HEART RATE VARIABILITY BIOFEEDBACK

An investigation into its adoption and benefit in people with autistic spectrum disorder

Helen Louise Coulter (MA MSc D. Clin Psych. AFBPsS)

Faculty of Life and Health Sciences

Thesis submitted for the degree of Doctor of Philosophy, October 2018

I confirm that the word count of this thesis is less than 100,000 words

Table of Contents

Acknowledgements

This research would not have been possible without the support and guidance of my supervisors at Ulster University, Professor George Kernohan and Dr Mark Donnelly – you have supported and guided me through a very long journey, thank you for your wisdom, kindness and patience. Thanks also to Dr John Mallett for advice on statistics, and Dr Cathal Breen for advice on cardiac physiology.

I would also like to thank the Public Health Agency Northern Ireland for supporting me with the fellowship award that enabled me to begin my research. In addition, I would like to thank to all the staff in South Eastern Health and Social Care Trust who enabled this research to take place. In particular, my thanks to Dr Mandy Irvine and to Bria Mongan who supported this research from the outset and to Paul Carlin and the staff at the research office for their advice and guidance. Thank you also to the people with ASD and their families who took part in this research – your involvement has made a difference and I wish you all well for the future.

My friends, both within the university and outside, have been there every step of the way and I could not have completed this without your support. Thank you to Sharon, Esther, Anne, Olivia, Sarah and Helena, also to Olufikayo and Keiko – you know how hard it is to do this so thank you for being there. Thanks to my friends Arlene, Elaine, Alison, Karen, Mel, Gloria, and Bronach, I can't wait to finally spend time with you all. Thanks also to Dad, Trish and Chris for all your support.

Finally, my heartfelt thanks to Nicky, Conn and Beth – thank you for all your support, for all your hugs, and for all the doughnuts!

Lastly, this thesis is dedicated to my mother Rebecca Jane Coulter who became ill during the years over which this research study took place and died in 2016. She wanted me to be happy and to keep going. She was kind, determined, enthusiastic and was my greatest friend. I miss her with all my heart. She taught me to,

follow where your heart leads, it will not lead you astray.

Abstract

Autistic spectrum disorder (ASD) is a complex neurodevelopmental disorder associated with high levels of anxiety. This study assessed the feasibility of using a complex investigation in a healthcare environment by testing the adoption and usability of heart rate variability (HRV) biofeedback as an intervention to help people with ASD manage anxiety.

The first phase entailed patient and public involvement of key stakeholders to develop the study protocol. The second phase involved a small-scale pilot trial with participants with ASD who had been attending mental health services (n = 20, 13-24 years; 16 males; 4 females; IQ>70). Participants were randomly allocated to an immediate biofeedback group, or a waiting list group who then also received the biofeedback intervention after a 6 week wait. Participants were allocated to one of two different home trainer HRV biofeedback devices (StressEraser or Inner Balance). All participants were offered training and were provided with a biofeedback device for home use over a 12-week intervention period. Pre and post levels of anxiety and depression were measured using questionnaires, whilst HRV was measured using single lead ECG.

Pre-post participant reports indicated a significant reduction in anxiety in children (p = 0.04; d = 0.96) and adults (p = 0.006; d =1.39) but no change in depression over the course of the intervention. Pre-post ECG monitoring indicated no change in HRV indices and a significant increase in heart rate (p = 0.01; d = 0.73) during a stress profile assessment.

Surveys and usability ratings were collected to assess acceptability of the intervention. The majority of participants were able to use HRV biofeedback devices with reported benefit, however some participants had difficulties using a fingertip sensor device. The feasibility of using HRV biofeedback to manage anxiety in this population in a larger trial was found to be acceptable.

List of Abbreviations

ASD	Autistic Spectrum Disorder
ANS	Autonomic Nervous System
DOH	Department of Health
HR	Heart Rate
HRV	Heart Rate Variability
IAPS	International Affective Picture System
NAS	National Autistic Society
NICE	National Institute of Clinical health Excellence
PHA	Public Health Agency
PNS	Parasympathetic Nervous System
RMET	Reading the Mind in the Eyes Test
SEHSCT	South Eastern Health and Social Care Trust
SNS	Sympathetic Nervous System
UK	United Kingdom
US	United States of America

Declaration

I hereby declare that for two years following the date on which this thesis is deposited in the Library of the University of Ulster, the thesis shall remain confidential with access or copying prohibited. Following expiry of this period I permit the Librarian of the University to allow the thesis to be copied in whole or in part without reference to me on the understanding that such authority applies to the provision of single copies made for study purposes or for inclusion within the stock of another university. This restriction does not apply to the British Library Thesis Service (which is permitted to copy the thesis on demand for loan or sale under the terms of a separate agreement) nor to the copying or publication of the title and abstract of the thesis.

IT IS A CONDITION OF THE USE OF THIS THESIS THAT ANYONE WHO CONSULTS IT MUST RECOGNISE THAT THE COPYRIGHT RESTS WITH THE AUTHOR AND THAT NO QUOTATION FROM THE THESIS AND NO INFORMATION DERVIVED FROM IT MAY BE PUBLISHED UNLESS THE SOURCE IS PROPERLY ACKNOWLEGED

Chapter 1. Introduction

1.1 Overview

This thesis presents research into a technology proposed to help relieve distressing symptoms in one of the most prevalent developmental disorders affecting communication and behaviour.

This initial chapter first describes the condition which is now known as autistic spectrum disorder or '*ASD*'. The growing prevalence rates and the increasing social and financial costs of ASD will be highlighted. A summary of research developments within the field of ASD will be described and some of the areas which have been proposed as important directions for future research into ASD are outlined. The growing importance of the ASD community in helping to shape and to define our understanding of the condition will also be acknowledged.
The structure and scope of the current study will then be reviewed, and the overall study aim will be defined.

1.2 Autism and Autistic Spectrum Disorder (ASD)

> *"There are now approximately 700,000 people with autistic spectrum disorder within the UK and the costs of meeting their needs has been estimated to be more than that of cancer heart disease and stroke combined"* (Iemmi *et al.* 2017 p.14).

Autism is a condition which affects how a person communicates with and relates to other people. It also affects how they make sense of the world around them (National Autistic Society 2010). Individuals with different forms of autism vary, however they show all two core features; difficulties with social communication and interaction, and restricted, repetitive patterns of behaviour, interests or activities (Research Autism 2016).

Substantial changes to how autism is understood and defined have taken place over the years since the term was initially described by the psychiatrist Leo Kanner in 1943. The term '*Asperger's Syndrome*' has been used particularly within the UK to describe people with autism and no learning disability, after the of the work of Hans Asperger was described by Wing (1981a).

At the time of writing autism is viewed as a neurodevelopmental disorder which develops in childhood. It is described in a dimensional rather than a categorical framework (Lord and Jones 2012) and is behaviourally defined according to standardised diagnostic criteria. Thus, the Diagnostic and Statistical Manual for Clinicians, fifth edition (DSM-5 2013) has replaced the terms Autistic disorder; Asperger disorder; Childhood disintegrative disorder, and Pervasive developmental disorder not otherwise specified (PDD-NOS), with the collective term '*Autistic Spectrum Disorder'* (ASD) and also recognises the importance of sensory issues in people with the condition. The International Classification of Diseases, which is widely used in Europe is expected to also reflect these changes in the next edition.

Whilst the term Asperger syndrome is still used by both clinicians and some able people with autism, the term '*ASD*' will be used throughout this text to describe the condition.

1.3 The Growing Prevalence and Costs of ASD

Around 1% of the UK population are likely to have some form of ASD, with studies reflecting this prevalence both in children (Baird *et al.* 2006) and in adults (Brugha *et al.* 2012).

Epidemiological studies over the past 50 years have shown a dramatic increase in the numbers of people being diagnosed with ASD. For example, Lotter (1966) reported a prevalence rate of 4.5 in 10,000, whilst a review of 23 studies carried out by Fombonne (1999) reported 18.7 in 10,000. In the US, the Centre for Disease Control produced a widely publicised report of a prevalence rate of ASD in children of 1 in 88 (U.S. Department of Health and Human Services 2012) which was updated to 1 in 59 in 2018. The reasons for these apparent increases, and the differences between incidence and prevalence rates have been debated (e.g. Taylor *et al*. 2013) but are likely to be related to changing definitions of the disorder; increased awareness of the condition in women and girls, and recognition of the condition in people with no learning disability (Thrum 2012).

The economic cost of ASD was reviewed in 2007 by Knapp and colleagues at the National Autism Project in the London School of Economics, with initial estimates of costs at £28 billion per year. A further review carried out in 2017 indicated that the costs of ASD are growing and have now been estimated to be £32 billion a year (Iemmi *et al.* 2017).

A review of research into ASD in the UK was carried out by Pellicano *et al*. (2013; 2014). The level of research output in the UK, as indicated by numbers of research publications, was found to have doubled between 2001 and 2011; however even with these increases, the level of funding for research in the UK was found to be much lower than in the US, and comparatively little research was focused on treatments and interventions (Pellicano *et al.*2013). The National Autism Project review has also emphasised that, despite the growing prevalence and high costs, the funding for ASD research and interventions lags behind the level of support given to other conditions (Iemmi *et al.* 2017).

1.4 ASD Research

1.4.1 *What do we currently know?*

Research over the past 50 years has led to significant changes in how ASD is viewed and understood. A number of different theoretical models have been developed to explain differences seen in people with ASD, compared to typically developing peers.

During the first half of the 20th century reports from Kanner (1943) noted 'a lack of warmth' in mothers of autistic children, and authors such as Bettelheim (1972) popularised what became known as the '*Refrigerator mother*' theory of autism, suggesting that autism was caused by a lack of maternal affection. During the latter half of the 20th century such theories were largely rejected, and theories on ASD related to some of the cognitive differences which were demonstrated in experimental studies assessing the responses of people with ASD (Sivaratnam 2015).

For example, differences described as '*Theory of Mind*' difficulties have been demonstrated in people with ASD in a number of widely reported experimental studies (Baron-Cohen 1985). The term '*Weak Central Coherence'* has also been used to describe some of the unique visual differences demonstrated in people with ASD (Frith and Happé 1994). '*Executive function deficit*s' have also been described in ASD (Ozonoff *et al*.1991; Hill 2004).

Studies of monozygotic twins in the 1970's highlighted a high level of heritability in ASD (Folstein and Rutter 1977)**.** A large body of research has since been focussed on trying to identify specific genes involved in the development of ASD (Geschwind 2011). The search for ASD specific genes has however shown much more complex picture with current research suggesting a very large number of genes involved (State and Levitt 2011). Research has indicated that there is also an important environmental component to ASD (Field 2015).

Interest in the interactions between genes and the environment has led to an increase in epigenetic research investigating how the environment may play a role in triggering expression or suppression of genes in the development of ASD (Schanen 2006).

ASD has been described as a specific '*systematising*' style of cognitive functioning which is more common in males (Baron-Cohen 2002). The term '*neurodiversity*' has been used to highlight the view that some differences seen in intellectually able people with ASD should simply be accepted and respected rather than modified to what has been termed '*neurotypical'* behaviour (Jaarsma 2012).

The increasing availability and use of neuroimaging techniques, and the development of complex signal processing and physiological monitoring, has enabled researchers to assess differences in the central nervous system and the autonomic nervous system of people with ASD, compared to those without ASD.

For example, research using neuroimaging has demonstrated **s**igns of early brain 'overgrowth' in children with ASD (Hazlett *et al*.2011). Functional neuroimaging studies have demonstrated differences in the brain's response to social information in people with ASD (McPartland *et al*.2011). Eye tracking technology has been used to show early differences in the visual preferences of children with ASD (Pierce 2016). Autonomic nervous system dysfunction has been recognised as a difficulty affecting many people with ASD (Hirstein *et al*.2001; Cheshire 2012; Lydon *et al*.2014). A widely reported theory has linked difficulties seen in ASD to dysfunction in a proposed system of neurons involved in multisensory integration, called the '*Mirror Neuron System'* (Obermann and Ramachandran 2007).

The numbers of people with ASD reported to have no intellectual disability have varied widely depending on methods of measurement and people with ASD have been found to score significantly higher on non-verbal intelligence tests (Dawson 2007). Reviews of prevalence increasingly indicate that over 50 percent of people with ASD have no intellectual disability (Kim *et al.* 2011; Postorino 2016).

The gender ratio in ASD has previously been reported as 4:1 male to female (Ehlers and Gillberg 1993), however it is thought that many girls and women with ASD have not been recognised because of their ability to mask symptoms of the disorder (Gould and Ashton-Smith 2011; Dean 2017). Gender identity disorder has also been reported to be more common in people with ASD (de Vries 2010).

Moving into the 21st century many of the epidemiological studies have also highlighted the importance of recognising the high levels of anxiety, depression and sensory difficulties experienced by people with ASD (Ghaziuddin 2005; Simonoff *et al.* 2008). For example, there is an increased risk of early death and suicide in people with ASD (Richa 2014; Hirvikoski 2016) and the importance of sensory problems is now formally recognised in clinical guidelines (DSM-5 2013).

1.4.2 *ASD Research – Where should we go from here?*

A review of future directions for research into ASD has been carried out by Damiano *et al.* (2014). A new method called *'Experimental therapeutics'* for the design of studies assessing ASD has been highlighted as a useful and cost-effective technique of assessing novel approaches prior to carrying out larger scale trials (Damiano *et al.* 2014). This method involves developing preliminary small-scale studies to test out new interventions by measuring key areas relating to the neurology or physiology of people with ASD as outcome indicators.

Assessment of the thoughts and feelings of people with ASD using traditional retrospective questionnaires may not accurately reflect their reactions due to their intrinsic social and communication difficulties. A potentially more useful type of assessment has therefore been proposed, termed *'Ecological momentary assessment'* which may provide a more accurate method of capturing the emotional states of people with ASD (Damiano *et al.* 2014). This method involves carrying out more frequent assessments to capture the reactions of people with ASD as they occur in real time rather than relying on a single retrospective report.

The wider use of technology has also been advocated as a potential method for the delivery of future interventions to help people with ASD (El Kaliouby et al. 2006). Due to difficulties with face to face social interaction the use of computers is often an area of interest for people with ASD. For example, the rapid growth of the '*neurodiversity*' movement via online groups has highlighted the importance of the internet for people with ASD (Jaarsma 2012).

The use of computer-based techniques can reduce the demands made by verbally mediated techniques that can be actually more stressful and confusing for people with ASD (National Autistic Society 2010). Technology may be used to deliver interventions and to augment both communication and social interaction, and growing interest in this area has led to increased contact between the ASD community and researchers (Bölte 2010)

The high level of mental health conditions in people with ASD has also been emphasised by number of reviews as an important area for future research, which may in turn also help in our understanding the possible mechanisms underlying the aetiology of ASD (Pelton and Cassidy 2017).

Finally, the importance of patient and public involvement in the design; development and impact assessment of interventions has been emphasised as important to help improve overall outcomes within health care (Mockford *et al*.2012). The term *co-production* has become a popular byword to emphasise the need for user involvement in the development of a range of different clinical interventions (Verschuere 2012). A number of reviews within the field of ASD research have also acknowledged the necessity to listen to, and to involve the increasingly vocal ASD community (Pelicano 2014; Fletcher–Watson 2018).

1.5 Listening to the ASD community

> *"If you got rid of all the autism genetics, you wouldn't have science or art. All you would have is a bunch of social yak yaks"* (Grandin, 2010, p.1).

Temple Grandin is one of the most widely known people with ASD. She has written numerous books regarding her own experiences and has given detailed insights into the experiences of people with ASD (Grandin 2006; 2010). Grandin highlights the importance of recognising that whilst ASD can be a disability, many people with ASD also have abilities and special talents which can make a great contribution to society. However, despite their potential talents, many people with ASD struggle both in education and in employment. For example, statistics reported by the National Autistic Society (NAS 2010) suggest that only 16 per cent of people with ASD are in full time employment.

An evaluation of the views of people with ASD in the UK, their families and practitioners was reported by Pellicano *et al.* (2014) to highlight areas of focus for future research into ASD. Reports from people with ASD and their carers indicated a high level of dissatisfaction with the current type of funding carried out in the UK, which had focussed mainly on areas within biological and cognitive sciences. The report concluded that future research should take account of both the current needs of people with ASD, and importantly also involve them in research development and planning, *"future...research should lie in those areas that make a difference to people's day to day lives"* (Pellicano *et al*. 2014 p.756).

There has also been a growing recognition of the importance of listening to the voices of the ASD community and allowing people with ASD to be different. For example, accounts from people with ASD have highlighted how many people with ASD enjoy activities which others without ASD often termed 'neurotypicals' find strange and repetitive (Grandin 2011). These special interests and repetitive behaviours are often reported to reduce stress and should not always be targeted as things to change or remove (Grandin 2011).

1.5.1 *What issues are important for people with ASD?*

> *"Lots of autistic people get very stressed or anxious…Everyone should understand more about what can cause anxiety or stress for autistic people and the simple things they can do to help"* (Iemmi *et al.*2017, p.3).

One significant area of need directly reported by people with ASD and their carers is the high level of stress that they experience. The Autism Dividend Report reviewed the costs of ASD and one of the key recommendations was the need to understand more about stress or anxiety and to provide further support for people with ASD (Iemmi et al. 2017).

An assessment of direct reports from people with ASD and their carers has been conducted by Research Autism (2016). In this survey 98 % of people with ASD and their carers reported that *"stress is a significant issue"* whilst 89% reported that it was *"difficult or impossible to find effective support"* (Research Autism 2016). Key areas of difficulty reported to be related to stress were "*poor sleep; lack of confidence; problems with work and relationships and overall health"* (Research Autism 2016).

The term '*meltdown*' is also frequently used by the ASD community to describe an important issue affecting many people with the condition. This phenomenon can be described as becoming completely overwhelmed and losing control. Many able people with ASD have written about this difficulty and the need for further support and research (Lipsky 2011).

These reports and the growing use of direct reports from people with ASD suggest that providing people with ASD with support to manage stress, anxiety or meltdowns may be a valuable area for further research which could make a difference to their lives.

Thus, it is important to first review what we already know regarding evidence on interventions to help people with ASD, before assessing what further interventions may be useful.

1.6 Interventions to help people with ASD

Research into interventions to help people with ASD has not been without controversy. Some interventions have on occasion been adopted without clear evidence for effectiveness and have led to unwanted side effects or at times even fatal results (Williams 2012; Farmer 2013).

Interventions have at times been advocated by those with a vested interest in a particular mode of therapy or treatment. For example, a report regarding a postulated link between ASD and use of the MMR vaccine in a small sample of 12 children (Wakefield 1998) led to a worldwide reduction in the uptake of vaccination rates (Godlee 2011). The postulated link between MMR and ASD has since been researched with no evidence for any link (Taylor *et al.* 2014: Uno *et al.* 2015).

Many studies have advocated treatments based on small non-randomised samples, and whilst studies using small samples can provide useful information on a potential intervention, larger scale randomised studies have been needed to enable interventions to be adequately assessed for effectiveness. Systematic reviews of behavioural and psychosocial interventions have shown inconclusive results and have highlighted the wide variability in populations; interventions and outcome measurement in studies (Ospina *et al.* 2008: Bishop-Fitzpatrick *et al.* 2013).

A valuable development for both clinicians, people with ASD and their carers has been the production of evidence guidelines for interventions by organisations such as the National Institute for health and Clinical Excellence (NICE). In addition, charities such as National Autistic Society, Research Autism and Autistica now regularly provide people with ASD and their carers with more objective advice on research evidence about what interventions can actually help people with ASD.

Clinical guidelines produced in 2013 concluded that no one intervention was seen as better for treating symptoms of ASD, and several interventions such as chelation therapy; hyperbaric oxygen; secretin and antidepressants for treatment of core symptoms of ASD were not recommended (NICE Clinical Guidelines: 170, 2013).

1.6.1 *The use of technology to help people with ASD*

> *"The computer is kind of like what sign language is to the deaf. It's the autistic way of communicating"* (Bagatell 2010, p.37).

The use of technology has been advocated by many people with ASD as a less stressful medium for learning which is suited to their visual strengths (Murray 1999, National Autistic Society 2010). There is also growing research evidence for technology both to aid compliance with traditional treatments and as innovative interventions in their own right. (Mintz 2013; Grynszpan *et al*.2014).

The over use of technology in children and young people has also become a concern, particularly regarding the effects of excessive video gaming. A number of meta analyses have highlighted negative effects associated with gaming such as increased aggressive thoughts and decreased prosocial behaviour (Anderson et al. 2001; 2010). A recent longitudinal study has also highlighted associations between time spent gaming and levels of anxiety and depression in children (Lobel 2017).

Despite concerns regarding overuse, there has likewise been an acknowledgment of the potential for technology to help manage the growing levels of mental health in the general population. In a report entitled '*Rebooting psychotherapy research and practice*' the use of technology is advocated to help reduce the increasing burden of mental illness (Kazdin and Blase 2011). In addition, several systematic reviews have highlighted the potential of specific games for psychotherapy (Eichenberg et al. 2017) and use of video games for role play; stress reduction, and emotion regulation (Villani 2018). Technology may provide researchers and therapists with tools to assess and intervene with large numbers of people which current traditional models of face-to-face therapy simply cannot support.

Interventions to help people with ASD manage stress and anxiety or reduce meltdowns remains an area of need where further research is warranted. Technology may represent a useful method to help people with ASD as it does not involve the complex social and communication demands required in interventions such as social skills groups or cognitive behaviour therapy (CBT).

1.7 Study rationale

> *"Nearly a decade on the needs of people with autism are still unmet"* (Iemmi *et al*. 2017, p.14).

ASD is now a common condition (Brugha 2012). Reports suggest high costs of supporting people with ASD, yet little research has been undertaken into new types of interventions specifically designed to meet their needs (Pellicano 2014).
Methods of intervening to help people with ASD manage anxiety have often involved provision of therapy via groups or face to face talking therapy using therapies such as CBT which were originally designed for people without ASD, and which place additional burden on people with ASD due to their underlying social and communication difficulties. It is argued that new interventions should be designed from an ASD perspective using methods that are more suited to the strengths and interests of people with ASD.

It is argued that new studies are needed to investigate interventions to help people with ASD manage issues that concern them such as anxiety. Many people with ASD report that managing stress is one of the biggest issues facing them (Research Autism 2016); that they simply want help managing stress, and that current interventions are not meeting their needs (Pellicano 2014).

People with ASD represent an active and vocal community who are not always involved in the design and development of research studies into their condition.
This study was thus designed to with these issues to the fore and aimed to develop an intervention to help people with ASD manage anxiety designed from an ASD user perspective.

People with ASD frequently describe themselves as visual thinkers and report that visual information rather than verbal information is an important method for learning (Grandin 2006). The use of visual aids has become ubiquitous as a method to help people with ASD understand and manage difficulties including anxiety (e.g. Gray 1994; Buron 2003).

The use of visual information presented via technology is now being investigated as a method of teaching people with ASD to enable them to understand and control their reactions (Torrado *et al.* 2017) and to interpret social situations more easily (Daniels *et al.* 2018).

Mindfulness based stress reduction and mindfulness based cognitive therapy have become popular methods of helping many people manage anxiety (Kabat-Zinn 1992). Some studies have now directly investigated the use of mindfulness-based approaches for people with ASD (Singh *et al.* 2011). One important component of mindfulness-based interventions is a focus of attention on the breath, and meditation with a focus on breathing has been found to show changes in ANS function (Krygier *et al* 2013). However, mindfulness-based interventions typically involve use of complex cognitive skills in a group therapy setting which can benefit parents and caregivers but may not be suited to social and communication difficulties of people with ASD (Keenan-Mount *et al.* 2016).

Many people with ASD have visual strengths and an interest in technology therefore this study considered technology as a potential method of helping to provide an intervention to manage anxiety. The focus for technology however was not on use of 'gaming' which has been associated with reports of increased inattention and anxiety in children (Anderson 2010; Lobel 2017).

Biofeedback was chosen as a method for intervention to help people with ASD manage anxiety. Biofeedback is argued to provide a number of advantages over traditional CBT and mindfulness-based interventions and breathing techniques for the management of anxiety in ASD. First, it can present information in a visual manner suited to the typical strengths of people with ASD (Grandin 2006). Second, it provides structured information in a systematic manner a factor recommended as important for provision of interventions for people with ASD (NICE guide 170). Further, biofeedback aims to increase awareness of physiological reactions which can be reduced or impaired in people with ASD (Dubois *et al.* 2016).

Biofeedback technology provides a technique for developing control over specific symptoms in a visual and systematic manner without the need for complex cognitive techniques or complex group interventions which are potentially anxiety provoking for people with ASD (Mottron 2017). The use of technological solutions to difficulties experienced by people with ASD may represent what has been termed a 'naturalistic developmental behavioural intervention' which can help with the generalisation of skills due to their use in real world interactions (Schreibman *et al.* 2015).

Assessment and measurement of the thoughts and feeling of people with ASD using retrospective questionnaires alone may not accurately reflect their reactions to an intervention due to their intrinsic social and communication difficulties. Therefore, assessment of self-reported 'stress levels' using technology was used for people with ASD in this study as this type of measurement can be completed quickly and remotely without the need for frequent clinic visits for assessments.

There is also a need to carry out pilot studies to investigate new interventions prior to any large-scale trial. Therefore, this study targeted a small sample of people with ASD and collected detailed information on both demographics and mental health.

Many people with ASD show difficulties with physiological reactivity suggesting ANS dysfunction (Lydon *et al*.2014). Measuring physiological changes before and after an intervention may represent a more objective measurement of outcome and may also help our understanding of some of the underlying difficulties that people with ASD experience (Di Palma *et al.* 2017). One of the objectives of the study was therefore to also measure changes in key physiological indicators, which have already been suggested as potential differences in people ASD, as well as using more traditional measures using questionnaires. The targets for change in this study were not focussed on social and communication skills but were instead focussed on assessing measurable changes in behaviour and physiology, related to anxiety.

1.8 Scope and Structure of Current study

This study took the form of a small-scale piloting and feasibility study, which investigated anxiety management for people with ASD using technology. Providing an intervention based on use of technology may be more interesting for people with ASD and may be more suited to their needs (Oberleitner et al. 2006).

The study involved people with ASD in the initial assessment of design, measures, equipment and procedure,

The study then collected detailed information on participant characteristics and used technology to monitor progress and use of the intervention over time. In addition, some of the outcome indicators for measurement of change involved targeting key areas such as change in physiology and change in observed behaviour, as well as using more traditional questionnaire assessments.

The study was limited by the fact that this is a PhD level project with one investigator available to provide the intervention and to collect and analyse data. It therefore did not have the scope to trial the intervention against another existing treatment or to recruit a large sample of participants.

The investigator has a high level of experience both working with people with ASD, and with people with mental health difficulties, and the study did therefore recruit a clinical population of people with ASD who had mental health needs.

In addition, the investigator undertook an extensive programme of training to develop skills in physiological assessment and the delivery of technology-based interventions, prior to embarking on this research project.

1.9 Overall Aim of the Study

The overall aim of this study was to investigate a new approach to helping people with ASD manage anxiety using technology.

Biofeedback was chosen as an intervention because it typically presents information in a visual manner and provides a very structured and systematic process for developing control over specific symptoms. Biofeedback aims to increase awareness of physiological reactions something which has been found to be reduced or impaired in people with ASD (Dubois *et al.* 2016).

The study assessed key physiological outcomes as well as using other more traditional forms of clinical assessment. It monitored progress using technology and reviewed problems, risks and benefits to assess the feasibility of carrying out a larger scale trial in the future.

The next chapter will explore in more detail three key background themes relevant to this study and will outline the study rationale, and key research objectives.

Chapter 2. Background Information

2.1 Overview

This chapter reviews background information on three main themes upon which this thesis is based. These themes relate to three of the indicators, Population, Intervention and Outcome, within the 'PICO' framework used for reporting interventions (Richardson *et al.* 1995).

First, relevant background research on the population of ASD is presented and theories regarding ASD, anxiety and the autonomic nervous system are then reviewed.

Second, a sensor technology-based intervention termed 'biofeedback' will be described and research regarding biofeedback is reviewed. The use of biofeedback in different populations without ASD is outlined and evidence for the use of biofeedback in people with ASD is discussed.

Third, a physiological measurement modality, namely Heart Rate Variability or 'HRV', is defined and standards for measurement of HRV are described. The growing use of HRV as an indicator of autonomic nervous system functioning is discussed. The development of a specific type of biofeedback, termed HRV biofeedback, is described and the use of HRV biofeedback in different populations is outlined. The links in relation to these three areas are then described.

Finally, the rationale for using a home-based technology intervention using HRV biofeedback to help manage symptoms such as anxiety in people with ASD will be presented, and the overall research hypothesis for the study is proposed.

2.2 ASD and anxiety

> *"Just imagine how you felt when you did something really anxiety provoking… now just imagine if you felt that way most of the time, for no reason"* (Grandin 2011, p.2).

The personal account quoted above illustrates the significant impact that anxiety can have on the lives of people with ASD, and the importance of understanding anxiety when assessing and treating people with ASD.

People with ASD have spoken about their awareness of 'difference' from others from an early age which can be viewed as a problem or disability, or simply as a difference which requires acceptance (Grandin 2006: Kapp *et al*.2013)

2.2.1 *Definitions of anxiety and stress*

The terms 'anxiety' and 'stress' are often used interchangeably however 'stress' is also sometimes used to describe a cause of strain or tension. Thus, the Oxford English Dictionary (OED) defines stress as,

> *"a state of mental or emotional strain or tension resulting from adverse or demanding circumstances" OR "something that causes a state of strain or tension"* (OED online, 2018).

Anxiety is defined as "a *feeling of worry, nervousness, or unease about something with an uncertain outcome*" (OED online 2018). Whilst these two terms are often used interchangeably the term 'anxiety' is used for the majority of this text as defined above. The term 'stress' has previously been used in surveys of people with ASD and it is therefore also used in this text in surveys of direct reports from people with ASD to describe, '*a state of mental or emotional strain or tension*' rather than a cause of strain or tension.

Assessment of anxiety levels is now seen as a vital part of any initial assessment of ASD (Vasa 2016).

2.2.2 *What levels of anxiety do people with ASD experience?*

High levels of anxiety particularly in people with ASD and no learning disability have been reported since the first reports in English of what was termed Asperger's syndrome (Wing 1981a). This group of people with ASD were reported to show,

> *"…clinically diagnosable anxiety and varying degrees of depression…which seem to be related to the painful awareness of handicap and difference from other people."* (Wing 1981a, p. 118).

Research since this time has continued to report mental health difficulties in people with ASD with the most commonly reported disorders being anxiety and depression (Stewart *et al.* 2006). Reviews have also indicated a high level of other co-morbid mental health conditions associated with ASD including problems with obsessive compulsive disorder; attentional problems and phobias (Simonoff *et al.*2008; Lugnegard *et al*.2011). Reviews of the levels of anxiety reported in people with ASD have however shown wide variations (Ghaziuddin 2005; Stewart *et al.*2006). There are likely to be several reasons for this wide variation:

(i) People with ASD, by definition, have intrinsic communication difficulties and may struggle with understanding and explaining their thoughts and feelings;

(ii) Parent observations and questionnaire reports may also not provide accurate information, due to difficulties interpreting the underlying feelings of people with ASD, which may not be accurately reflected in their observable behaviour (Mazefsky *et al.*2011; Bitzika *et al.* 2015);

(iii) The expression of anxiety in ASD may also be uniquely different to anxiety seen in people without ASD. A review of the presentation of anxiety in ASD found a range of recognised types of anxiety disorder but also patterns of anxiety unique to ASD such as unusual fears and phobias (Kerns *et al*.2014):

(iv) The use of questionnaires traditionally used for people without ASD which require retrospective recall of thoughts and feelings may also be particularly difficult for people with ASD to understand and to report on accurately (Damiano *et al.* 2014).

Current questionnaires designed for the non-ASD population may not adequately capture the symptoms of ASD type anxiety which can also overlap with core symptoms of ASD symptoms (Jitlina et al. 2017). This issue has led to some researchers designing questionnaires specific to ASD such as the '*Autism Stress Survey Schedule*' (Goodwin 2007).

Due to the ongoing difficulties measuring anxiety in ASD any assessment of anxiety should ideally also check for the presence of other mental health conditions and use a number of different methods of assessment including direct reports; observations from carers, as well as using traditional questionnaires (Vasa 2016).

Despite variations in reports of levels of anxiety in ASD, a meta-analytic review indicated prevalence rates of anxiety in young people with ASD of 40%, compared to rates of anxiety of 27% in typically developing peers (van Steensel *et al*. 2011).

A further systematic review and meta-analysis of 83 studies carried out by van Steensel and Heeman (2017) has also indicated increased risk of anxiety in children and young people with ASD compared non ASD peers, particularly with increasing age and with higher IQ.

2.2.3 *What causes anxiety in ASD?*

Models describing potential mechanisms to explain the development of anxiety in ASD have been proposed by a number of research groups.

One proposed reason for anxiety reported in people with ASD, is that it is not a secondary problem related the effects of social and communication difficulties, but that it is a sign of an underlying difficulty with the autonomic nervous system and is a core feature of the condition (Sugarman *et al*. 2013).

A further model proposed by Boulter et al. (2014) is that people with ASD show increased anxiety in situations of ambiguity, a cognitive concept described as '*intolerance of uncertainty'* (Dugas 1998). South and Rodgers (2017) have proposed a detailed model for the development of anxiety in ASD, using a framework which links sensory and emotional dysfunction, to the construct of intolerance of uncertainty, which can then in turn, lead to the anxiety or repetitive behaviours seen in ASD.

However, there may also be significant environmental and social factors which cause anxiety in ASD which are not related to the person with ASD directly, but to other people's reactions to them. For example, a study has shown how people without ASD frequently make immediate and unfavourable judgements about people with ASD irrespective of the intellectual ability of the person with ASD (Sasson *et al.* 2017).

The exact reasons for high levels of anxiety in ASD are still unclear but may be related to both underlying difficulties within the individual themselves and to secondary environmental effects related to some of the consequences of having an ASD such as those highlighted by (Sasson *et al.* 2017).

2.2.4 *What interventions are available for anxiety in ASD?*

A range of different treatments are available to help manage anxiety in people with ASD, however they vary in terms of their availability due to limits both on resources and in expertise in working with people with both ASD and mental health conditions (Wong *et al.* 2015; Vasa 2016).

Medical treatments have been used for many years in people with ASD to help manage both anxiety and some of the behaviours associated with ASD. For example, Melatonin has been used and found to be a treatment which is both safe and effective for the treatment of sleep problems in ASD (Gringras and Gamble 2012). Medications commonly used to manage anxiety in people with include selective serotonin reuptake inhibitors (SSRI) antidepressants such as sertraline and escitalopram. Anti-psychotic medications such as risperidone have also used to manage some of the challenging and repetitive behaviours associated with anxiety in ASD. However systematic reviews of the medical treatments for ASD used to manage anxiety have suggested that existing evidence for the effectiveness of these medications is limited and that side effects and adverse events can occur (McPheeters *et al.* 2011; Dove *et al.* 2012; Siegel and Beaulieu 2012). Personal accounts from people with ASD on the effectiveness of medications to help anxiety have been mixed, with some reporting benefits (Grandin 2011) and some reporting significant negative effects (Lipsky 2011).

A number of non-medical interventions have also been used to help manage anxiety in people with ASD. For example, Cognitive behaviour therapy (CBT) has been adapted and used as an intervention for adults, teenagers and for younger children with ASD, both to improve social responsiveness, and to reduce anxiety (Sofronoff *et al*. 2005; White *et al.* 2009; Wood *et al.* 2009). Further studies have reported on adaptations of CBT for younger children with ASD (Scarpa and Reyes 2011). Group based CBT has been reported to show positive effects as measured by changes in social responsiveness reported by parents (Freitag *et al.* 2016).

Some studies assessing the effects of CBT have suggested that positive changes in young people with ASD have been reported by parents for up to three months' post treatment (White *et al.* 2015; Maddox *et al.* 2017).

Evidence from systematic reviews of studies using CBT treatment have indicated some support for the use of CBT in people with ASD (Lang et al. 2010; Ung et al.2015). However additional input from parents may be an important factor to improve treatment outcomes of CBT in young people with ASD (Reaven 2011).

A systematic review and meta-analysis on the use of CBT for people with ASD has been carried out by Weston *et al.* (2016). This quantitative synthesis review assessed 48 studies and results indicated that overall effect sizes of CBT treatment for ASD varied depending on the outcome measures used and the population questioned. Thus, evidence from direct reports from people with ASD using CBT indicated non-significant effects, whilst results of reports from parents supporting the CBT treatment indicated small or medium effect sizes (Weston *et al.* 2016).

Mindfulness interventions based on the work of Kabat-Zinn (1982) have become a popular method to help neurotypical people without ASD manage anxiety, and mindfulness-based interventions have now also been investigated for people with ASD. A meta-analytic review assessed the effect of mindfulness interventions on anxiety and depression in clinical populations (Hofmann *et al.* 2010) and highlighted moderate effect sizes for improvements in anxiety. A review of the use of mindfulness for people with ASD identified nine studies using this type of approach for people with ASD (Keenan-mount *et al*. 2016). The majority of interventions identified actually involved teaching mindfulness techniques to parents or teachers of young people with ASD (e.g. Jones *et al.* 2014; Hwang *et al.* 2015). Some mindfulness interventions for people with ASD have been reported however these have involved removing the more abstract cognitive components and using yoga and breathing techniques for people with ASD (Singh *et al.* 2011; de Bruin *et al.* 2014).

The evidence for non-medical interventions such as CBT to manage anxiety in people with ASD is growing however many studies report on small samples using parent report only. Investigation of the views of people with ASD and the use of individual therapy rather than group therapy has been recommended (Weston *et al.* 2016).

The availability of many non-medical interventions remains limited due to need for skilled therapists and the large numbers of people requiring interventions. There is significant cost both in terms of therapist training and time involved in providing these interventions and many therapists report that they lack confidence and training (Cooper *et al.* 2018). The growth in alternative treatments both pharmacological and non-pharmacological, reflects the continuing demand from people with ASD and their carers for support (Lofthouse *et al.* 2012). A guide has now been produced aimed at supporting carers and people with ASD in choosing interventions, which reviews the numerous interventions available with information on the available research evidence for each (Fleming *et al.* 2015).

A systematic review of existing treatments for anxiety in ASD carried out by Vasa (2014) indicated modest evidence for the effectiveness of CBT and highlighted a lack of randomised controlled trials of medication for treatment of anxiety in ASD.

There remains a lack of robust evidence for the effectiveness of current treatments of anxiety in ASD, as compared to the level of evidence supporting interventions for anxiety in typically developing peers (Vasa 2014). Evidence reviews suggest caution, particularly regarding the use of medication, and highlight the increased risks relating to bipolar disorder and suicide risk in people with ASD (Vasa 2016).

Current UK clinical guidelines on treatments for children and young people with ASD recommend consideration of CBT for anxiety in ASD and recommend following the existing guidelines for non ASD populations when considering medical treatment of comorbid disorders seen in people with ASD such as depression and obsessive-compulsive disorder (NICE clinical guideline 170: 2013).

2.2.5 *Reports from people with ASD about their anxiety*

> *"Eye contact is something that I have always had trouble with.... All of the stress that is put on doing it makes me more nervous, tense, and scared... just because I am not making eye contact with you does not mean that I am not listening to you or paying attention to you. I can concentrate better not having to keep eye contact at the same time"* (Bovee 1999, p.18).

A different way to explore the nature of anxiety in ASD, is to examine direct accounts from people with ASD and their families. Some of these accounts have led to increases in our understanding of the nature of ASD and these accounts can also highlight new areas for further research. For example, as illustrated in the quote above, many able people with ASD have written about the high levels of anxiety they experience if forced to look into someone's eyes.

Poor eye contact during social interaction has been described as a symptom of ASD since some of the early accounts of the condition were reported (Kanner 1943). Reports of poor eye contact have in turn led to *improvement in eye contact* becoming a common target for some of the behavioural interventions designed to help people with ASD. Presuming that improved eye contact will help people with ASD develop better social and communication skills has recently been argued to be a 'neurotypical' solution which does not consider the underlying needs and wishes of the individual with ASD (Mottron 2017).

It is has been argued that teaching individuals with ASD to simply change their behaviour to non ASD or *neurotypical* behaviour, may not always be an appropriate target for change without a better understanding of the underlying reasons behind ASD behaviour (Mottron 2017).

If the many personal accounts from people with ASD are to be believed, it is possible that some interventions designed to change behaviour such as eye contact in people with ASD, may have actually increased stress in some individuals and may at times be a trigger for a set of behaviours described by many within the ASD community as '*meltdowns'*.

2.2.6 *ASD Meltdowns*

> *"For someone with autism, when they reach the point of sensory, emotional and information overload, or even too much unpredictability, it can trigger a variety of external behaviours that are similar to a tantrum...it can trigger a complete shutdown and withdrawal"* (National Autistic Society, 2016).

A difficulty linked to anxiety, which has been widely reported by both families and people with ASD themselves, is a set of behaviours commonly referred by the ASD community to as *meltdowns* (Lipsky 2011). Meltdowns often involve extreme anxiety and agitation and are described by the National Autistic Society (NAS) as a reaction to being 'overwhelmed' (NAS 2016).

An important distinction is made by many people with ASD between meltdowns and tantrums, in that tantrums are typically seen in children as a result of not getting something they want. Tantrums occur in an attempt to gain something and can be controlled to some degree by interventions such as distraction, rewards or discipline. In contrast, meltdowns are viewed as a sign that the person has become completely overwhelmed and overloaded, and someone in the midst of a meltdown has little or no control over their behaviour. People with ASD have reported extreme fatigue and exhaustion and may not remember what has happened during a meltdown (Lipsky 2011, p127).

The management of ASD meltdowns require a very different approach because of their different underlying origin. For example,

> *"The goal for the support person at the height of a meltdown is to ensure safety, knowing the meltdown will continue until the energy is spent. There is no stopping a meltdown in progress"* (Endow, 2016).

Understanding both the '*sensory and environmental triggers for meltdowns'* is said to be essential for helping both people with ASD and their carers to manage this behaviour, which can occur in both adults and in children (Lipsky 2011 p.169).

One influential account of the development of poor eye contact, meltdowns and anxiety originated from two researchers who were also parents of a young child who was eventually diagnosed with ASD (Markram 2007).

These reports led to the development of a theory known as the '*intense world syndrome'* (Markram 2007), which describes how extreme sensory overload developing in very early life leads to severe anxiety, which in turn leads to social withdrawal. This theory focuses on the importance of sensory overload and anxiety, which are argued to actually cause many of the problems seen in people with ASD, such as poor eye contact; poor communication and repetitive behaviours (Markram 2007).

Green and Ben-Sasson (2010) have likewise highlighted the links between anxiety and sensory responsivity in people with ASD and have suggested a number of possible mechanisms regarding the interactions between both anxiety and sensory responses.

The repetitive behaviours often observed in people with ASD, have been described by some with ASD as a method of coping with both anxiety and sensory issues. For example, Grandin reports,

> *"When I did stims[1] such as dribbling sand through my fingers, it calmed me down. When I stimmed, sounds that hurt my ears stopped. Most kids with autism do these repetitive behaviors because it feels good in some way. It may counteract an overwhelming sensory environment"* (Grandin, 2011).

These personal accounts, in conjunction with the development of models regarding the development of anxiety in ASD (e.g. South and Rodgers 2017), have led to growing interest in the importance of both sensory function and autonomic nervous system functioning in the development and maintenance of difficulties faced by people with ASD.

[1] a term used to refer to repetitive behaviours seen in ASD such as hand flapping or rocking

2.2.7 *ASD and sensory functioning*

It is now recognised that sensory issues, such as over sensitivity or under sensitivity to noise; light; touch; smell and pain are important areas of difference experienced by many people with ASD (Bogdashina 2016; Schauder and Bennetto 2016). People with ASD are frequently described as having deficits or difficulties, however in some sensory areas such as hearing they have been found to demonstrate superior skill in comparison to their neurotypical peers (Remington and Fairnie 2017).

A review of sensory functioning in young children with ASD found that 95% had some form of sensory processing dysfunction (Tomcheck and Dunn 2007). Sensory difficulties which persist beyond childhood have also been shown in people with ASD compared to peers (Crane 2009). Diagnostic criteria now recognise sensory issues as part of the disorder (DSM-5 American Psychiatric Association 2013).

Questionnaire assessments have been used to compare responses of people with ASD to peers without ASD. For instance, the *Sensory Profile* (Dunn 1999; Brown and Dunn 2002) is a commonly used questionnaire completed either by carers or the individual themselves to assess a range of different sensory responses.

Experimental research has also been used to assess sensory responses in ASD by assessing underlying physiological responses to different sensory stimuli. A seminal study reported by Hirstein *et al*. (2001) suggested there may be different subtypes of ASD as indicated by both '*hyposensitiv*ity and *hypersensitivity'* to sensory stimuli. Further research has also suggested subtypes of sensory responsivity in ASD with more adaptive sensory responses being linked to lower anxiety (Uljarevic 2016).

Some evidence exists for what has been termed '*hyperarousal*' in ASD (Kushki *et al.* 2014), however, a systematic review of 10 studies has also suggested evidence for '*hypoarousal*' in people with ASD (Watts 2016).

A systematic review of 57 studies assessed the physiological reactions of people with ASD to a wide range of sensory; emotional; social and stress stimuli (Lydon *et al.* 2014).

In this review, over 78% of people with ASD responded differently to sensory stimuli compared to non ASD peers (Lydon *et al.* 2014). The variability of responses, with both over sensitivity and under sensitivity to stimuli was noted.

Differences in the physiological responses of people with ASD to social and emotional stimuli and to stress tests were also reviewed (Lydon et al. 2014). Overall, a high level of variability in the physiological responses assessed in people with ASD was highlighted and it was noted that observable behaviours reported were not always related to internal physiological state (Lydon et al.2014). Further research into the physiological responses of people with ASD was advocated,

> *"Further investigation…will further our understanding of the disorder, potential subtypes within it, associated behaviours, and health outcomes"* (Lydon 2014 *et al*. p.19).

A growing body of research has involved assessment of different physiological reactions in people with ASD. People with ASD have been noted to show different responses to non ASD peers to a range of tasks, with contrasts and comparisons being made between behavioural responses observed in people with ASD, and their physiological reactions and autonomic functioning.

It is thus important to review the different types of assessment which can be used to evaluate autonomic nervous system functioning in people with ASD.

2.2.8 *ASD and autonomic nervous system functioning*

The autonomic nervous system (ANS) is the part of the nervous system that controls involuntary actions such as the heart beat and widening of blood vessels (Fox 2006).

The sympathetic nervous system is responsible for 'activation and mobilization' of the body, whilst the parasympathetic nervous system is responsible for 'recovery and restoration' (Fox 2006). There is also increasing interest in the enteric nervous system, which is thought to link emotional and cognitive areas of the central nervous system with the intestinal system (Carabotti 2015).

ANS activity can be measured indirectly via a range of different methods (Peper 2008). For example, increased sweat responses typically occur when the sympathetic nervous system is activated, and some studies have used physiological sensors to measure changes in electrodermal activity produced by the sweat response in people with ASD.

One study using assessment of electrodermal responses, found both hyper and hypo responsivity in children with ASD, and also noted decreased responses during repetitive behaviour, which was suggested as a possible indication of decreased sympathetic nervous system activation (Hirstein *et al.* 2001). This study has been widely reported as possible physiological evidence for the stress reducing effects of engaging in repetitive behaviours, such as those reported in personal accounts from people with ASD (Grandin 2011).

Other studies have measured cardiac responses, recording both heart rate and heart rate variability using electrocardiogram. For example, individuals with ASD showed increased heart rate compared to control participants over a number of tasks, suggesting increased cardiovascular arousal levels in people with ASD (Ming 2005; Goodwin 2006). Increased baseline heart rate and decreased cardiac reactivity to stress stimuli tasks has also been shown in people with ASD and suggested as demonstrating '*overall autonomic hyperarousal*' (Kushki 2014, p.1).

People with ASD have also been noted to show different responses to non ASD peers to a range of tasks. For example, ASD subjects showed increased parasympathetic nervous system activity in a mental arithmetic 'stress' task compared to the 'rest' condition which involved staring at a white wall, suggesting that some people with ASD may show '*autonomic hyperarousal*' in rest conditions (Toichi and Kamio 2003, p.417).

Pupil light reflexes and measurements of salivary cortisol have also been used to assess ANS functioning in people with ASD. For example, atypical pupil constriction responses in children with ASD have been linked to observations of sensory dysfunction in ASD and suggested as a possible indication of lower parasympathetic nervous system responding in ASD (Daluwatte 2013). Levels of salivary cortisol have also been measured and have been found to be related to child self-reports of anxiety in boys with ASD (Bitsika *et al*. 2015). Respiratory dysfunction has also been highlighted in children with ASD and linked to reduced cardiac vagal activity, compared to age matched peers (Ming *et al.*2016).

A wide range of research paradigms, using different assessment methods and employing many different sensors have been used in research to assess ANS functioning in people with ASD, making it difficult to draw general conclusions regarding any specific area of difference or dysfunction. A review of the different types of methodologies employed to assess ANS dysfunction in children with ASD, was carried out by Cheshire (2012). This review noted the complex and at times contradictory findings and emphasised the need to integrate and interpret any ANS findings with other data,

> *"Autonomic phenomena are most meaningful when viewed from perspectives of molecular neuroscience, structural and functional neuroimaging, and developmental psychopathology."* (Cheshire2012 p.7).

People with ASD can be seen to show altered ANS responses in a range of different areas. Research has now focussed on whether interventions to change some of the ANS responses observed in people with ASD may in turn, also help manage some of the difficulties reported by people with ASD.

2.2.9 *Interventions to treat ANS dysfunction in ASD*

A number of pharmaceutical interventions have been employed to help manage difficulties which may be related to ANS dysfunction in ASD. Thus, reports of symptoms such as increased resting heart rate have led some researchers to investigate whether drugs such as the beta-blocker propranolol could be a possible method for helping people with ASD. This drug is typically prescribed to treat blood pressure but has also been used to treat anxiety and PTSD (Davidson 2006). Studies have shown this medication may have potential to manage anxiety (Narayanan 2010) and working memory deficits (Bodner 2012) in people with ASD.

The underlying ANS and sensory differences seen in people with ASD have been argued to be one of the key reasons for using an intervention termed a '*low arousal approach*' to manage challenging behaviours seen in people with ASD (McDonnell *et al.* 2015). Thus, interventions which reduce sensory information are advocated as more suitable methods of intervention which may help to both prevent and reduce challenging behaviours and decrease the need for invasive physical interventions being used on people with ASD (McDonnell *et al.* 2015).

A study using animal models, based on the '*intense world syndrome'* theory (Markram 2007), has suggested that interventions which make the environment 'enriched and predictable' may also help to reduce symptoms of ASD (Favre 2015).

Sugarman *et al.* (2013) have outlined a theory termed the *autonomic dysregulation theory of autism*. This theory also focuses on how ANS dysfunction can be seen to be linked to features of ASD. Anxiety is proposed as a core feature of ASD rather than a secondary effect, and restricted repetitive behaviours observed in ASD are proposed as methods used by the individual to reduce increased autonomic arousal (Sugarman *et al*. 2013). One intervention proposed by Sugarman *et al*. (2013) to help regulate the ANS in people with ASD and reduce symptoms of anxiety, is the use of technology using '*biofeedback*'.

2.3 Biofeedback

> *"It is becoming main stream to measure our physiology. Biofeedback is a logical next step."* (Thompson 2016, p. 55).

The Association for Applied Psychophysiology and Biofeedback (AAPB), the Biofeedback Certification International Alliance (BCIA), and International Society for Neurofeedback and Research (ISNR) convened a task force of scientists and clinicians in late 2007 to agree a consensus definition of biofeedback,

> *"Biofeedback is a process that enables an individual to learn how to change physiological activity for purposes of improving health and performance. Precise instruments measure physiological activity…and rapidly 'feedback' information to the user. The presentation of this information often in conjunction with changes in thinking, emotions, and behaviour supports desired physiological changes. Over time, these changes can endure without continued use of an instrument*." (Tan *et al.* 2016, p.3).

Biofeedback has also been described as,

> *"A self-regulation technique through which patients learn to voluntarily control what were once thought to be involuntary body processes*" (Frank *et al*. 2010, p.85).

A short biographical review of some of the key individuals who developed biofeedback has been provided by Siever (2008). Whilst biofeedback has been known about since the 1960's, there is growing interest in its use in sports performance (Blumenstein and Orbach 2014) and in movements such as '*personalised medicine*' and '*the quantified self*' (Swan 2009).

Biofeedback can be seen to provide a form of individualised health care which is focussed on the unique responses of each individual patient. It represents a method that goes beyond simply monitoring physiology because it actively involves the user, enabling them to learn to change their unique physiological responses to improve their health.

2.3.1 *Types of biofeedback*

Biofeedback equipment can be categorised into two types, professional systems and small personal use devices. Professional systems allow for a number of different sensors to be used either individually or simultaneously to capture different physiological measurements to facilitate a wide range of different types of assessments and training (e.g. ProComp Infinity®; NeXus-10®). In addition, however, an increasing number of small-scale devices are also now commercially available and marketed for personal use (e.g. emWave 2®; Wild Divine®; Alive®).

A number of different physiological sensors can be used individually or in combination in biofeedback training (Tan *et al.* 2016). Electromyography (EMG) biofeedback measures muscle tension as it changes over time. Electrodermal activity (EDA) measures sweat responses, whilst thermal or temperature biofeedback measures body temperature changes over time. Heart rate and heart rate variability (HRV) are measured in HRV biofeedback using either ECG or photoplethysmography (PPG) sensors, often in conjunction with respiration. Electroencephalography (EEG) biofeedback is often referred to as '*neurofeedback*' and measures brain wave activity over time.

There are many different types of physiological assessment sensor and different protocols have been developed for using biofeedback for an increasing number of conditions (Peper 2008). Biofeedback practitioners may also use multimodal sensor assessments to plot what has been termed a '*biofeedback stress profile*' in which an individual's unique profile of responses to stress can be mapped before planning a biofeedback treatment to change any maladaptive responses (Matto 2013).

Irrespective of the type of biofeedback used, the importance of having a trained biofeedback practitioner is argued to be essential to provide expert training and support to the user to enable them to gain control over their individual physiological reactions (Yucha and Montgomery 2008; Pastor 2008). The importance of using additional therapeutic techniques such as '*mindfulness*' to enable users to develop skills in biofeedback has also been recognised (Khazan 2013).

2.3.2 *Biofeedback efficacy – what do we know?*

La Vague *et al.* (2002) developed a template for systematic evaluation of the efficacy of psychophysiological interventions, such as biofeedback. This template denotes five levels of clinical efficacy with higher levels requiring adherence to much more stringent criteria. Thus, level one indicates treatment which is '*not empirically supported'* and level five indicates treatment which has been found to be both '*efficacious and specific*' to the condition described.

Biofeedback has been used for a wide range of physical and mental health conditions and in a range of different populations (Peper 2008). Due to variations in the design and reporting of many studies, the main professional societies involved in biofeedback and neurofeedback produce regular guidelines for use of biofeedback, which report on latest research findings and evidence based practice, using the template for reporting levels of efficacy (Yucha and Gilbert 2004;Yucha and Montgomery 2008; Tan *et al.* 2016).

Several systematic reviews and meta analyses have indicated evidence in support of biofeedback. For example, biofeedback has been reported as 'efficacious and specific' for a number of conditions such as stress incontinence (Weatherall 1999); pelvic floor dysfunction (Koh *et al.*, 2008), and headache (Nestoriuc *et al.*, 2008).

Biofeedback for the treatment of anxiety has been given a rating as *efficacious* (Tan *et al.* 2016). A systematic review of literature from 2000-2017 on biofeedback for stress management indicated significant positive effects for biofeedback in 16 out of the 17 studies identified and has provided comparisons on psychological and physiological measures used; frequency and type of biofeedback training given, and implications for future studies (Kennedy 2018).

Biofeedback for the specific treatment of ASD symptoms has been given a rating as '*probably efficacious'* (Tan *et al.* 2016). Whilst many different types of biofeedback have been noted, most studies using biofeedback in people with ASD have focussed only on the use of EEG biofeedback or '*neurofeedback'*.

2.3.3 *Evidence for the use of biofeedback in ASD*

The most widespread use of biofeedback for people with ASD involves use of neurofeedback.

Neurofeedback is a sub speciality of biofeedback which involves initial EEG recordings and often detailed 'quantitative electroencephalogram' (QEEG) brain mapping using multiple EEG sensors. Neurofeedback assessment aims to identify abnormal patterns of cortical activity and then train the individual to alter these abnormal patterns to normalise brain activity (LaVaque, *et al*. 2003).

Several reviews regarding the use of neurofeedback in ASD have been conducted. A report of outcomes of over 150 cases over a 15 year period is reported in two papers by (Thompson *et al.* 2010a, 2010b). The accounts summarise data from clients with Asperger's syndrome and Attention Deficit Hyperactivity Disorder (ADHD) who were given between 40-60 sessions of both neurofeedback and other types of biofeedback. Decreased symptoms on the Australian Scale for Asperger's Syndrome and the Conner's rating Scale for ADHD were noted after using neurofeedback, and a rationale for the use of neurofeedback in ASD was provided. However, these reports despite providing information on both questionnaire and EEG changes, describe case histories from clinical practice rather than specific research designs. Multiple interventions were used in clients with a range of difficulties, and clients were seen over variable periods with no comparator groups, making conclusions regarding efficacy of neurofeedback problematic.

The need for well-designed studies assessing neurofeedback using randomisation; has been emphasised (Coben *et al*.2010). A detailed review of research literature from 13 case studies and 5 controlled trials by Holtmann (2011) provided valuable comparisons of types of study design and measures used. This review concluded that neurofeedback may hold some promise for improvement of ADHD like symptoms however,

> *"existing evidence does not support the use of neurofeedback in ASD"* (Holtmann *et al.* 2011, p.986).

A randomised controlled trial of neurofeedback in ASD aimed to address methodological problems in earlier studies such as lack of comparator group, and clear diagnostic assessment of cases (Kouijzer *et al.*, 2013). In this study no statistically significant changes in reported symptoms of ASD were observed, although significant improvements were noted in measures of cognitive flexibility (Kouijzer *et al.*, 2013). A further systematic review of identified 17 studies suggested that neurofeedback may be considered as a treatment with "*modest experimental support"* (García-Berjillos *et al.*, 2015, p.151).

Brain–computer interface (BCI) applications for people with ASD have also employed neurofeedback within a *serious game* environment (Ritterfeld 2009; Friedrich *et al.* 2014; 2015). This type of neurofeedback has been proposed as a method of activating the human 'mirror neuron system' which may improve social interaction in ASD (Datko *et al*. 2018; Goodman *et al.* 2018).

In summary, research on the use of neurofeedback to help people with ASD is continuing to develop, with a need for larger scale, controlled trials to ascertain its efficacy. Studies vary considerably with only a small number of studies testing neurofeedback against a comparator treatment.

The review by Holtmann (2010) suggests that neurofeedback may be more appropriate as a treatment for symptoms seen in people with ADHD, and the studies reported by Thompson *et al.* (2010) report on cases with comorbid ASD and ADHD. Existing guidelines in the UK, do not currently recommend neurofeedback for treatment of core problems of ASD (NICE Clinical Guideline 170: 2013).

Interestingly, in their review of case histories reporting the use of neurofeedback in people with ASD, Thompson *et al*. (2010b) report that whilst the focus was on describing their rationale for using neurofeedback, they acknowledge that improved treatment outcomes in people with ASD and ADHD may also have been related to the teaching of diaphragmatic breathing and to their use of biofeedback to modify heart rate variability or 'HRV' (Thompson *et al.* 2010b, p. 16).

2.4 Heart Rate Variability

"A healthy heart is not a metronome" (Shaffer 2014, p.1).

2.4.1 *Definitions of Heart Rate Variability*

The quote above from Shaffer highlights the common misconception that normal heart functioning should show no variation. In fact, whilst some types of irregular heart beat rhythm do indicate potential problems, the healthy heart should show a natural variability in the time intervals between individual heartbeats often termed '*inter-beat intervals*.' These short millisecond variations give an indication of the action of the vagus nerve on the sinoatrial node of the heart. This naturally occurring variability in heart rhythm is known as '*heart rate variability*' or 'HRV' (Malik 1993).

Heart rate and HRV can be used as signs of the functioning of the autonomic nervous system (ANS). HRV was first used in maternity services when it was noted that a decreasing level of HRV was frequently an early indicator of foetal distress (Hon 1963).

HRV has been shown to be an accurate method of assessing cardiac autonomic functioning (Malik *et al.*1996; Stein and Kleiger 1999) and has been used as an indicator of physiological arousal (Appelhans and Luecken 2006; Thayer and Sternberg 2006). Heart rates that show no variability are usually a sign of declining health or a sign that the individual has an artificial pacemaker (Hampton 2013).

HRV levels are high in infants and decline with increasing age (Nunan 2010). The natural variability in heart rate is seen as a sign of the inidviduals adptability or resilience (Shaffer *et al.* 2014). HRV is affected by a number of different internal and external factors including breathing, the blood pressure control system and the regulation of the autonomic nervous system (Khazan 2013).

The normal variability in the heart rate termed HRV is shown in Figure 2.1 below. Measurement of the Inter Beat Intervals (IBI's) refers to the time between the R-waves peaks, shown in Figure 2.2.

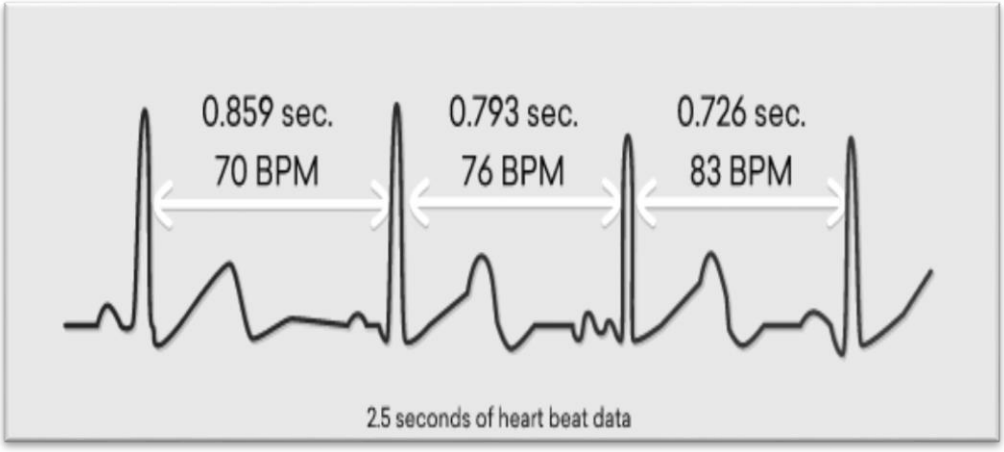


Figure 2.1 ECG recording showing millisecond variations in heart beat intervals

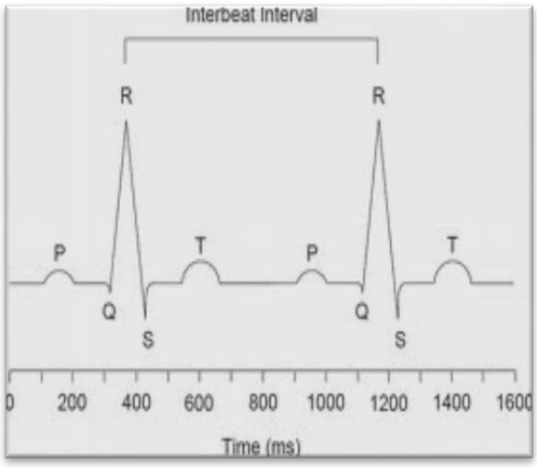


Figure 2.2 Measurements from one R wave to the next – known as R-R intervals or interbeat intervals (in HRV statistics the "NN" means "Normalised RR")[2].

[2] Figures 2.1 - 2.3 reproduced with permission from D. Matto www.biofeedback.workshop.nl

Respiratory sinus arrhythmia (RSA) describes a specific phenomenon that occurs when HRV changes in phase with respiration. RSA was initially felt to be a phenomenon only seen in young people and children but was subsequently linked to breathing frequency in adults (Angelone and Coulter 1964). RSA has been investigated in a number of experimental studies and has been shown to be linked to efficiency of pulmonary gas exchange and improved circulatory efficiency (Hayano *et al*. 1996). The role and function of the autonomic nervous system and particularly the vagus nerve in controlling RSA has been debated (Porges 1995). Yasuma and Hayano (2004) provide a useful review of developments in our understanding and provides a definition of RSA as,

"Heart rate variability in synchrony with respiration, by which the R-R interval on an ECG is shortened during inspiration and prolonged during expiration" (Yasuma and Hayano 2004, p.684).

The synchrony between heart rhythms and respiration can be clearly seen in the changes of R wave frequency on an ECG. Biofeedback systems can also show both ECG and respiration simultaneously and can be used to show change from normal breathing to RSA. Figure 2.3 shows the increase in synchrony between heart rate and breathing during slow breathing relaxation.

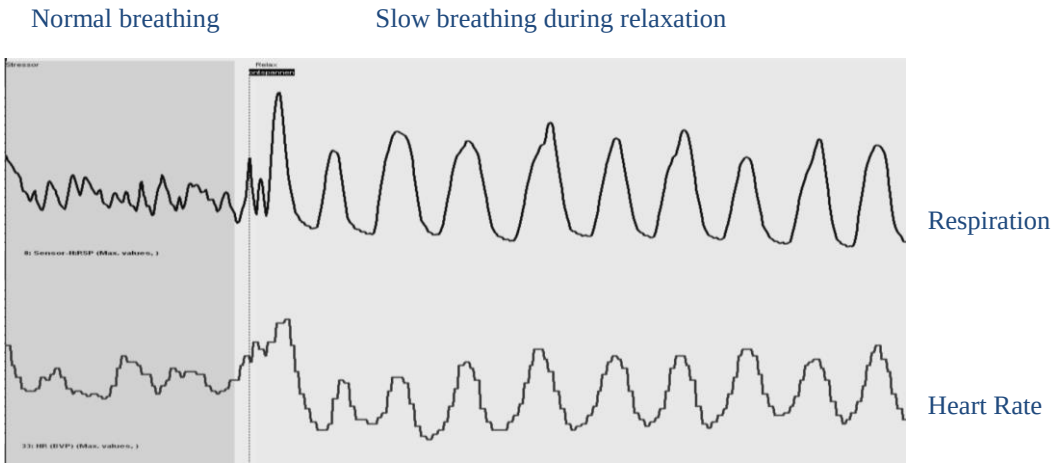


Figure 2.3 Simultaneous recording of heart rate and breathing showing the change from a normal breathing pattern to an RSA pattern highlighting the changes in heart rate in synchrony with changes in breathing[3].

[3] Figures 2.1 - 2.3 reproduced with permission from D. Matto www.biofeedback.workshop.nl

2.4.2 *Standards for measurement of HRV*

> *"HRV is an emergent property of interdependent regulatory systems which operate on different timescales to help us adapt to environmental and psychological challenges"* (Shaffer and Ginsberg 2017, p.1).

There is a growing body of research investigating HRV and it has been viewed as an important biomarker for self-regulation (Holzman and Bridgett 2017). In order to interpret this information accurately, it is first important to have consensus on how this physiological variable is measured, analysed and reported.

Attempts to agree a consensus on the standards for measurement and reporting of HRV were undertaken in 1996 by a joint task group comprising both clinicians and technical experts. Standards for the parameters of measurement of HRV were agreed and published jointly in the journals 'Circulation' and the 'European Heart Journal' in 1996 (Camm *et al.*1996; Malik *et al.* 1996). This report commonly known as the '*Task Force Report*' outlines definitions of terms and measurement criteria, as well as outlining some of the clinical applications of measuring HRV. Further definitions were also reported by Berntson *et al.* (1997).

A review of 44 different studies involving 21,438 participants by Nunan (2010) provided initial guidelines and normative data on HRV.

Reference values for studies assessing HRV in children have also been reported (Seppala 2013), and gender differences in HRV in adults have been assessed (Koenig and Thayer 2016). References values for short term HRV recordings have been reported on a large sample of healthy adults from a single study (Dantas *et al.* 2018). Guidelines for calculating effect size distributions for HRV and suggested samples sizes for planning future studies have also been produced (Quintana 2017).

2.4.3 *Measures used to report HRV*

HRV can be measured via either ECG or PPG sensors, however ECG recording is recommended as a reference standard for more detailed signal analysis. HRV indices are calculated from a recording of inter-beat intervals or an 'IBI' file and may be reported in the actual values of milliseconds, or in 'normalised units' (Shaffer and Ginsberg 2017).

Respiratory sinus arrhythmia or '*RSA*' is a phenomenon which has been proposed to reflect 'vagal tone' (Porges 1995). When RSA occurs, there is typically a reduction in heart rate and an increase in aspects of HRV. Thus, these signs are often taken as indications of the action of the vagus nerve and the functioning of the parasympathetic nervous system. HRV indices can be measured over a 24-hour period, however many studies report HRV from short term recordings of approximately five minutes. Respiration depth and frequency may also be reported.

HRV is frequently measured and reported in two main formats; time domain and frequency domain. Time domain measures are derived from time interval calculations. Frequency domain measures, or power spectral density analysis measurements, are usually calculated using a method known as '*Fast Fourier Transform'* spectral analysis (Welch 1967). HRV may also be calculated using non-linear measurements. This type of measurement can give additional information on time domain and frequency domain measures and can be used to index the unpredictability of a specific time series (Shaffer and Ginsberg 2017). A geometrical model termed a '*Poincaré'* plot, can also be produced which gives a visual display in the form of a scatterplot which can then produce a number of variables of non-linearity (Kamen 1996).

A large number of HRV variables can be derived from ECG data and there remains much variation in the types of analysis conducted and the types of indices reported. Whilst time domain and frequency domain measurements are commonly described, studies have also reported non-linear measurements which have been linked to health outcomes (Stein and Reddy 2005; Kemp *et al.* 2010).

A summary of common terms used to report HRV with a description of what they mean, and the unit of measurement is shown in Table 2.1 - Table 2.3.

*Table 2.1 Time domain measures derived from heart rate data used to report HRV**

Time Domain variables	Description of term	Unit of measurement
HRV	Heart Rate Variability	ms
HRV max-min	The range of HRV – highest to lowest interval	bpm
RR	The interval between heart beats often termed 'beat to beat' intervals / 'interbeat intervals' or 'IBI'	ms
Mean RR	The mean RR or mean interbeat interval	
NN	The interval between normal heart beat contractions i.e. 'normal to normal' IBI	ms
SDNN	The standard deviation of the NN interbeat intervals – a direct reflection of overall variability in heart rate	ms
RMS-SD	The root mean square of successive differences in NN intervals – associated with HF variations in HRV – this may reflect the activity of the parasympathetic nervous system	

*Table 2.2 Frequency domain measures derived from heart rate data used to report HRV**

Freq. Domain variables	Description of term	Unit of measurement
VLF	Very Low Frequency (range 0 - 0.04Hz)	ms^2
LF	Low Frequency (range 0.04 - 0.15Hz)	ms^2
HF	High Frequency (range 0.15 - 0.4Hz) – this may indicate parasympathetic activity	ms^2
TP	Total power of all frequencies – this may reflect overall autonomic activity	ms^2
LF/ HF	Low Frequency**:** High Frequency – this may reflect balance of the autonomic nervous system	ratio

*Table 2.3 Sample of Non-linear Measures used to report HRV**

Non-linear variables	Description of term	Unit of measurement
Poincare plot (SD1)	Reflects high frequency fluctuations	ms
Poincare plot (SD2)	Reflects low frequency fluctuations	ms
Sample entropy (SampEn)	Overall complexity of time series	

*Adapted from the 'Task Force' for the European Society of Cardiology / North American Society of Pacing and Electrophysiology guidelines (Malik *et al.*1996).

2.4.4 *Methodological problems assessing HRV*

There are many important methodological considerations to be taken into account in the assessment; measurement; analysis and interpretation of HRV. A number of researchers have now produced guidelines on how to lessen some of the methodological problems in assessing HRV (Billman 2013; Quintana and Heathers 2014; Quintana 2016).

Measures used

Time domain measures which are commonly reported include the standard deviation of the normal to normal beats or 'SDNN' and the root mean square of successive differences in HF variations or 'RMS-SD'. A number of other measures are also seen as important because of their significance in determining HRV. Thus Nunan (2010) recommends reporting of mean RR interval; HR; and the actual values of HRV instead of normalised units.

Frequency domain, or power spectral density measures regularly reported include both high frequency or HF and low frequency or LF HRV. Reporting the LF/ HF ratio is now not thought to clearly reflect the ratio of sympathetic and parasympathetic activity or '*autonomic balance'* and reporting this ratio should be interpreted with caution (Billman 2013a). Reporting of frequency domain measures particularly VLF and TP are not thought to provide clear information in short term HRV recordings, and recordings of different time periods should also not be compared (Nunan 2010). It has also been proposed that the LF band width can reflect both PSNS and SNS activity and that the LF band width in short term HR recordings may be an indication of overall vagal activity (Porges 1995).

Tools used

The high level of accuracy provided by automated algorithms to calculate HRV indices from an ECG recording are now seen as an appropriate and accurate method to edit raw data, despite the initial Task Force recommendation of manually editing HRV (Nunan 2010).

Environment setting

The environmental conditions involved in the initial assessment and collection of data are important and should always be reported. For example, speaking or paced breathing can of itself increase HRV (Mulder 1992; Nunan 2010).

A standardised test environment for all individual participant assessments is also vital to accurate measurement of HRV. For example, factors such as age; time of day; body position; hunger; bladder emptying; physical activity; alcohol; caffeine and medication all have an impact on HRV and attempts to standardise and report these should be taken (Billman 2011; Heathers 2014).

Study design

A very wide range of inter-individual differences also have been reported in studies measuring HRV (Nunan 2010). Therefore, further studies measuring pre-post changes within the same individuals have been recommended (Quintana and Heathers 2014). The need for longitudinal studies, to evaluate changes in HRV over time in new populations, has been emphasised (Kemp and Quintana 2013).

Recent guidelines for reporting articles on psychiatry and heart rate variability or 'GRAPH' guidelines have provided a valuable framework for future research studies (Quintana 2016). The guidelines make recommendations in four areas:

(i) Inclusion of detailed diagnostic and demographic information on participants and controls is seen as essential

(ii) Reporting information on equipment used; configuration and type of electrodes; sampling rate and length of data recording is also important

(iii) The reporting of the method of data extraction and methods of data analysis should also be documented

(iv) Finally, as the methods for calculating and reporting HRV can vary (e.g. Porges 1995) this should also be recorded (Quintana 2016).

Despite the difficulties measuring HRV outlined above, and the differences in reporting and analysing this variable, there is increasing interest in the importance of HRV as a predictor of both health and illness (Moss and Shaffer 2017).

HRV has been argued to be an indicator of the body's ability to adapt to changing environmental demands (Beauchaine 2007; Shaffer and Ginsberg 2017). Many of the initial investigations into HRV arose from the use of this measure as an indicator of cardiac difficulties (e.g. Tsuji *et al.*1996), however an increasing number of studies have also begun to highlight important links between HRV and both physical and mental health (Gevirtz 2013).

2.4.5 *HRV and Physical Health*

HRV has been shown to decline with age (Umetani 1998; Jandackova 2016). HRV has also been investigated extensively in cardiac patients. For example, reduced HRV has been associated with increased risk of mortality following myocardial infarction (Kleiger et al.1995; Bailey 2001) and the longitudinal 'Framingham Heart Study' highlighted that reduced HRV was associated with mortality (Tsuji *et al.*1996).

As far back as 1976 research indicated that decreases in HRV could predict the onset of neuropathy in diabetes before the appearance of overt symptoms (Ewing *et al.* 1976). Kemp *et al.* (2016) highlighted that reduced HRV was linked to insulin resistance may be an early indicator of illness such as type 2 diabetes.

More recently, interest has grown into investigations to assess whether HRV indicators might change as a result of any intervention. A systematic review of 33 RCTs investigating a range of different therapies designed for secondary prevention of heart disease, indicated that HRV indices were found to significantly increase as a result of secondary cardiac prevention interventions (Nolan 2008).

Whilst the early focus on HRV has highlighted its role as a predictor of cardiac health, many patients with heart disease were also found to have co morbid mental health difficulties such as anxiety, (Tully and Cash 2013); depression (Meijer 2013) and PTSD (Edmondson 2013) which increased risk of further cardiac illness.

This has in turn led to increasing interest in the links between HRV and different types of mental health conditions.

2.4.6 *HRV and Mental Health*

The risk of cardiovascular illness is increased in patients with co-morbid depression (Whooley 2006). The relationship between HRV and depression has also been investigated in people without co-existing cardiac illness. A review and meta-analysis of 18 studies indicated that people with depression showed lower HRV compared to controls, and severity of depression was also related to reductions in HRV (Kemp *et al*. 2010). Importantly, patients taking antidepressant medication did not show any improvements in HRV, despite reported improvement in symptoms. In addition, one specific type of medication, tricyclic antidepressants, was associated with reductions in HRV (Kemp *et al.* 2010). Such medications may actually increase the risk of cardiovascular illness (Kemp *et al*.2014).

The relationship between anxiety disorders and HRV has been investigated in meta-analyses of 36 studies which reported a range of anxiety-based disorders to be associated with reduced HRV (Chalmers et al.2014). People with a diagnosis of social anxiety disorder have also shown reduced HRV compared to controls Alvares *et al.* (2016). High frequency HRV has been linked to frequency of respiration in people with severe mental illness but not in controls (Quintana 2016). In a study of bipolar disorder, mania was found to be associated with increased heart rate and decreased HRV (Lopes Wazen 2018).

Studies assessing HRV and mental health have varied from large scale population studies comparing HRV to control groups, to smaller scale studies assessing changes in HRV within individuals with specific conditions. A review of a body of work assessing HRV and its relationship to mental and physical health has highlighted the important links between HRV; mental health, and physical illnesses and emphasises the need for further research in this area,

> *"Over the longer-term, reduced HRV leads to immune dysfunction and inflammation, cardiovascular disease and mortality ... Further research is urgently needed on the long-term effects of autonomic dysregulation in otherwise healthy psychiatric patients, and appropriate interventions to halt the progression of a host of conditions associated with morbidity and mortality"* (Kemp and Quintana 2013, p.288)

2.4.7 *HRV and Emotion*

HRV has been reported to be an indicator of change in emotions (Rainville *et al.* 2006; Rockliff *et al.* 2008) and has been proposed as a biomarker for emotional response (Appelhans and Luecken 2006).

HRV has also been found to be associated with emotion recognition. For example, level of resting state HF-HRV was associated with scores on the *Reading the Mind in the Eyes Test* (Baron-Cohen *et al.* 2001), a test used to assess the emotion recognition difficulties often seen in people with ASD (Quintana *et al.*2012).

Reduced resting state HRV has been associated with hypervigilance and maladaptive responses to emotional stimuli (Park and Thayer 2014). A review by Beauchaine (2015) proposed that reduced HRV is associated with what is termed 'emotional dysregulation' and psychopathology.

A detailed review of recent research investigating the links between HRV and emotion has been carried out by Mather and Thayer (2018). This review highlights how HRV has been linked to connectivity in the prefrontal cortex and the amygdala which are associated with emotion regulation (Mather and Thayer 2018).

A new theoretical model, which highlights the links between genetic environmental and social influences on HRV and connects them to overall health and well-being. termed the 'GENIAL model' has also now been proposed (Kemp *et al.*2017).

Understanding the interactions between HRV; emotion recognition; social interaction and mental health difficulties may help our understanding of health and illness. Many people with ASD also have emotion recognition difficulties (Mazefsky 2013); social interaction difficulties (Knott 2006); and can have high levels of mental health problems such as anxiety (van Steensel 2013).

Thus, understanding the links between HRV and ASD may further help our understanding of the nature of ASD.

2.4.8 *HRV and ASD*

A number of investigators have used HRV assessment and quantification methods described by Porges (1992; 2007), in experimental studies which have supported a possible association between levels of HRV and ASD symptoms.

For example, van Hecke *et al.* (2009) assessed children with ASD whilst they watched videos of familiar and unfamiliar people. Children with ASD showed reduced regulation of their heart rate compared to typically developing children and when shown an unfamiliar face. The investigators suggested that according to this finding may indicate a "*precautionary mobilisation to fight or flee"* induced by seeing unfamiliar people (van Hecke *et al*. 2009, p. 1128).

Further research by Bal *et al.* (2010) examined facial affect recognition in children with ASD and typically developing children. Children with ASD showed increased heart rate and lower levels of RSA during a two-minute baseline recording compared to peers and made more errors and were slower on the facial recognition task (Bal 2010). More recently RSA has also been found to be associated with social functioning and language skills in children with ASD (Patriquin *et al.* 2013).

Other experimental paradigms have suggested a link between HRV, anxiety and social interaction in people with ASD (Kushki *et al*. 2014). HRV has also been found to increase after administration of oxytocin, a hormone linked to which has been investigated to help social engagement in people with ASD (Kemp 2012).

A qualitative synthesis review by Benevides and Lane (2015) investigated cardiac autonomic measures in ASD. Methodological problems highlighted included the need to take into account age race and gender differences in participants; the need to use appropriate HRV measures for the length of recording; artefact identification in analysis, and the importance the type of task designed as stressful for people with children with ASD (Benevides and Lane 2015). The authors also emphasise the need for new theoretical frameworks to help guide future research into HRV.

2.5 Theoretical Frameworks relating to HRV

> *"When the heart is affected it reacts on the brain and the state of the brain again reacts through the (vagus) nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body."* (Darwin 1872, p.69).

Two important theoretical frameworks, which have influenced our understanding of how HRV and the ANS affect behaviour are Polyvagal theory (Porges 1995; 2007;2011) and Neurovisceral Integration theory (Thayer and Lane 2000; 2009).

2.5.1 *Polyvagal theory*

Polyvagal theory is a theoretical model that was proposed by the behavioural neuroscientist Stephen Porges which relates the internal functioning of the ANS to social engagement and self-regulation in mammals (Porges 1995; 2001, 2007).

The quote from Darwin above has been used by Porges to illustrate how the links between the heart and the brain have been known about for many years, and that the interactions between the heart and the brain are influenced by what is now known as the 10^{th} cranial nerve (CNX) or the '*vagus'* nerve. The word vagus comes from the Latin word for wandering, which highlights the fact that the vagus is the longest nerve in the ANS which has links to the heart, lungs and digestive system.

Polyvagal theory (Porges 1995) provided an evolutionary perspective on the organisation of the nervous system and described the evolutionary development of the vagus nerve into different branches (hence the term poly-vagal). Porges proposed that the ANS evolved over time to aid the development of the complex social behaviours seen in mammals and linked the regulation of behaviour to the branches of the vagus nerve (Porges 2001; 2007).

Porges proposed that, via evolution, links emerged in the brain between nerves that control the heart and brain (Porges 2001; 2007). A set of linked neural systems was proposed that link bodily feelings with facial expression, vocal intonation, gesture, and eye contact and referred to as the '*social engagement system'* (Porges 2001).

The different branches of the vagus correspond to different evolutionary stages of development and are activated in order depending on environmental demands (Porges 2001; 2007). Thus, when the environment is appraised as safe the phylogenetically newer '*myelinated vagus*' is activated and older defensive vagal circuits are inhibited, and this enables social engagement activities such as eye contact expression of emotion and facial expression to occur (Porges 2001). However, if the environment is viewed as threatening then older vagal pathways will be activated resulting in activation of what has been termed as 'fight, flight or freeze behaviours' (Porges 2001). Social communication is thus only able to occur appropriately when the environment is perceived as safe (Porges 2011).

Porges proposed that specific HRV measures such as respiratory sinus arrhythmia (RSA) serve as a marker of vagal functioning and may thus be an indication of an individual's ability to respond to and engage with their environment in an appropriate social manner (Porges 2001; 2007). Polyvagal theory has therefore been used in a number of studies to explain some of the difficulties observed in people with ASD (Van Hecke *et al*. 2009; Bal *et al*.2010; Patriquin *et al*.2013).

Polyvagal theory is however, not without its critics. Grossman *et al.* (1991) highlighted that RSA is primarily related to respiration and is not always an indication of 'vagal tone'. Grossman and Taylor (2007) provided further evidence calling into question some of the evolutionary tenets of Porges theory and emphasised that factors such as respiration and physical activity must be considered when calculating RSA, and that RSA and vagal tone are not always associated.
Despite criticisms, Polyvagal theory is still regarded as an important framework which has helped in developing our understanding of the role of HRV. Beauchaine (2006) emphasises the need for theories to help our understanding of psychiatric conditions and argues that too much attention has been given to description and categorisation rather than to theory explaining behaviour. Polyvagal theory has provided a much-needed framework and,

> *"...has emerged as an important explanatory construct for a wide range of psychiatric conditions."* (Beauchaine 2006, p.175).

2.5.2 *Neurovisceral Integration Theory*

The Neurovisceral Integration Model (Thayer and Lane 2000; 2009) describes a set of neural structures called the central autonomic network or '*CAN*' (Benarroch, 1993) which are involved in the '*integration of brain and body functioning*'. This network comprises a number of structures including the prefrontal cortex, insular cortex, amygdala, hypothalamus, ventrolateral medulla, as well as the peripheral ANS, and coordinates both central and autonomic nervous system responses to environmental change (Thayer and Lane 2000; 2009). This theory has provided an important basis for understanding interactions between the brain and the body,

2.5.3 *Neurovisceral Integration Across a Continuum of Time*

More recently Kemp, Koenig and Thayer (2017) have provided a 'multidisciplinary synthesis' on research into HRV. The authors propose that whilst the Neurovisceral Integration Model provides an important *structural framework* for understanding interactions between the brain and the body, there is also a further *temporal framework,* described as 'Neurovisceral Integration Across a Continuum of Time' or *NIACT* (Kemp *et al.* 2013, p.547). This extended model emphasises the importance of neurovisceral integration across time stating that, "*the extent to which the brain and body are integrated will contribute to eventual mortality*" *(*Kemp *et al*. *p.548).*

This framework draws evidence from research into HRV and integrates research from a range of different disciplines. Evidence from recent meta analytic studies are shown to link HRV to a number of physical and mental health outcomes. The authors highlight the role of the vagus nerve in regulating multiple brain and body systems and propose that vagal dysfunction leads to risk of morbidity and mortality. Importantly HRV is seen as an index of vagal function and this new model views, *"HRV as a psychophysiological marker of health and wellbeing"* (Kemp *et al.* p.548). If indeed HRV is a marker of health and well-being, it may be useful to further investigate the circumstances in which it might be possible for an individual to increase HRV.

2.6 Is it possible to increase HRV?

Respiratory sinus arrhythmia or 'RSA' describes a phenomenon that occurs when breathing and heart rate changes synchronize (Porges 1992). When this happens, there is typically an increase in HRV.

In the 1980's reports emerged in Russia suggesting that with specific training in developing RSA, people were able to produce large increases in their levels of HRV using biofeedback techniques (Lehrer *et al.* 2000).

This biofeedback technique which was described as *resonant frequency biofeedback training* was then reported with a specific protocol for training by Lehrer *et al*. (2000). The technique involves teaching an individual to find their own unique breathing rate at which *resonance* occurs between two systems, the heart rhythms or associated with respiration, and low-frequency heart rhythms proposed to be related to the activity of the baroreflex system (Lehrer *et al.* 2000). When these two systems are in a specific 0^{o} phase sequence then large increases in HRV are said to occur (Lehrer *et al*.2000).

This process has since been described as 'resonant frequency feedback'; RSA biofeedback; HRVB and HRV biofeedback, occurs when breathing is slowed to a rate of somewhere between 5-7 breaths per minute, which is slower than normal breathing rates (Lehrer *et al*. 1997; Lehrer and Gevirtz 2014).

This technique teaches the individual to breathe within the low-frequency heart rhythm range and HRV recordings typically show a peak in HRV frequency waveforms at 0.1Hz, in conjunction with slow regular breaths synchronised with changes in heart rate (Lehrer and Gevirtz 2014).

Heart rate activity in the low frequency range is thought to reflect the influence of both the parasympathetic and sympathetic nervous system (Berntson *et al.* 1997). Porges suggests that RSA may be an indicator of the overall functioning of the Poly-vagal system described as the *vagal brake* or an index of *parasympathetic tone* (Porges 1995; 2007).

Experimental research has further investigated the effects of breathing on HRV indices. For example, Sasaki and Maruyama (2014) compared controlled breathing at 15 breaths per minute (0.25Hz) and at 6 breaths per minute (0.1Hz) to spontaneous breathing. During controlled breathing at 0.1Hz, the LF/ HF ratio was found to increase greatly, and HF decreased, whilst HR and respiration remained unchanged. The authors suggest that this occurs because some HF components become synchronised with respiration frequency at 6 breaths per minute which corresponds with LF band width (Sasaki and Maruyama 2014).

As noted earlier anxiety has been found to be associated with reduced levels of HRV (Chalmers *et al.* 2014), and research has investigated whether specific interventions can reduce anxiety and increase HRV. For example, autogenic training was found to increase HRV in participants with high trait anxiety under experimental conditions (Miu *et al*. 2009)

McCraty and Childre (2010) from the Institute of HeartMath use a term called '*Coherence'* to describe a change or shift in heart rate rhythms which they propose increases a system's ability to self-regulate. The importance of experiencing positive emotions is emphasised to increase a system's ability to self-regulate, reduce stress and improve health (McCraty *et al.* 1995;2009).

Coherence as described by HeartMath is largely similar to what is described by RSA, although importantly this shift in heart rhythm is said to only occur when positive emotions such as gratitude are generated (McCraty and Childre 2010). Coherence can also be seen in the spectral analysis of HRV by a, *"large increase in power in the low frequency band around 0.1Hz"* (McCraty *et al*.2009, p.14).

Reports produced by the Institute of HeartMath describe various methods of helping to generate positive emotions, such as the 'Heart Lock-In®' technique (McCraty *et al.* 2009). HeartMath LLC also produce a number of commercially available devices for helping users achieve this state of psychophysiological '*Coherence'* using the technique now known as HRV biofeedback.

2.6.1 *HRV Biofeedback*

> *"Mind-body medicine is so prominent right now, and this is a way to help people learn mindfulness more quickly. This is a tool that should be in most psychologists' toolboxes."* (Austad, 2016, p. 52).

HRV measurement has been used in conjunction with sensor technology to develop a specific method of biofeedback now referred to as HRV biofeedback (Lehrer and Gevirtz 2014).

The protocol originally described by Lehrer *et al*. (2000), involving ten sessions of individual training, has been widely used as the 'gold standard' for training in HRV biofeedback. More recently, a five-session protocol for training has also been produced (Lehrer and Vaschillo 2013). Following baseline assessment using multi-channel biofeedback recording apparatus, respiration and heart rate variables are recorded simultaneously, and the individual is then taught to breathe at the unique breathing rate which produces the largest variations in HRV. The protocol then involves practicing and sustaining this technique to enable the user to increase their levels of HRV (Lehrer *et al*.2000).

To support the maintenance and development of resonant frequency breathing, individuals can practice paced breathing, or use 'home trainer' HRV biofeedback devices. These devices employ a less invasive measurement approach referred to as photoplethysmography (PPG) which uses infra-red sensors to detect blood volume pulse from which HRV can be derived. Several certified devices exist within the market place, which have conformity with health, safety, and environmental protection standards for these products. These types of 'home trainer' device have now made HRV biofeedback more accessible for individual use. These devices can be adjusted by the user to different breathing rates but are usually set at a default rate of six breaths per minute. Assessment of the accuracy of some devices has also been carried out (Heilman 2007; 2008). A number of research studies have also investigated their effectiveness when used as stand-alone interventions without employing the full Lehrer training protocol using multichannel recording (Reiner 2008; Ratanasiripong 2012; de Bruin *et al.* 2016).

2.6.2 *HRV Biofeedback mechanism and efficacy*

A number of reviews discussing the possible mechanisms of effect underlying HRV biofeedback have been described (Gevirtz, 2013; Moss *et al.* 2013; Lehrer and Gevirtz 2014; Lehrer, 2017). The exercising and strengthening of the '*baroreflex response'* originally proposed by Lehrer *et al*. (2003) has been noted as one possible mechanism of effect (e.g. Lehrer and Gevirtz 2014). The baroreflex links via the brainstem to the amygdala, a centre for emotional control, which may be one of the mechanisms by which HRV biofeedback may help people with mental health conditions such as anxiety and depression. Further proposed mechanisms of effect include a strengthening of vagal responses; stimulation of cholinergic anti-inflammatory responses, improved gas exchange with increased cardiac and pulmonary function, or a placebo effect (Moss 2013; Lehrer and Gevirtz 2014).

Research has been conducted on the use of HRV biofeedback to reduce stress and anxiety in a range of non-clinical populations such as students (Ratanasiripong 2012; Meier and Welch 2016); stressed adults (de Bruin *et al.*2016) and call centre workers (Kennedy and Pretorius 2008).

HRV biofeedback has also been reported to improve the outcome of a number of physical health conditions such as hypertension (Nolan *et al.*2010; Cullins *et al.* 2013); alcohol dependency (Penzlin 2017); chronic fatigue (Windthorst *et al*.2017) coronary heart disease (Lin *et al*.2015). HRV biofeedback has also been used to improve performance in sports (Morgan 2017). HRV biofeedback has been reported to reduce symptoms in a number of mental health conditions such as anxiety (Reiner 2008; Henriques 2011); PTSD (Zucker *et al.*2009; Tan *et al*.2011) and depression (Karavidas *et al.* 2007; Patron 2013; Caldwell and Steffen 2018). Many initial studies reported on either on small samples of people with specific conditions or did not randomise participants into different conditions (Reiner 2008). However, a number of randomised controlled trials (RCTs) of HRV biofeedback have now been carried out. A summary of RCTs since 2009 using HRV biofeedback is presented in table 2.4 below using the population; intervention; comparator and outcome or 'PICO' framework (Richardson 1995).

Table 2.4 Evidence from RCTs using HRV biofeedback devices presented using the population; intervention; comparator and outcome or 'PICO' framework.

Author year and location	Design	**P**opulation	**I**ntervention - aim	**I**ntervention - length	**I**ntervention - device	**C**omparator(s)	**O**utcome
Caldwell, Y. & Steffen, P. (2018) UT: USA	RCT n=32 (18-25yrs)	MDD (major depressive disorder)	Compared effects of HRVB + psychotherapy to psychotherapy	5 x 45 min	Biofeedback system (J&J engineering)	Psychotherapy Non MDD control	HRVB + psychotherapy showed significant increase in HRV and decrease in depressive symptoms over a 6-week intervention
De Bruin, E. (2016) Amsterdam: NL	RCT n=75 (18-40yrs)	Stressed adults	Assessment of 3 self-help interventions for stress	35 x 10-20min	StressEraser (Helicor)	Mindfulness / Physical activity	HRVB was as effective as Mindfulness or Physical activity for decreasing stress over a 5-week intervention
Tan G. (2013) SC: USA	RCT n=42 (>18yrs)	PTSD	To reduce symptoms of PTSD	25min training + 35 x 15min	emWave (HeartMath)	Sham biofeedback No treatment	HRVB group showed decreases in PTSD symptoms compared to controls
Lehrer, P. (2018) USA	RCT n=68 (18-75yrs)	Asthma	To assesst effectiveness of HRVB to control asthma	20 x 20min	StressEraser (Helicor)	Controller medication for asthma	HRVB not more effective than controller medication for Asthma
Lemaire, J. (2011) Calgary: CA.	RCT n=40 (>18yrs)	Physicians	Reduction of self-reported stress	28 x 15min	emWave (HeartMath)	Info booklet on wellbeing programme	HRVB group showed significant decrease in stress scores compared to control
Meier, N. & Walsh, A. 2016) IA: USA	RT n=32 (18-29yrs)	Stressed students	Reduction of anxiety Increase in HRV	3x 10min	Nexus system (Mind media)	Walking	HRVB reduced anxiety more than walking intervention. Both HRVB and exercise increased HRV

Author year location	Design	**P**opulation	**I**ntervention - aim	**I**ntervention - length	**I**ntervention - device	**C**omparator(s)	**O**utcome
Nolan, R. (2010) Toronto: CA	RCT n=65 (35-64yrs)	Hypertension	Reduction of hypertension	6 x 60min	Unspecified biofeedback system	Autogenic relaxation	HRVB group decreased BP and increased HRV compared to controls
Prinsloo, G. (2013) Cape town: SA	RCT n=18 (23-41yrs)	Work related stress	To assess the effects of HRVB on cognitive ability and affect	1 x 10min	StressEraser (Helicor)	Sham biofeedback device	HRVB group showed ↑reaction times and ↓anxiety compared to controls after a single short session of HRVB
Ratanasiripong, P. (2012) CA: US	RCT n=30 (18-42yrs)	Stressed students	Reduction of self-reported stress	4 x 30min + counselling	emWave (HeartMath)	Counselling	HRVB plus counselling group showed significantly greater reductions in anxiety compared to counselling
Wells, R. (2012) Sydney: AUS.	RCT n=46 (19-67yrs)	Musicians	Reduction of performance anxiety	1 x 30min	Biofeedback system (J&J engineering)	No treatment / Slow breathing	HRVB / slow breathing both showed significant ↑ in HRV compared to control – no difference between HRVB and slow breathing
Whited, A. (2014) N.C, USA	RCT n=27 (18-30yrs)	Students	To assess physiological response to stressor tasks	4-8 x 30min	emWave (HeartMath)	No treatment	HRVB showed ↑parasympathetic responses to stress but no change in resting HRV, and no difference on reports of stress compared to controls
Yu, L. (2018) Kaohsiung: Taiwan	RCT n=210 (35-70 yrs)	CAD (coronary artey disease)	To improve prognosis of CAD	6 x 60min	ProComp Infiniti (Thought technology)	Psychoeducation + medical care	HRVB group showed significant ↓ in admissions & ↓depression and hostility compared to controls
Zucker, T. (2009) CA: USA	RCT n=38 (18-60yrs)	PTSD	To reduce symptoms of depression in PTSD	28 x 20min	StressEraser	Progressive muscle relaxation	HRVB showed ↓depression and significant increases in HRV compared to controls

RCT – Randomised controlled trial; RT – Randomised trial; HRVB – Heart rate variability biofeedback.

A randomised study by Meier and Walsh (2016) compared short term interventions of walking and biofeedback for students experiencing stress and found biofeedback to be more effective for reducing anxiety and increasing calmness on questionnaire reports. However, importantly no clear effect was shown for either intervention on physiological measures of HRV (Meier and Walsh 2016).

An RCT assessing three separate interventions using either biofeedback; mindfulness or physical activity showed that all three interventions showed positive effects on questionnaire measures including mindful awareness and attentional control (de Bruin *et al.* 2016). No physiological measures were used in this study.

Positive effects of HRV biofeedback have been reported in a one year follow up of an RCT using short term HRV biofeedback in patients with chronic heart disease. Increases in LF HRV indices, as well as reduced hospital admissions were found in post intervention and at one year follow up (Yu 2018). However, an RCT carried out to investigate the efficacy of HRV biofeedback for control of asthma, has reported that biofeedback was not better than medication (Lehrer *et al*. 2018).

The number of studies on HRV biofeedback continue to grow, however there are wide variations in study design, and it is important to recognise that the methodologies employed have involved different devices, training protocols and diverse outcome measurements.

Due to the large number of existing studies and the diverse methodologies used it is therefore useful to review existing critical appraisals to investigate the overall efficacy of HRV biofeedback.

One of the first critical reviews of studies using HRV biofeedback was carried out by Wheat and Larkin (2010). This review noted that whilst positive outcomes are reported in many studies, when physiological outcome measures and questionnaire reports or observations have both been used to evaluate outcomes, they have not always shown a high degree of concordance (Wheat and Larkin 2010). The need for further studies using both physiological assessment in conjunction with measurement of clinical outcomes has been emphasised, to assess the possible mechanisms of effect in HRV biofeedback (Wheat and Larkin 2010).

A review of clinical evidence from all types of biofeedback for mood and anxiety disorders has been conducted by the Canadian Agency for Drugs and Technology in Health (CADTH 2017). This review highlighted some improvements in both PTSD and depression using HRV biofeedback and some improvement in PTSD and anxiety using neurofeedback. However, only five RCTs were included in the final review and no studies were identified which assessed the use of home biofeedback equipment in patients (CADTH 2017). Overall, there was a recommendation for larger scale randomised control trials with an alternative treatment as a comparator, and for the development of guidelines on the use of biofeedback and neurofeedback for anxiety and mood disorders (CADT 2017).

A systematic review of 63 studies employing all types of biofeedback as an intervention for a range of psychiatric disorders has been carried out (Schoenberg and David 2014). Over 80% of articles included in this review described clinical improvement related to biofeedback with 65% to a statistically significant level. A range of biofeedback modalities including HRV biofeedback were investigated in this review, and multimodal biofeedback was noted as most effective in improving symptoms (Schoenberg and David 2014). This report aimed to highlight how biofeedback can be used with positive results as an adjunct to treatment in a range of psychiatric disorders, however only ten studies reviewed involved HRV biofeedback.

A furthermore specific systematic review assessed the efficacy of HRV biofeedback as a psychophysiological treatment for depression and PTSD (Blase et al. 2016). Critical appraisal of outcomes was carried out using the GRADE method (Dijkers 2013) and out of an initial 789 studies using HRV biofeedback identified, 6 RCTS and 4 other relevant studies were selected.
Significant outcomes were seen in biofeedback conditions compared to controls. The authors noted,

> *"Significant outcomes of this limited number of randomised studies indicate there may be a clinical improvement when HRV biofeedback training is integrated into the treatment of PTSD and depression"* (Blase *et al.* p.300).

A quantitative meta–analysis has been carried out to assess the effect of HRV biofeedback training on stress and anxiety (Goessl *et al.* 2017a). In this review a random effects meta-analysis was carried out on 24 studies identified. The authors concluded that,

> *"HRV biofeedback training is associated with a large reduction in self-reported stress and anxiety. Although well-controlled studies are needed, this intervention offers a promising approach for treating stress and anxiety with wearable devices"* (Goessl *et al*. 2017, p1).

In summary, there are a growing number of studies using HRV biofeedback as an intervention for a wide range of conditions in a number of different populations. There are a number of confounding factors such as use of different devices and protocols which make comparisons between studies problematic.

Overall, there is a need for further randomised controlled studies and assessment of outcome should ideally utilise both physiological and psychological measurements. Further information on the qualitative experiences of users of HRV biofeedback may also be useful to further assess some of the effects of this intervention. However, the most recent reviews suggest further research is warranted to investigate the potential of HRV biofeedback, and a meta-analysis does suggest potential efficacy of this intervention as a method to reduce stress and anxiety.

2.7 Rationale for the use of HRV Biofeedback in ASD

HRV biofeedback has been proposed as an important adjunct to other interventions available, which may help people with mental health conditions manage difficulties such as anxiety more effectively (Lehrer 2017; Caldwell 2018).

The relationship between anxiety and ASD is now viewed by some as central to development of many ASD symptoms, rather than being a secondary consequence of social and communication symptoms (Markram 2007; Sugarman *et al.* 2013).

A number of interventions have been used to try to help manage anxiety in people with ASD. Conventional therapies such as CBT have shown moderate success, however adaptations have been needed to accommodate the social and communication difficulties seen in people with ASD. In addition, many conventional 'talking therapies' require significant time and therapist expertise making them costly, in a time of limited healthcare resources.

Despite widespread use (Farmer *et al.* 2013), evidence for the effectiveness of medication to treat some of the difficulties experienced by people with ASD remains limited, and there is a possibly of increased risks in people with ASD (Vasa 2016).

It is proposed that a new approach to managing difficulties faced by people with ASD is needed, that appeals to their strengths and interests rather than simply trying to adapt existing therapies designed for the non ASD population.

The use of technology has been advocated as a potential method of helping people with ASD (Murray 1999; Bagatell 2010). Biofeedback has been highlighted as a potential intervention that reduces the need for complex verbal interaction and involves use of real time visual or auditory feedback which may appeal to the nonverbal strengths, and the technology interests seen in many people with ASD.

Current evidence has highlighted that people with ASD show signs of ANS dysfunction (Hirstein *et al*. 2001) and show significant difficulties with symptoms such as anxiety (van Steensel 2017).

HRV biofeedback may help regulate ANS function and has been investigated as an intervention to help manage symptoms such as anxiety in people without ASD (Reiner 2008; de Bruin 2016).

HRV biofeedback is visual and requires fewer verbal and social demands that many traditional talking therapies. It has shown some positive effects helping people without ASD and may also be a potential intervention to help people with ASD.

It is therefore hypothesised that HRV biofeedback could be used as a possible intervention to help regulate ANS dysfunction and reduce symptoms such as anxiety in people with ASD.

Whilst the exact mechanism of effect is still debated, the provision of an intervention such as HRV biofeedback via technology may be a useful method of engaging people with ASD in an area of interest, without the complex social and communication demands of traditional cognitive and behavioural therapies, and without some of the potential risks of medication.

Previous research has focussed on use of neurofeedback in people with ASD and current research into its effectiveness is ongoing.

HRV biofeedback combines a method of delivery using visual information and technology, which may be suited to the visual strengths of people with ASD (Grandin 1995), with an aim to intervene in area of possible underlying dysfunction.

2.8 Summary

This chapter has highlighted relevant background information on literature relating to ASD, biofeedback and HRV. It is argued that HRV biofeedback could be a useful method to help manage anxiety in people with ASD.

The next chapter will present a systematic review of literature relating to the intersection between the three themes of ASD, biofeedback and HRV to examine what specific research exists on the use of HRV biofeedback in people with ASD - see Figure 2.4.

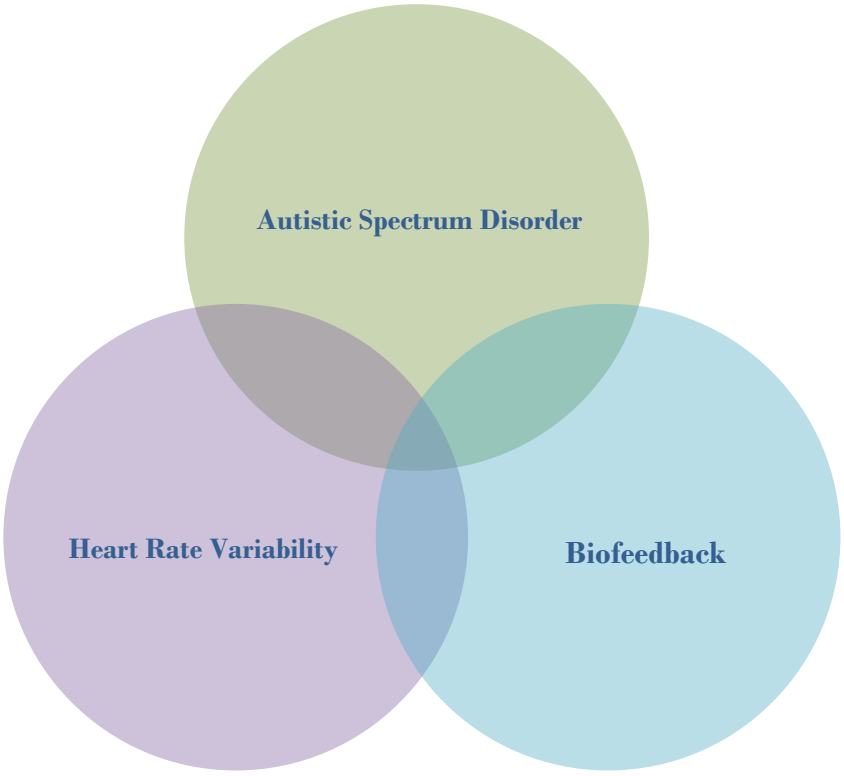


Figure 2.4 Three main themes upon which the thesis is based.

Chapter 3. Systematic Literature Review

3.1 Overview

It has been proposed in Chapter 1 that a new approach to managing difficulties faced by people with ASD is needed, one that appeals to their strengths and interests rather than simply trying to adapt existing therapies designed for the non ASD population. Chapter 2 has reviewed current research on HRV, biofeedback and ASD to inform the background context and develop a rationale for the current study. It concluded that there is emerging support for HRV biofeedback, although further research is needed.

Chapter 3 will now report the findings of a systematic review to assess what literature exists on the use of HRV biofeedback in people with ASD. Literature from library electronic databases; key journals and unpublished doctoral theses is reviewed and presented in a PRISMA flow diagram (Liberati 2009). Literature identified is then appraised and future directions for further research are discussed.

3.2 Systematic literature search

Literature search question: What literature exists on the use of HRV biofeedback in people with ASD?

3.2.1 *Search Methodology*

Initial reviews of published database literature carried out from 28th to 30th January 2015 indicated a very heterogeneous range of studies with few randomised controlled trials into the use of HRV biofeedback and no randomised trials reported specifically on ASD. Therefore, search methods employed included systematic electronic database searching, and review of reference lists from key texts, hand searching selected journals and unpublished theses.

A systematic approach to the search strategy was employed following the PRISMA guidelines (Liberati *et al.*, 2009). The search strategy used was also linked to a clearly defined research question related to the Population, Intervention, Comparator and Outcomes (PICO) framework (Schardt *et al.*, 2007).

A preliminary search was carried out using electronic library databases using two terms related to the population – namely people with 'autistic spectrum disorder and the intervention 'heart rate variability biofeedback'.

This initial search yielded insufficient results from databases interrogated. Therefore, the second theme was broken into two separate parts describing the intervention type – 'biofeedback' and the specific measurement modality – 'heart rate variability'.

Searches were therefore carried out using three key themes related to population intervention and outcome measurement as outlined below,

- Theme 1: Population – ASD (common synonyms were also included)
- Theme 2: Intervention – Biofeedback
- Theme 3: Outcome measure – Heart rate variability

3.2.2 *Search strategy*

A comprehensive search of electronic library databases was then undertaken to identify relevant literature on the three key themes identified in the research question and PICO framework specific to this review. The following five databases were searched,

- Medline; Psychinfo and Embase via the OVID platform;
- CINAHL plus
- Scopus

Searches were carried out on 11th August 2016 and were repeated on 19th July 2017.

Inclusion criteria

- All languages were included in the review
- All date ranges were included; i.e. no restriction was set on the date range for each database.
- Both published and unpublished literature was included in the review.

Exclusion criteria

- Literature without an English abstract was excluded.
- Studies not including ASD were excluded from the final review.
- Studies not containing HRV biofeedback were excluded from the review.

3.2.3 *Search terms used*

Keywords were identified initially by consulting with experts in the areas of ASD and heart rate variability and were then further refined with advice from a librarian. Searches were carried out using the advanced search option of each database. Keyword searching was carried out by exploding search terms and then using truncation characters specific to each database to identify relevant MESH terms and keywords. Terms were then combined using the Boolean operator 'AND' to combine themes and limit the search.

A summary of databases searched, search terms used, and final dates of each search are outlined in Table 3.1.

Table 3.1 Library electronic database search strategy showing themes based on PICO framework; search terms; databases used; dates of search and inclusion and exclusion criteria.

Research question	**P**opulation	**I**ntervention	**C**omparator	**O**utcome
"An Investigation into the use of Heart Rate Variability Biofeedback in People with Autistic Spectrum Disorder"	*"Autistic Spectrum Disorder"*	*"The use of HRV biofeedback"*	*any*	
Search terms used	*Theme 1* *Autism** *Asperger** *Autis*/ASD* *Autistic Spectrum Disorder* *Pervasive Developmental Disorder** *PDD*	*Theme 2* *'Biofeedback'*		*Theme 3* *'Heart rate variability'* *HRV*
Databases searched	Final search date	Inclusion criteria	Exclusion criteria	
• Medline via Ovid • Psychinfo via Ovid • Embase via Ovid • CINAHL plus • Scopus	*19th July 2017*	*All languages* *All dates*	*No English abstract* *Not ASD* *Not HRV* *Biofeedback*	

Results of database searches shown in Table 3.2.

Table 3.2 Results of literature searches from five library electronic databases with duplicates removed and exclusion criteria applied.

Literature theme	Database 1 Medline	Database 2 Psychinfo	Database 3 Embase	Database 4 CINAHL	Database 5 Scopus	Total	Number remaining once duplicates removed	Number remaining once exclusion criteria applied
HRV + ASD	39	31	99	8	19	196	120	
HRV + Biofeedback	153	191	341	72	275	1032	598	
ASD + Biofeedback	56	54	296	30	10	446	442	
HRV+ ASD + Biofeedback	3	4	8	0	4	19	11	2

3.2.4 *Literature search results*

Literature search results were reviewed to assess what literature currently exists on the use of HRV biofeedback in people with ASD. The titles and abstracts of the literature accessed were reviewed and duplicates were removed. All potential articles were screened in full and exclusion criteria were then applied excluding all articles not relating to persons with ASD.

Only articles which involved the use of HRV biofeedback as the main intervention for people with ASD were included in the final review. Articles which mentioned the use of HRV Biofeedback within the context of an overall review but did not focus on HRV biofeedback as the main intervention were excluded.

A summary of final records identified from library electronic databases with reasons for exclusion is described in Table 3.3.

Table 3.3 Summary of records identified from electronic library database searches, with two records highlighted for inclusion.

Library database searching of literature:	Inclusion / Exclusion with reason
1. Bacchini, P.H.F., Lopes, E.C., De A. Barbosa, M.A.G., Ferreira, J.O., Da Silva Neto, O.C., Da Rocha, A.F. and De A. Barbosa, T.M.G 2014"Developing an affective Point-of-Care technology," *IEEE Symposium on Computational Intelligence in Healthcare and e-health* (CICARE), Orlando, FL, p. 77-84.	Not HRV biofeedback Exclude
2. Friedrich E.V.C., Suttie N., Sivanathan A., Lim T., Louchart S. and Pineda, J.A. (2014). Brain-computer interface game applications for combined Neurofeedback and biofeedback treatment for children on the autism spectrum. *Frontiers in Neuroengineering*, 7, (21), p. 1-7.	Autism + biofeedback review Exclude
3. Krivonogova, E. (2013). Non-communicable disease epidemic: epidemiology in action (EuroEpi 2013 and NordicEpi 2013): Aarhus, Denmark 11 to 14 August 2013. *European Journal of Epidemiology*, 28 (1), p.130.	Not Autism Exclude
4. Power, E.M., (2016). *Evaluating the Effectiveness of Biofeedback in Improving Emotional Regulation for a Student with Autism Spectrum Disorder.* (Doctoral dissertation, The Chicago School of Professional Psychology). ProQuest Information and Learning; US. No. 10085662.	Autism + HRV+ biofeedback **Intervention Include √**
5. Reid A. and Nihon, S. (2013). The effects of heart rate variability on sensorimotor rhythm: A pilot study. *Journal of Neurotherapy*, 17(1), p.43-48.	Not Autism Exclude
6. Santhirasegaram, L. (2011). A book finally written: Case study of effective intervention five years' post closed head injury. *Journal of Neurotherapy*, 15(4), p.441-443.	Not Autism Exclude
7. Thompson L., Thompson M. and Reid, A. (2010). Functional neuroanatomy and the rationale for using EEG biofeedback for clients with Asperger's syndrome. *Applied Psychophysiology Biofeedback,* 35 (1), p.39-61.	Autism + biofeedback review Exclude
8. Thompson L., Thompson M. and Reid, A. (2010). Neurofeedback outcomes in clients with Asperger's Syndrome. *Applied Psychophysiology Biofeedback*, 35(1), p.63-81.	Autism + biofeedback review Exclude
9. Thompson M. and Thompson, L. (2011). Setting up for success with asperger's and autistic spectrum disorder. *Journal of Neurotherapy*, 15(4), p.426-427.	Autism + biofeedback review Exclude
10. Thompson M., Thompson L., Reid A. and Santhirasegaram, L. (2011). Neural networks: An exploration of functions influenced by Neurofeedback. *Journal of Neurotherapy*, 15(4), p.447-448.	Not HRV biofeedback Exclude
11. Westlake, G. (2013). *Evaluation of a biofeedback intervention in college students diagnosed with Autism Spectrum Disorders*. (Doctoral dissertation, Arizona State University). ProQuest Information and Learning; US. No. 3595257.	Autism + HRV+ biofeedback **Intervention Include √**

Additional manual searches were then carried out by reviewing reference lists from the publications obtained from combined search terms and by reviewing the Journals '*Applied Psychophysiology and Biofeedback'*, '*Journal of Neurotherapy*' and the magazine '*Biofeedback*' published by the Association of Applied Psychophysiology and Biofeedback. The titles and abstracts of all the literature accessed were reviewed and duplicates were then removed. Full texts were then screened for eligibility using the inclusion and exclusion criteria. A summary of the additional records identified from other sources with reasons for exclusion is described in Table 3.4.

Table 3.4 Summary of additional literature identified from three sources: manual searching of references, journals and grey literature, with three records highlighted for inclusion.

Additional manual searching of references, journals and grey literature	Inclusion/Exclusion with reason
1. Aguinaga, Nancy (2006). An Investigation of the Effectiveness of Computer-assisted Biofeedback for Students Diagnosed as Having Autism Spectrum Disorder (Doctoral dissertation, University of Central Florida). Electronic Theses and Dissertations. 951.	ASD + HRV + biofeedback Intervention **Include** √
2. Berger, M.J. (2007). The Efficacy of Selected Biofeedback Techniques in Mitigating Symptoms Associated with Autism Spectrum Disorder. Biofeedback, 35(2), p.62-68.	ASD + HRV + biofeedback Intervention **Include** √
3. McCoy, K.M., Westlake, G., Zucker, S.H. and DiGangi, S.A. (2014). Evaluation of a Biofeedback Intervention in College Students Diagnosed with an Autism Spectrum Disorder. DADD Online Journal, 1(1), p.121- 135.	ASD + HRV + biofeedback Intervention **Include** √
4. Sugarman, L.I., Garrison, B.L., Williford, K.L. (2013). Symptoms as Solutions: Hypnosis and Biofeedback for Autonomic Regulation in Autism Spectrum Disorders. American Journal of Clinical Hypnosis, 56, p. 152-173.	ASD + HRV biofeedback - review Exclude ×

The combined results of library electronic database searching, and manual searching are summarised in the PRISMA flow diagram in Figure 3.1 PRISMA diagram for systematic literature review conducted in 2017.

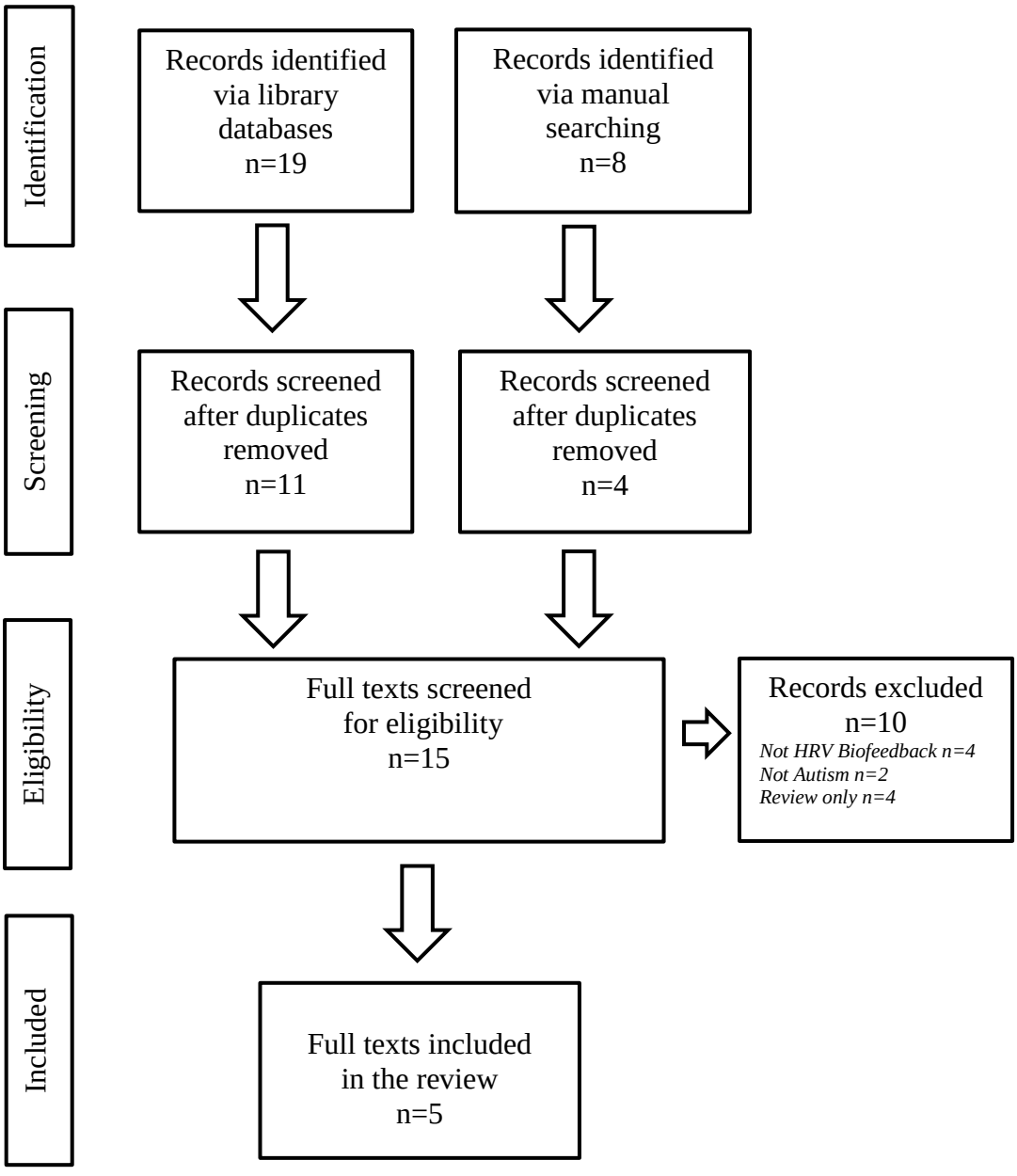


Figure 3.1 PRISMA diagram for systematic literature review conducted in 2017.

3.3 Critical appraisal of literature

A critical appraisal of the final studies included in the review is described below. Each study was initially reviewed using the PICOTS framework (Schardt *et al.* 2007; Davies 2011).

A number of more detailed evaluation tools exist for reviewing the quality of published studies such as the critical appraisal skills programme (CASP 2006), or the outcome of studies (Dijkers 2013). However, as the records identified were mainly unpublished dissertations the studies met few of the appraisal criteria. Studies were therefore appraised by reviewing an adapted form of the framework for '*10 questions to help you make sense of qualitative research*'(Chenail 2011). The framework used for appraising the studies identified is outlined in Table 3.5.

Table 3.5 Summary of framework questions used to appraise literature.

Appraisal area	Guiding questions
Rigour	1. Was there a clear statement of the aims of the research?
	2. Is the methodology appropriate to the stated aims?
	3. Was the research design appropriate to address the aims of the research?
	4. Was the recruitment strategy appropriate to the aims of the research?
	5. Was the data collected in a way that addressed the research issue?
	6. Has the relationship between researcher and participants been adequately considered?
	7. Have ethical issues been taken into consideration?
	8. Was the data analysis sufficiently rigorous?
Credibility	9. Is there a clear statement of findings?
Relevance	10. How valuable is the research?

The final studies included in the overall review are shown in Table 3.6. Two of the reports; Westlake (2013) and McCoy (2014), describe research from the same PhD project and are therefore reviewed as a single study.

Table 3.6 Final studies included in the literature review.

Final results of combined literature search terms
1. Aguinaga, Nancy, (2006). *An Investigation of the Effectiveness of Computer-assisted Biofeedback for Students Diagnosed as Having Autism Spectrum Disorder* (Doctoral dissertation, University of Central Florida). Electronic Theses and Dissertations. 951.
2. Berger, M.J., (2007). The Efficacy of Selected Biofeedback Techniques in Mitigating Symptoms Associated with Autism Spectrum Disorder. *Biofeedback, 35(2), p.62-68.*
3. Power, E.M., (2016). *Evaluating the Effectiveness of Biofeedback in Improving Emotional Regulation for a Student with Autism Spectrum Disorder* (Doctoral dissertation, The Chicago School of Professional Psychology). ProQuest Information and Learning; US. No. 10085662.
4. Westlake, G. (2013) *Evaluation of a Biofeedback Intervention in College Students Diagnosed with Autism Spectrum Disorders.* (Doctoral dissertation, Arizona State University). ProQuest Information and Learning; US. No. 3595257. and McCoy, K.M., Westlake, G., Zucker, S.H. and DiGangi, S.A., (2014). *Evaluation of a Biofeedback Intervention in College Students Diagnosed with an Autism Spectrum Disorder*. *DADD Online Journal*, 1(1), p.121- 135.

These four studies are now reviewed, first with reference to the PICOTS framework to describe and summarise and secondly with reference to the adapted CASP framework to appraise each study.

3.4 Study 1: Aguinaga (2006)

3.4.1 *PICOTs framework*

Author and Year; Location and literature format	Aguinaga, N., (2006). University of Central Florida; unpublished doctoral dissertation
Population studied	Participants were three young people with autism aged 9-10 years (2 females; 1 male) who were assessed in a special needs' classroom environment.
Design of study Intervention	This study employed a single subject multiple baseline design. Participants were assessed on their ability to engage in academic tasks before and after using a computer assisted biofeedback programme (Freeze-Framer). Performance on academic tasks was also measured. Parent and teacher reports were collected on perception of *'generalization of self-regulation behaviour*' (Aguinaga, 2006 p. iii), before and after the intervention period.
Sample size and Comparator	The sample size was n=3. Within subject comparisons were made before and after using the HRV biofeedback intervention There was no separate control group.
Key findings and Outcome	All participants showed increased '*speed to engagement*' in academic tasks. Time spent '*on task*' also improved for all participants. One out of the three participants also showed improved academic performance on tasks. Teacher reports indicated a perception of '*generalisation of self-regulation of behaviour*' in all participants, whilst parent reports did not indicate any perception of change in the home environment. Participants with greater cognitive ability showed more improvement on tasks.
Time frame for study	This study involved biofeedback sessions lasting 3-4 minutes once per day, five days per week for five weeks in total, with each participant beginning the intervention in phases one after another.
Setting	This study was carried out in a classroom setting in a school for children with disability.

3.4.2 *Study 1: Aguinaga (2006) Appraisal*

Rigour

Aims	This dissertation makes a clear statement of aims to examine the impact of a type of heart rate variability biofeedback on the engagement of students with autism in academic tasks.
Design and Methodology	The design took into account the nature of employing a new intervention in a vulnerable young population. Biofeedback was used once a day, five days per week at the set time on the same computer in the participant's usual classroom. Baseline data was collected from participants at the same time each day five times per week in the same classroom. Participants were given support in use of the device by a member of the research team. Participants then immediately completed an individualised academic task which was scored according to the specified research aims. A checklist was followed to ensure training and recording of data was collected in the same manner by all members of the research team. The method was congruent with the aims of the research.
Recruitment	Participants were recruited by the researcher and special education teacher identifying suitable potential participants according to pre-set selection criteria. Written information was then given to parents and teachers and written consent forms were signed prior to intervention. A verbal assent form was also read aloud to all participants.
Data collection and Measures	All participants were assessed before and after using biofeedback. Data was collected on speed to engagement, time on task and academic performance. A short questionnaire was used to collect information from parents and teachers, regarding the outcome of the intervention.
Researcher participant relationship	The researcher and several other members of a research team spent time with participants – all contact was in the participant's usual classroom. The short nature of sessions and the involvement of other researchers made it unlikely that the researcher had a profound influence on treatment results.

Ethical issues	Consent was deemed adequate. Written information was given to carers prior to obtaining consent. Assent was also sought verbally from all participants. All consent and assent record forms used were provided. The researcher noted that parents would have benefitted from having more information on the biofeedback programme and its aims and recommended more involvement of parents in any future research.
Data analysis	Descriptive statistics were used to assess pre-post participant behaviour before and after using biofeedback.

Credibility

Is there a clear statement of findings?	The study findings are stated clearly. The wider relevance of findings is limited due to the small sample size. Strengths of this study related to the detailed level of observations of behaviour carried out in a natural classroom setting, rather than in a clinical environment. The study also employed a clear and replicable methodology regarding the use of biofeedback for to help young children with autism engage in academic tasks.

Relevance

How valuable is the research?	This research study has relevance as it adds information on the use of this intervention in a learning-disabled population in a classroom environment. The value is limited by the small sample size and lack of a control group.

3.5 Study 2: Berger (2007)

3.5.1 *PICOTS framework description*

Author and Year *Location and literature format*	Berger, M.J., (2007). The Bronx High school of Science. Magazine article
Population studied	This report presented results intervention with a single adolescent male diagnosed with ASD.
Design of study *Intervention*	Single case design and report of future treatment potential. The intervention employed HRV biofeedback using biofeedback games produced by Somatic Vision. The treatment regime used several additional biofeedback measurements such as skin conductance and hand temperature to measure outcomes. In addition, the participant practiced biofeedback guided meditation exercises.
Sample size and Comparator	The sample size in this study was n=1 There was no comparator.
Key findings and Outcome	Pre-post comparisons were made using a single parent rated questionnaire, the Autism Treatment Evaluation Checklist. Results indicated '*measurable improvement on sensory/ cognitive awareness and on health/ physical behaviour ratings and dramatic improvement in sociability'* (Berger, 2007 p. 62) The participant showed improvement on self-ratings of calmness. In addition, physiological assessments used before and after biofeedback training showed a slowed breath rate and improved hand temperature.
Time frame for study	The case study involved 18 x 1hour biofeedback sessions over a period of 6 weeks, plus home practice of biofeedback guided meditation exercises.
Setting	The location for the biofeedback sessions was unclear.

3.5.2 *Study 2: Berger (2007) Appraisal*

Rigour

Aims	The stated aims were to outline the potential of biofeedback as an intervention for ASD and to help the participant to self soothe and relax.
Design and Methodology	This single case study design did meet the aim of showing the potential for this type of treatment and to assess whether it would help the participant to relax. The nature of study design did not allow for any comparisons with other subjects; however, the methodology was appropriate to meet the stated aims.
Recruitment	The nature of participant recruitment in this study is unclear
Data collection and Measures	Pre-post comparisons were made using parent report via a standardised questionnaire and using several pre-post physiological measurements from biofeedback devices used with the participant and a participant rating scale. The study shows strength in this area due to the use of pre-post questionnaire measurement in conjunction with pre-post physiological measurements, and pre-post participant ratings
Researcher participant relationship	The nature of the study design and intervention indicates that there would have been close contact between the participant and the researcher, particularly in the initial set up of the treatment regime.
Ethical issues	The nature of the researcher's initial recruitment method and subsequent contact with the participant is not discussed. There may have been a relationship which then influenced the outcome. It would have been useful to have had clarification as to how long the researcher spent with the participant in the hour-long biofeedback sessions and how much training from the researcher was involved.
Data analysis	Statistical tests were carried out in this study on the pre-and post-ratings of behaviour on the parent rating scale. Significant changes were reported ($p \leq 0.03$).

Credibility

Is there a clear statement of findings?

There is a clear statement of findings in this study.

Whilst HRV biofeedback was the main treatment modality, the additional use of home meditation practice is a confounding variable that may have also influenced results of the study. This study showed strengths in that pre-post measures were obtained from both participant and parent. In addition, several physiological measurement modalities were used and the detail in recording and the pre-post recording enabled statistical analysis of change over time.

The study was limited because of the small sample size and lack of additional information regarding participant characteristics, such as cognitive ability and level of anxiety. There was evidence of a significant positive effect from the intervention over several pre-post measures.

The strength of this evidence is however limited due to the fact that this was a single case study and confounding variables such as participant researcher relationship and the additional use of mediation practice were not discussed.

Relevance

How valuable is the research?

This study shows relevance as a proof of concept case design in a new area where there exists no current published research. The researcher clearly acknowledges the need for larger studies to increase evidence base for the potential of this intervention.

3.6 Study 3: Power (2016)

3.6.1 *PICOTS framework description*

Author, Year and Location and literature format	Power, E.M., (2016). Chicago School of Professional Psychology. unpublished doctoral dissertation
Population studied	This study involved assessment of an intervention with a single 8-year-old boy with autism.
Design of study Intervention	This was a single case study design. The intervention involved use of a hand held HRV biofeedback device (emWave2) with recordings made using the device during the baseline assessment and during the intervention to assess change in 'cardiac coherence'.
Sample size and Comparator	The sample size was n=1. The subject acted as their own control. No other comparator is described.
Key findings and Outcome	A significant negative change in cardiac coherence was noted during the intervention period compared to the baseline period. Thus, the participant showed greater levels of cardiac coherence during the baseline assessment period compared to the intervention period.
Time frame for study	Four initial baseline sessions took place over four days with each session lasting on average 12 minutes. Ten intervention sessions took place over the course of ten days each lasting on average 7 minutes.
Setting	Each session involved the participant being taken out of their classroom to be assessed by the researcher in separate room within the school environment.

3.6.2 *Study 3: Power (2016) Appraisal*

Rigour

Aims	This study aimed to assess the impact of HRV biofeedback using a commercial device on a single participant with ASD.
Design and Methodology	The study employed a single subject experimental A-B design, deemed appropriate to test out a new intervention in a new and vulnerable population. The methodology involved an initial detailed neuropsychological assessment followed by baseline measurement of HRV using the emWave2 device whilst the boy played with Lego blocks. This detailed assessment was then followed by an intervention period of 10 sessions training him to think positive thoughts and breathe deeply.
Recruitment	The recruitment strategy used in this study involved teachers recommending a student who had difficulty with emotional regulation for the intervention. Written parental consent was obtained. Verbal consent was also sought from the participant.
Data collection and Measures	Detailed neuropsychological testing was carried out as part of the regular assessment of each student which collected information on the participant's cognitive ability levels. Finally, questionnaires rated the severity of autism symptoms. Intervention measures used included pre-and post-teacher rating scales and data from the biofeedback device itself.
Researcher participant relationship	The researcher spent short periods of time (30 minutes) with the participant during the intervention and baseline periods, however the neuropsychological assessment process would have entailed several hours of direct contact prior to this.

Ethical issues

A number of ethical issues arose in this study, many of which were noted by the researcher.

Sensory issues and cognitive rigidity commonly seen in people with autism were highlighted by the researcher as possible reasons for the poor results of the intervention. For example, '*the student's sensory response to the emWave2 equipment proved to cause some difficulties during the baseline and intervention phases'*, (Power p.67).

An important issue raised by this study was the anxiety noted in the participant regarding sessions with the examiner. This may have been related to the change in his routine '*the student appeared to become anxious on days that he would be meeting with the examiner and would check with his teacher an average of four times on intervention days to see if the examiner was coming'* (Power, p.66.)

The examiners visits varied depending on her schedule and school events *'this ultimately dictated when the student could be pulled from his classroom which impacted the student's anxiousness regarding inconsistency in his weekly schedule'* (Power p.67). The participant was given a visual schedule regarding visits by the examiner, but it was acknowledged that the times of visits were inconsistent, which may have increased anxiety.

In addition, issues were noted within the actual intervention sessions '*The participant reported that he was 'upset because he did not know how to change the colors of the machine* … and stated that *'he was trying his hardest to think positively and take deep breaths'* (Power p.64).

Data analysis

Statistical assessment was carried out using tests which were appropriate to single case design.

Credibility

Is there a clear statement of findings?

The author gives a clear account of findings and highlights factors such as sensory sensitivity; need for routine seen in many people with autism, and a lack of time that may have led to problems with this intervention. Strengths of this study relate to the very detailed level of observations of task behaviour, carried out in an educational environment.

Confounding variables

Some ethical issues are raised by this study concerning the stress of continuing to use biofeedback and the impact this may have on a vulnerable participant. The boy reported feeling stressed at not being able to do the biofeedback properly and it is possible that instruction to carry out deep breathing may have led to hyperventilation and anxiety.

Future implications

A potential confounding variable in this study relates to the possible influence of the lengthy neuropsychological assessment prior to the baseline and intervention. This may have had an impact on the participant independently from the any actual biofeedback training. It is also possible that the chosen baseline play activity was more relaxing for the participant than the biofeedback sessions with the examiner.

This study involved the youngest participant studied (8 years) and this age group may require different training techniques. Some of the implications of this research relate to the need for training to ensure participants can use devices correctly.

Relevance

How valuable is this research?

This study is limited because of the small sample size and the lack of information on other aspects of participant's behaviour that could have been obtained from contact with parents. This research is however valuable because of the information on the potential for negative effects from use of biofeedback.

3.7 Study 4: Westlake (2013)

3.7.1 *PICOTS framework description*

Author Year and Location	Westlake, G. (2013) and McCoy (2014). Arizona state university unpublished dissertation and an online journal.
Population	College students with and without ASD participated in this study
Design of study *Intervention*	The study was a two-group experimental design. The intervention involved initial basic training in use of the desktop HRV biofeedback equipment. After basic instruction participants then completed a 10-minute session using the system once per week for 10 weeks. No other training or input from support staff or the researcher was provided. No background information was collected on participants other than gender. Participants completed biofeedback sessions on their own in the same room and recorded their HRV scores and session time on a record sheet manually after each session for later data analysis.
Sample size and Comparator	Intervention: n = 10 students with ASD (all male) Comparison: n = 37 students not ASD (28 male, 9 female)
Key findings and Outcome	The study used exploratory data analysis to review trends in data collected over the ten-week period. Within and between groups comparisons were made to examine trends between the first five weeks and the second five weeks of the intervention. Participants with ASD showed a greater increase in mean HRV scores compared to students without autism in the second five weeks of the study. Participants with ASD also showed higher median scores and less variability in their scores compared to students without ASD, in the second five weeks of the study. Both groups showed a decline in participation over the course of the study with only 60% of autism students remaining at the end of the study and 66% of non-autism students remaining at the end of the ten-week period. A possible pattern between participant drop out from the study and their biofeedback progress was also discussed with the suggestion that those with little progress may have to dropped out
Time frame *Setting*	The Intervention lasted 10 weeks. The study was located in a Disability Resource Centre.

3.7.2 *Study 4: Westlake (2013) Appraisal*

Rigour

Aim	This feasibility study aimed to assess whether HRV biofeedback intervention would help young adults with ASD manage anxiety.
Design and Methodology	This study design was deemed as appropriate to the stated aims. The methodology used did not however address the stated aims as no direct measure of anxiety is used and no pre-post measurement of anxiety is carried out. There was also an inconsistency in the reporting of the sample size of the control group through the study.
Recruitment	The study design involved recruiting two groups, those with a diagnosis of ASD and students from psychology classes. Two different recruitment strategies were used. Students in the control group were recruited directly from introductory psychology courses. Students with ASD were referred directly into the study by advisors who were supporting students with ASD at the university. It was not clear whether any participants in the control group may also have had ASD.
Data collection and Measures	There were a number of limitations with data collection in this study. No data was collected on participant characteristics such as race or age cognitive ability or pre-existing anxiety levels. Participants recorded their HRV coherence scores and session time from the experimental device on a record sheet manually after each session. No independent physiological measures of HRV or anxiety were carried out.
Researcher participant relationship	The researcher had no contact with any of the participants thus excluding any potential direct effect of a researcher participant relationship on results.

Ethical issues	The referral into the study of people with ASD by advisers may have led to inclusion of participants with ASD who did not want to participate or who did not have high anxiety.
Data analysis	Exploratory data analysis was used rather than hypothesis testing and statistical tests. The methods used to visually review trends in the data may have been open to interpretation and this was acknowledged. In addition, the level of 'coherence' measured by the device was taken to be an indication of participant's level of HRV and their anxiety. The assumption that measures of HRV recorded from the biofeedback device are a sign of actual participant HRV and participant anxiety may not be correct.
Credibility	
Is there a clear statement of findings?	The findings of this study were unclear. The rationale for reporting findings of trends between the first five weeks and the second five weeks of the study, rather than the first and last week of the study is unclear. The discussion of potential links between attrition from the study and biofeedback progress is unclear, as both participants with high scores and low scores dropped out of the study. There were a number of limitations in this study due to the lack of demographic information and lack of independent measurement of anxiety prior to commencing the intervention. The different recruitment strategies employed and the lack of any independent measurements of anxiety or HRV make it difficult to draw conclusions about outcomes.
Relevance *How valuable is this research?*	This research is relevant because of the information it adds in a new area with no published literature. Despite limitations, this was the only known study with a sample size greater than three and with a comparator group

A summary of key similarities and differences emerging from the design, measures and interventions employed in these studies is described in Table 3.7.

Table 3.7 Critical appraisal summary of four studies showing key differences in design measures and intervention.

Theme	Study Author and Year			
	Aguinaga 2006	**Berger 2007**	**Westlake 2013**	**Power 2016**
Design	*multiple case study*	*single case study design*	*2x group design*	*single case study design*
Sample size	*n=3*	*n=1*	*n=10*	*n=1*
Age	*9-10 years*	*teenage*	*unknown*	*8 years*
Recruitment and consent	*Teacher + carer consent*	*Unknown*	*ASD Mentor*	*Teacher + carer consent*
Control group or comparator	*No*	*No*	*Yes (n=37) assumed not ASD*	*No*
Random allocation used	*No*	*No*	*No*	*No*
Allocation concealment	*No*	*No*	*No*	*No*
Location of intervention	*School / college*	*Unclear /home practice*	*School / college*	*School / college*
Measures				
Demographic information	*Age, gender*	*Gender only*	*Gender only*	*Age, gender*
Type of assessment used in addition to biofeedback	*Timing of behaviour on academic tasks*	*Participant self-rating of calmness* *Parent report*	*None*	*Psychometric testing of participant prior to intervention*
Carer reports collected	*Parent and Teacher*	*Parent only*	*None*	*Teacher only*
Participant report collected	*None*	*Participant self-rating*	*None*	*Indirect reports via teacher*
Type of physiological measurements + assessments	*Scores on biofeedback device used as measure of HRV*	*Skin conductance, and temperature*	*Scores on biofeedback device used as measure of HRV*	*Scores on biofeedback device used as measure of HRV*
Intervention				
Length of biofeedback	*3-4 minutes x25 sessions*	*60 minutes x18 sessions*	*10 minutes x10 sessions*	*7 minutes x10 sessions*
Biofeedback device used	*Freeze-framer*	*Somatic Vision + RESPeRATE*	*emWave2 desktop*	*emWave2*
Adoption of device / usability	*No*	*No*	*Attrition rate calculated*	*No*

3.8 Synthesis of evidence on HRV biofeedback in ASD

In order to provide a synthesis of the evidence available from this literature the three areas of study design; measures used, and interventions employed shown in Table 3.7 are now reviewed further to assess whether any clear themes are apparent.

3.8.1 *Design of studies assessing HRV Biofeedback in ASD*

The studies reviewed in this literature appraisal are typical of those in a new area of research namely small group or single case study design. The existing studies are limited in terms of sample size with no studies having more than ten people with ASD. They have added useful information regarding the potential of HRV biofeedback for both positive and negative outcomes in people with ASD.

Sample size

Single case study and small group comparisons have been appropriate in a new area for a vulnerable population. However, there is now a clear need for larger scale studies with greater sample size. Future studies should aim to follow randomised control design with adherence to principles such as the CONSORT guidelines for the reporting of trials (Schulz *et al.*, 2010).

Recruitment

Current studies show the potential for selection bias in the recruitment of participants. These studies involved children being selected by teachers or recommended by mentors for inclusion in research, rather than using more widespread recruitment strategies. In addition, the study involving two groups did not use a similar selection strategy for each group. To minimise potential for bias, studies should clarify a clear procedure for recruitment, to reduce selection bias.

Consent and information for participants

The studies reviewed did not clarify how much information was given to parents or carers regarding each intervention, prior to obtaining consent.

One of the studies noted increased difficulty using biofeedback after intervention and reports of increased anxiety in the participant. Thus, participants and carers and participants with ASD should be given detailed information on the nature of the intervention with possible risks as well as benefits outlined in any further development of this research area. This information should also be presented in a format that is accessible to both carers and people with ASD.

Random allocation

The studies identified used small-scale samples to explore the potential for an effective treatment and therefore they did not employ random allocation. As further evidence of potential effectiveness becomes available, it will become necessary to formally test the effectiveness of HRV biofeedback. The risk of bias must be addressed through random allocation to groups and use of allocation concealment. Only one study used a comparator group, and this was limited by the lack of random allocation and the different recruitment strategies used. In addition, the lack of detail regarding participant characteristics in this study made it impossible to determine if the two groups in this study were different with regard to either levels of anxiety or presence of ASD symptoms.

Location of intervention

Three of the four studies reviewed were set in an educational environment. One of the potential reasons for the negative outcome of using biofeedback seen in the study by Power (2016) was suggested as being due to use of an unfamiliar environment and an erratic training and intervention schedule. It is of note that the study design used by Aguinaga (2006) used the participant's classroom which was a familiar environment and all training biofeedback and intervention sessions were all given every day and at the same time each day. Some of the key issues reported by people with ASD and their carers are difficulties coping with new situations and any change in their environment (National Autistic Society, 2017). The importance of using a safe and familiar environment should be acknowledged in any study aiming to help people with ASD manage anxiety.

3.8.2 *Measures used to assess HRV biofeedback in ASD*

Demographic information

Minimal demographic information was collected in three out of the four studies reviewed. The information collected by Power (2016) involved collecting information on neuropsychological functioning rather than demographic information. The lack of detailed demographic information collected in these studies made it difficult to understand the specific characteristics of participants and draw conclusions about how these participants compared to the wider population of people with ASD, and whether specific participant characteristics may be related to outcome of biofeedback. Collecting data on levels of ASD symptomology and levels of premorbid anxiety would enable more information to be gathered on the potential for biofeedback to elicit change in specific groups and could help to elucidate whether there was any relationship between level of ASD symptoms and anxiety and use of biofeedback.

Participant reports

Information in current studies was mainly obtained via proxy parent or teacher reports. Whilst this information is important, direct reports from people with ASD on the effectiveness and usability of any interventions are essential when designing and developing new intervention specifically tailored to the needs of people with ASD. The report of a single case by Berger (2007) was useful in that direct participant reports were used in conjunction with parent reports and physiological assessments. Three studies focused on younger participants with more limited verbal skills which made it more difficult to obtain written or verbal reports.

The study by Westlake (2013) assessing college students with ASD did not collect any direct reports or data from either group of participants other than scores on the device and length of practice sessions. This would have been a valuable opportunity to collect information from users on both use and effectiveness of biofeedback.

Future research could focus on obtaining the views of people with ASD to obtain their insights and opinions on both usability and effectiveness of HRV biofeedback.

Measurement of HRV in people with ASD

The studies reviewed all used the biofeedback intervention device itself as a measurement of underlying participant HRV. Scores recorded by the device were assumed to be equivalent to the individual's actual HRV measurement and were also seen as an indication of participant anxiety. To test the effectiveness of any HRV biofeedback intervention, future studies should include independent measures of HRV independent from the biofeedback device itself, and independent measures of stress or anxiety.

3.8.3 *Interventions used for people with ASD*

Analysis of the actual biofeedback interventions used in the studies reviewed highlights the heterogeneity of intervention design which again makes any comparisons between studies difficult. This difficulty is widespread within the current research literature and has been highlighted in several of the reviews of the of studies in other population's (Yucha, 2002; Yucha and Montgomery, 2008).

Length and frequency of intervention sessions

One example of this variability in intervention type is the length of session time used for biofeedback practice which varied from 3 minutes to 60 minutes within studies. Sessions also varied in frequency from 10 to 25 minutes with sessions either daily or several times per week. It is not clear whether longer sessions are needed to improve treatment outcomes in this type of intervention.

Training provided

In addition, the length of time spent training participants in use of biofeedback is not clearly specified in studies reviewed. It is possible that people with ASD will have difficulties with understanding how to use biofeedback devices and those current methods of training are not appropriate and need to be changed. The amount of training time needed and any difficulties with training could be assessed in future studies to determine whether any training difficulties relate to the overall outcome of the intervention.

Type of device used

Different HRV biofeedback devices were used in each study, all of which involved differing user interface and reward systems. The devices used included a number of HeartMath devices (emWave Desktop; emWave2 and Freeze-framer) all produced by (Quantum Intech Inc. Boulder Creek; CA). Somatic Vision produces a range of software programs which integrate gaming software into HRV biofeedback and skin conductance technology (Somatic vision Inc. Encinitas; CA).

Usability of biofeedback device

An important factor not considered in any of the studies reviewed is an analysis of the usability of different devices in terms of interface, form and overall functioning. There are significant differences in the size shape and visual information provided by different devices. It is possible that this will have an impact upon adoption and compliance. Whilst all HRV biofeedback devices claim to help users regulate breathing they vary widely in how they present information to users. Devices also may not use the same underlying algorithms for calculating HRV which again highlights the issue that independent calculation of HRV would be useful to understand how this intervention might work, and whether it has any actual impact on HRV.

Adoption of biofeedback intervention

None of the studies reviewed lasted for longer than ten weeks. Information on attrition rates was gathered in the study by Westlake (2013) however, because no participant reports were collected, and no premorbid information was gathered it was not possible to clearly explain reasons for drop out. It would be useful for future research to consider how individuals with ASD adopt this type of intervention, including information about attrition / drop-out rates and comparing differences between those who used the device and those who did not.

3.9 Conclusion

Based on a review of the existing literature on the use of HRV biofeedback in people with ASD, a number of themes emerge regarding gaps in the research literature in this area. First, there is a need for larger more controlled studies investigating the use of HRV biofeedback in people with ASD. Whilst studies with people with ASD are at an early stage of development, the recent systematic review and meta-analysis supporting the efficacy of HRV biofeedback (Goessl, *et al.* 2017) suggests that further work in this area is warranted.

Second, no studies have yet been conducted in a clinical population of people with ASD, using portable home use HRV devices. Third, no studies have involved measurement of HRV separate from the biofeedback device. Rather than relying on the device itself as a measure of change in HRV, independent assessment of the variable which HRV biofeedback devices purport to measure would be valuable to help elucidate whether this type of device could help individuals to change HRV.

Finally, no studies have reported on the adoption and usability of HRV biofeedback devices as a potential intervention for individuals with ASD. Longer term interventions and use of follow-up debriefing interviews would be useful to help understand some of the reasons why and how participants use this intervention. Analysing information from those who dropped out may also be useful to understand potential problems or risks related to this intervention.

Reflecting upon these four preliminary studies, the following chapter will outline a study involving an initial usability evaluation, followed by a pilot study to investigate the adoption, usability and effectiveness of an HRV biofeedback intervention for a clinical population of children and young adults with ASD. The intervention will employ small portable HRV biofeedback devices to help young people with ASD manage symptoms such as anxiety, in a home-based environment. It will also aim to measure levels of HRV and anxiety directly in people with ASD before and after using an HRV biofeedback intervention.

Chapter 4. Methodology

4.1 Overview

A rationale for investigating the use of a technology-based intervention to help manage anxiety in people with ASD has been proposed (Chapter 1). A review of background information has shown that people with ASD show signs of both ANS dysfunction, and high levels of anxiety (Lydon 2014; van Steensel 2011) and the growing evidence for HRV biofeedback as an intervention to manage anxiety in a range of different populations has been presented (Chapter 2). A systematic review of the literature has indicated that this intervention has not been thoroughly trialled in this population (Chapter 3).

Building upon existing work, it is proposed that HRV biofeedback could offer a potential means to help regulate ANS function and manage symptoms such as anxiety in people with ASD.

This chapter describes the overall study aim and the specific research objectives. The underlying theory underpinning the study is reviewed and the development of a two-phase design is described. The initial evaluation phase of the study involved researcher training, followed by evaluation of participant information; measures; equipment; risks and initial testing of procedure to inform the main part of the study. This evaluation phase is presented, and amendments made to the final pilot study design are summarised. The phase 2 study design is then presented according to consolidated guidelines for reporting of pilot and feasibility trials 'CONSORT' (Eldridge et al.2016). Finally, the measures, equipment procedure and a data analysis plan for the Phase 2 pilot study are described.

4.2 Study Aim and Objectives

The overall aim of the study and the specific research objectives are stated below.

Aim

To investigate the use of HRV biofeedback in people with ASD.

Objectives

1. *To provide a home-based HRV biofeedback intervention to people with ASD.*
2. *To assess anxiety and physiological arousal before and after using a HRV biofeedback device.*
3. *To assess usage of HRV biofeedback in a sample of people with ASD.*
4. *To evaluate the risks, benefits and acceptability of this technology.*
5. *To develop recommendations on the further use of HRV biofeedback for people with ASD.*

4.3 Theoretical Framework

Previous researchers have provided theories which can help to understand the possible mechanisms underlying HRV biofeedback (Porges 2001; Thayer and Lane 2000; Lehrer *et al.* 2000; Gevirtz 2014).

Two prominent theories '*Polyvagal theory'* and the '*Neurovisceral Integration Model*' were presented in Chapter 2, which can help to explain some of the findings relating to our understanding of HRV. Both of these theories propose that vagally mediated HRV is an indication of self-regulatory mechanisms exerted to control emotions or behaviour.

A recent meta-analysis of research has provided support for these theories suggesting that HRV indices can be used as biomarkers of self-regulation (Holzman 2017). In addition, advances in brain imaging and neurobiology have now shown the direct links between stress, the heart and the brain (Tawakol 2017).

Whilst both theoretical models provide valuable frameworks to guide future research, Polyvagal theory was chosen to help guide this thesis due to the specific predictions it makes regarding people with ASD. Impairments in the '*social engagement system*' described by Porges, are suggested as features of several disorders including ASD. For example, Porges states,

> *"Many of the behavioral attributes of autism appear to be convergent with a compromise in this hypothetical social engagement system" (Porges 2013, p. 262)*

Underlying difficulties with the CNS and the ANS in people with ASD are theorised to lead to an inability to switch into a more adaptive state in which social behaviours can take place (Porges 2013). Thus, one of the central consequences of impairments in the social engagement system may be heightened anxiety (Porges 2013). It is therefore hypothesized that methods of slowing and controlling heart rate via HRV biofeedback may be one possible way to help people with ASD regulate underlying ANS function and reduce levels of anxiety.

A theoretical model showing how an HRV biofeedback intervention might work is presented in Figure 4.1.

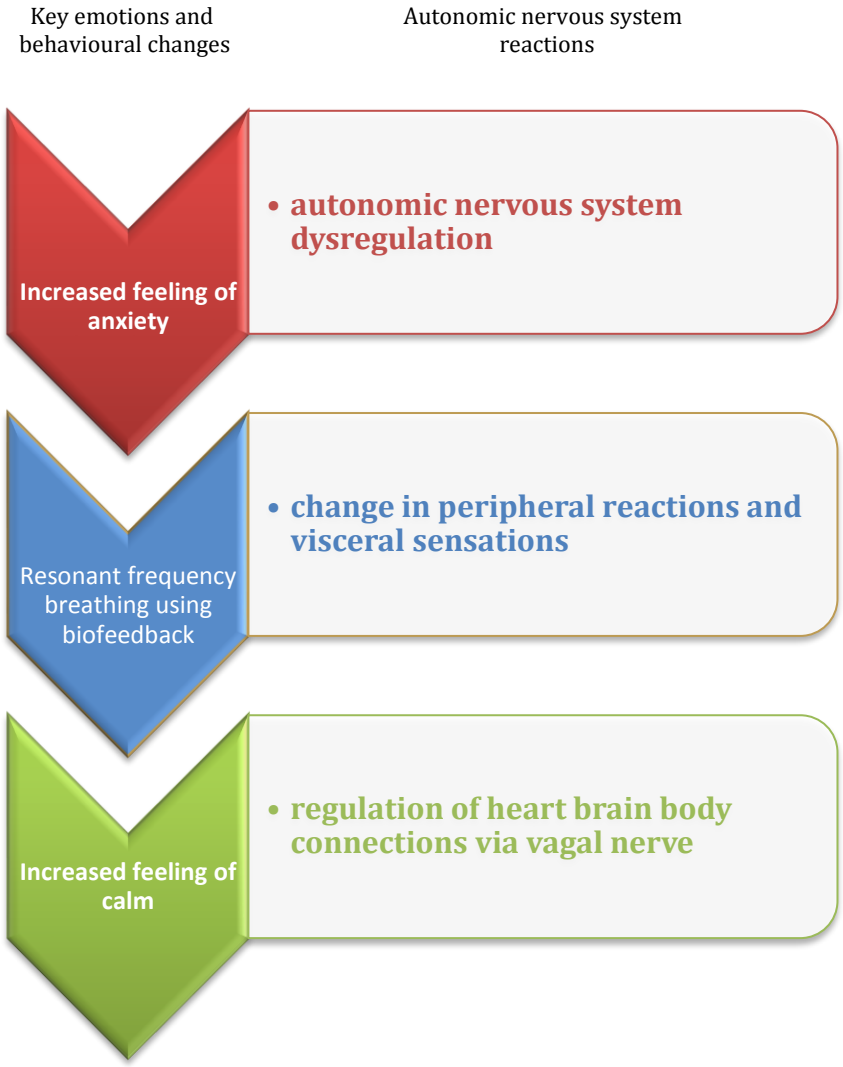


Figure 4.1 Model showing one possible mechanism of effect of HRV biofeedback to enhance vagal regulation of ANS via resonance frequency breathing, linking key emotions and behaviours involved in the intervention on the left, with key physiological changes expected on the right.

Polyvagal theory may explain one possible mechanism behind the anxiety states often seen in people with ASD. It may in turn give insights into the translation of research into more effective interventions (Bridges 2015).

The research hypothesis underpinning the study, initially proposed Chapter 2, can be thus expanded, to give further explanation on the possible mechanism of effect of the intervention.

HRV biofeedback will enable young people with ASD to control their breathing and heart rate using resonant frequency breathing, thus helping to activate their '*social engagement system*'.

This in turn will regulate autonomic nervous system arousal and reduce reported symptoms such as anxiety, or behavioural difficulties such as *meltdowns*.

The mechanism of how the intervention is hypothesized to work is essential to determining the outputs of the study to be assessed and measured, and Polyvagal theory has provided a conceptual framework for the development of potential measures needed, and information to be collected. This theory has also informed the development of the study design and specific predictions made from the research hypothesis.

As outlined above, it is hypothesised that HRV biofeedback will be able to help people with ASD to establish resonant frequency breathing and thus regulate underlying ANS dysfunction. The specific predictions derived from this hypothesis are that use of HRV biofeedback will enable participants to increase HRV indices and that this will lead to feelings of calm or reductions in anxiety.

4.3.1 *Outcomes Expected and Plan for Data Collection*

The expected outcomes from this study were directly related to the research hypothesis. Thus, outcomes expected were an increase in participant resting state HRV; a reduction in participant anxiety, and signs of change in participant behaviour as observed by carers.

Quantitative data was therefore collected on measures of participant resting state HRV and participant self-reports of anxiety pre and post use of HRV biofeedback.

In addition, carers were asked to rate the frequency of participant anxiety attacks or 'meltdowns' both at the beginning and then again at the end of the intervention. Data was also collected from direct participant reports on their usage of the device over the period of the intervention.

Debriefing reports from both participants and carers and researcher notes were also used to provide qualitative and quantitative information on perceived benefits and any problems with the intervention devices and any other changes in participant behaviour.

Finally, data was also collected on participants who dropped out to ensure information is collected on any potential risks or unexpected outcomes of the intervention.

4.4 Overall Design

The study followed revised MRC guidelines (Craig and Dieppe 2008) for the development and evaluation of complex interventions, namely a feasibility and piloting study to test methodology and procedure, to assess dropout rates, and to determine risks and potential benefits prior to conducting any large-scale trial.

The study thus involved an initial evaluation (Phase 1) followed by a small-scale pilot (Phase 2) which involved a detailed follow up of a sample of people with ASD using repeated measures of the specified outcomes in a randomised control experimental design.

The study involved the collection of both quantitative and qualitative data to maximise information on potential problems from a range of different data sources, which has been emphasized as particularly important in the development of an intervention in a new population (O'Cathain 2015).

Due to the differences in physiology reported in many people with ASD (Lydon *et al.* 2014) and the stated hypothesis predicting a change in HRV, pre and post intervention assessments of physiological responses were seen as important measurement outcomes. The study therefore used pre-post questionnaire assessment but also recorded participant physiological reactions before and after the intervention to assess any changes in underlying physiology.

The overall study design is shown in Figure 4.2 below.

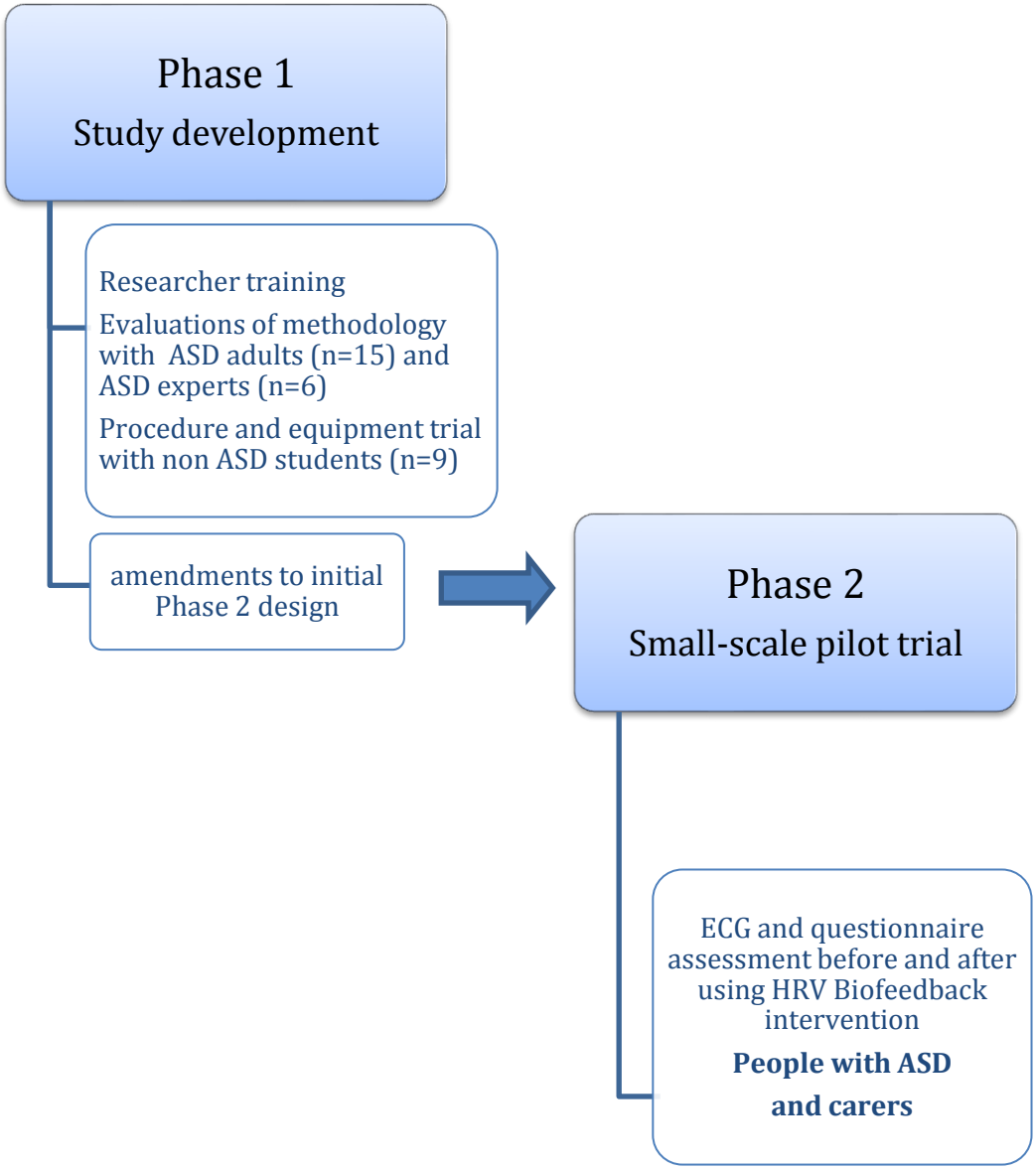


Figure 4.2 Two phase study design, comprising researcher training and evaluation of equipment, methods and procedure, leading to the development of a randomised pilot trial to investigate HRV biofeedback in people with ASD.

4.5 Phase1: Study development

4.5.1 *Researcher Training*

The initial phase of this study began with training of the researcher, a consultant clinical psychologist, with experience in assessment and intervention in mental health and ASD. Prior to commencing the final phase of the study, the researcher received training to acquire skills in (i) ECG recording (ii) HRV assessment and analysis (iii) use of portable and (iv) multichannel biofeedback systems.

ECG training involved attending over 20 hours' cardiac physiology classes and additional one to one training in ECG placement. Clinical interpretation of ECG recordings was beyond the scope of researcher training and was carried out anonymously by a senior chartered cardiac physiologist. HRV training involved attending accredited courses from the Biofeedback Certification International Alliance. HRV analysis was carried out by the researcher with supervision according to guidelines from training and using recommended software (Kubios Premium version 3.0.0). Biofeedback training involved undertaking accredited courses as part of the process for gaining Biofeedback Certification International Alliance certification. Each of the four areas of training fed into and supported the others to enhance overall learning. A summary of key areas of training undertaken by the researcher is shown in Figure 4.3 below.

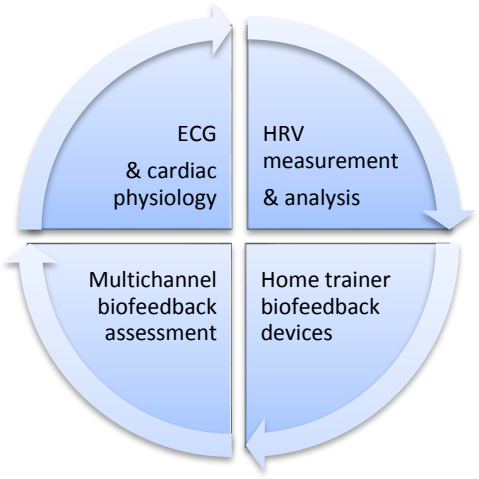


Figure 4.3 Summary of researcher training in cardiac physiology; HRV analysis; use of portable biofeedback devices and multichannel biofeedback assessment systems.

4.5.2 *Stakeholder Evaluations of Methods and Procedure*

A wide variety of equipment exists for both assessments of HRV and for biofeedback practice. To assess these areas for use in people with ASD independent advice was sought from a number of different groups. The aim of this phase was to evaluate information; measures; equipment and to check any difficulties with the initial study procedure and potential risks, for people with ASD. In order to do this a series of usability evaluations was approved by Ulster University in 2014 and then conducted in 2015 (appendix I).

The first part of this evaluation involved a series of meetings with ASD experts from both the voluntary sector (n=3) and NHS clinical teams (n=3), and also with two groups of adults with ASD (n=15).

The study initial design, a number of questionnaire measures and written materials including participant information forms and consent forms were all reviewed. The usability of several types of intervention device and assessment equipment was also assessed. Potential risks of undertaking the HRV biofeedback intervention with people with ASD were also considered.

The second part of this evaluation involved a trial of equipment and procedure for the physiological assessment, which was carried out with a small group of volunteer undergraduate students not diagnosed with ASD (n=9).

The aim of this second part of the evaluation phase was to assess the timings required to undertake assessment and recording of physiological data, and also to assess any problems associated with assessment equipment, software and any risks with the overall physiological assessment process, prior to carrying out a trial in people with ASD. This evaluation involved detailed pre-post physiological assessment of physiology using what has been termed a '*psychophysiological stress profile*' paradigm (Matto 2015) which involved the simultaneous assessment of skin temperature; electrodermal skin response and breathing rates as well as assessment of HRV using ECG.

Physiological assessment equipment trialled was a commercially-available multi-channel biofeedback monitoring system (Nexus-10 Mark II® Mind Media B.V. Herten; Netherlands), which is widely available in both Europe and the United States for monitoring a range of different physiological reactions (Hughes 2008).

Initial evaluations were sought from ASD adults and experts within voluntary sector and the NHS which then led to the initial testing of procedure with volunteer students. A summary of the different groups involved in the evaluation process is shown in Figure 4.4.

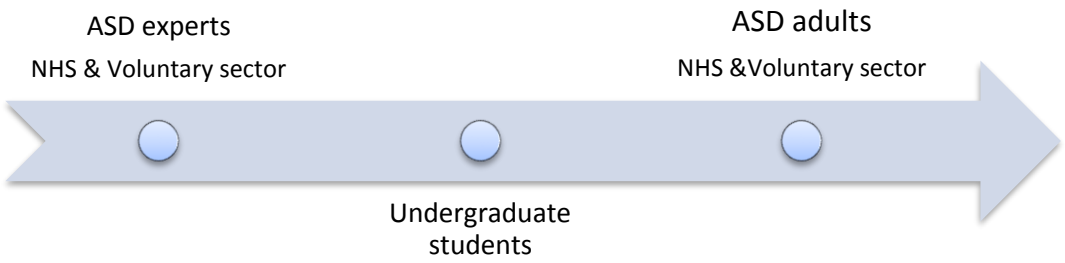


Figure 4.4 Different groups involved in initial Phase 1 evaluations, including NHS and voluntary sector experts; adults with ASD and undergraduate students.

4.5.3 *Preliminary study design*

The initial design for the Phase 2 pilot which was evaluated, involved randomising participants into two different groups, with each group trying a different home use HRV biofeedback device over a 12-week intervention period. A delayed intervention 'control' group would first wait 12 weeks, before being randomised into the two device groups and then also starting the same 12-week intervention. The initial Phase 2 design which was proposed is shown in
Figure 4.5

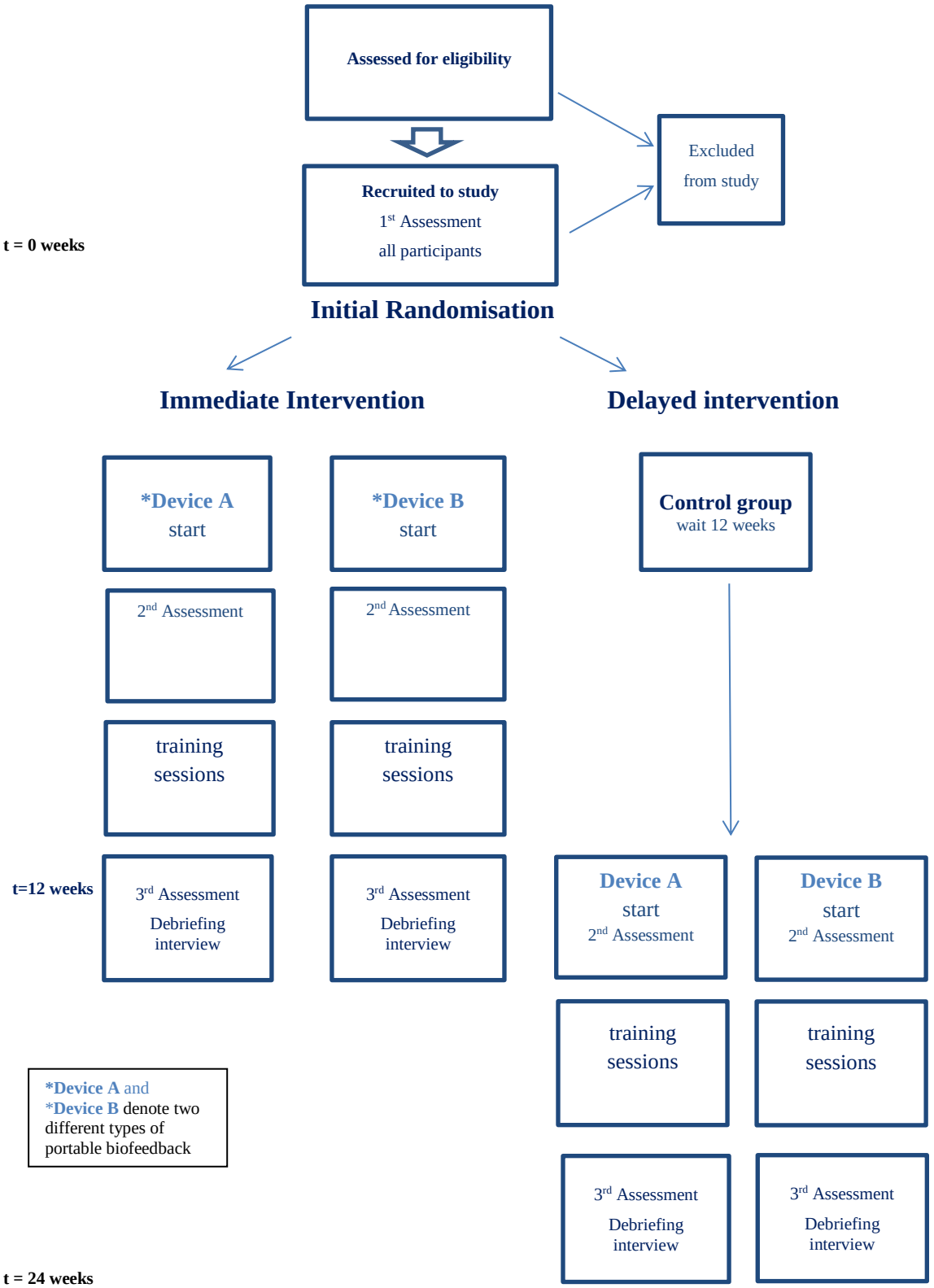


Figure 4.5 Preliminary pilot study design showing randomisation into delayed and immediate intervention groups and allocation of two types of biofeedback.

The initial stakeholder engagement enabled people with ASD and those with expertise in the area to offer direct reports and insights regarding the final pilot study. The reports obtained from the series of evaluations were categorised into areas relating to study design; participant information; measures; equipment; procedure and risks involved. A summary of information obtained in the series of evaluations is reported below.

Amendments to Phase 2 preliminary design

The initial pilot design proposed involved randomisation of participants into immediate and delayed intervention groups. The delayed intervention group would act as a waiting list control and would wait 12 weeks before being given a device. Both professionals and people with ASD reported that this delayed waiting time was too long and that this time should be reduced to ensure the delayed intervention group did not drop out of the study. The waiting time was therefore reduced from 12 to 6 weeks.

Involvement of carers for both adults and children

The stakeholder meetings with professionals and people with ASD highlighted the need to involve carers of people with ASD in any evaluation of an intervention, irrespective of whether participants were adults or children. The importance of obtaining reports from carers was emphasised to obtain perspectives on any observed effects of the intervention, which may not have been apparent to participants. All adult participants were therefore also asked to nominate a trusted adult or carer to also complete interviews and to be present during the physiological assessment. Carers were asked to provide information on participant behaviour and demographic information.

Amendments to participant information

The need for more accurate and specific visual images in all areas affecting participant information was emphasised. Further photographs of the researcher were included. A video of the participant information booklet and links to video clips from manufacturers of the devices were included with participant information.

At the end of the study all participants were also offered a summary of the results of the study using accessible formats.

Choice of measures

The measures selected for initial evaluation were chosen on the basis that they showed good reliability and validity; were simple and easy to use or were designed specifically for the population in question.

Thus, measures evaluated were the State Trait Anxiety Inventory (Spielberger et al.1983); the Beck scales (Beck 1993; 1996) and the Child Behaviour Check List (Achenbach 2001), which were chosen as they have been widely used in non ASD populations for assessing anxiety and depression and show good reliability and validity. The Personal Wellbeing Index was also reviewed due to its short and easy to use format (Cummins and Lau 2005). The Autism Stress Survey Schedule was reviewed as it was identified as one of the only existing ASD-specific questionnaires assessing stress and anxiety symptoms (Goodwin 2007).

Use of simple short questionnaires or short Likert rating scales was reported by all of the stakeholder groups as easier for people with ASD to understand and use. Adults with ASD involved in the evaluations reported that completing short reports or tick boxes would be preferable to completing long questionnaires, interviews or audio recordings. The ASD Stress Survey Schedule was reported to be confusing and too long. The Personal Well-being Index was viewed as not specific to anxiety.

A decision was made to use the Beck questionnaires due to use of short, easy to understand scales with good reliability and validity (Beck 1993; 1996). A decision was made not to carry out lengthy interviews and to rely on short questionnaires and quantitative rather than more detailed qualitative data for participant data.

Including a measurement of depression was also felt to be important because anxiety and depression are frequently associated in the same individual (Sterling 2008) and because measurement of levels of depression would also allow for assessment of mental health risk in participants.

NHS and voluntary sector experts noted that conducting pre- and post-interviews with carers rather than using questionnaires could be a more useful method of obtaining information on any observed behavioural effects of the intervention.

A series of short questions was therefore agreed that focussed on asking carers for information on current participant behaviour; main concerns and the frequency of anxiety attacks or 'meltdowns' in participants. This latter area was assessed due to the reports that this can be one of the most difficult areas to manage for people with ASD and their carers (Myles and Southwick 2005). Again, a decision was made not to carry out lengthy interviews and to rely on short reports from standardised questions.

Changes to Equipment

Potential biofeedback devices were selected for evaluation on the basis that the device or an earlier version of a device had already been used in previous research studies. A number of portable biofeedback devices suitable for personal use were chosen for review chosen for review (see appendix II and figure 4.7). Devices were chosen due their previous use in research studies in non ASD populations (Kennedy 2008; Beckham 2013; Whited 2014; van der Swan 2015).

The nonverbal nature of the intervention; the immediate visual feedback and portability of devices, were all seen as positive aspects of the intervention suited to the needs of people with ASD.

Physiological assessment equipment

The initial monitoring equipment evaluated was one of the main multi-channel professional biofeedback monitoring systems available, the Nexus-10® II (Mind Media B.V., Herten: NL). This system was chosen due its ability to make multi-channel recording and assessment using multiple physiological sensors and due to the availability of equipment and support services within Europe.

The protocol initially proposed involved assessment and training of participants in a clinic setting, using three physiological sensors, measuring HRV, EDA and respiration, before and after using a small personal use HRV device at home.

Both professional experts and ASD adults who viewed the physiological assessment equipment expressed concerns about anxiety that could be caused by this assessment due to the use of multiple wires, electrodes and Velcro combined with using an unfamiliar clinic setting. Direct testing of the physiological equipment and the assessment procedure using a standardised 'psychophysiological stress profile' paradigm (Matto 2015) was therefore undertaken with a small group of undergraduate students. This assessment highlighted similar concerns from non ASD students regarding the complexity of this type of assessment, and its potential to cause anxiety to participants.

As result of meeting with the second ASD user group (March 2015) and a consultation with international experts (KH June 2015) a decision was made to not use the multi-channel biofeedback monitoring equipment (Nexus-10 Mark II®). Instead a wireless single lead ECG recorder (Actiwave Cardio; CamNtech UK) was chosen, which recorded less information, but had already been used successfully to record physiological information both with children and with people with ASD (Hegarty–Craver 2017).

Changes to Procedure

Both professional experts and people with ASD emphasised that initial assessment and the intervention itself would be more likely to be acceptable if it was introduced in the participant's home.

The clinic setting for physiological assessment was seen as problematic as this would be likely to increase participant anxiety simply due to the use of an unfamiliar setting. Subsequently a decision was therefore made to carry out all assessments and delivery of the intervention in the participant's home.

Evaluation of Risks

Professional experts in ASD noted that whilst portable, home-use HRV biofeedback devices had been used successfully in other populations these devices had not yet been adequately trialled in people with ASD. It was therefore agreed that devices would only be assessed using a small sample of young adults and teenagers with ASD and would not be used with young children, or with those with a learning disability who may not fully understand the study. It was also agreed that regular monitoring of participant progress during the intervention would take place to ensure no problems arose with use of the device.

The use of technology such as text messaging or email to enable participants to complete regular progress reports was seen by professional experts and adults with ASD as a useful method of monitoring use of the biofeedback device, which could highlight any potential problems and would not involve lengthy interviews with participants.

Concerns were expressed regarding the need for training to be able to ensure participants did not become more anxious if they were unable to use the device quickly. The need to help participants achieve success early in training was noted, by both people with ASD and ASD experts.

The potential for participants to become either distressed; aggressive or overly attached to the researcher was highlighted by NHS and voluntary sector experts. It was agreed that all participants would be offered a follow-up session if needed and provided with information on additional support services available.

Further details of direct reports from the Phase 1 evaluations from different groups are shown in appendix V.

4.6 Risk Evaluation and Ethical Considerations: Phase 2

Before commencement of Phase 2, a further review of risks and ethical considerations involved was conducted by consulting the Clinical Director of Cardiac Physiology at Ulster University and the South-Eastern Health and Social Care Trust Infection Prevention Control team.

There was a risk of potential anxiety or inconvenience to participants when they are asked to undertake physiological assessments. All potential participants were therefore shown all the equipment to be used and had an opportunity to try it at home before consent was obtained.

The pilot study involved the assessment of a vulnerable clinical population who have intrinsic social and communication difficulties and may have poor insight into their stress levels and mental health which may compromise participant autonomy. Therefore, both assent and consent were sought from all participants and their carers. Participants were also allowed to take time to consider participation in the study after an initial home visit and demonstration of equipment.

To ensure that participants felt at ease during physiological assessment all assessments and training were provided at home. In addition, all participants had a carer present during the attachment of sensors and the physiological recording. The presence of another adult during visits also reduced potential risk to the researcher carrying out home assessments alone with adult participants. A lone worker protocol was therefore followed.

There was a risk that some participants could show a pattern of chronic over breathing or shallow breathing prior to any biofeedback training causing them to potentially feel dizzy when starting treatment. This was addressed by carrying out a breathing assessment using questionnaire (van Doorn 1983) and providing advice on correct breathing technique in training prior to intervention.

Regular reports on progress from participants were used to monitor any potential mental health concerns. This information was first sent to participants via their phone or email address. Reports were then returned by participants via a secure email link to a South Eastern Health and Social Care Trust address with only the participants unique identifier code and no other personal information or IP addresses recorded. Any increased concerns raised about a participant's mental health during the course of the study led to referral to the appropriate local mental health service and subsequent exclusion from the study.

All participants and their carers were given a support pack outlining mental health support services available to them in their local area and out of hours' services should they have mental health concerns at any time during the course of the study. To ensure there were no other unknown contraindications to participation each participants' GP was informed of their involvement in the study and notified of participant drop-out or any follow up referrals made at the end of the study.

Whilst participants with known cardiac conditions were excluded from the study, there was a possibility that monitoring could detect an unknown potential cardiac risk in participants. Anonymous review of all ECG recordings was therefore undertaken by a Senior Cardiac Physiologist. Where analysis of ECG recordings indicated any unusual heart rate patterns, a further 12 lead assessment was carried out via a participant GP. Any participants with confirmed cardiac concerns were subsequently excluded from the study.

There was a risk of cross infection. Participants with compromised skin conditions were therefore excluded from the study. In addition, all equipment was cleaned with 70 % isopropyl alcohol wipes between each use and new electrodes were used for each participant assessment. There was a risk of allergic reaction or bruising during placement of electrodes. This was addressed by careful placement of electrodes and cleaning the site for electrode placement with water and soap (rather than alcohol).

There was a potential risk of participants with ASD becoming anxious or upset whilst watching the images used in the physiological assessment task (Louwerse et al.2014). The images chosen were therefore those that did not have high negative emotion valence score (Lang 1997). Participants were also informed that they could stop the study at any stage without compromising any of the treatment or services available to them and would be given a support pack and offered an opportunity to talk to the investigator or someone else outside the research team.

All participants who reported that they wished to continue using the biofeedback device at the end of the study, were allowed to keep it (no other incentives were offered to participants or carers). A follow up biofeedback support session was offered to all participants up to six months after the study finished.

Data confidentiality and storage

To ensure confidentiality and stay within the law, all personal information recorded from participants and carers has been stored in accordance with the Data Protection Act (1998). All research data will continue to be held securely for 10 years' post-completion in compliance with Ulster University storage regulations and will then be securely destroyed. Each participant in the pilot study was issued with a unique personal identification number or PIN. Consent forms, confidential patient details and data that link the participant names to PIN codes were kept separate from anonymized questionnaires and interview reports and are only accessible to the researcher and principal investigator. Hard copies of questionnaires, interview notes and printings of ECG recordings were anonymised and contained only the participant identification number and are stored in a locked filing cabinet in the researcher's office within Ulster University. Anonymized physiological recordings are stored in a password protected portable hard drive in a locked filing cabinet within Ulster University.

4.7 Phase 2: Pilot Study

The findings from stakeholder evaluations in Phase 1 were used to develop the second Phase of the study which involved a small-scale pilot trial. As outlined in section 4.4, the purpose of this pilot was to assess outcomes, adoption and usability of the intervention and to review the potential risks and benefits in this new population. The methods for this pilot trial of an HRV biofeedback intervention in people with ASD are now described below.

4.7.1 *Participants*

Inclusion criteria

Participants were aged 13-24 years; male or female and English speakers. All participants were required to have already received a diagnosis of ASD using recognised assessment tools such as the Autism Diagnostic Observation Schedule (Lord 2001) via one of the existing ASD assessment clinics within South Eastern Health and Social Care Trust. Demographic information was collected on; age; gender; smoking; drug and alcohol intake; physical activity; medication and technology use (Quintana 2016).

Exclusion criteria

In order to avoid confounding factors and minimise risk of harm, participants were excluded if they had a drug or alcohol addiction; a known cardiac condition; learning disability; suicidal risk; psychosis; severe eczema or psoriasis; significant infections such as MRSA or an immunosuppressing condition or if they were taking medication known to suppress HRV such as narcotics, benzodiazepines; beta blockers, or tricyclic antidepressants (Kemp 2010; Gevirtz 2014). Participants were not automatically excluded if they were attending therapy or taking other medications, however record was made at assessment of any treatment and of prescribed medication taken. Participants were withdrawn and referred on to appropriate support services if they or their mental health worker indicated that one of the exclusion criteria was met during the course of the study.

4.7.2 *Recruitment*

Participants were selected from the clinical population of adolescents and young adults aged 13-24 years referred to services for people with ASD without a learning disability within South Eastern Health and Social Care Trust.

The initial aim was to recruit 40 participants, 20 adults and 20 children. A phased approach to recruitment was taken, due to initial caution expressed within the evaluations and ethical approval guidance.

The study ethical application had therefore specified that participants recruited for the first three months should be adults only. This phased approach was intended to assess if there were concerns about using this intervention that might highlight difficulties or risks which would preclude use of the intervention with children (who may have less insight into the nature of the study).

Potential participants were identified by a number of methods. First, the researcher held meetings with the adult ASD team and the child and adolescent ASD intervention teams to explain the project and answer any queries or concerns. Next, members of the adult ASD team gave out participant information packs during clinic sessions to clients on their caseload who had been confirmed to meet inclusion criteria.

All potential participants were given an information pack with an invitation letter; participant information leaflet outlining the study and copies of relevant assent or consent forms for participants and carers. Video links to further information about individual devices were included; samples of information sent to participants and carers is reported in appendix IV.

Participants and carers were invited to contact the researcher directly via phone or email (or via their keyworker, if preferred). Once any queries were addressed the researcher arranged a home visit to obtain written consent from both participants and carers.

4.7.3 *Randomisation*

In order to decrease the risk of group allocation bias, random assignment to treatment or control group was carried out *after* all pre-intervention assessments so the researcher was initially blind to who was allocated to each group during all baseline assessments.

Allocation was made in blocks to ensure that adequate numbers of participants were allocated to each condition. A randomised number sequence was generated via computer. Randomised numbers were then placed in a drawer in sealed numbered opaque envelopes. Envelopes were then opened in order once each new participant had completed the first baseline assessment.

Following allocation to groups, assessment using questionnaire, interview and ECG assessment was then carried out as outlined in figure 4.6 below. After each initial assessment was completed a further participant device allocation envelope was then opened to determine which of the two different biofeedback devices they would receive. Allocation to devices was also planned in two blocks of twenty to ensure balance between groups.

4.7.4 *Pilot study design*

The Phase 2 pilot trial involved a detailed follow up of a sample of people with ASD, using repeated measures in a randomised experimental design. The design shown in figure 4.6 follows the CONSORT extension to randomised pilot and feasibility trials reported by Eldridge *et al.* (2016).

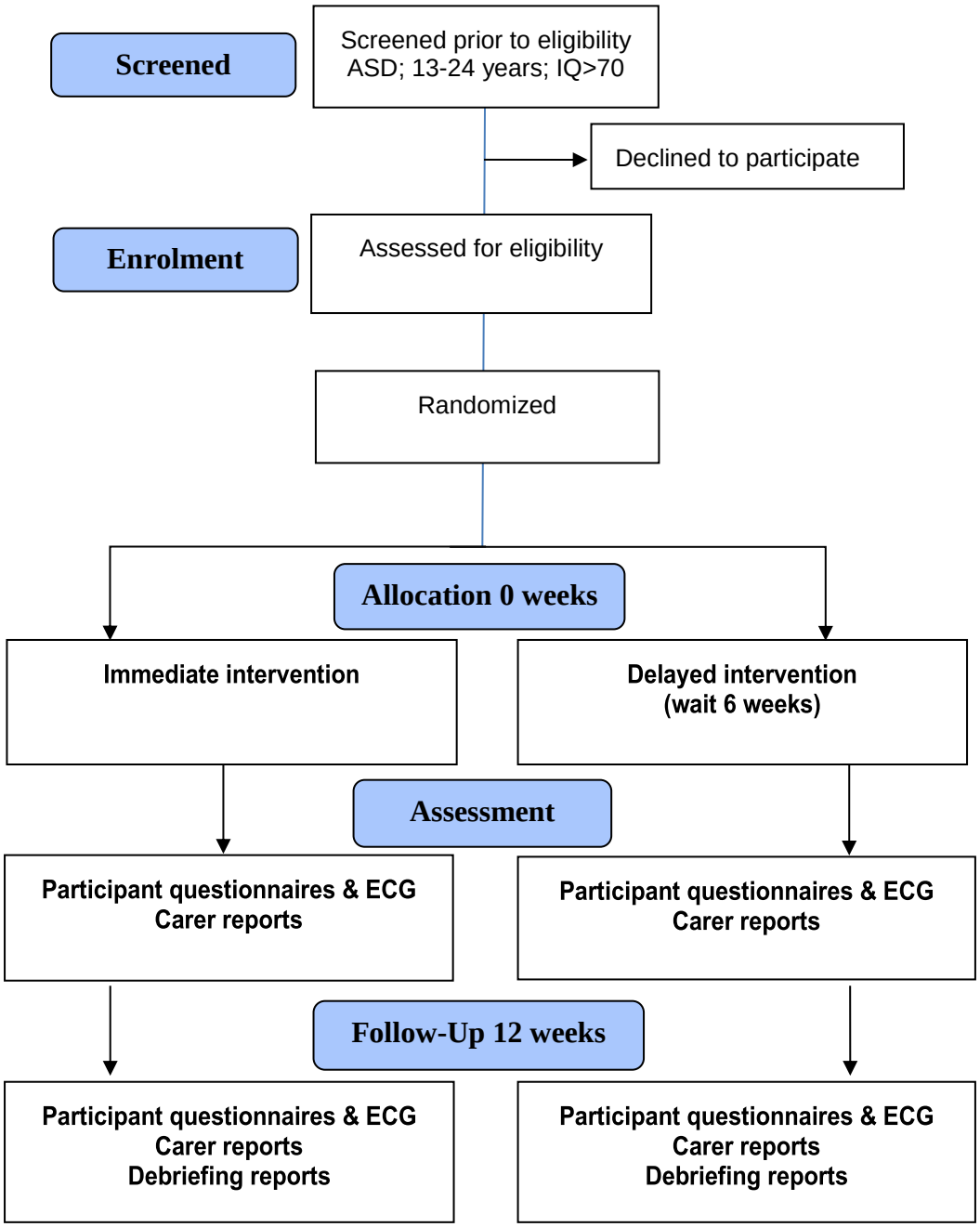


Figure 4.6 CONSORT (2010) flow diagram summarising Phase 2 Pilot study design, starting with screening and enrolment, before allocation into intervention groups, showing type of assessment and final follow up.

4.7.5 *Measures*

Measures used related to the outcomes predicted by the research hypothesis and were refined according to Phase 1 evaluation findings.

Pre-Intervention baseline assessment

Participant self-report questionnaires – Anxiety and Depression

Participants were asked to complete short self-report questionnaires on anxiety and depression. Measures used included the *Beck Anxiety Inventory* (Beck et al.1993); the *Beck Depression Inventory-II* (Beck 1996). Younger participants were asked to complete the *Beck Youth Inventories-II* for young people aged 13-17 years (Beck 2005). Despite not being designed specifically for people with ASD, these questionnaires were viewed as appropriate for this population in the evaluation, due to the clear and concise listing of symptoms in a literal manner, combined with a simple and quick rating format.

The *Beck Anxiety Inventory* consists of a list of 21 common symptoms of anxiety in which respondents rate each symptom as occurring 'not at all' 'mildly' 'moderately' or 'severely'. Ratings are then scored from 0-3 on each symptom with a total possible score of 63. Scores from 8-15 are considered to indicate 'mild anxiety';16-25 'moderate anxiety' and scores of 26-63 indicate 'severe anxiety' (Beck 1993, p.5). The *Beck Anxiety Inventory* has been widely used to assess anxiety since its first development and demonstrates good reliability and validity (Cronbach's alpha of 0.94; concurrent validity of 0.58; Fydrich et al. 1990).

The *Beck Depression Inventory-II* consists of 21 short statements which are rated by participants and are then scored on a four-point scale of 0-3, with a maximum score of 63. Scores, from 14-19 are described as '*mild depression'; 20-28 as 'moderate depression' and 29-63 as 'severe depression'* (Beck 1996, p.11). Internal reliability alpha coefficients of the *Beck Depression Inventory-II* are higher than the earlier version at 0.92 and 0.93 for clinical samples and students respectively (Beck 1996, p.14).

The *Beck Depression Inventory-II* has been widely used to assess depression and shows good test retest stability and discriminant validity compared to anxiety (Beck 1996, pp.25-28).

The *Beck Youth Inventories-II* consists of a series of short self-report questionnaires which assess depression, anxiety anger, disruptive behaviour and self-concept. This scale was developed to address the clinical concerns that the reading level of the adult versions was too difficult for some children (Beck 2005, p. vii). Individual subscales within this questionnaire can be used independently or combined (Beck 2005, p.1). In order to minimize any additional burden on participants only the anxiety and depression subscales were used in the study. Both of these subscales have been found to show good internal consistency with Cronbach's alpha coefficients from 0.89 to 0.95 for differing age groups (Beck 2005, p.39), good test-retest reliability (Beck 2005, p.40), and good discriminant validity in identifying anxiety and depressive symptoms (Beck 2005, pp.56-57). Each subscale contains 20 short statements which are rated in terms of their frequency, with each subscale taking '*5-10 minutes to complete*' (Beck 2005, p.1). Scores are calculated by totalling raw scores which range from 0-3 with a total possible raw score of 60 on each scale. Raw scores are converted to standardised T-scores which enable comparisons to age and gender matched norms. T-scores are interpreted as follows; 55-59 '*mildly elevated'*; 60-69 '*moderately elevated'* and 70 plus *'extremely elevated*' (Beck 2005, p.12).

Participant breathing symptoms questionnaire

Because of the potential for participants breathing too deeply or quickly when learning HRV biofeedback participants were also given a short questionnaire to check for potential symptoms of hyperventilation *'Nijmegen Hyperventilation Syndrome questionnaire'* (van Doorn et al.1983). This short questionnaire contains 16 items which are rated on a 1-5 scale. The efficacy of this measure has been assessed and found to show good discriminant validity distinguishing between those with and without hyperventilation syndrome (van Dixhoorn 1985).

Carer Interview and Questionnaires

Carers were asked to provide information on the participant's behaviour in a standardised interview. Demographic data was also collected using a short form devised by the researcher asking for information regarding gender; age; education; physical activity; use of technology; alcohol and medications known to affect HRV.

In addition, carers completed a standardised questionnaire to check the level of social and communication symptoms in participants, the '*Social Communication Questionnaire'* (SCQ) by Rutter *et al.* (2003). The SCQ is a 40-item parent report questionnaire that can be used as a screening questionnaire for ASD. Carers were given the SCQ Autoscore Form: 'Lifetime' format (Western Psychological Services Product No. W-381B). This short questionnaire asks carers questions regarding the individual's entire developmental history and is rated in a simple yes / no format taking 'less than 10 minutes to complete' (Rutter *et al.* 2003, p.1). The SCQ has been extensively researched and demonstrates good internal consistency with alpha coefficient scores ranging from 0.84 to 0.93 with increasing age (Rutter et al. 2003, p.20) and good discriminant validity compared to other screening measures (Charman 2007). In this study the SCQ was used to look at levels of ASD symptomatology in a sample of young people already diagnosed with ASD. In line with this use the authors also advise that it can be used on a "*group basis to compare levels of ASD symptomatology"* (Rutter *et al*. 2003, p.2). Whilst all participants had already undergone detailed assessment and had been given a diagnosis of ASD this questionnaire was used to provide background information on the level of ASD symptomatology in each participant.

Carers and participants together also completed '*The Sensory Profile for Adolescents and Adults'* (Brown and Dunn 2002) to check levels of sensory symptoms in participants. This questionnaire asks 60 questions rated on a 5-point Likert rating scale. Scores are obtained in four different 'quadrants' relating to areas of sensory behaviour; Low registration; Sensation seeking; Sensory sensitivity and Sensation avoidant. Internal consistency alpha coefficients range from 0.64 to 0.77 for quadrant scores (Brown and Dunn 2002, p.52)

Intervention monitoring – Participant progress reports

During the intervention participants were also asked to complete short daily progress reports on their stress levels and their use of the device over the 12-week intervention period. The progress report was devised by the researcher based on initial Phase 1 evaluations and served a twofold purpose; to track participant stress levels, and also to monitor usage of the device over the course of the intervention. This brief report asked questions on sources of stress; levels of stress and usage of the biofeedback device.

Post intervention Debriefing and Usability Assessment

Participants repeated the questionnaire measures and undertook repeat ECG recording whilst carers completed a final interview. Participants and carers were then asked to complete short reports devised by the researcher to rate positive and negative aspects of the intervention and other problems encountered.

An overall review of usability of the technology was also carried out with both participants and carers at the end of the study, using the '*System Usability Scale'* developed by Brooke (1986). This questionnaire was developed to enable quick and standardized assessment of the usability of different technology products. The scale is comprised of 10 short statements which are rated on a 5-point scale. The total possible overall score is 100 with higher scores indicating higher levels of usability. Empirical evaluations of the *System Usability Scale* indicate good reliability (Bangor *et al.* 2008). The scale gives a single score overall score which can be used for, *"assessing competing products that may have the same functional properties implemented with very different interfaces"* (Bangor 2008, p.590).

A summary of questionnaires and interviews used; person reporting, and time taken for each measure is presented in Table 4.1. Samples of all measures used are shown in appendix III.

Table 4.1 Summary of information provided in different formats by participants and carers before, during and after the biofeedback intervention.

Stage of Intervention	Person Reporting	Measure Used	Time needed*
Pre-intervention*	Carer	*Demographic information and Carer Interview; Social Communication questionnaire (Rutter, M.D., 2003)*	45 minutes
Baseline		*Sensory Profile (Brown, C.E. 2002)*	15 minutes
	Participant	*Beck Anxiety Inventory (Beck, A.T., et al.1988); Beck Depression Inventory II (Beck, A.T. 1996) OR (Beck Inventory 13-17 years (Beck, J.S. 2005) Nijmegen Q'aire (Van Doorn,1983).*	10 minutes 5 minutes
		HRV recording using single lead ECG	15 minutes
Intervention monitoring	Participant	*Online progress report*	1 minute
Post intervention*	Carer	*Carer Interview*	15 minutes
		Debriefing interview form	5 minutes
	Participant	*Beck Anxiety Inventory (Beck, A.T., et al.1988); Beck Depression Inventory II (Beck, A.T. 1996) OR (Beck Inventory 13-17 years (Beck, J.S. 2005)*	10 minutes
		Debriefing interview form	10 minutes
		System Usability scale (Brooke, J.,1986)	5 minutes
		HRV recording using single lead ECG	15 minutes

*A total time of 2 hours was allocated to each home visit to allow for all assessments and interviews to take place.

4.7.6 *Equipment*

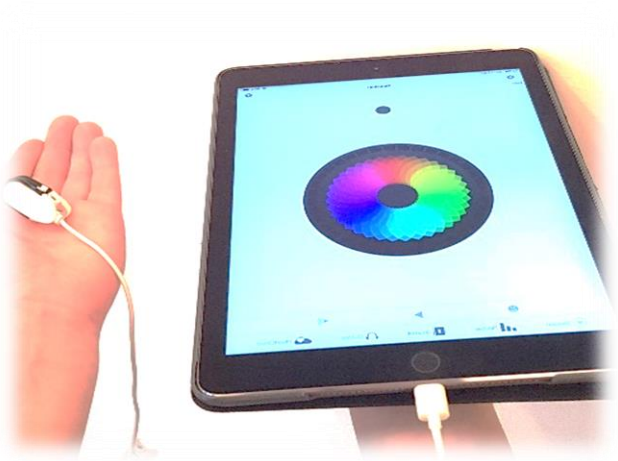
Intervention equipment (HRV Biofeedback devices)

A number of different types of HRV biofeedback devices are currently available for home use.

These devices typically derive HRV from an infra-red photoplethysmography (PPG) sensor, which measures rate of blood flow usually via either the fingertip or the earlobe. Peripheral blood flow can be used to assess heart rate and the thin tissue in both the fingertips and earlobes are commonly-used sites for measuring blood volume pulse (BVP), which can be used to estimate HRV (Peper 2010).

HRV personal use devices available differ in terms of form factor; feedback mechanisms; data storage; training guidelines and underlying software, all of which may affect user experience and effectiveness. To explore these aspects, participants were randomly allocated to a device after their initial allocation into an intervention group. The study then collected data on device usability and user experience. Group A were provided with a home trainer biofeedback device, which used PPG ear sensors (Inner Balance®, HeartMath™: Quantum Intech Inc., Boulder Creek; CA). Within this group, participants in ownership of a tablet computer or smartphone were invited to use the newer version of the platform (Inner Balance). Participants not wishing to use their tablet or smartphone were provided with a standalone device (emWave2®). Both devices used the same processing algorithms but differ in the way in which information is presented to the user. Group B were provided with a second home trainer biofeedback device which used a fingertip PPG sensor contained within a standalone device (StressEraser®: Helicor Ltd.; New York). Images of the biofeedback devices which were available for participant use are presented in Figure 4.7. Further information on HRV biofeedback devices is provided in appendix II.

Group A



Inner Balance

emWave2 (if no iOS device)

Group B

StressEraser

Figure 4.7 Portable 'home trainer' biofeedback devices available for use in the study.

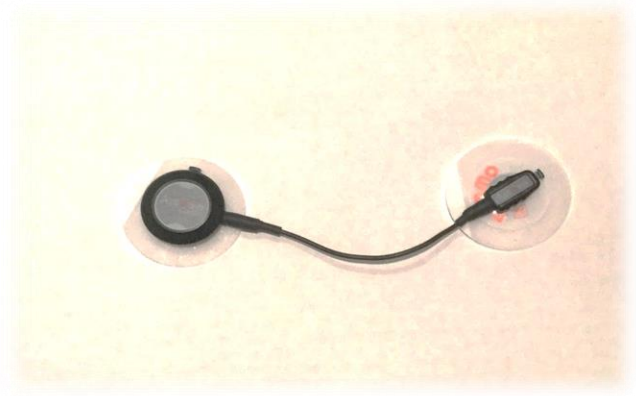
Physiological assessment equipment

Following the concerns about the multi sensor assessment equipment reported in Phase 1 of the study (Nexus-10® Mark II), a wireless single channel ECG was used for all physiological assessments in Phase 2 (Actiwave® Cardio: CamNtech Ltd., Cambridge UK). This small single channel wireless ECG waveform recorder, which is worn on the chest does not require any external leads or Velcro to connect to the recorder. The small size and wireless recording enabled monitoring to be carried out in a wide range of applications in different environments.

The single channel ECG recorder has been passed as a "*Class 2a Medical Device conforming to the essential safety and health requirements and provisions of EC Council Directives 93/42/EEC, Annex V"* (Actiwave user guide 2.0.2 p.2). The device is supplied with a docking station and reader software to enable information recorded on the device to be extracted to a PC for further analysis.

The Actiwave Cardio can be worn on either the upper or lower chest and attaches via spring loaded contacts to standard 4mm studs on ECG electrode pads (Actiwave user guide 2.0.2 p.8). Additional equipment needed included standard ECG electrodes with 4mm male snap connectors, and cardio prep-pads for initial skin exfoliation. Initial practice with this equipment involved self-testing; testing with an ECG simulator device and testing with a senior cardiac physiologist.

The equipment used for physiological assessment is shown in Figure 4.8. Further information on HRV assessment equipment is provided in appendix II.



Actiwave Cardio (wireless ECG recorder)

Actiwave Cardiodock (reader)

Figure 4.8 Wireless ECG recorder and reader used to carry out physiological assessment.

4.7.7 *Procedure*

Provisional ethical approval from the Office for Research Ethics Committees Northern Ireland was granted in December 2015. Further clarification of participant information booklets and equipment was requested, and final approval was granted in January 2016 for commencement of Phase 2 of the study on 21st March 2016 (see appendix I).

Initial assessment

All assessment and training was carried out by the researcher. All participants were offered assessment and training in their home environment, with their carer present. After further checks on exclusion criteria were made, consent and assent was obtained. All participants completed baseline questionnaires followed by a physiological assessment. Carers completed a standardised interview and questionnaires on social, communication and sensory difficulties.

Intervention and Monitoring

Following baseline assessment, participants were randomised into an immediate intervention group or a delayed intervention control group (see Phase 2 design page 120). Immediate intervention participants were then offered two separate 60-minute training sessions of home instruction in use of their allocated biofeedback device (either device A or B). Delayed intervention participants waited six weeks before being reassessed again on baseline measures and allocated a biofeedback device and provided with home training in its use. Once the intervention had commenced, all participants were asked to complete regular reports on their stress levels and how frequently they used the device.

Training

Each training session lasted for 60 minutes once per week for two weeks. Each session involved initial demonstration of the allocated device by the researcher and a review of device functions using existing training protocols, guidelines and video clips (see appendix II).

This demonstration was then followed by an initial practice session involving the participant using the device with direct coaching from the researcher. Finally, a practice plan was agreed outlining a time for practice that suited the participants' routine with a recommendation of at least 10 minutes' practice per day.

Debriefing

All participants were reassessed after they finished the intervention by repeating the questionnaires and physiological assessment procedure. Participants then completed a short debriefing interview and a usability rating of their device. Carers were asked the same standardised interview questions which had been completed at baseline and also completed a short debriefing interview. In order to control for differing home environments, the procedure followed a standardised format using the same initial interview script; assessment procedure; training guidelines and the same debriefing interview script (see appendix IV).

4.7.8 *ECG Recording*

Measurement of heart rate and HRV in participants was carried out with adherence to guidelines for assessment and reporting of HRV (Task Force; Camm et al. 1996) and guidelines on the reporting of HRV in psychiatric populations (Quintana 2016).

Set up of equipment took place whilst participants completed questionnaires. All equipment was cleaned with 70% isopropyl alcohol prior to each assessment and again after each use. Set up involved programming the ECG recorder by inputting start time, date and recording ID – only the participant's PIN, gender and task number were entered. The ECG recorder then recorded participant heart beats using two electrodes attached to the chest connected by a short lead. The recorder identified heart beats and R wave peaks within the ECG signal to enable calculation of R-R intervals. The sampling rate was set at 1024Hz with a 10-bit resolution, a recommended rate for this type of assessment (Berntson et al. 1997; Heilman – personal correspondence 2015). A 50Hz band pass filter was applied to remove contamination from background power line interference.

Once set up was complete, the recorder was attached. To avoid contamination or cross infection new electrodes were used for each individual assessment.

Checks were made to ensure the participants skin was not broken or red prior to each assessment. Each participants skin was first cleaned with simple soap and water wipes, prior to electrode placement. Skin was then lightly wiped using specialist exfoliation pads designed for ECG assessments to remove any existing dead skin, sweat and sebum. Alcohol wipes were not used as it was advised that these would be more likely to cause irritation (Actiwave user guide v.2.0.2). Electrodes were then applied to the central sternum area of the chest, according to manufacturer's instructions (Actiwave user guide v.2.0.2). The first electrode was placed directly onto the centre of the chest and the recorder was then attached onto it. The second electrode was attached to the left side so that the ECG recorder was positioned across the chest in approximately V1 – V5 positioning – see Figure 4.9. Two different placement positions are recommended as suitable depending on the user's anatomy and size.

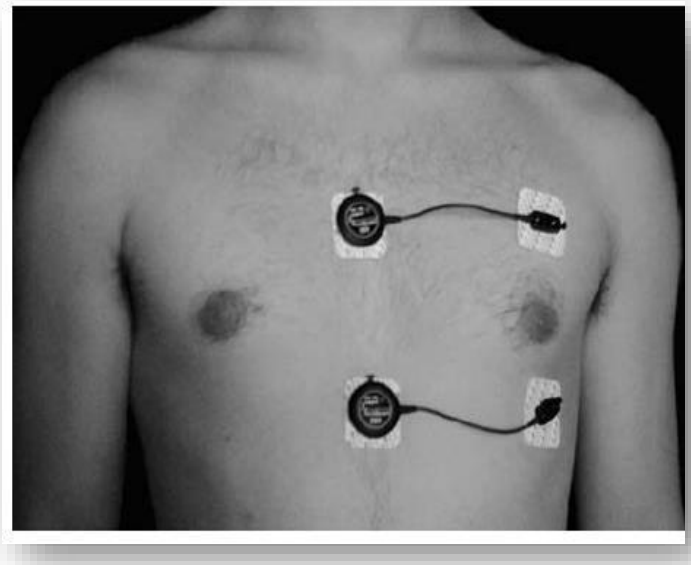


Figure 4.9 Illustration of two different electrode placement positions for HRV assessment recommended for single lead ECG Actiwave Cardio recorder (reproduced with permission of CamNtech Ltd).

To minimise problems with diurnal variation participants were seen at the same time of day for each repeat assessment, and records were made of any medications taken. Participants were instructed to sit upright at a dining room or kitchen table, in a straight-backed chair and watch a series of images displayed on a computer (PowerPoint™ presentation) via a 15-inch laptop.

Adjustments were made to the laptop height to ensure participants viewed the screen at a comfortable height without having to look up or down. The screen was positioned within one metre of each participant.

Participants were encouraged to remain seated and upright throughout the three assessment stages. Two 30 second breaks were allowed between individual sections of the assessment task, to allow for movements and stretching. Instructions for the task were presented on the laptop screen. Participants were reassured that the task was not a test and that they should simply relax and enjoy watching the images.

Deliberately controlling breathing rates and talking have been argued to alter HRV (Denver *et al.*2007). Therefore, instructions were given to '*just relax*' and to breathe normally to ensure participants did not try to actively adjust their breathing rates. The software used to analyse ECG recordings produced a derived estimate of respiration to enable checks that breathing rates were within the normal parameters used for analysis of HRV (Task Force guidelines: Camm *et al.* 1996). Separate respiration gauge belts were not attached to participants following concerns about straps and Velcro reported in the Phase 1 evaluations.

The assessment lasted for a total of 14 minutes. Researcher notes were also made of any difficulties with the assessment and responses to the task, including problems with electrode placement and any excess movement. At the end of the recording, the recorder was removed from the electrodes and placed on its docking station which was connected to the laptop. Participants were given hypoallergenic wipes to aid removal of electrodes at the end of the assessment. Records were made of any reactions or reports of discomfort during attachment or removal of electrodes.

Finally, the ECG reader software downloaded data from the recorder to the laptop via the dock and USB cable. All ECG recordings were initially downloaded using the proprietary software (CamNtech, Cambridge: UK) and saved as European Data Format files. A timing manager program recorded the exact viewing times of each PowerPoint slide thus enabling each section of the task to be recorded accurately.

HRV data was extracted from each of the three sections of the assessment and analysed using specialist software (Kubios HRV Premium version. 3.0.0).
Artefact identification and correction was conducted on all HRV recordings by using a 'smoothness priors based detrending approach' to analysis by setting the software to 'smooth priors' and also by using the 'automatic' artefact correction (Tarvainen 2006, p.20). Using this type of standardised approach to removal of artefact with HRV analysis software has been advocated as an appropriate alternative to using a manual editing process (Nunan 2010; Huang 2018).

4.7.9 *Psychophysiological assessment task*

The task used for assessment of HRV followed a standard 'psychophysiological stress profile' paradigm used for assessing resting state HRV developed after consultation with experts in this area[4].

Participant HRV was assessed for a 14-minute period at the beginning and at the end of the intervention. Delayed intervention participants were also assessed at the initial assessment six weeks prior to starting the biofeedback intervention, whilst immediate intervention participants were assessed after six weeks of intervention. Thus, three separate assessments were planned for each participant. These additional assessments were carried out to enable group comparisons to be made between immediate and delayed groups, comparing six weeks of intervention (in the immediate group) to six weeks of no intervention (in the delayed group).

The task involved three separate parts, each part lasting a minimum of three minutes, with additional time allocated for set up and short breaks. The format for tasks followed a commonly used protocol of '*baseline assessment*' task followed by a '*mild stress*' task, and finally a '*recovery*' task (Matto 2015).

[3]Personal correspondence with Richard Gevirtz, June 2015

The mild stress task used was the '*Reading the Mind in the Eyes Test'*. This assessment has been used to assess emotion recognition has been found to be a more difficult task for people with ASD (Baron-Cohen 2001; Kushki *et al.* 2014).

The baseline and recovery tasks involved using images from the '*International Affective Picture System*' (Lang *et al.* 1997; 2005) a database of visual images which have normative ratings regarding their emotional content. Images used were selected rated as having positive and non-social content.

First, participants watched a series of images of scenes from nature that did not contain any people or animals – this initial part of the recording enabled a baseline to be established and allowed participants to get used to the recording.

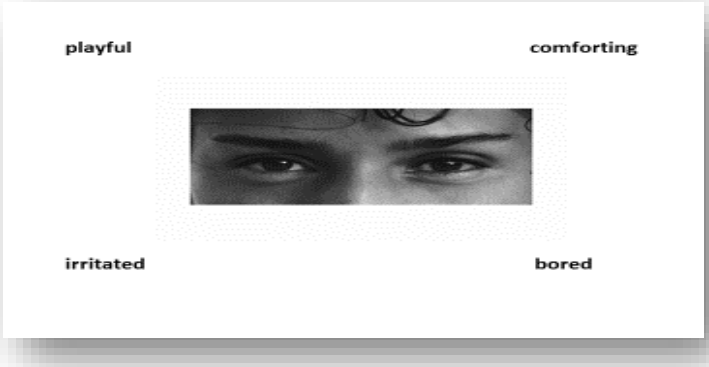
Second, a series of images from the '*Reading the Mind in the Eyes Test*' or RMET (Baron-Cohen 2001) was presented. This part of the assessment involved showing a series of images of eyes from human faces. Participants were asked to choose one of four words on the screen which best described the emotion shown on the face. Images used were all taken from the images in this test and varied in each assessment.

The third and final part of the assessment task, involved presenting a further series of images from the '*International Affective Picture System*' or IAPS which were rated as having positive and non-social content (Lang *et al.* 1997; 2005). Examples of images similar to those used in the physiological assessment task, are presented in Figure 4.10. The actual images used in the IAPS task are not to be reproduced except within the context of a research study – however the reference numbers of the specific images used are listed in appendix III.

Psychophysiological assessment via 15minute ECG recording

(i) Baseline recording task (IAPS)

(ii) 'Stress test'
(Reading the Mind in the Eyes Test)



(iii) 'Recovery' task (IAPS)

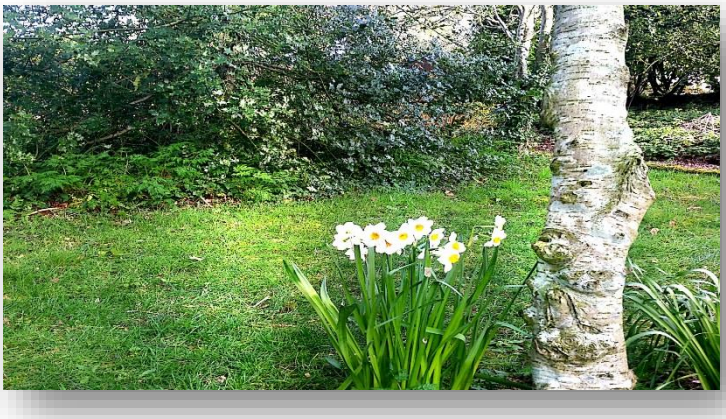


Figure 4.10 Sample of images from three-part psychophysiological stress profile assessment involving (i) Baseline recording (ii) Stress task and (iii) Recovery task.

4.8 Chapter Summary

This chapter has described the methods used to develop a two-stage piloting and feasibility study, the first stage of which involved a training and evaluation phase, which in turn led to the development of the second stage, a small-scale randomised pilot study.

Chapter 5 will now report findings on the demographic information collected and baseline measurement data from both carers and participants. Analysis of pre and post data and an assessment of usability, risks and benefits of the intervention will be then presented in Chapter 6.

Chapter 5. Participant Data

5.1 Overview

This chapter will first present information on recruitment into the study. The figures for overall recruitment, randomisation and retention of participants are reported and then summarised in a CONSORT flow diagram.

Next the overall data analysis plan is outlined, and the demographic data collected in the study is described.

Key concerns reported regarding participant behaviour; triggers for anxiety and strategies used to manage anxiety meltdowns are then described. Finally, baseline ASD profile measurements of participant social, communication and sensory difficulties are reported. Sources of stress reported by participants are also described.

Analysis of demographic information was carried out on the initial sample recruited into the study. This demographic information is important to assess whether the sample of participants in this study reflects the wider population of people with ASD in the UK. Further statistical analysis of data on particpiants who provided data on pre and post measures is reported in Chapter six.

5.2 Recruitment of Participants

The initial study aim was to recruit forty participants, twenty adults and twenty children. The initial ethical application had specified that the initial participants recruited for the first three months should be adults with their carers to evaluate if there were any concerns about using this intervention that might highlight difficulties or risks which would preclude use of the intervention with children.

Recruitment therefore began with meetings and participant information booklets being given out to the members of the adult ASD team in May 2016. There were however significant difficulties recruiting adult participants in the 18-24-year-old age group. No participants were recruited from May to September 2016 (see

Figure 5.1). Of note was the fact that during this period repeated enquiries were made by members of children's teams regarding the availability of potential participants within children's teams.

The study protocol stated that initial recruitment would begin by directly recruiting from clients attending clinical teams, but that if recruitment was poor it would proceed by contacting participants discharged from services.

It had also been agreed with the PI and CI that no recruitment would take place from current waiting lists as this could be deemed as offering a potential early intervention service and would potentially put undue pressure on people waiting for services to participate in the study.

Therefore, by September 2016 a further meeting was held with the PI and it was agreed that recruitment would commence of adults who had recently been discharged from adult or children's services who were now 18 years or over. This recruitment strategy led to immediate contact from a number of young adults who had recently been discharged from services due to their age. After evaluating these adults with ASD over a three-month period, recruitment then opened to both adults and children with ASD for the remainder of the study.

Participants involved in the study were either recruited directly by their keyworker, or by a letter sent by the ASD clinic secretary to recently discharged clients. All clients were given the same information packs and cover letter.

A time line showing the different phases of recruitment over the course of the study with time periods and numbers recruited is shown in Figure 5.1.

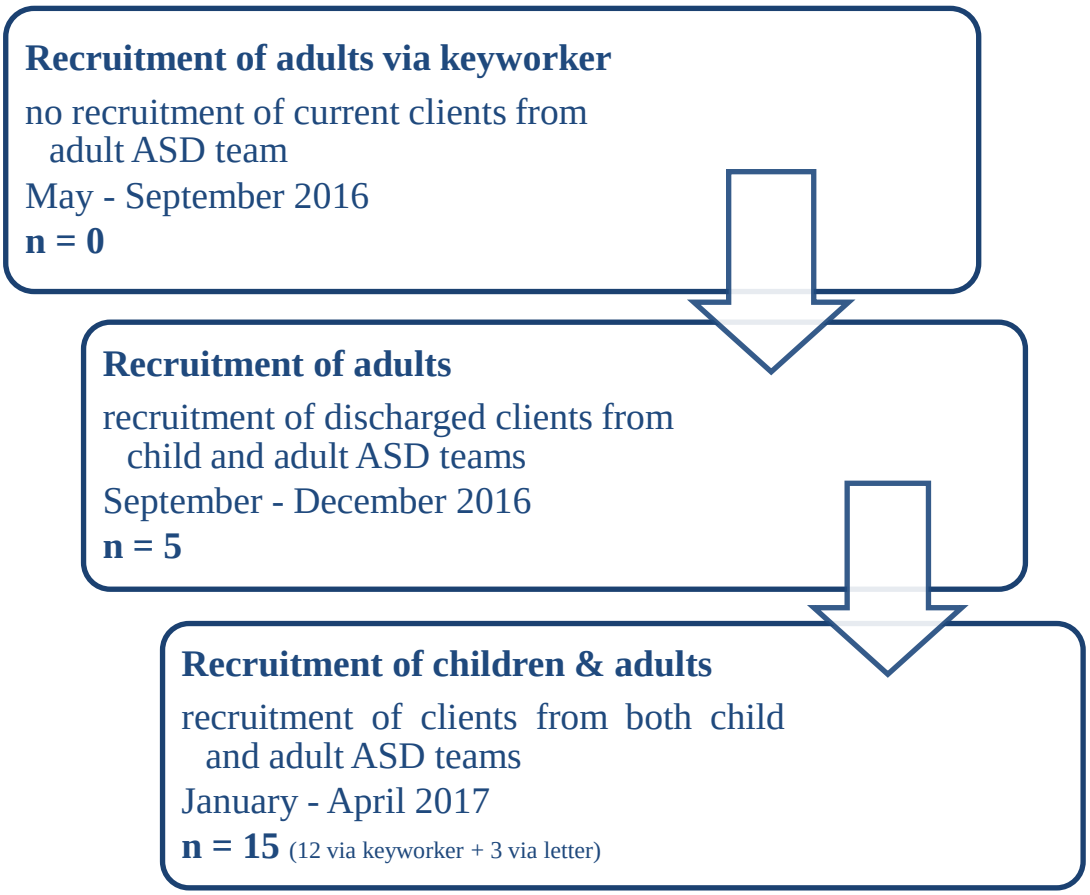


Figure 5.1 Recruitment methods time line showing initial recruitment of adults only followed by recruitment of children and adults from May 2016 - April 2017.

Twenty participants were recruited over the course of the study, 10 into the child group and 10 into the adult group. A decision was made to stop recruitment in April 2017 after the first twenty participants were recruited. This was due to a high level of requests for repeat ECG checks from the cardiac physiologist and also due to the need to include all intervention sessions before the trial end date in July 2018.

Twelve participants were recruited directly by their keyworker. Eight participants recruited were not receiving any service and were recruited by letters sent by the team secretary to recently discharged clients Recruitment of participants by method of recruitment and referral team is shown in Figures 5.2 to Figure 5.3.

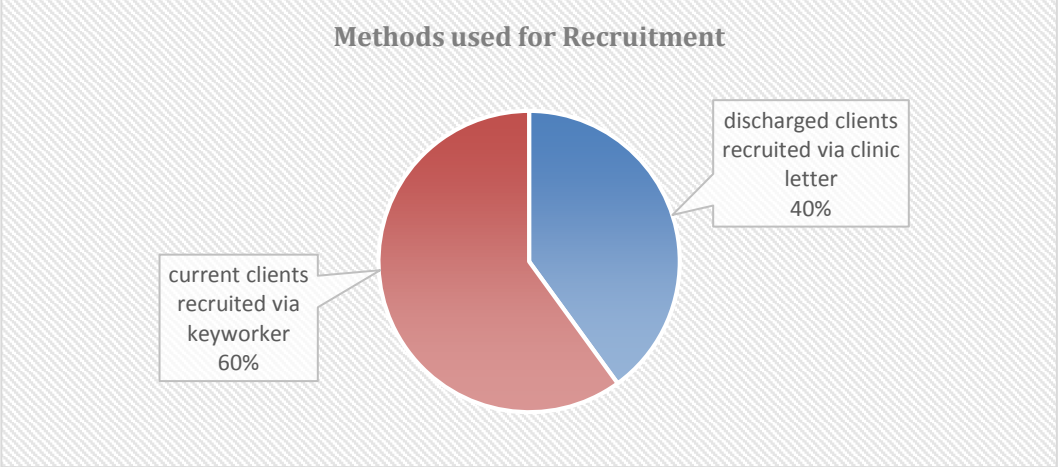


Figure 5.2 Summary of two different methods to recruit participants.

Of those attending clinical services the majority (10) were attending Child and Adolescent Mental Health Services (CAMHS). Of those attending CAMHS only two reported that the service was helping with their problems. Only one adult was recruited from the adult ASD team and one was recruited from a client being discharged from the children's disability team – see Figure 5.3.

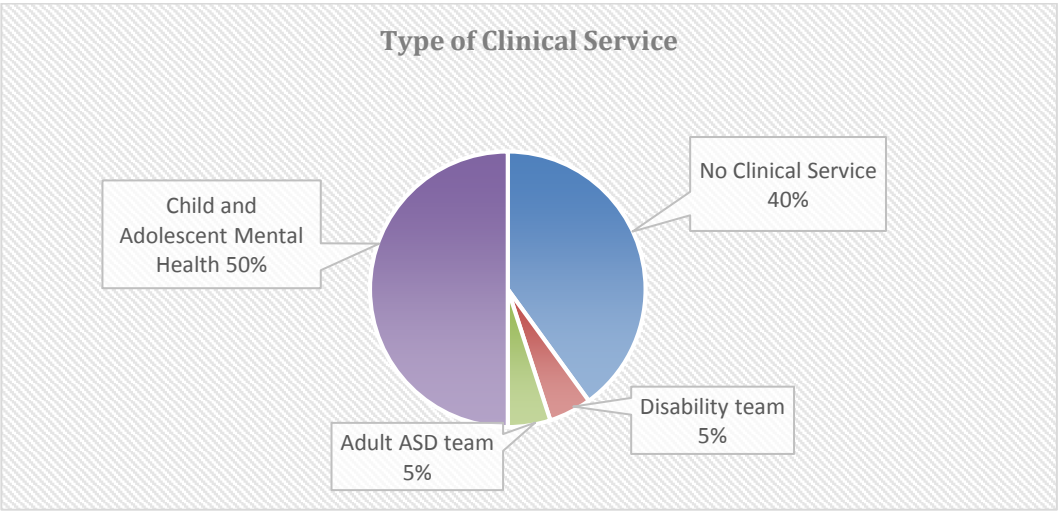


Figure 5.3 Summary of different types of clinical service involved with participants at time of recruitment.

5.3 Randomisation of Participants

Randomisation into groups was planned in two blocks of 20 to ensure not all participants were allocated to one group initially. No concerns were reported by participants about randomisation into immediate or delayed intervention groups.

Randomised allocation of devices was also planned in two blocks of 20. However, two participants who were initially allocated to the StressEraser group were unable to use this device due to concerns using the finger sensor. Both participants wanted to continue with the trial and a decision was made to allow participation by allocating them to the second group. Thus, despite an initial attempt to randomly assign participants to different devices this randomisation procedure was discontinued.

5.4 Retention and Drop-out of Participants from Pilot

The study aimed to follow guidelines for reporting of pilot and feasibility studies with data collected on numbers contacted and recruited with reasons for drop-out recorded (Eldridge, 2016). Records were kept of the numbers of potential participants contacted and the method of recruitment contact. Overall, 59 participants were contacted for screening either by letter or directly by their keyworker. Of this sample 20 participants eventually volunteered for the study. Thus 34% of the initial screening sample volunteered to take part in the study. Four participants were excluded after randomisation into groups, three due to cardiac concerns highlighted by ECG, and one due to a significant change in mental health highlighted at the 6 weeks follow up. Three participants of the initial twenty recruited dropped out after 6 or 8 weeks but before the full 12 weeks of intervention had been completed. Reasons reported for drop out were ‘not wanting to continue’ (n=2) and ‘family stress’ (n=1). Of the three who dropped out, two consented to all data being used in the study, however one declined further questionnaire and physiological assessment, leaving 15 participants whose full data was included in the final analysis. A summary of initial screening and enrolment; randomisation into groups; participant retention over the course of the study, follow-up and analysis of data is shown in Figure 5.4.

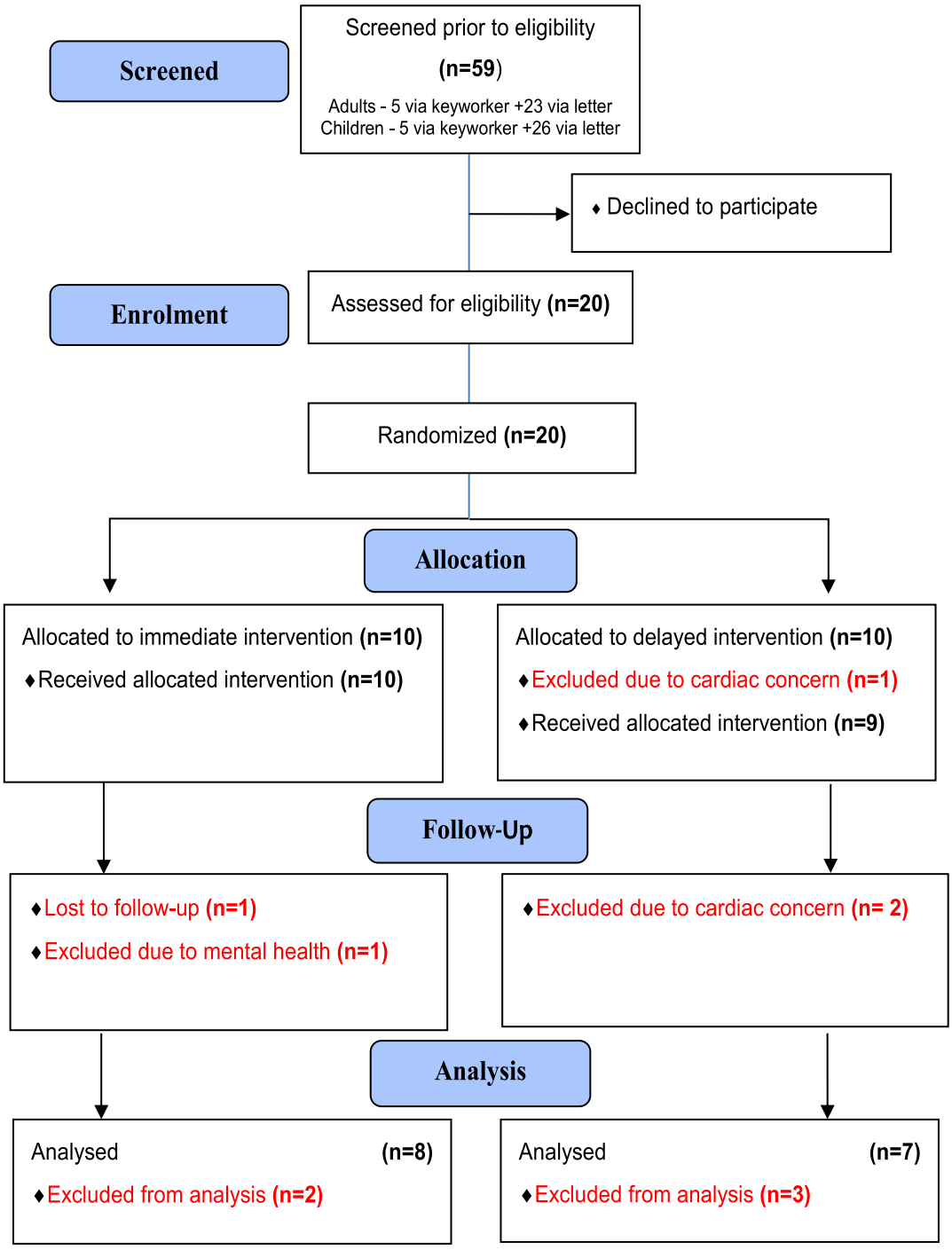


Figure 5.4 CONSORT 2010 flow diagram summarising numbers for screening and enrolment; allocation into groups; follow-up and final analysis.

5.5 Data analysis plan

An intention to treat approach was adopted in analysing results (Ferguson 2002). Thus, participants who dropped out early or had continuing difficulties using their biofeedback device after randomisation had their data included for further analysis provided, they had consented for this data to be collected. This type of approach has been described under the adage of "*as randomised so analysed*" (LaValley 2003, p12) and argued to provide more real-world information on the outcomes of a clinical intervention following CONSORT guidelines and may reduce the level of type 1 errors in analysis (Newell 1992; Gupta 2011).

Qualitative data was obtained from demographic information questions; standardised interview and from short debriefing reports. Due to the limited nature of qualitative data collected it was felt that more detailed thematic analysis such as Braun and Clarke's framework (2006) was not appropriate. Qualitative data was therefore analysed using frequency counts and manifest content analysis of reports given (Graneheim 2004; 2017). Quantitative data from questionnaires and physiological recordings was analysed using statistical tests assessing paired samples of data from the same subjects. Correlational analyses were also carried out to review associations between baseline measurements and HRV data.

A number of participants were excluded post randomisation due to meeting exclusion criteria and their pre-post data was therefore not included in the quantitative data analysis. Several participants dropped out prior to 12 weeks and this data was included, provided consent had been obtained. A summary of how data was analysed from the participants who did not complete the full 12 weeks of intervention is shown both in the CONSORT diagram and in Figure 5.5 below.

Table 5.1 Number of participants who were excluded or lost to drop out during the course of the intervention and subsequent analysis of outcome data.

Type of Participant	Number	Follow up data and consent	Data analysed
Excluded after randomisation	4	yes	no
Dropped out before 12 weeks	2	yes	yes
Dropped out before 12 weeks	1	no	no

5.6 Demographic information

Demographic information collected from the 20 participants who were initially recruited into the Phase 2 study is now described below.

5.6.1 *Gender and Age*

Overall 20 people were recruited into the study, 16 males and 4 females. The age range of participants recruited was 13-22 years, with a mean of 16.3 years – see Table 5.2 Participant gender.

Table 5.2 Participant gender.

Gender	Frequency	(Percentage)
Male	16	(80)
Female	4	(20)

This gender distribution mirrors that found in a Northern Ireland school census which indicated a gender ratio of 4:1 males to females diagnosed with ASD (Waugh 2017).

5.6.2 *Age of ASD Diagnosis*

Only one participant had received a diagnosis of ASD before five years of age. The majority of participants (13 out of 20), were diagnosed during their primary school years between 5-11 years of age. Six participants were not diagnosed with ASD until 12-17 years of age – see Table 5.3.

Table 5.3 Age when participant was diagnosed with ASD.

Age	Frequency	(Percentage)
Under 5 years	1	(5)
5-11 years	13	(65)
12-17 years	6	(30)

These findings reflect research indicating that most children with ASD are still being diagnosed with ASD in primary school years (Daniels and Mandell 2013).

5.6.3 *Education*

The majority of participants were in school or college. However, 4 out of 20 of participants were at home and were not receiving any form of education or employment. Participants reported anxiety regarding the educational environment as the reason they were not attending either school or college – see Table 5.4.

Table 5.4 Type of education or employment reported by participants.

Education	Frequency	(Percentage)
Not in education or employment	4	(20)
Secondary / grammar school	13	(65)
College / university	3	(15)

An NAS review has indicated that only 16% of adults with ASD are in full time employment or education (Madders, 2010). The sample in this pilot highlights non-attendance in teenage years at school, which may be a precursor to this problem.

5.6.4 *Physical Activity*

Eight participants reported that they undertook less than 1 hour of physical activity per week. A further six reported that they completed 1-2 hours per week. The two participants reporting more than 3 hours of physical activity per week were the youngest participants in the study – see Table 5.5.

Table 5.5 Levels of physical activity reported by participants.

Physical Activity	Frequency	(Percentage)
Less than 1 hour per week	8	(40)
1-2 hours per week	6	(30)
2-3 hours per week	4	(20)
3+ hours per week	2	(10)

Department of health guidelines recommend 2 ½ hours per week of moderate physical activity for adults and 1 hour per day for children (DiSantis *et al.*, 2013).

The levels of activity reported by participants were below this level, with 14 out of 20 participants not completing recommended levels for adults (DiSantis *et al.*, 2013).

5.6.5 *Sleep Problems*

Fifteen out of 20 participants also reported some form of sleep problems, a difficulty also highlighted in a recent ASD stress survey (Research Autism 2016).

Table 5.6 Level of sleep problems reported by participants.

Sleep	Frequency	(Percentage)
No problem sleeping	5	(25)
Sometimes problems sleeping	5	(25)
Frequent problems sleeping	10	(50)

5.6.6 *Prescribed Medication*

Participants were also asked if they took any prescribed medication. Ten out of 20 reported that they did not take any prescribed medication. Of the ten participants taking medication, 6 were taking antidepressants, followed by 4 out of 10 who were taking some form of stimulant medication. Despite a majority of participants reporting some degree of sleep disturbance (Table 5.6), only three were reported to be taking Melatonin, a drug frequently prescribed for sleep problems in people with ASD. A further finding was that three participants also reported needing to carry auto injectors with adrenalin (EpiPen®) – see Table 5.7.

Table 5.7 Types of prescribed medication taken by participants.

	Frequency	(Percentage)*
Not taking medication	10	(50)
Antidepressant	6	(30)
Stimulant medication	4	(20)
EpiPen	3	(15)
Melatonin	3	(15)

*Several participants were taking more than one form of prescribed medication.

5.6.7 *Additional Diagnoses*

Participants also reported having a number of additional comorbid diagnoses, which were related to some of the prescribed medication listed in Table 5.7 Types of prescribed medication taken by participants above. Thus, four participants had an additional diagnosis of Attention Deficit Hyperactivity Disorder, and three participants had a form of severe anaphylaxis.

5.6.8 *Use of Technology*

Participants were asked questions regarding their use of technology. Results are reported in Table 5.8 - Table 5.12.

Participants were first asked about their access to different types of technology. Six out of ten child participants and eight out of ten adult participants reported that they had access to tablet computer iOS devices.

Table 5.8 Participant access to iOS or android technology device.

Participant Group		Frequency	(Percentage)
Children 13-17 years	*iOS device*	6	(60)
(n=10)	*no iOS device available*	4	(40)
Adults 18-24 years	*iOS device*	8	(80)
(n= 10)	*no iOS device available*	2	(20)

The majority of participants had access to a smartphone. One child participant was not allowed access to their phone due to inappropriate use. Two adult participants also reported that they also had limits set on their phone.

Table 5.9 Participant access to smartphone for personal use.

Participant Group	*Use of Smart phone*	Frequency	(Percentage)
Children 13-17 years	*not allowed phone*	1	(10)
(n=10)	*limits on phone use*	9	(90)
	unlimited phone use	0	
Adults 18-24 years	*limits on phone use*	2	(20)
(n=10)	*unlimited phone use*	8	(80)

Participants were also asked about the amount of time they spent using technology or '*screen time'*. Three out of ten children and 4 out of ten adults reported that they spent more than five hours per day using some form of device such as computer, tablet or gaming console.

Table 5.10 Participant reports on time spent using technology per day.

Participant Group	Time on screens	Frequency	(Percentage)
Children 13-17 years	*3-5 hours per day*	7	(70)
(n=10)	*5+ hours per day*	3	(30)
Adults 18-24 years	*3-5 hours per day*	6	(60)
(n=10)	*5+ hours per day*	4	(40)

Nine out of the ten child participants reported that gaming was their favourite type of technology. This was also the favourite activity reported by six out of the ten participants in the adult group.

Table 5.11 Participant reports on favourite type of technology.

Participant Group	Favourite technology	Frequency	(Percentage)
Children 13-17 years	*gaming*	9	(90)
(n=10)	*TV/ YouTube / video*	1	(10)
Adults 18-24 years	*gaming*	6	(60)
(n=10)	*TV/ YouTube/ video*	3	(30)
	social media	1	(10)

Participants were then asked whether they had experienced any problems using technology. Seven out of ten child participants reported that they had experienced some form of problem with using technology, with use of social media reported as the most common source of problems.

A similar pattern was seen in the adult group with six out of ten adults reporting that they had experienced a problem with some form of technology. Social media was reported as the most common source of problems, with both adults and children reporting difficulties with the use of social media.

Table 5.12 Participant reports on problems with technology.

Participant group		Frequency	(Percentage)
Children 13-17 years	*problems with gaming*	1	(10)
(n=10)	*problems with TV/ YouTube*	1	(10)
	problems with social media	4	(40)
	problems with phone	1	(10)
	no technology problems	3	(30)
Adults 18-24 years	*problems with gaming*	1	(10)
(n=10)	*problems with TV/ YouTube*	0	(0)
	problems with social media	4	(40)
	problems with phone	1	(10)
	no technology concerns	4	(40)

5.6.9 *Smoking, Illegal Drug use and use of Alcohol*

Participants were also asked whether they smoked or used e-cigarettes, took illegal drugs or drank alcohol. None of the participants reported smoking or taking drugs. Two participants in the adult group reported drinking alcohol at a level which was within the UK Department of Health (DOH) recommended limit of 14 units per week (Kalinowski and Humphreys 2016).

5.6.10 *Demographic information on drop-out and exclusions*

A review of those particpiants who dropped out or were excluded from the study was carried out to assess whether any specific group was more likely to drop out or meet exclusion criteria.

The gender of participants who dropped out was two males to one female. Ages ranged from 13 – 18 years. Reasons for drop-out were also recorded and were reported as 'family stress' (1 participant) and 'device useful but don't want to continue with further assessment' (1 participant) and 'device not useful' (1 participant). A summary is reported in table 5.13.

Table 5.13 Participant age gender and reported reasons for drop-out.

Gender	Age	Reported reason for dropout from study
Male	13	*Family stress*
Male	18	*Device not useful*
Female	18	*Device useful but don't want further assessments*

A number of participants who were initally screened and recruited then later met exclusion criteria post randomisation. A summary of the age and gender of participants who were excluded from the study with the reason for exclusion is reported in table 5.14.

Table 5.14 Participant age gender and reasons for exclusion from study.

Gender	Age	Reason for exclusion from study
Male	13	*Cardiac problem*
Male	18	*Cardiac problem*
Male	15	*Mental health problem*

5.7 Carer Interview

Carers were asked standardised questions regarding their main concerns; whether there were any triggers for participant anxiety attacks or *'meltdowns'* and any strategies used to manage anxiety.

5.7.1 *Triggers for anxiety*

The main concern reported by all families was anxiety. The three main triggers for anxiety attacks reported by 14 out of 20 families were sensory issues such as *'loud noise'*, '*bright lights*', '*touch'*, '*change in routine'* and *increases in workload or exams.* Busy or crowded places e.g. '*shopping centres*' or '*school'* were also mentioned as frequent triggers for anxiety reported by 11 out of 20 families. *Problems with friends'*, and '*'being away'* or *'separated'* from parent or carer were also common triggers for anxiety. All families reported more than one trigger for anxiety. Triggers for anxiety reported are summarised in Figure 5.5.

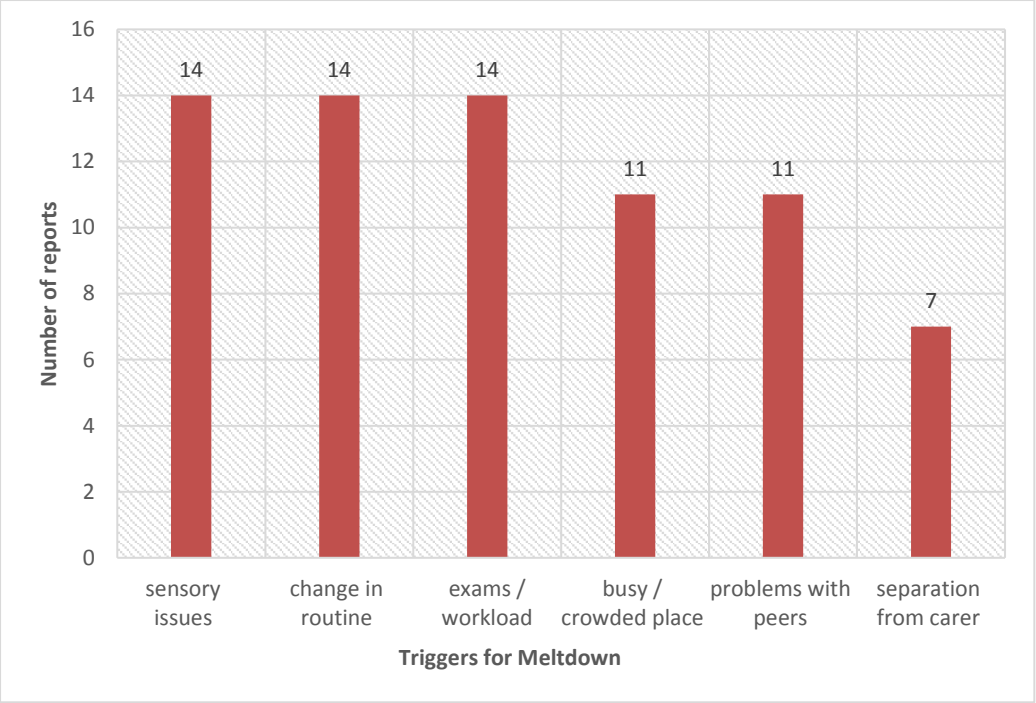


Figure 5.5 Frequency of different triggers for meltdowns reported by carers (n=20) at initial interview.

5.7.2 *Strategies used to manage anxiety*

Carers and participants were also asked what strategies they used to manage participant anxiety. Carers and participants reported using a number of different strategies to help them cope when feeling anxious.

The most frequently reported strategy described by 17 out of 20 families involved reducing sensory information e.g. '*reduce noise* or *'turn down lights*. The second most common strategy reported by 8 out of 20 families was engaging in favourite activities to ease feelings of anxiety. Further strategies reported were physical activity; spending time with parent or carer; time with pet; music; and escaping from the source of stress, by fighting or running away. Carers and participants all reported more than one strategy for managing anxiety. A summary of strategies reported is shown in Figure 5.6.

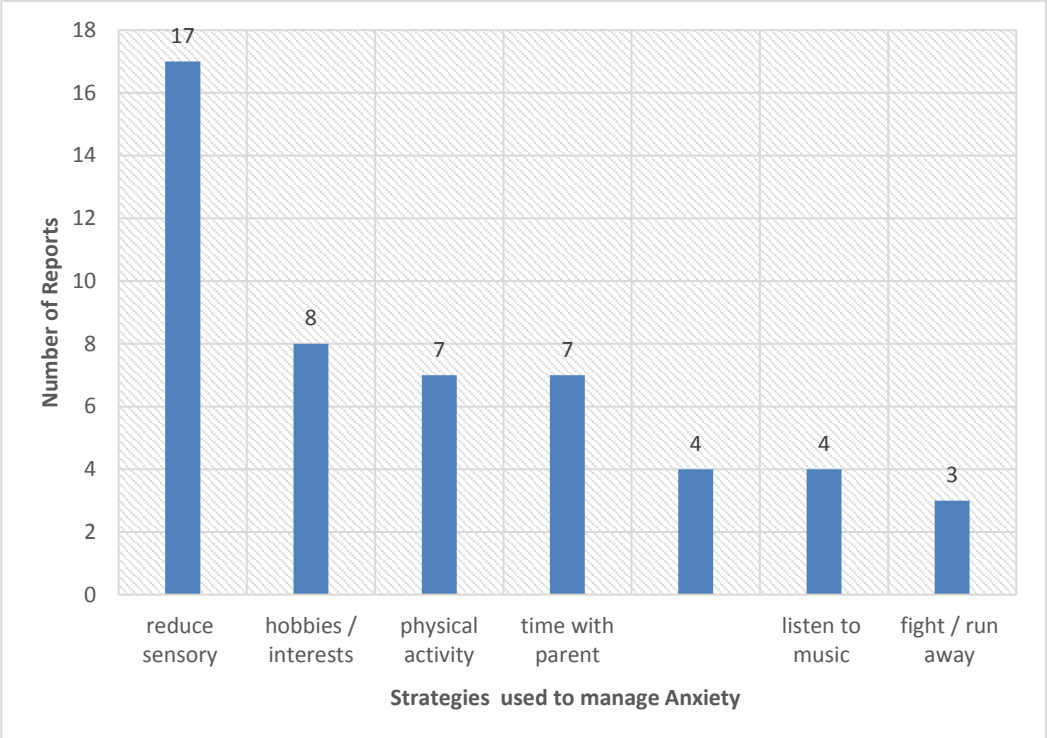


Figure 5.6 Frequency of different strategies reported by carers and participants to help manage participant anxiety (n=20).

5.8 Carer Questionnaire Reports

Following initial interview, carers were then asked to complete two questionnaires, the Social Communication Questionnaire (Rutter et al. 2003), and the Sensory Profile (Brown and Dunn 2009), to provide information on the level of social, communication and sensory difficulties in each participant. Further information on both questionnaires used is reported in chapter 4 and samples copies of reports are shown in appendix III.

All participants had previously been diagnosed with ASD. However as ethical permission had not been sought to access medical records, detailed diagnostic data was not accessible to the researcher. These two questionnaires were therefore used to give a profile for each participant on some of the key difficulties seen in ASD.

5.8.1 *Social Communication Questionnaire*

Findings from the Social Communication Questionnaire (SCQ: Rutter et al. 2003) are reported in Table 5.15.

Table 5.15 Carer reports of participant social and communication difficulties (n=20).

SCQ (Lifetime) Symptoms	Score
Mean *(standard deviation)*	20.80 *(6.45)*
Median	19
Range *(minimum – maximum)*	21*(12-33)*

The mean score for the SCQ in the participant sample was 20 with a maximum score of 33. The recommended cut-off level on the SCQ for possible diagnosis of ASD is 15. The minimum score reported in the sample was 12 however, as all participants had previously been referred for a more detailed assessment and had been diagnosed with ASD within a specialist assessment clinic, this participant was included in the study.

5.8.2 *Sensory Profile Questionnaire*

This 60-item questionnaire assessed sensory related difficulties which were then summarised into four types of sensory functioning, '*Low registration'; 'Sensation seeking'; 'Sensory sensitivity'* and *'Sensation avoidant'*, based on the Model of Sensory processing (Dunn 1997a). Group mean raw scores and standard deviations for child and adult participants, and classification categories with regard to the normative distribution of scores on the four domains are reported in Table 5.16.

*Table 5.16 Sensory profile scores reported by children and adults with ASD over four different categories of sensory difficulty (n=16.) **

Sensory Category	Children (13-17 years)	Adults (18-24 years)
1.Low registration		
Mean (standard deviation)	32.16 *(5.23)*	44.9 *(6.31)*
Classification	*Similar to most people*	*Much more than most people*
2.Sensation seeking		
Mean (standard deviation)	44.66 (*11.57)*	40.6*(10.33)*
Classification	*Similar to most people*	*More than most people*
3.Sensory sensitivity		
Mean (standard deviation)	32.83*(8.56)*	46.1*(11.44)*
Classification	*Similar to most people*	*More than most people*
4.Sensation avoiding		
Mean (standard deviation)	38.66*(13.51)*	50.0*(9.45)*
Classification	*Similar to most people*	*Much more than most people*

*Four families did not complete the Sensory Profile questionnaire.

Children showed scores which were categorised as '*similar to most people*' on all four domains of sensory behaviour. In contrast, adults showed scores which were either '*more than most people*' (between the 84th and 98th percentile) or '*much more than most people*' (greater than the 98th percentile) compared to the original study population (Brown and Dunn 2003, p.32).

5.9 Participant Baseline measurements

Participants provided questionnaire reports on their levels of anxiety and depression prior to the start of the intervention. The questionnaires used provided raw scores and clinical category ratings for both anxiety and depression compared to normative ranges (see Chapter 4).

5.9.1 *Anxiety*

Clinical category ratings for anxiety reported by both children and adults are shown in Figure 5.7 - Figure 5.8.

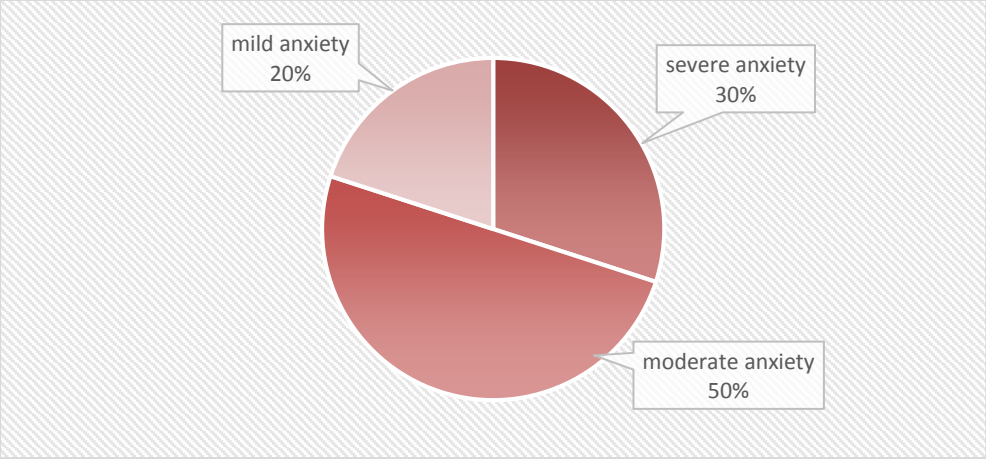


Figure 5.7 Anxiety reported by children aged 13-17 years (n=10) at initial assessment, using the Beck Youth Inventory–II, showing mild moderate and severe levels of anxiety.

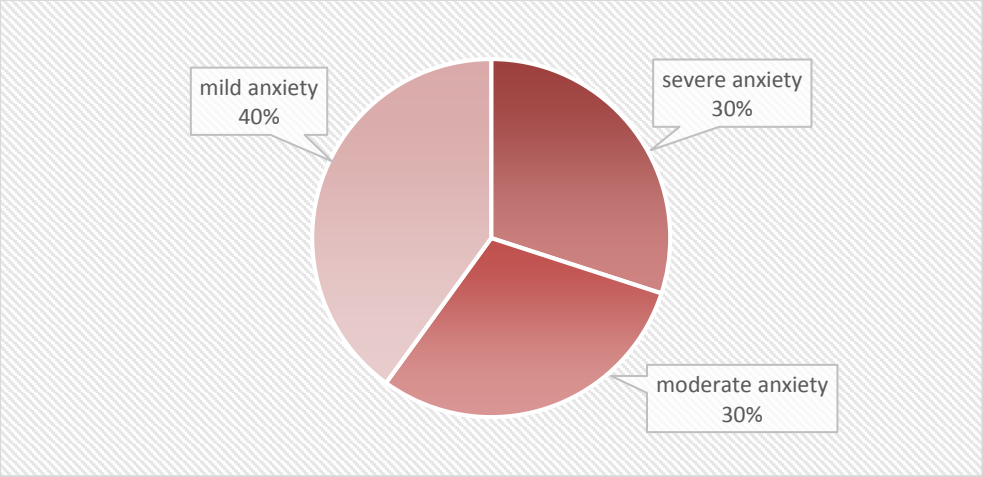


Figure 5.8 Anxiety reported by adults aged 18-24 years (n=10) at initial assessment, using the Beck Anxiety Inventory, showing mild, moderate and severe levels of anxiety.

5.9.2 *Depression*

Clinical category ratings for depression reported by both children and adults are shown in Figure 5.9 and Figure 5.10.

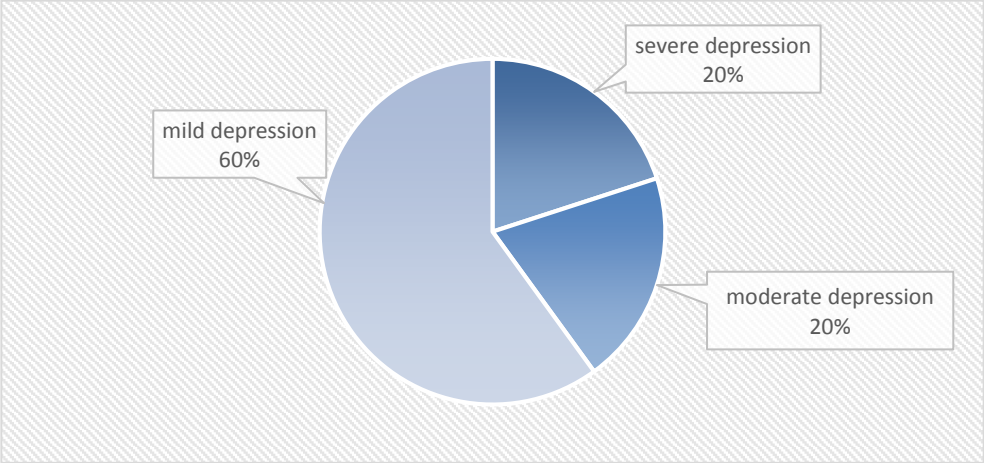


Figure 5.9 Depression reported by children aged 13-17 years (n=10) at initial assessment, using the Beck Youth Inventory–II showing mild, moderate and severe levels of depression.

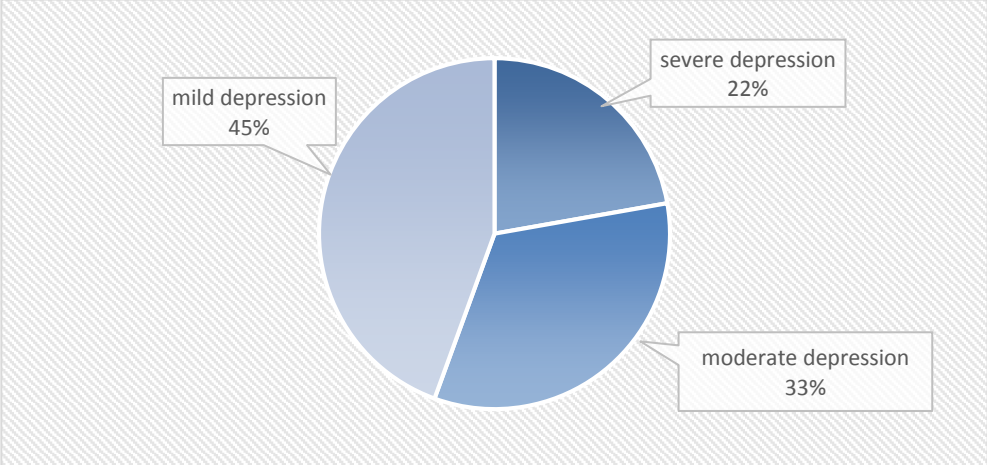


Figure 5.10 Depression reported by adults aged 18-24 years (n=10) at initial assessment, using the Beck Depression Inventory-II showing mild, moderate and severe levels of depression.

5.9.3 *ECG measurements*

Initial ECG were carried out on all 20 participants. Four sets of data were excluded from analysis due to participants meeting exclusion criteria. One further participant dropped out and declined to provided further information.

Initial measurements from the first four minutes of ECG recording are presented in Table 5.17. Results are shown in comparison to some of the existing reference values for heart rate and HRV. Some reference values are available for children (e.g. Seppala 2014) however these values are for a younger sample of 6-8-year olds and do not provide similar measurement scores. The current sample of young people aged 13-24 is therefore compared to the large-scale norms produced by Nunan (2010) and to an age stratified sample from a single cohort of adults produced by (Dantas *et al.* 2018).

Table 5.17 Initial measurements from the first four minutes of ECG recording that include Heart Rate, HRV time domain and HRV frequency domain calculations.

Heart Rate and **Heart Rate Variability** (Baseline measurements from short term ECG recording)	ASD sample 13-24 years n = 15	(Nunan 2010) reference values n = 21,438	(Dantas 2018) 35-44 years n = 982
	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*
Heart Rate (bpm)	75.55 *(9.92)*	n/a	66 *(9)*
HRV time domain measurements	Mean (SD)	Mean *(SD)*	Mean *(SD)*
SDNN (ms)	50.86 *(20.7)*	50 *(16)*	45.7 *(17)*
RMSSD (ms)	49.28 *(31.5)*	42 *(15)*	34.9 *(17.5)*
HRV frequency domain measurements	Mean (SD)	Mean *(SD)*	Mean *(SD)*
HF (n. u.)	40.49 *(18.4)*	40 *(10)*	45.1 *(19.2)*
HF (ms^2)	1254.13*(2077.2)*	657 *(777)*	575.5 *(667.6)*

Results from the current ASD sample show values within one standard deviation of the mean, although mean heart rate and actual values of HF-HRV for the ASD sample are above one standard deviation of the mean for adults aged 35-44 years. This difference is likely to reflect the relatively younger age range of the current ASD sample (13-24 years) compared to the norms for adults (35-44 years).

Chapter 6. Results

6.1 Overview

Information has already been presented on the development of design, methods and procedures for the Phase 2 pilot trial (Chapter 4). The demographic characteristics of the participant sample have been described with figures on recruitment, numbers excluded and levels of dropout (Chapter 5).

This chapter now focuses on the main study findings. This information is at the core of any clinical study where new data is presented as a basis for future research.

The research objectives for the overall study are restated below.

Research study objectives

1. *To provide a home based HRV biofeedback intervention to people with autistic spectrum disorder.*
2. *To assess participant anxiety, depression and physiological arousal before and after using a biofeedback device.*
3. *To assess the adoption of HRV biofeedback technology.*
4. *To evaluate the risks and benefits of this technology.*
5. *To develop recommendations on the use of HRV biofeedback for people with autistic spectrum disorder.*

Research objective 1 has been addressed through the development of study methods, presented in Chapter 4. The results of the Phase 2 pilot now presented aimed to address research objectives 2, 3 and 4.

This chapter now reports findings from the Phase 2 pilot following guidelines for randomised controlled pilot trials (Eldridge *et al.* 2016). Results are presented in separate sections each linked to a specific research objective, as outlined below.

Research objective 2: 'Pre-post data collection'

Information is presented on pre-post data from a number of measures including participant anxiety and depression from questionnaires, carer reports on frequency of meltdowns from interview, and physiological measurement of participants from ECG, before and after the intervention.

Research objective 3: 'Adoption of Technology'

Information is presented on the level of training given; participant use of device during the intervention, and participant ratings of device usability. This information was collected from researcher records and from online surveys collected from participants during the intervention and from ratings and interviews carried out at the final debriefing session.

Research objective 4: 'Assessment of Risks and Benefits'

Information is presented on risks and potential harms encountered, reported benefits and any unintended consequences of the intervention. This information was provided via debriefing interviews with carers and participants, and by reviewing procedural difficulties recorded by the researcher during the study.

Results are then summarised and associations between the ASD profile measurements with HRV data are presented.

6.2 Research Objective 2 'Pre-post Data Collection'

6.2.1 *Summary*

This section provides the results of group data collected to assess pre-and-post changes over the course of the intervention.

Information is presented on three main areas of assessment, each of which used different methods of measurement. These approaches included (i) carer reports on participant frequency of anxiety attacks or 'meltdowns' via pre-post interviews (ii), participant self-reports via pre-post questionnaires and (iii) direct physiological assessment of participants via pre-post recording of Heart Rate and HRV.

Carers reported frequency rate of participant anxiety meltdowns before and after the intervention. Young people with ASD were asked to give direct self-reports via questionnaires on their levels of anxiety and depression using standardised questionnaires (Beck *et al.*1988; 1996; 2005) before and after using their biofeedback device over the course of the intervention. Due to the different scales used for adults and children results of anxiety and depression questionnaires were analysed separately.

Group data on the above measures was collated and analysed using a standard statistical analysis software package (IBM SPSS, version 24). Analyses were carried out to review group changes over time. In addition, more detailed analyses of physiological data acquired from single lead ECG were carried out using specialised software (Kubios HRV Premium, version 3.0.0).

The key areas of information in this section with results on each area are now presented as outlined below.

- CARER REPORTS – assessed via pre-post interview questions
- PARTICIPANT SELF-REPORTS – assessed via pre-post questionnaire
- PARTICIPANT PHYSIOLOGY – assessed via pre-post ECG recording

6.2.2 *Carer Reports of Frequency of 'Meltdowns'*

Carers were asked to assess the frequency of anxiety attacks often referred to as *meltdowns* in the initial interview, and then again at a debriefing interview at the end of the study.

Reports from carers on the frequency of anxiety attacks / meltdowns were collated and then rank ordered into ordinal data with scores ranging from 1 (once per month) to 5 (daily). Four participants were excluded; one did not provide any follow-up data for analysis therefore data was included from fifteen sets of carer ratings for analysis. Carer pre-and-post reports on frequency of anxiety attacks are shown in order of recruitment in Figure 6.1.

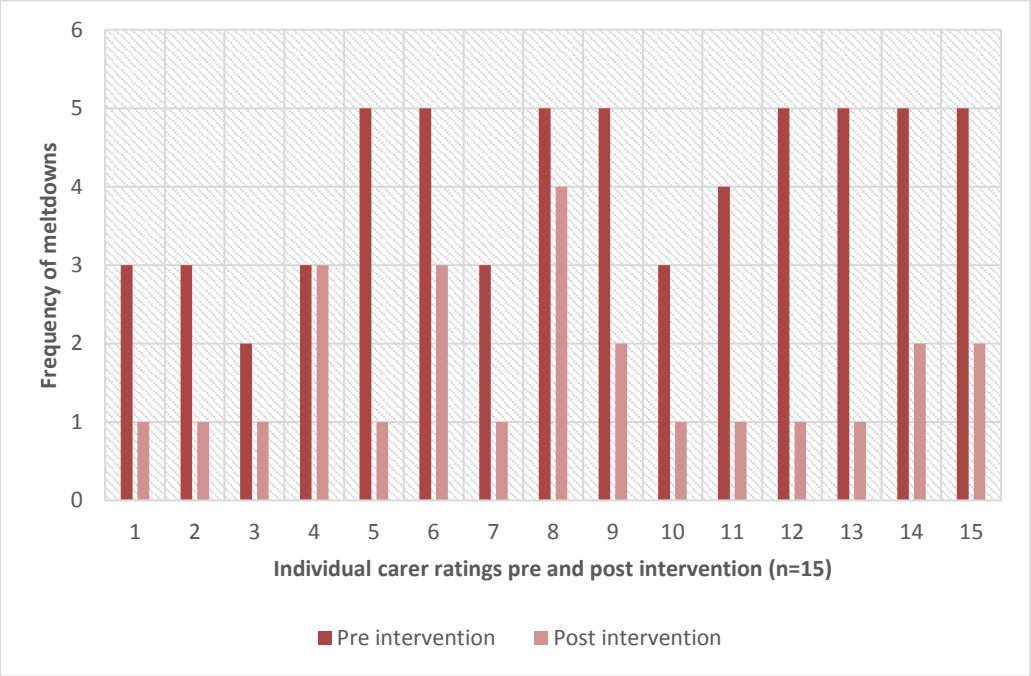


Figure 6.1 Carer ratings of frequency of participant meltdowns at initial interview (pre-intervention) and at debriefing interview (post-intervention).

Statistical analysis – Frequency of Meltdowns

Statistical analysis was carried out to assess change in reports over time. Calculations made were based on within subject comparisons. The non-parametric Wilcoxon Signed Ranks test was performed due to the use of ordinal data. Results are shown in Table 6.1, below.

Table 6.1 Results of Wilcoxon Signed Ranks Test, based on within subject comparisons of carer reports on the frequency of participant meltdowns, at initial interview and at debriefing.

Carer reports on frequency of Meltdowns (n=15)	Percentiles			Z	*p* value (2 tailed)
	25th	50th	75th	-3.33*	0.001
Initial interview	3.00	5.00	5.00		
Debriefing	1.00	1.00	2.00		

*based on positive ranks

Carers reported a significant difference in the frequency of meltdowns between the initial interview and the final debriefing interview, Z = -3.33; $p = 0.001$. Effect size calculations carried out indicated a large effect size, $r = 0.6$[5]. All scores except one (tied no change) reported lower anxiety scores at time two.

[5] *Effect size calculations for the Wilcoxon Signed Ranks test were based on paired difference values, using the formula,* $Z \div \sqrt{n(cases\ x\ 2)}$ *where n = the number of observations over the two different time points rather than the number of cases.*

Thus, the calculation using this formula was therefore $3.33 \div \sqrt{(15x2)}$ *using criteria of 0.1 = small, 0.3 = medium and 0.5 = large effect for non-parametric tests (Cohen 1988).*

6.2.3 *Sources of stress during intervention*

Participants were also asked to report directly on sources of stress for them during the intervention period, by completing online reports which were sent daily to their smartphone or PC. The online report asked for responses via smartphone to indicate one of five different sources of stress. Overall 417 reports were sent by 18 out of the 20 participants over the course of the intervention period.

The most frequent source of stress reported was a *'school problem'*, with 34% of the sample reporting this as their main source of stress. '*Home'* or '*relationship*' problems were also reported as sources of stress for participants in 18% of responses. A similar number of responses, from 18% of participant responses simply indicated *'I don't know why I am stressed'*.

Results of data collected on sources of stress during the intervention are summarised in Figure 6.2.

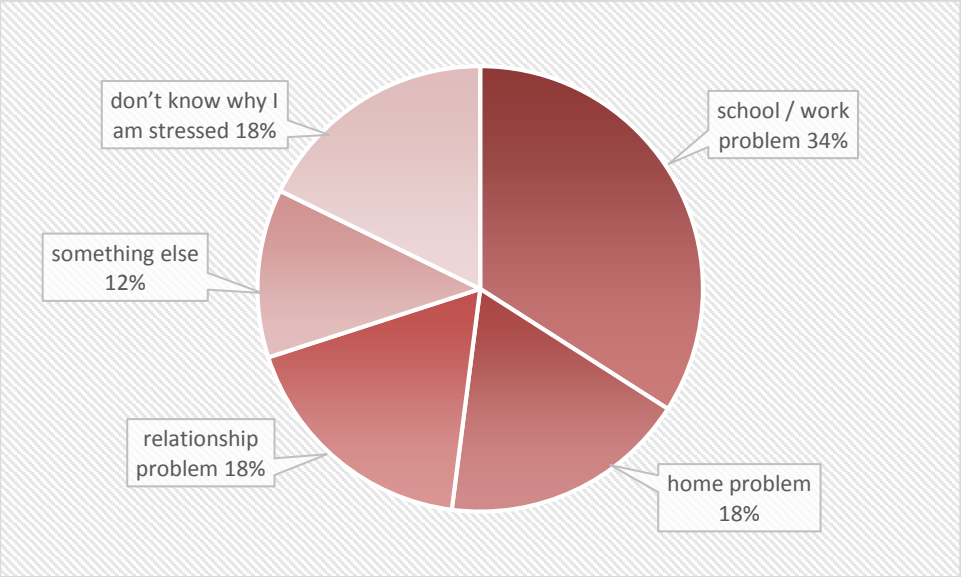


Figure 6.2 Daily sources of stress reported by participants during the intervention (n=18).

6.2.4 *Participant Questionnaire Reports – Anxiety*

Levels of anxiety reported by children and adults pre-and-post intervention are shown in order of recruitment in Figure 6.3 and Figure 6.4. Participant pre-and-post intervention scores are reported separately for children and adults due to the use of different measures.

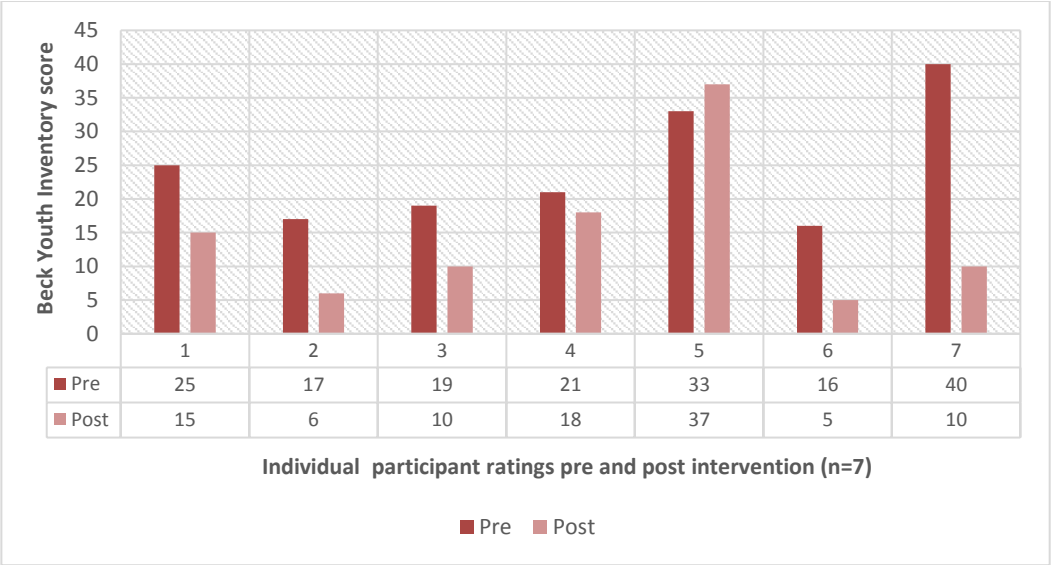


Figure 6.3 Individual ratings of anxiety from children aged 13-17 years (n=7), using the Beck Youth Inventory Anxiety Scale, pre and post intervention.

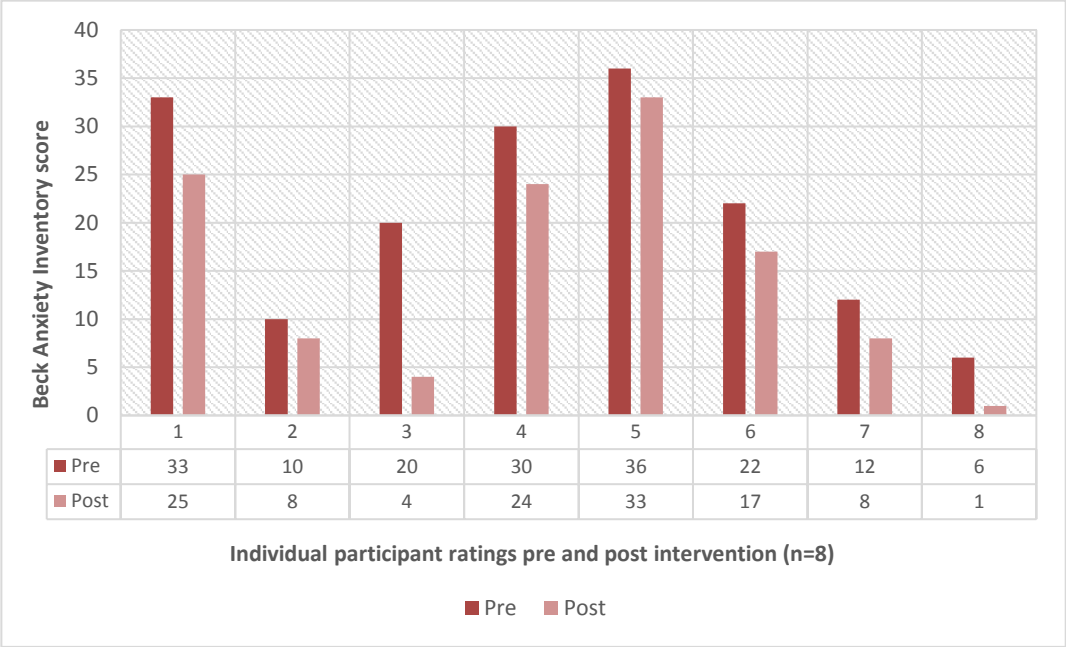


Figure 6.4 Individual ratings of anxiety from adults aged 18-24 years (n=8), using the Beck Anxiety Inventory, pre and post intervention.

Statistical analysis – Anxiety measures

Overall, 15 participants were analysed; 8 adults and 7 children. Statistical analyses were carried out to assess mean group differences in reports of anxiety from both children and adults at the beginning and at the end of the intervention. Anxiety score at baseline did not deviate from normality as indicated by both the Kolmogorov–Smirnov and Shapiro Wilks tests ($p > 0.05$). There were no extreme outlier's in observed data. One child participant showed an increase in anxiety in the post intervention score. Parametric statistical tests were conducted using Paired Sample T-tests for repeated measures. Results are summarised in Table 6.2.

Table 6.2 Paired Samples T-tests for self-reported anxiety via questionnaire from child and adult participants pre and post intervention.

Age group	Pre – intervention	Post – intervention	Mean difference	r	t score	***p*** value 2 tailed
Children (n=7)						
Mean *(SD)*	24.43 *(8.98)*	14.43 *(10.97)*	10.00 *(10.39)*	0.472	2.55	0.04
Adults (n=8)						
Mean *(SD)*	21.12 *(11.2)*	15.0 *(11.49)*	6.125 *(4.39)*	0.925	3.95	0.006

Children showed a significant difference in reports of anxiety pre and post intervention: t (6) = 2.55; $p = 0.04$; $d = 0.96$. Adults also showed a significant difference in mean scores pre and post intervention: t (7) = 3.95; p = 0.006; $d = 1.39$. Effect size calculations carried out indicated a large effect size[6].

[6] *Effect size calculations were conducted to estimate Cohen's d values using the formula* $d = \frac{m_1 - m_2}{\sqrt{{s_1}^2 + {s_2}^2 - (2rs_1s_2)}}$ *which takes into account the correlation between the two means for within subject's comparisons (Morris and DeShon 2008, p.111) and using Cohen's d standard deviation units of small 0.2; medium 0.5 and large 0.8 effect sizes (Cohen 1988, p.22).*

6.2.5 *Participant Questionnaire Reports – Depression*

Levels of depression reported by children and adults pre-and-post intervention are shown in Figure 6.5 and Figure 6.6. Participant pre-and-post intervention scores are reported separately for children and adults due to the use of different measures.

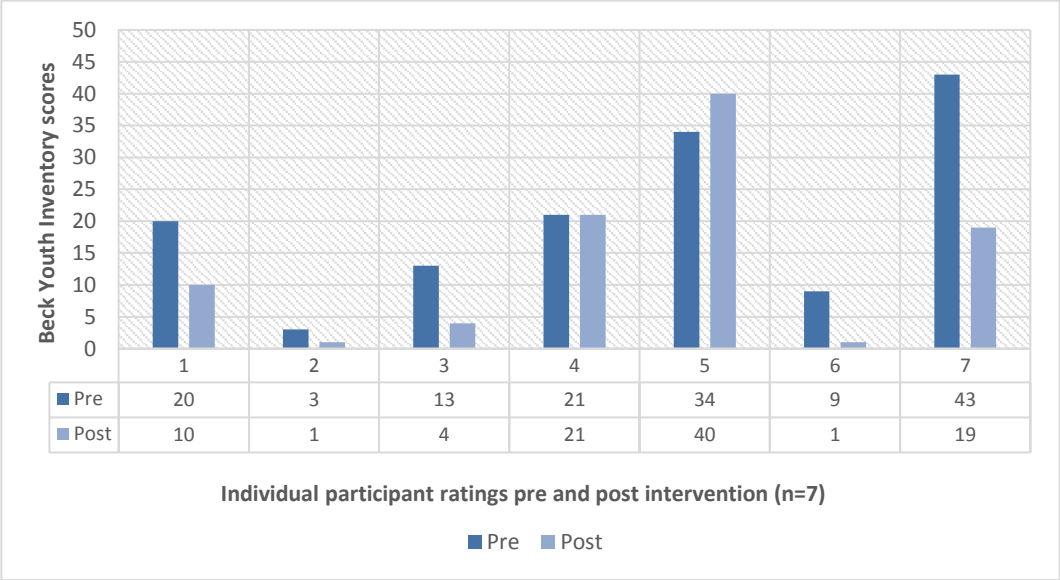


Figure 6.5 Individual ratings of depression from children aged 13-17years (n=7) using the Beck Youth Inventory Depression Scale, pre and post intervention.

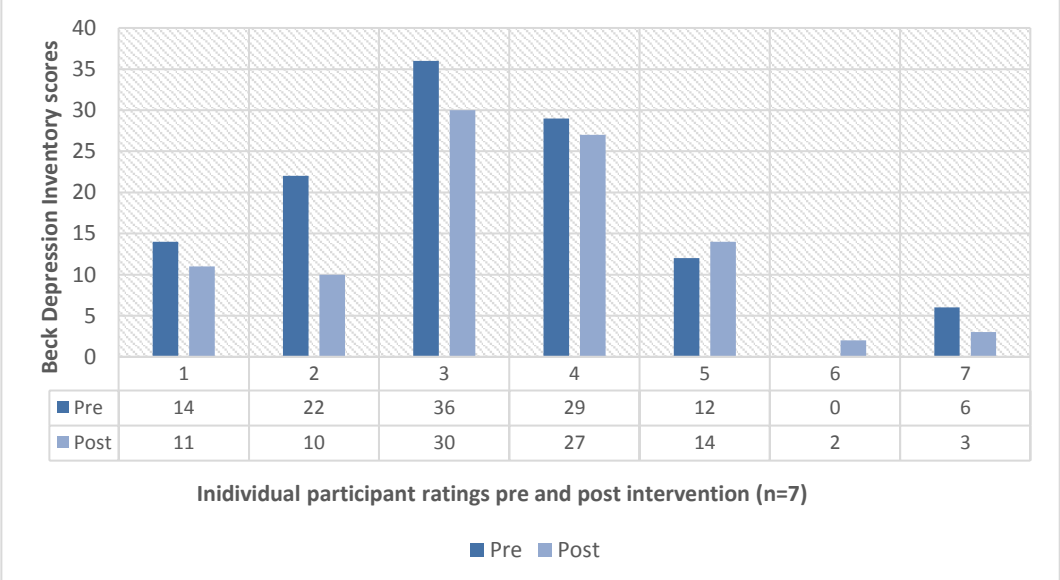


Figure 6.6 Individual ratings of depression from adults aged 18-24 years (n=7) using the Beck Depression Scale, pre and post intervention.

Statistical analysis – Depression measures

Statistical analyses were carried out on pre-and-post intervention reports of levels of depression for both adults and children using Paired Samples T-tests for single sample repeated measures. Both the Kolmogorov–Smirnov and Shapiro Wilks tests were performed which reported no significant deviations from normality ($p > 0.05$). Four participants were excluded, and one further participant dropped out and provided no further data for analysis. One adult participant did not complete depression questionnaires at the start of the intervention therefore only matched pairs from seven adults and seven child participants were analysed. Results are reported in Table 6.3.

Table 6.3 Paired Samples T-tests for self-reported depression via questionnaire from child and adult participants pre and post intervention.

Age group	Pre-intervention	Post-intervention	Mean difference	r	t score	*p* value 2 tailed
Children (n=7)						
Mean *(SD)*	20.43 *14.04)*	13.71*(14.16)*	6.71*(9.53)*	0.0772	1.86	0.11
Adults (n=7)						
Mean *(SD)*	17.0 *(12.74)*	13.86 *(10.91)*	3.14*(4.85)*	0.928	1.72	0.14

Neither children or adults showed a significant difference in depression over the 12-week intervention period. There was variability in scores at both time points suggesting more heterogeneity in depression scores.

Between group comparisons were planned to compare six weeks of intervention in the immediate group to six weeks of no intervention in the delayed group. The small sample size and dropouts from the study prevented these comparisons from being carried out.

6.2.6 *Participant Pre-Post ECG Assessment*

Participants each carried out a short 15-minute single lead ECG assessment to record resting state heart rate and HRV before and after the intervention.

Participant ECG recordings followed a set structure designed by the researcher, as outlined in Chapter 4. Each recording contained three sections. The first section allowed a baseline recording of heart rate and HRV to be acquired. The second section involved the Reading the Mind in the Eyes Test (Baron- Cohen 2001). This served as a 'stress' test for the study as it has been found to be more challenging for people with ASD compared to neurotypical peers (Baron-Cohen 2008). The third section involved watching images viewed as neutral or relaxing from the International Affective Picture System (Lang 1997;2005). This section served as a 'recovery' task to assess heart rate and HRV following the stress task.

Four participants met exclusion criteria post randomisation and therefore their data was not included for further analysis. One participant dropped out and declined the ECG recording and therefore data was unavailable for analysis. Thus, group HRV data is presented on the remaining 15 paired sets of participant data.

Baseline measurements from the initial part of the recording are reported in Chapter 5. HRV measurements are expressed in multiple formats that include time domain, frequency domain, and non-linear interpretations that provide multiple measurements in each domain. Graphical results and statistical tests are reported on heart rate and on the root mean square of successive differences (RMSSD); a commonly reported time domain measurement for short term recordings, which refers to the successive differences between adjacent normal R to R or interbeat intervals (Camm et al.1996; Shaffer and Ginsberg 2017). Heart rate values are reported in beats per minute (BPM). RMSSD is reported in measured in milliseconds (ms).

Results from participant pre and post ECG recordings are reported for both the 'stress test' and the 'recovery' task below.

Psychophysiological assessment – Stress Task

Values for heart rate and time domain HRV (RMSSD) from 15 participants during the Reading the Mind in the Eyes Test are shown in Figure 6.7 and Figure 6.8.

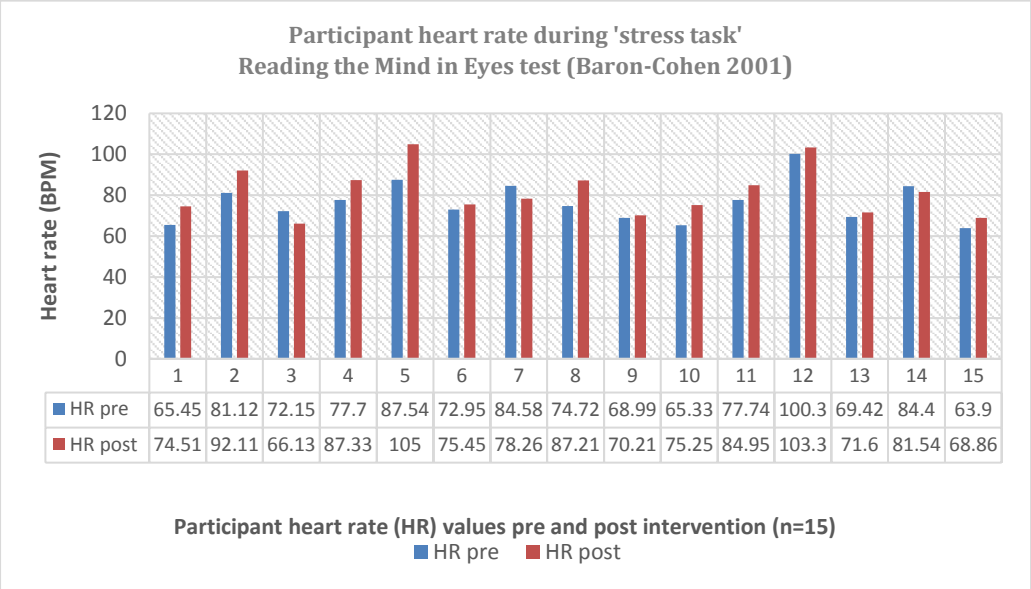


Figure 6.7 Participant Heart Rate (n=15) during 'stress test' using Reading the Mind in the Eyes Test (Baron-Cohen 2001), pre and post intervention.

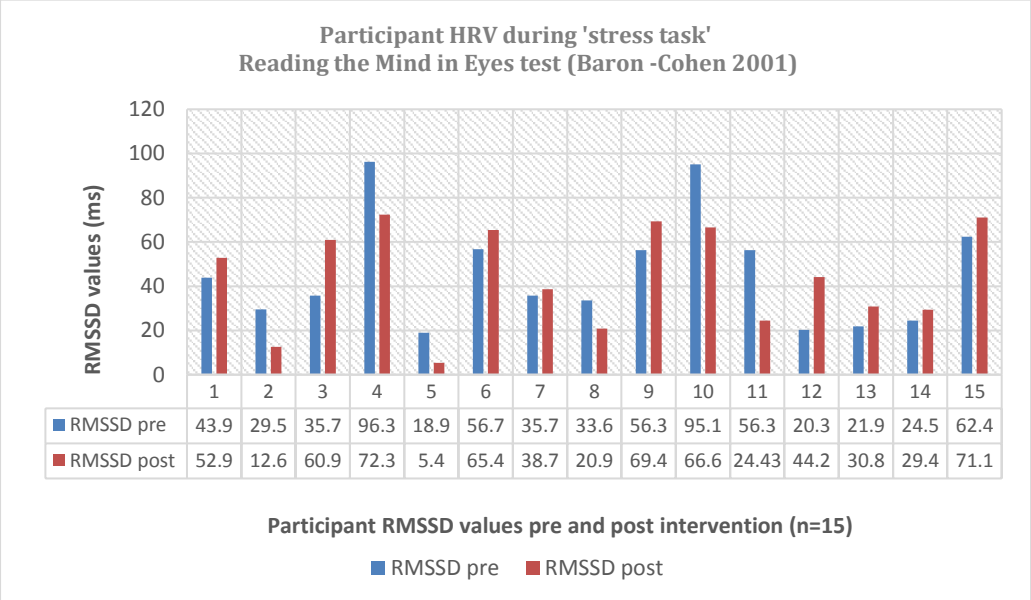


Figure 6.8 Participant HRV time domain measurements showing RMSSD values (n=15) during Reading the Mind in the Eyes Test (Baron-Cohen 2001), pre and post intervention.

Statistical analysis – Reading the Mind in the Eyes Test

Statistical analyses were carried out to assess mean group differences in both heart rate and HRV at the beginning and at the end of the intervention. One participant had unreadable recordings at the pre-intervention assessment point and data from their earlier control recording was imputed into the baseline time point for analysis. Initial tests were carried out using the Kolmogorov–Smirnov and Shapiro Wilks statistics to establish the normal distribution of scores, with both tests returning p-values > 0.05 for HR and RMSSD. Parametric statistical tests were then carried out using Paired Samples T-tests for repeated measures. Results are summarised in Table 6.4.

Table 6.4 Paired Samples T-tests for repeated measures pre and post intervention of Heart Rate and RMSSD during the Reading the Mind in the Eyes Test.

READING THE MIND IN EYES TEST	Pre – intervention	Post – intervention	r	Mean difference	t score	***p*** value 2 tailed
Heart Rate (n=15)						
Mean *(SD)*	76.42 *(9.95)*	81.45*(11.87)*	0.817	-5.03	-2.84	0.01
RMSSD (n=15)						
Mean *(SD)*	45.81*(24.81)*	44.34 *(22.87)*	0.706	1.47	0.31	0.76

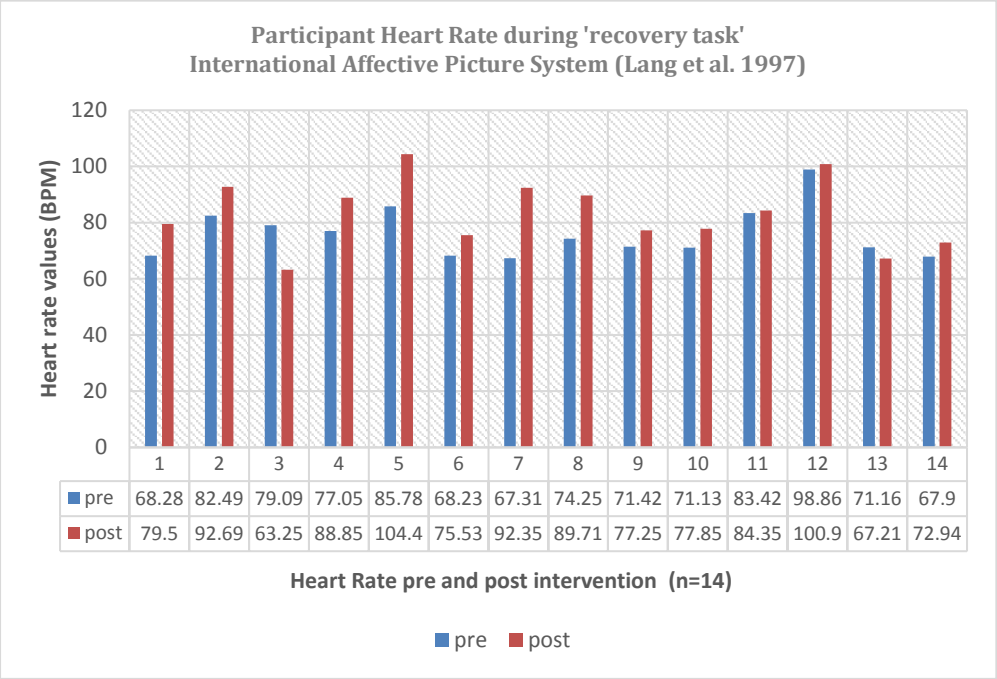
Statistical tests showed a significant difference in heart rate pre and post intervention: t (14) = -2.84; $p = 0.01$; $d = 0.73$. Effect size calculations carried out indicated a medium effect size[7].

There were no significant differences in RMSSD values pre and post intervention.

[7] *Effect size calculations were again conducted using the same formula taking into account the correlation between the two means for within subject's comparisons (Morris and DeShon 2008, p.111) and using Cohen's d standard deviation units of small 0.2; medium 0.5 and large 0.8 effect sizes (Cohen 1988, p.22).*

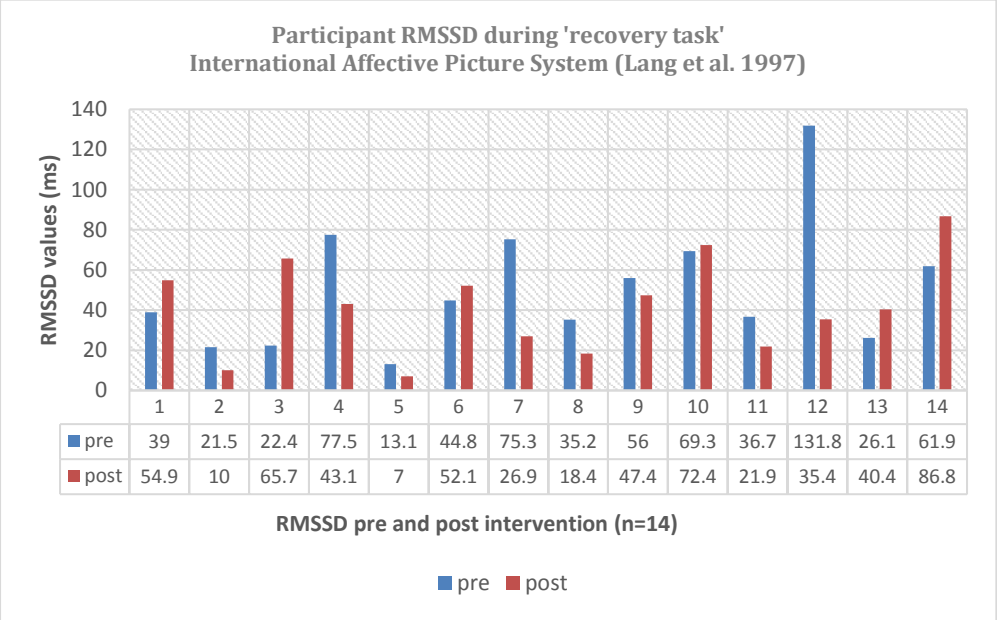
Psychophysiological assessment – Recovery task

Values for heart rate and RMSSD during the International Affective Picture System (Lang et al. 1997) '*recovery*' task are shown in Figure 6.9 and Figure 6.10.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
pre	68.28	82.49	79.09	77.05	85.78	68.23	67.31	74.25	71.42	71.13	83.42	98.86	71.16	67.9
post	79.5	92.69	63.25	88.85	104.4	75.53	92.35	89.71	77.25	77.85	84.35	100.9	67.21	72.94

Figure 6.9 Participant Heart Rate (n=14) during 'recovery' task, using International Affective Picture System (Lang et al. 1998), pre and post intervention.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
pre	39	21.5	22.4	77.5	13.1	44.8	75.3	35.2	56	69.3	36.7	131.8	26.1	61.9
post	54.9	10	65.7	43.1	7	52.1	26.9	18.4	47.4	72.4	21.9	35.4	40.4	86.8

Figure 6.10 Participant HRV time domain measurements showing RMSSD values (n=14) during recovery task using International Affective Picture System (Lang et al. 1997), pre and post intervention.

Statistical analysis – recovery task

Statistical analyses were carried out to assess mean group differences in both heart rate and HRV at the beginning and at the end of the intervention on the recovery task using the International Affective Picture System (Lang et al.1997). Initial tests were carried out using the Kolmogorov–Smirnov statistic to establish the normal distribution of scores. One participant had unreadable data from the final part of the physiological assessment and therefore only 14 sets of paired data were available for analysis. Parametric statistical tests were carried out using Paired Samples T-tests for repeated measures. Results for both heart rate and RMSSD are summarised in Table 6.5.

Table 6.5 Paired Samples T-tests for repeated measures pre and post intervention of Heart Rate and RMSSD during 'recovery task'.

RECOVERY TASK	Pre – intervention	Post – intervention	r	Mean difference	t score	***p*** 2tailed
Heart Rate (n=14)						
Mean *(SD)*	76.17 (*9.02)*	83.34 *(12.10)*	0.59	-7.17	-2.69	0.01
RMSSD (n=14)						
Mean *(SD)*	50.76*(31.23)*	41.60 *(23.65)*	0.24	9.16	0.99	0.34

Statistical tests showed a significant difference in heart rate pre and post intervention, t (13) = -2.69; $p = 0.01$; $d = 0.72$. Effect size calculations indicated a medium effect size[8]. There were no significant differences in RMSSD values pre and post intervention. Further analyses carried out on both time domain (SDNN) and frequency domain (HF-HRV; LF-HRV) variables also showed no significant differences pre and post intervention.

[8] *Effect size calculations were again conducted using the formula taking into account the correlation between the two means for within subject's comparisons (Morris and DeShon 2008, p.111) and using Cohen's d values of small 0.2; medium 0.5 and large 0.8 effect sizes (Cohen 1988, p.22).*

6.3 Research objective 3: 'Adoption of technology'

6.3.1 *Summary*

This section reports the results of information collected to evaluate the adoption and use of this technology by participants during the intervention. Information is provided on problems using the device and level of training given to participants; participant use of the biofeedback device over the intervention period, and participant reports on the usability of the biofeedback device and the ECG recorder. Reports were obtained from 18 families. All available debriefing data was included to further review information on those who had a risk identified, provided they consented to provide data.

Several different methods were used to collect data at different time points during the course of the study. These included (i) researcher records made regarding training and notes of reported problems using device; (ii) participant feedback on use of their device collected during the intervention via a daily online survey; and (iii) participant questionnaire reports on overall usability of the device taken at the end of the intervention.

Results are reported as outlined below in sections covering the initial training period; participant use of biofeedback device over the 12-week intervention period, and evaluation of usability of the equipment used in the intervention assessed at the final debriefing session.

- TRAINING and PROBLEMS USING DEVICE – assessed via researcher notes taken at start of intervention.
- USAGE OF DEVICE – assessed via participant survey during intervention.
- USABILITY OF EQUIPMENT – assessed at final debriefing interview.

6.3.2 *Problems with training in use of Biofeedback Device*

Record was made of the level of training given to each participant and any reported problems using each device. A breakdown of amount of training given to participants by type of device is shown in Figure 6.11 and Figure 6.12.

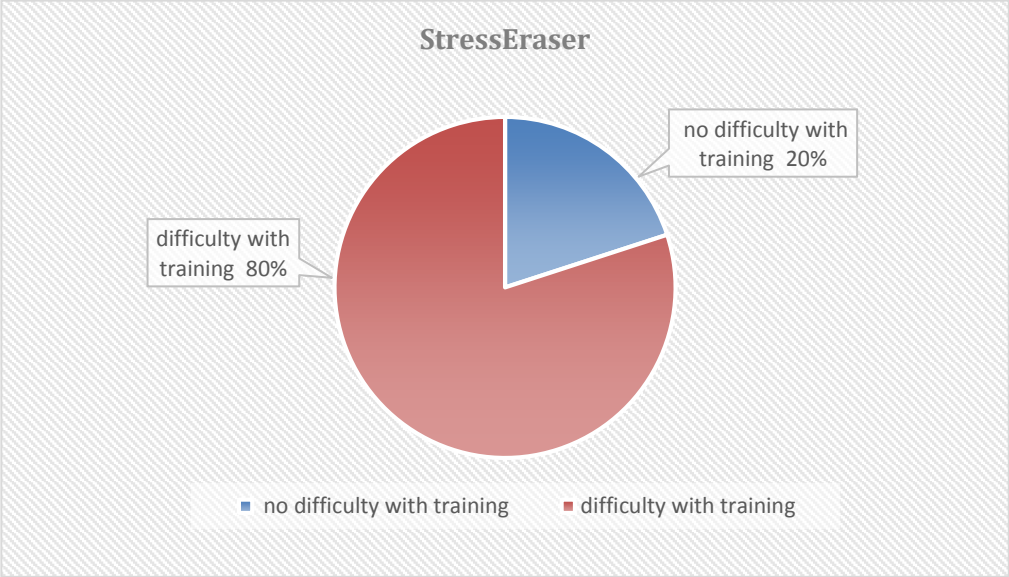


Figure 6.11 Participant reports of difficulties during training with StressEraser biofeedback device.

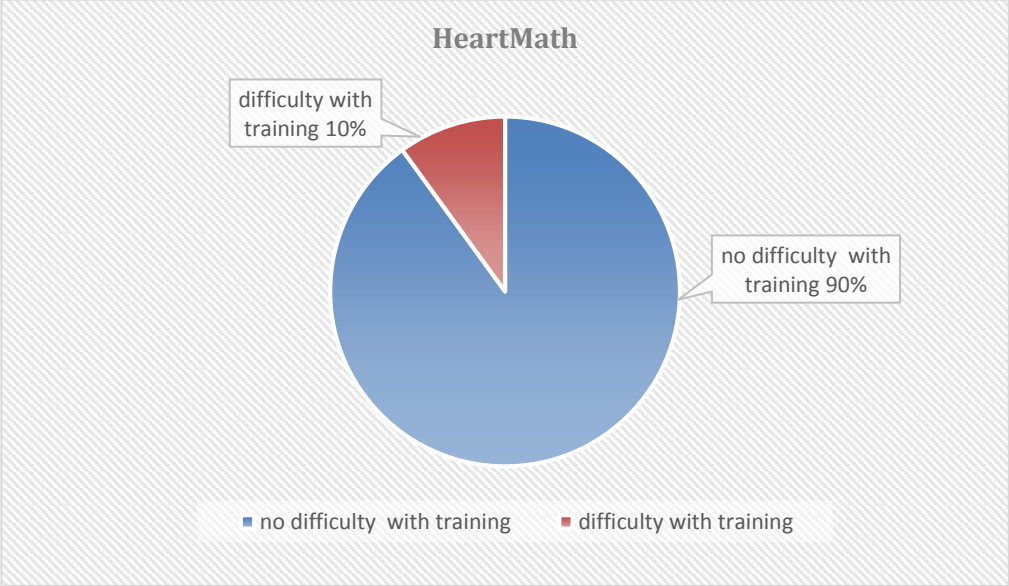


Figure 6.12 Participant reports of difficulties during training with HeartMath biofeedback device.

The initial study protocol described in Chapter 4 had planned to provide all participants with the same amount of training. However, eight out of the ten participants initially allocated to a StressEraser device reported difficulties and required two or more sessions of training. In contrast, only one of the ten participants allocated to a HeartMath device reported difficulties which required additional training. Importantly, the participants who required less training all reported positive effects.

Random allocation to devices was initially planned, however, two participants who were initially allocated to the StressEraser group experienced difficulties during training and were unable to obtain a reading from the finger sensor unable to use this device due to difficulties experienced during training.

Following the 'intention to treat' principle (Newell 1992), a decision was made to allow participants to continue in the study with an alternative device. Both of the participants who were unable to use the StressEraser expressed a desire to continue to participate in the trial and were therefore allocated to the second device group. Thus, despite an initial attempt to randomly assign participants to different devices this type of randomisation was not possible. The final allocation of devices is shown in Table 6.6.

Table 6.6 Final numbers of participants allocated to different biofeedback devices.

Type of device	Number	Percentage
StressEraser	8	*40*
HeartMath	12	*60*

Furthermore, one participant allocated to the HeartMath group had no access to phone or tablet computer and subsequently used the emWave2 device; all other participants in the HeartMath group used the Inner Balance; both HeartMath devices employed a HeartMath PPG ear sensor and employed the same underlying processing algorithms.

6.3.3 *Usage of Biofeedback Device*

Once the intervention had commenced, participants were then asked to provide information about their regular usage of the biofeedback device over the course of the intervention period.

Participants completed short online survey reports which monitored use of the biofeedback device during the intervention period. Data was included and analysed from all participants who consented to provide this information, in order to capture data from those who dropped out of the study. There was a wide range in the frequency of reporting between different individual participants, with users sending between 2 – 70 reports over the course of the study.

Participants were asked how much time they had spent using their biofeedback device. Overall, 418 reports were collected from 18 participants regarding time spent using their biofeedback devices. Results are reported in Figure 6.13.

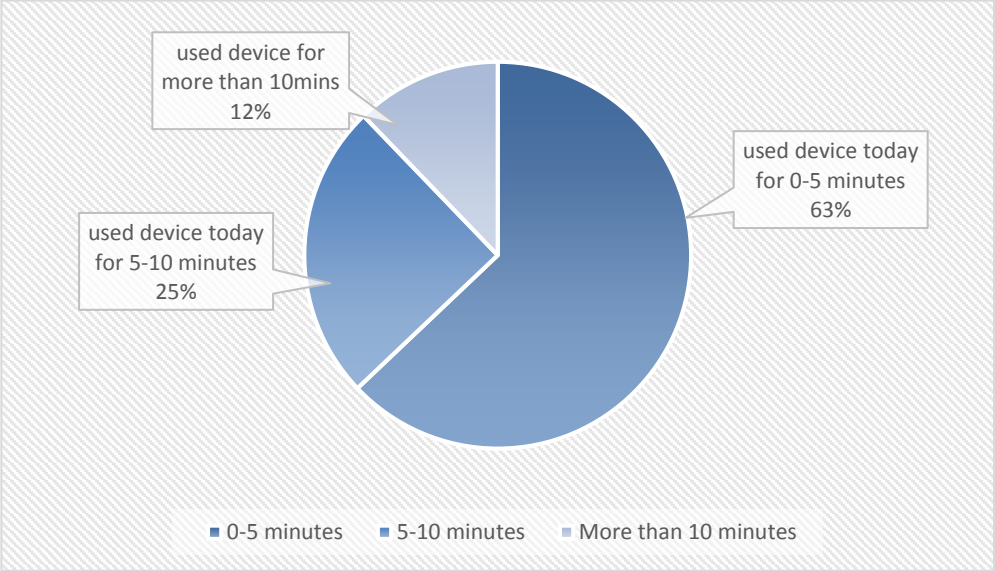


Figure 6.13 Participant reports on time spent using biofeedback device.

The majority of responses from participants indicated that the device had been used for up to five minutes with a quarter of the responses indicated use for between five to ten minutes. Overall 88% of participants reported using their device for somewhere between 0-10 minutes, with only a small minority using the device for longer than ten minutes.

6.3.4 *Reasons for not using Biofeedback Device*

Participants who hadn't used their device were also asked to report the reasons for not using the device. A summary of 145 reports provided by participants detailing reasons why the device had not been used is reported in Figure 6.14.

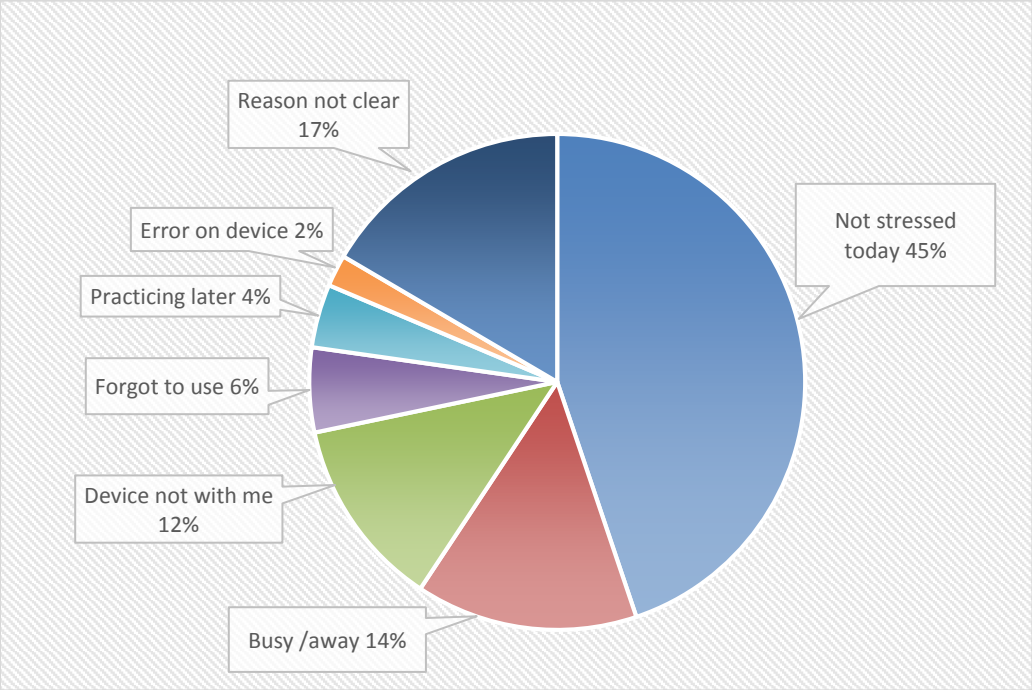


Figure 6.14 Summary of reasons for not using biofeedback device reported by participants via daily text survey.

The most frequent reason reported for not using the device was simply that the participant did not feel stressed. Other reasons reported were 'too busy' (14%); 'device not with me' (12%); 'forgot to use it' (6%); 'practicing the device later' (4%) and 'error on device' (2%). Seventeen percent of participants gave no clear reason for not using the device.

6.3.5 *Usability of Equipment*

The System Usability Scale (SUS) originally devised by Brooke (1996) was used to gather information from participants at the end of the intervention period regarding the overall usability of the biofeedback device. This 10-item questionnaire asked questions regarding ease of use, complexity of system, and amount of learning needed to use the device.

The SUS scale was also used to gather information regarding the overall usability of the Actiwave ECG recorder, which had been used for pre-post physiological recordings of heart rate variability, and the usability of the SMS text message survey used to monitor use of the device over the intervention period. Seventeen SUS reports rating the usability of biofeedback devices were provided (two participants completed ratings on both devices due to a change of device). Fifteen participants completed ratings on the Actiwave ECG recorder. Fifteen participants completed ratings on the text survey. Mean scores were then calculated to give an overall usability score for each separate type of equipment used in the study. Results are shown in Table 6.7.

Table 6.7 System Usability Scale (SUS) ratings of biofeedback devices; ECG recorder and Text survey.

Type of equipment	SUS score Mean (*SD*)	'benchmark' SUS score Mean *(SD)*
StressEraser	76.6	68 *(12.5)*
HeartMath	83.6	
Actiwave ECG recorder	70.0	
Online text survey	78.5	

The mean SUS scale score for the StressEraser was 76.6, whilst the overall mean score for HeartMath was 83.6. A review of 446 studies using the SUS has been carried out (Sauro 2011). In this review the global benchmark mean score on the SUS scale is calculated as 68, with scores above this considered to be above average (Sauro 2011, p. 54). All usability ratings indicated above average or above average mean scores for equipment and biofeedback devices used in the study. These findings provide ratings of the basic usability of the equipment involved in the study but do not elucidate potential risks or benefits, which will now be described.

6.4 Research Objective 4: What are the Risks and Benefits of using this technology with this population?

6.4.1 *Summary*

Information is now presented on risks and potential harms encountered, and on unexpected findings. In addition, information is presented on perceived benefits and problems with the intervention, from the perspectives of both participants and carers. This information was provided using qualitative data collection obtained from final debriefing interviews with carers and participants, and by reviewing data collection and procedural difficulties recorded by the researcher during the study.

Reports were obtained from 18 families. All available debriefing data was included to further review information on those who had a risk identified, provided they consented to provide data. Results are presented as summarised below.

- RISKS; POTENTIAL FOR HARM and UNEXPECTED FINDINGS – assessed via researcher records, carer and participant reports

- BENEFITS and PROBLEMS – assessed via researcher records, and debriefing reports from both participants and carers.

6.4.2 *Risks*

Risks highlighted in protocol prior to intervention.

Two main risks had been identified in the initial study protocol as potential risk areas requiring monitoring during the study. These were the potential for finding previously unknown cardiac conditions highlighted by the ECG recording, and the potential for finding a more severe mental illness in participants during the course of the intervention – see Figure 6.15.

Risks identified during intervention

Risks were identified in four participants during the course of the study. These participants were then excluded, three due to previously unidentified cardiac risks and one due to the development of a severe mental health problem.

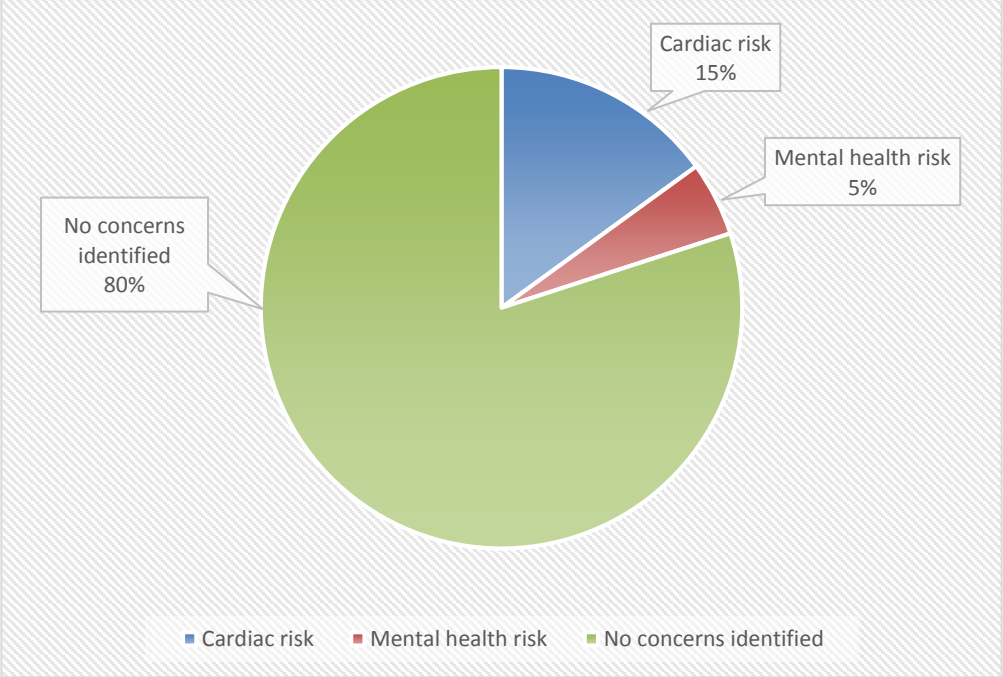


Figure 6.15 Identification of risks in participants during the course of the intervention showing 15% excluded due to cardiac risks and 5 % excluded due to mental health risks.

6.4.3 *Potential for Harm*

ECG induced anxiety

All ECG recordings were reviewed anonymously by a senior chartered cardiac physiologist. All ECG recordings were screened as being within normal limits, however a high level of precaution was adopted due to the exploratory nature of this research. Therefore, all recordings showing any unusual wave forms were recommended for further 12 lead ECG assessment, to ensure there was no risk of undetected cardiac problems. Of the 20 participants assessed, 10 were recommended for further assessment 12 lead ECG assessment. One participant was immediately identified as having cardiac problems and was then excluded from the study. Two further participants were also subsequently identified and referred to cardiologists for assessment after cardiac concerns were identified from 12 lead ECG.

There was potential for these further ECG checks to have caused undue anxiety for participants. To assess this possibility, a review of records was undertaken to check if any of the participants who had shown an increase in anxiety had also been in the group that required an additional ECG check. Demographic information and debriefing reports were also included from these participants to assess any concerns.

One case was identified that showed an increase in anxiety in the group of cases requiring further ECG checks. This participant also had difficulties with using their device, and debriefing interviews indicated concerns regarding their device rather than the ECG assessment.

Two cases also reported concerns regarding pain or itchiness during removal of electrodes, however, neither of these participants reported concerns regarding use of device or equipment or required further ECG follow-up.

Biofeedback induced anxiety

Another potential risk identified in the study protocol was the possibility of the biofeedback intervention itself causing increased anxiety. Increased anxiety was reported in several participants, and therefore notes and reports were reviewed to assess any potential links between use of device and increased anxiety.

One child participant showed increases in self-reports of anxiety and depression over the course of the intervention and reports obtained at debriefing did indicate difficulty regarding use of the device. In this case, there was evidence of biofeedback induced anxiety and potential for harm from the intervention.

One adult participant also showed increases in anxiety and depression over the intervention period, and reports at debriefing indicated some difficulties using the biofeedback device. Both of these participants were allocated to the StressEraser device.

Device records and clinical notes were also reviewed in the participant who developed severe mental health difficulties at the six weeks follow up. This participant had only practiced the device at the initial training session and had not used the device after initial training. These reports were also confirmed by review of device records which showed no further use of device. Thus, no linkage was found from records between use of the biofeedback device and the development of the mental health difficulties that led to exclusion of this participant from the study.

6.4.4 *Unexpected findings*

Cold fingers

One unexpected finding of the intervention was that many participants were found to have cold fingers during initial training. Of the ten participants initially allocated to the StressEraser, seven reported some degree of difficulty over the course of the study. Cold fingers can, in some individuals, be a sign of a shut down in peripheral circulation as a result of stress (Barlow 2006). This symptom alone, however, is not generally a cause for concern and was not reported by participants at initial recruitment as a known problem. However frequent difficulties using the finger sensor in participants allocated to the StressEraser device led to checks indicating this difficulty. This symptom was reported by two participants as the reason for not being able to use their device at all, and two further participants were only able to use their device after warming their fingers. Three further participants experienced intermittent difficulties. Participants were asked to complete the Nijmegen scale (van Doorn 1983) if they reported having any difficulty with their device. This short 16 item questionnaire looked at levels of symptoms that can be seen in individuals with chronic hyperventilation. Further assessment of this scale has indicated discriminant validity as a screening instrument for chronic hyperventilation syndrome (van Dixhoorn 1985). A sample of the Nijmegen questionnaire is presented in appendix III.

Definitive assessment of hyperventilation difficulties is only possible using capnography measurement of exhaled $C0_2$, however, authors of the scale propose that scores above 23 out of a total possible score of 64 suggest possible signs of hyperventilation syndrome (van Dixhoorn 1985). Results summarised in Table 6.8 indicate that some participants in the study who had difficulties with cold fingers may have also been experiencing symptoms of hyperventilation.

Table 6.8 Hyperventilation symptoms assessment – Nijmegen Scale.

Assessment of Hyperventilation symptoms	**Score**
Mean *(Standard Deviation)*	23.85*(10.14)*
Minimum-maximum scores *(Range)*	2.00 – 41.00 *(39)*

6.4.5 *Perceived Benefits and Difficulties with Intervention*

Reports on Effect of Biofeedback (during Intervention)

Participants were asked in the online survey during the intervention period if the device had helped when they used it. Results are reported in Figure 6.16.

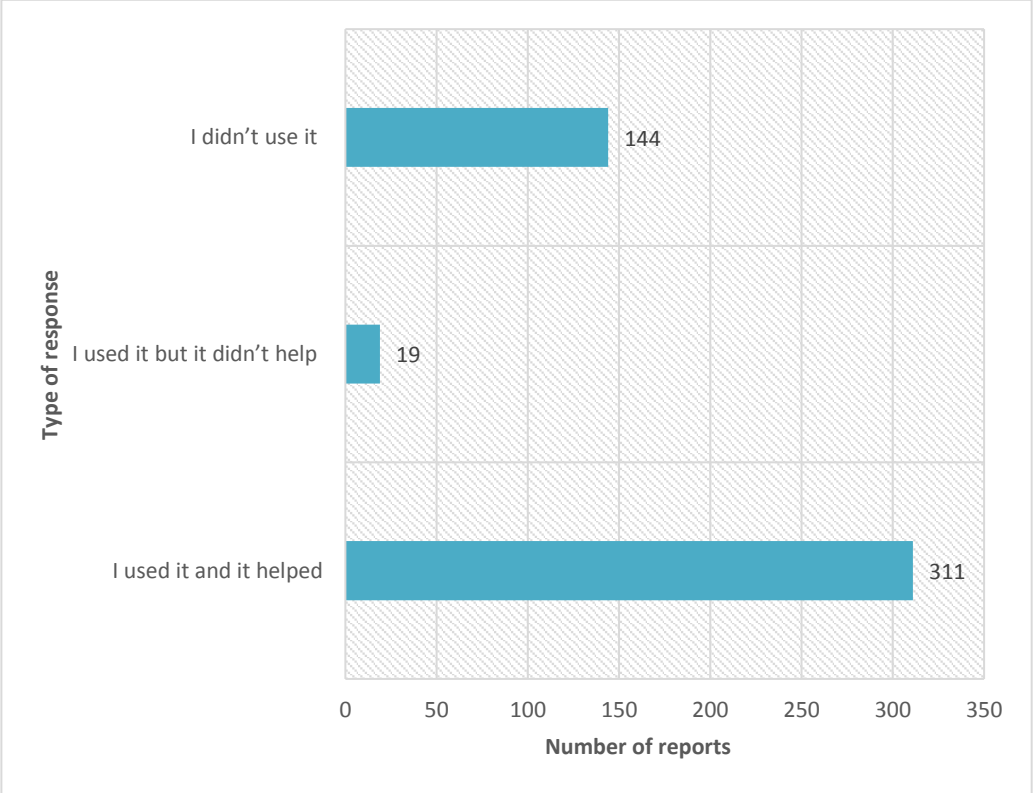


Figure 6.16 Participant reports effect of biofeedback device during intervention.

Overall 474 reports were provided from 18 participants on use of the biofeedback device and its effect. The majority of reports from over 65% of responses indicated that that the biofeedback device had been used and that *'it helped'* when used. Only 4% of questionnaire reports indicated that it *'didn't help'* when used. Thirty percent of responses from participants indicated that they had not used the device.

6.4.6 *Debriefing Reports*

In the final part of the study, participants and carers were both asked to give brief written comments on their experiences, both positive and negative at the final debriefing. Samples of debriefing reports are shown in appendix III. Reports obtained from eighteen participants, on problems with the intervention is shown in Figure 6.17.

Participant Reports of Problems

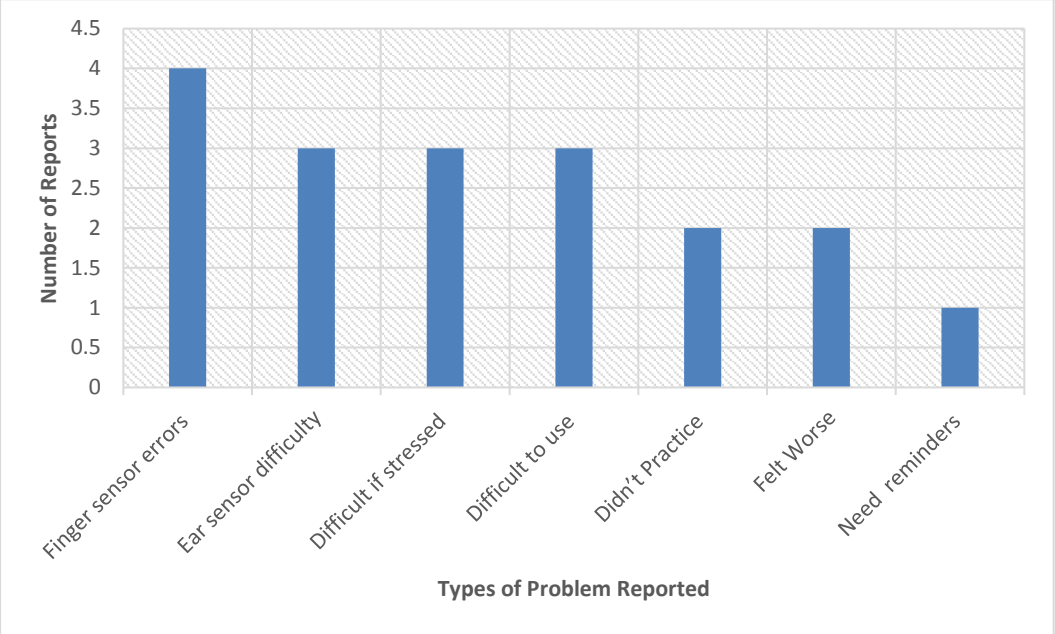


Figure 6.17 Problems reported by participants at debriefing.

A sample of direct quotes from participants is reported below; full results are reported in appendix V.

"the first device made me more stressed ...errors because my hands so cold"

"ear clip kept slipping hard to get pulse awkward on the finger and on the ear"

"didn't work if extreme stress… too difficult to use"

"don't remember to use it... I didn't use it when stressed"

"hard to get smooth waves …

didn't practice it… couldn't get a lot of points"

"need to set precise times for practice"

"caused increased stress as couldn't get points"

Participant Reports of Benefits

Reports obtained from 18 participants, on positive experiences or perceived benefits of the intervention are shown in Figure 6.18.

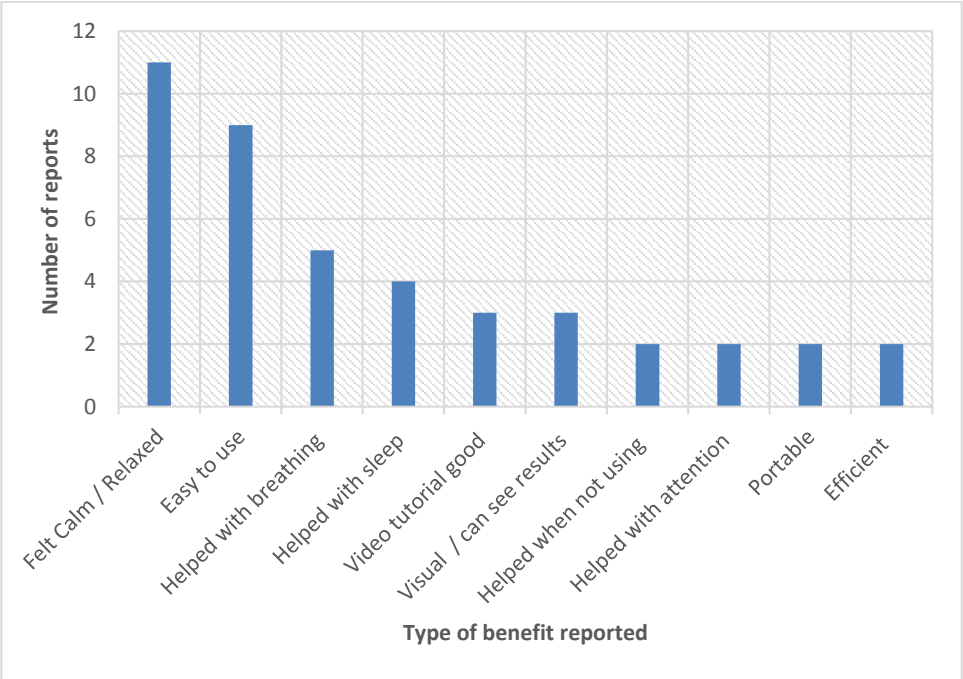


Figure 6.18 Benefits of biofeedback intervention reported by participants at debriefing.

A sample of direct participant quotes regarding positive experiences / benefits is reported below, full results are reported in appendix V.

"used after stressful day and helped … helped when people were annoying me"

"the information presented was calming allowed for me to collect my thoughts"

"it helped me sleep every time I used it… it helped with my problems"

"easy to use / comfortable / look like earphones. comfortable using it in public"

"visuals good / if stressed used it and helped / helps get to sleep at night "

"used same breathing but without device when in bed as don't want to get up"

"will continue… helped focus"

"showed my heart rate / it gave me a rating / has helped me control anxiety"

"I felt better / excellent and simple to use"

"it helped me be happier"

Carer Reports of Problems

Carers were also asked to review the intervention at the final debriefing interview. Carer descriptions of 'main problems', 'triggers for anxiety' and 'obstacles to managing anxiety' remained the same. However, as reported earlier many carers did report a reduction in the frequency of anxiety attacks / meltdowns (see page 155). Carers were also then asked to give asked to give brief written comments on any perceived benefits or problems encountered during the intervention. Reports from carers are summarised in Figure 6.19.

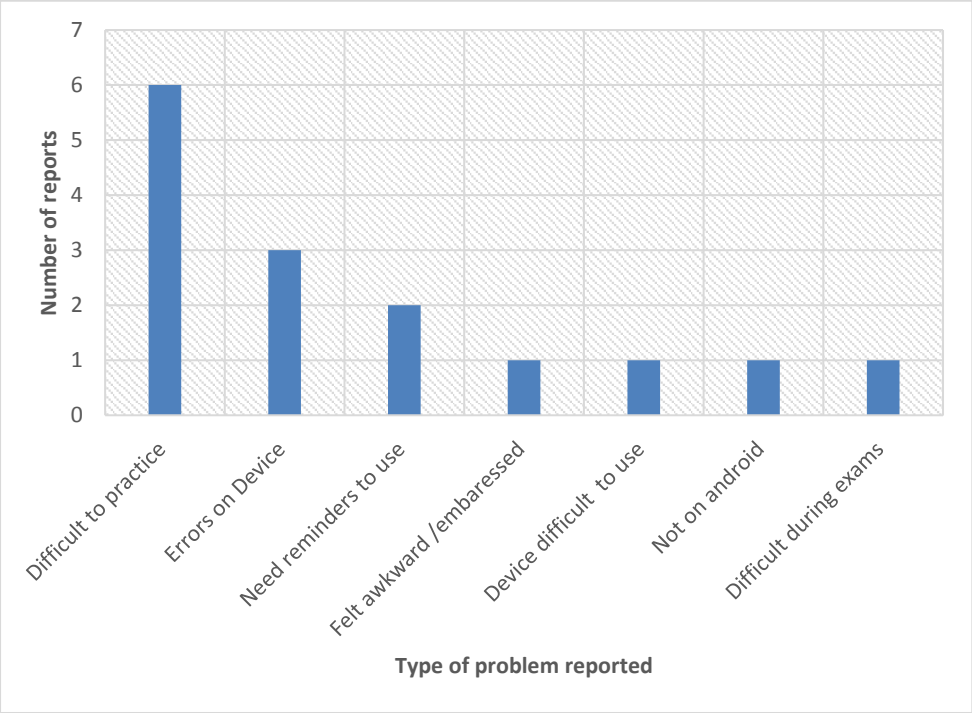


Figure 6.19 Problems with biofeedback intervention reported by carers at debriefing.

A sample of direct quotes s from carers is reported below, full results are reported in appendix V.

"problems with errors if fingers cold"

"prompts to use it would be good "

"hard to remember to use it every day"

"… felt self-conscious using it in public"

"not compatible with android devices"

"would have benefitted if started at a less stressful time"

Carer Reports of Benefits

Reports from carers on perceived benefits or positive experiences were collated and summarised. Results are reported in Figure 6.20.

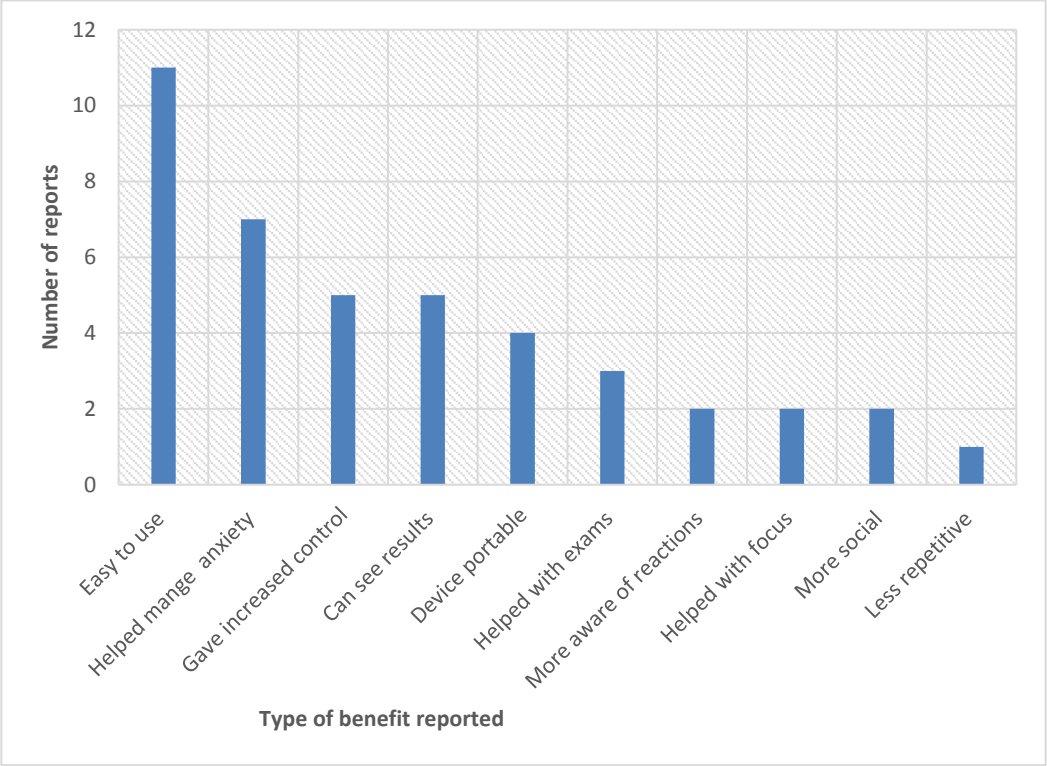


Figure 6.20 Benefits of biofeedback intervention reported by carers at debriefing.

A sample of direct quotes from carers on the positive effects of the intervention are outlined below, full results are reported in appendix V.

"easy to understand and use / good because visual / sound can be controlled"

"… was good on the phone / could take it everywhere"

"helped … calm down before going to …

"especially good at decreasing stress for exams"

"being able to see effect of your breathing … helped learn to control breathing"

"giving more control to person directly / visual /

"something to focus on"

"simple to use"

Additional reports from researcher records

Participants and carers were asked whether they had any additional concerns or whether they needed any follow up support. None of the participants or carers reported concerns regarding the intervention, however, three families requested further information regarding other support services available.

Some participants also commented further during debriefing on their stress levels and reasons for wanting to participate in the study. Examples of quotes from participants are listed below,

> ***"I get frustrated when people don't understand me and won't listen to … what I need"***
>
> ***"I wanted to do the research project to understand my anxiety more and see if biofeedback would help me more"***
>
> ***"I took on this program because I felt like it will help my problems"***

Some carers also commented further during debriefing on reasons for wanting to participate in the study and the intervention itself. Examples of quotes from carers are listed below,

> ***"… could monitor his own progress which was great"***
>
> ***"no major meltdowns despite some very difficult exams"***
>
> ***"very visual instant feedback that was easy to understand"***

Several unexpected changes reported by some carers were increases in participant's awareness of the physical symptoms of stress and ability to generalize the breathing and use it without the device and reports of increased confidence and social skills.

> ***"real benefits in helping develop awareness of physical symptoms / increased ability to identify patterns as they developed"***
>
> ***"… increased ability to anticipate and take greater control managing anxiety"***
>
> ***"better at socialising and teacher has noticed also / more smiles and eye contact"***
>
> ***"…really helped with confidence"***

6.5 Integration of findings

6.5.1 *Demographic and physiological variables*

In order to review associations between some of the different types of data collected, correlations between initial baseline data and ECG data were carried out.

Thus, Pearson Bivariate correlations were conducted to compare physiological variables measured at the initial pre-intervention assessment with age, ASD and sensory symptoms. Similar correlations were also conducted to compare age, ASD and sensory symptoms with final post intervention physiological variables. Results are reported in Table 6.9 and Table 6.10.

Table 6.9 shows that at the initial assessment, participant age was significantly correlated with sensory (Low registration) symptoms ($p < 0.01$) and with HRV variables ($p < 0.05$). HRV variables were also strongly correlated with one another ($p < 0.01$) and negatively correlated with heart rate ($p < 0.05$). ASD symptoms were positively correlated with heart rate ($p < 0.05$).

Table 6.10 shows ASD symptoms, as measured by the SCQ, were negatively correlated with HRV variables recorded at the final assessment ($p < 0.05$). ASD symptoms, were also positively correlated with heart rate recorded at the final assessment ($p < 0.05$). HRV variables were also significantly correlated with one another ($p < 0.01$), and negatively correlated with heart rate.

Table 6.9 Pearson correlation statistics at initial assessment between physiological measures recorded during Reading the Mind in Eyes Test (Baron-Cohen 2001) with participant age; sensory symptoms and level of ASD symptoms.

Pre-intervention								
		Age	**ASD**	**Sensory**	**HFHRV**	**RMSSD**	**SDNN**	**Heart Rate**
Age	Pearson Correlation	1	-0.250	0.647**	-0.580*	-0.596*	-0.548*	-0.012
ASD	Pearson Correlation		1	0.088	-0.221	-0.134	-0.184	0.541*
Sensory (low registration)	Pearson Correlation			1	-0.291	-0.288	-0.119	-0.158
HFHRV	Pearson Correlation				1	0.929*	0.902**	-0.562*
RMSSD	Pearson Correlation					1	0.946**	-0.514*
SDNN	Pearson Correlation						1	-0.465
HR	Pearson Correlation							1

** Correlation is significant at the 0.01 level * correlation is significant at the 0.05 level (2-tailed).

Table 6.10 Correlations between physiological measures recorded at final assessment during the Reading the Mind in Eyes Test (Barn-Cohen 2001), with participant age and level of ASD symptoms.

Post intervention								
		Age	**ASD**	**Sensory**	**HFHRV**	**RMSSD**	**SDNN**	**Heart Rate**
Age	Pearson Correlation	1	-0.250	0.647**	-0.250	-0.381	-0.522*	-0.062
ASD	Pearson Correlation		1	0.088	-0.557**	-0.442*	-0.504*	0.743*
Sensory (low registration)	Pearson Correlation			1	-0.181	-0.023	-0.142	-0.118
HFHRV	Pearson Correlation				1	0.892**	0.905**	-0.733**
RMSSD	Pearson Correlation					1	0.897**	-0.467*
SDNN	Pearson Correlation						1	-0.694**
HR	Pearson Correlation							1

** Correlation is significant at the 0.01 level * correlation is significant at the 0.05 level (2-tailed).

6.5.2 *Summary of findings*

This chapter has described findings from three separate research objectives and involved reporting of pre and post changes in participants; reporting on usage of the device over the intervention period; a review of risks, unexpected consequences and any problems or benefits reported at the end of the intervention.

Research objective 2: Pre-post data collection

- Participants reported a reduction in anxiety over the course of the intervention, whilst carers reported a reduction in participant *meltdowns*.
- There was no significant change in measures of depression in either the adult or the child group, over the intervention period.
- Physiological assessment highlighted an increase in heart rate but found no clear change in the HRV measures analysed during physiological assessment at the end of the intervention, compared to initial assessment.

Research objective 3: Adoption of technology

- Whilst most participants used the device for short periods (0-5 minutes), the majority of participants (65%) reported the device helped when they used it.
- Differences were also noted between the two different devices used, with the StressEraser device being prone to sensor error.

Research objective 4: Risks and benefits

- Risks relating to unidentified cardiac and mental health concerns were identified in four participants. The possibility of the intervention itself inducing anxiety was identified in two participants.
- Unexpected findings were that seven out of ten participants using the StressEraser had cold fingers which led to difficulties using the device. The number of participants requiring input from cardiology was also unexpected.
- Debriefing reports obtained at the end of the intervention indicated a range of benefits and difficulties with the intervention with similar issues being highlighted by both participants and carers.

The results presented above will now be discussed in more detail in Chapter 7.

Chapter 7. Discussion

7.1 Overview

This thesis reports on a 'proof of concept' study which aimed to answer two questions. First, '*Can people with ASD use portable HRV biofeedback devices?*' and second, '*Does use of these devices help to manage anxiety in people with ASD?*'

This chapter aims to answer these questions by discussing the main findings from the pilot study undertaken. First, the chapter reviews the limitations with the design, methods and procedure, and highlights confounding variables which may have affected the results. Second, the overall aim and objectives are restated, and the importance of the study findings is critiqued, in light of what is already known within the research literature about ASD, anxiety and HRV. Potential explanations for the positive and negative results are considered by interpreting these findings with reference to current research and theory.

Finally, the strengths of the current study and how it has moved forward knowledge in this area are considered. Chapter 8 will then address potential solutions to some of the problems highlighted within the current study, with an aim to address the final research objective (Objective 5), to *'develop recommendations for the use of this intervention in future studies.'*

7.2 Study limitations

7.2.1 *Ethical considerations*

There were a number of ethical considerations which affected the overall study design. The study involved assessment of a vulnerable clinical population who have by definition intrinsic social and communication difficulties and who also may have poor insight into their stress levels and mental health.

The need to protect patient confidentiality led to ethical permission for access to medical records not being sought which could have added important demographic information, regarding developmental history; diagnostic assessments and medical information on those who were referred on for further ECG.

In addition, when a number of participants requested to not have further training sessions this information was recorded and was respected. In the same manner, when two participants reported that that they could not use a device, but wanted to continue in the study, this request was accommodated at the expense of formally conducting a randomised controlled design.

7.2.2 *Bias and independence*

The study was conducted by one investigator who carried out all assessment; training; data collection; data inputting, and the majority of data analysis. Attempts were made to introduce blinding and independence into as many aspects of the study as possible as outlined in Chapter 4, however, it is possible that unconscious bias regarding the study aims and objectives may have affected some of the findings.

It is possible that unconscious bias may have occurred within carer interviews and participant reports due to a wish for the treatment to succeed. However, it is of note that several carers reported that the device did not help their child despite initial hopes that it would be beneficial, and that these carer reports were in concordance with participant reports.

7.2.3 *Study design*

Participants were randomised into immediate and delayed groups, and this study design meant that all participants eventually received an intervention. The increased wait in the delayed group may have increased expectations which could have affected reports on questionnaires and possibly internal physiology as well. Participants who were randomised into the delayed group were given the same number of assessments to ensure there was no increased burden of participation in this group, however this compromised the number of comparisons that could be made at similar time points.

Due to the limited sample size, it was not then possible to carry out one of the key statistical tests planned which would have enabled comparisons to be made between six weeks of intervention in the immediate group, to six weeks of no intervention in the delayed intervention group.

The study design also meant that participants in the delayed group had already had experience of assessment when they were assessed a second time at the beginning of the intervention. This difference means that there may have been an effect on participants in the delayed group which was simply related to assessment, sometimes termed the 'Hawthorne' effect (McCambridge 2014).

7.2.4 *Recruitment and selection of sample*

A key limitation in this study was the small sample size. Initial estimates involved recruiting 50 participants, to enable at least 10 participants to be recruited into each subgroup. However, early recruitment issues with adults, combined with limited time and researcher capacity, meant that only 20 participants were recruited.

The difficulty recruiting adults may indicate potential for problems with future studies; however, two issues are important which may have affected recruitment. First, the sample of adults was limited to a narrow range between 18 to 24 years. Employing a wider age range may have resulted in increased recruitment.

Reports from the adult ASD team at the end of the study did suggest that recruitment of older adults would have been possible, and that the age range chosen may be one where young adults are reluctant to attend services. Second, it was of note that all initial contact with the researcher was made by parents irrespective of whether participants were adults or children. Whilst all participants involved did give clear assent and consent, it may have been difficult for some young adults with ASD to make initial contact with the researcher to discuss the study because of their social and communication difficulties.

7.2.5 *Equipment*

One of the limitations in this study relates to the use of physiological assessment equipment. The initial study had been designed to utilise one of the large-scale professional biofeedback systems advocated by certified biofeedback practitioners. This type of system can be used to conduct pre-post multi modal 'psychophysiological stress profiles', assessing a number of physiological variables.

However, initial equipment feedback by stakeholders suggested that this type of assessment using multiple sensors could be too anxiety provoking, which led to the adoption of single lead ECG recorder, already used with people with ASD. This device was indeed found to be acceptable by participants, as seen in the usability scale ratings from participants, however, this was at the expense of collecting fewer physiological measures.

Importantly, the single lead ECG provided less comprehensive information on ECG waveform characteristics and the subsequent interpretation of anonymised single lead ECG recordings by the cardiac physiologist, resulted in repeat 12 lead ECG being requested in 10 out of the 20 participants to confirm normality of ECG waveforms. Three participants from this group were subsequently identified as having cardiac concerns which required further follow-up. Thus, whilst this device did detect difficulties the less comprehensive reading from a single lead ECG recorder entailed further unwarranted investigation for seven participants.

7.2.6 *Measures*

The methodology chosen for collection measurement and analysis of data in the study was predominantly quantitative rather than qualitative. It is acknowledged that detailed case study analysis could have been carried out if a different methodology had been chosen. Further case study analysis was not possible in this study due to the methods chosen to collect data and the level of ethical permission requested for more detailed information regarding cases to be collected. Future studies could employ case study methodology to detail further the individual case stories of participants. This type of design and methodology might further elucidate the reasons for some participants dropping out and provide examples of how this intervention was used in real world situations. It could potentially also highlight how individuals practiced and incorporated use of this intervention into their daily lifestyle and routines.

The current study used separate questionnaire measures for child and adult groups to assess anxiety and depression. The Beck adult scales were reviewed by people with ASD and deemed to be suitable, however, a decision was made by the researcher not to use these scales for the child group and to instead use the child and adolescent Beck scales. This was influenced by the question relating to sexual functioning in the adult scale, which was felt to be inappropriate for children. In addition, the Beck Youth scales report that the language in these scales is more suitable for children.

However, an accepted limitation of this change meant that the participants who completed the study could not be compared as one overall group when assessing theses variables and mean scores for anxiety and depression had to therefore be divided into two separate smaller groups. This decision to prioritise a clinical decision, over a research-based decision which would have provided a larger unified group of data, is an accepted limitation of the study.

7.2.7 *Usage of biofeedback devices*

A further important area not addressed by this study is the need to accurately capture and record data from the biofeedback devices, used by participants. In this study, ethical and clinical decisions were again made which compromised the level of detail in the collection of participant data, in favour of protecting participant information.

Thus, participants using HeartMath devices could have uploaded their data onto a cloud-based server managed by the parent company, however, as this server was located outside of the UK it could have been vulnerable to foreign laws surrounding privacy and, therefore, the confidentiality of data uploaded could not be guaranteed.

A compromise was to, therefore, to record screen shots of sample recordings of data from participant devices data, which were then used to check participant usage rather than to measure progress.

7.2.8 *Training*

One further difficulty which may have confounded results was the variation in training given to participants as the amount of training time requested by some participants was much less than the time that had been allocated in the study design.

Biofeedback can only work effectively if the user understands and adheres to instructions in its use (Pastor 2008). Concerted attempts were made by the researcher to ensure fidelity of training offered by giving all participants the same instructions from the researcher regarding breathing, and by offering two 60-minute individual training sessions to each participant.

Despite this, there was a variation in the amount of training given in this study, as several participants declined the second training session offered, reporting that they already knew what to do. These participants all used the Inner Balance device from HeartMath and were able to quickly establish slow breathing which presented as '*coherence*' on the device.

The variation in training time constitutes an issue with intervention fidelity, in that not all participants received the same amount of training time in use of the device. However, a review of participant training records indicated that importantly, participants who required less training all reported positive effects. Results therefore did not suggest that lack of training was a factor in participants reporting problems; in fact, the converse was true, in that participants requiring extra training sessions all reported difficulties using the device and increased anxiety and depression.

7.2.9 *HRV assessment*

Despite attempts to standardise the HRV assessment process, several limitations were noted. One clear limitation in the assessment process was the variation in environments, due to the decision to carry out home based assessments. Whilst attempts were made to standardise the assessment as much as possible, factors such as ensuring bladder emptying; no prior caffeine intake; recording height and weight, were not all taken into account. In addition, whilst time of day was controlled within each participant assessment, the time of assessment was not consistent between participants.

The use of a mean score for 13-24 olds for resting HRV is acknowledged as a limitation of the study. Comparisons were not made with the study on 6-8-year-old children as there was inadequate information available from these norms. The two adult reference studies used provided similar measurement scores which could be compared to the current sample. In addition, it was felt that the 13-24-year sample would be more similar to adult norms, than the 6-8-year-old sample. However, it is recognised that the age range for the current sample of 13-24-year olds was compared to reference studies on adults and the natural variation in resting HRV due to age presents a confounding factor which would have affected interpretation of resting HRV scores for this younger sample.

7.3 Review of aim and objectives

The overall study aim was to investigate the use of HRV biofeedback in people with ASD. This was achieved by addressing the following objectives:

1. *To provide a home based HRV biofeedback intervention to people with ASD.*
2. *To assess anxiety, depression and physiological arousal before and after using a biofeedback device.*
3. *To assess usage of the HRV biofeedback technology.*
4. *To evaluate the risks benefits and acceptability of this technology.*
5. *To develop initial recommendations on the further use of HRV biofeedback for people with ASD.*

Detailed information was acquired on a small sample of young people with ASD, on both demographic characteristics and on a number of outcome indicators. The specific research objectives of providing a home-based intervention and assessing anxiety; depression and physiology were achieved. Usability of the technology was measured in this pilot, and the potential benefits and risks of HRV biofeedback were evaluated.

Despite a range of limitations, the overall aim of the study, to carry out an investigation into the use of HRV biofeedback in people with ASD, was achieved. To understand and interpret the meaning of study findings, it is essential to place them in the context of research literature. Therefore, the study results are discussed in these subsequent sections taking into account the relevant theory on ASD, anxiety, and HRV and by considering the context of ongoing developments involving HRV biofeedback.

7.4 Interpretation of findings

7.4.1 *Demographic information*

The initial demographic information reported by participants and their carers does suggest that this was a representative sample of young people with ASD. For example, the gender ratio of 4:1 male to female in this sample mirrors that reported by other studies (Waugh 2017).

Demographic reports obtained indicated both high levels of screen time and low levels of physical activity in this sample, compared to nationally recommended guidelines (DiSantis *et al.*, 2013). These behaviours have been linked to increased risk of cardiovascular events in adults (Stamatakis *et al*.2011), and also to lower academic performance in children and teenagers (Corder *et al.*2015).

High levels of gaming-based screen time have also been associated with internalising mental health problems such as anxiety (Lobel *et al*.2017). Teenagers with ASD have also been reported to show significantly higher obesity levels than other developmental disorders (Philips *et al.*2014), and the low levels of physical activity reported in this sample may highlight one of the possible risk factors for this problem.

Reporting of the demographic information from the initial sample recruited rather than the final sample who completed the study is seen as a potential limitiation of the study. Demographic information from the three participants who dropped out of the study did not show clear group differences from the initial sample of participants recruited and no consistent reason for drop-out. However, this was a small pilot sample and any future study larger scale study should collect further data on the characteristics of those who dropped out and reasons for drop-out. Future studies should report on both the initial sample recruited and the final sample who completed the study.

Overall, the information from demographic reports portrays a picture of a sample of participants typical of young people with ASD, with a number of important risk factors for possible future mental and physical health difficulties.

7.4.2 *Participant reports*

The direct reports from participants suggest that there was a reduction in anxiety over time in the direction predicted by the research hypothesis. This finding suggests there may be a positive effect of HRV biofeedback in self-reported anxiety in young people with ASD. This finding reflects similar outcomes which have been reported in studies of clinical populations (Reiner 2008); young people with anxiety (Ratanasiripong 2012) and findings from the systematic review and meta-analysis which indicated an overall positive effect of HRV biofeedback (Goessl *et al*. 2017). It is important to note, however, that reductions in self-reported anxiety do not explain the underlying mechanism of effect produced.

It is also possible that the presence of the researcher simply carrying out assessments may have of itself caused a reduction in anxiety, an effect described as 'the Hawthorne effect' (McCambridge 2014).

The small sample size in this study was a limitation which prevented important between group comparisons from being carried out to assess whether this change would have happened over time without any intervention being provided.

There were no significant changes in reports of depression on questionnaire reports. Depression was measured in this study primarily to monitor risk. Whilst depression and anxiety are often noted together in the same individual (Ghaziuddin 2005) it may be that the depression symptoms reported relate to signs of a more pervasive and intractable condition, which is less subject to change over a 12-week period.

7.4.3 *Carer reports*

The frequency of participant *meltdowns* reported by carers did show a change which was statistically significant and was in the direction predicted by the research hypothesis. This finding may also indicate a positive effect of biofeedback, and whilst this data does not elucidate the mechanism behind any reported changes, it draws attention to potential for an important area of behaviour change which is particularly relevant for people with ASD (Lipsky 2011).

However, changes reported by carers regarding the frequency of participant meltdowns may have been influenced by other external factors not related to biofeedback. Thus, the range of external triggers for meltdowns reported by carers such as increased workload; holidays; separation from parents may have changed over time irrespective of any intervention and may have affected these reports.

In addition, this data was reported by carers rather than participants and there may have also been an unconscious expectation of reduction in this behaviour, which influenced these reports.

The presence of the researcher asking questions of carers regarding their concerns may also have caused an effect due to the influence of the non-specific therapeutic variables sometimes termed 'unconditional positive regard' related to the researcher being an experienced therapist (Farber and Lane 2001).

7.4.4 *Risks and unexpected findings identified*

A subgroup of participants reported difficulties using biofeedback particularly with use of the PPG sensor in one of the devices (StressEraser). Two participants were completely unable to use the StressEraser device and requested that they immediately change device. Both of these participants subsequently reported positive effects when using a HeartMath device.

Two further participants who also had difficulties using the StressEraser opted to continue using this device and reported increased anxiety and depression on questionnaires and reported increased stress in debriefing reports at the end of the 12-week intervention. These participants were noted during training to have symptoms such as cold fingers and difficulties suggesting possible difficulties such as chronic hyperventilation. In these cases, use of one type of biofeedback device, (StressEraser) was associated with increased anxiety and depression as indicated by participant questionnaire and also in reports obtained from carers at debriefing.

The difficulty noted during initial training sessions which highlighted participants showing cold fingers was an unexpected finding and occurred only in the device which used a finger sensor (StressEraser). The difficulties encountered by these participants were unlikely to be related to the device itself as each time this problem arose, multiple checks were made to ensure the device was functioning effectively.

The StressEraser device was selected for use within the study because it had already been employed in a range of studies which had consistently demonstrated positive effects (Karavidas *et al.* 2007; Reiner 2008; van der Swan 2015; Meier and Walsh 2016). This device has now been discontinued, however, none of the studies utilising it reported the specific problems highlighted in this study with people with ASD. Moreover, prior to the study commencement, two researchers reported positive effects from its use (personal correspondence with J. van der Swan and R. Gevirtz January 2016), in other non-ASD populations. No other evidence of these difficulties was found in the literature review.

Importantly, the difficulties reported with the StressEraser device were not reported with the Inner balance device which used a PPG sensor which could be attached to the ear. Potential reasons for the difficulties recorded include possible presence of chronic hyperventilation in participants, and high levels of stress causing peripheral vasoconstriction. This finding may also be related to underlying ANS differences seen in people with ASD and may affect the type of device which would be useful for this particular population. This difficulty would not have been highlighted in a study which simply recorded these participants as drop outs. Thus, it is argued that including all participants and recording all problems reported has added valuable information to the study, which can also inform future research.

A further unexpected finding was the need to request repeat ECG recordings in ten out of the twenty participants and the subsequent identification of three participants who were referred to cardiology for further assessment.
This difficulty may be related to less comprehensive information provided by anonymised single lead ECG recordings, however the identification of concerns in three participants following 12 lead ECG may indicate underlying physiological difficulties in people with ASD, particularly those with anxiety.

Currently there is limited data on the risk factors for cardiac problems in people with ASD. The high levels of anxiety and depression seen in this population; the frequent use of medication and potential underlying ANS differences may place them at increased risk and further research into this area is warranted.

7.4.5 *Benefits of using biofeedback*

Despite the problems and unexpected findings noted above, the majority of young people with ASD who participated in this study were able to use small 'home trainer' HRV biofeedback devices and reported positive effects as a result of their use.

For example, 65% of responses collected from participants during the intervention, indicated that the device helped when they used it. The majority of carers also provided positive reports regarding HRV biofeedback, with carers noting changes in participants which were similar to participant direct reports.

In addition, verbal reports from carer interviews indicated a significant reduction in the frequency of meltdowns observed in participants. These reports may indicate a direct effect of the intervention or may be related to therapeutic effects caused by the researcher, or to unconscious bias in the reporting of effects of the intervention.

7.4.6 *HRV data*

> *"Short term heart rate variability: Easy to measure, difficult to interpret"* (Lombardi *et al.* 2018, p.1).

The complexity of assessing, analysing and interpreting HRV data should not be underestimated, and this growing issue is highlighted in the review quoted above. This study involved undertaking single lead ECG recording which was used to collect data on measures of both heart rate and HRV. There is ongoing debate regarding the meaning of HRV variables and the interpretation of results (Borrione and Kemp 2018). Interpretation of HRV data in this small sample is therefore made tentatively due to the nature of the study design, and the complexity of this area.

Baseline data from ECG recordings showed increased heart rate and deceased HRV indices compared to some of the normative reference values available for adults (Nunan 2010; Dantas *et al.* 2018). Baseline HRV calculations were made using combined mean score data from participants aged 13-24 years and compared to norms for older adults. Comparisons were not made with the study on 6-8-year-old children as there was limited information available from these norms.

There is now a growing recognition of the importance of using age matched HRV frequency bands and the need for more normative data (Shader *et al*. 2017). Resting HRV does naturally change with age and an important limitation of the method of baseline comparison used in this study is that the natural variation in age range for HRV was not accounted for. Future studies should divide baseline HRV measurements into younger and older age groups to compare them to similar norms.

Pre and post data indicated a significant increase in heart rate and no significant changes in HRV indices over time, either in the stress task, or in the recovery task. Therefore, the research hypothesis, which had predicted a reduction in HRV indices over time, was not supported. There are a number of possible explanations for these findings. First of all, this was a small pilot sample using two different devices, for a relatively short time period which has added to the complexity of study design and makes interpretation of results more tenuous.

Whilst attempts were made to control the environment and conditions for HRV measurement, tighter controls such as using a standardised clinic-based assessment and ensuring additional factors such as bladder emptying and no intake of caffeine prior to assessment were not undertaken which could have influenced findings.

In addition, whilst expert advice was sought on both ECG and HRV, the complex process of recording; extraction of data and analysis of results may have been subject to error due to the inexperience of the researcher. For example, a large number of non-linear HRV variables were not reviewed which may have provided further information.

Findings may, however, indicate an increase in stress due to anticipatory anxiety when the stress task was repeated. Similar findings of increased heart rate during stress tasks have also been reported in ASD (Groden 2005; Kushki *et al.* 2014). In addition, findings suggest that people with ASD may not show quick recovery from stress due to what has been termed *sympathetic nervous system hyperarousal* (Goodwin 2006; Kushki *et al.* 2014).

Correlations of HRV indices at baseline with demographic variables indicated that HRV indices were significantly correlated with age, a finding which has been reported in a number of large-scale population studies (Lombardi *et al*. 2018). This finding suggests that age may be one of the most important factors which predict HRV indices and it is possible that this factor alone may outweigh any effect of interventions such as HRV biofeedback. HRV indices at the final ECG recording were correlated with level of ASD symptoms. It may be that the nature of the psychophysiological 'stress' and 'recovery' assessment used with people with ASD was too anxiety provoking and that the assessment itself accounted for changes in HRV. The use of a psychophysiological stress profile assessment for people with ASD may simply be too anxiety provoking to use as an assessment of HRV physiology pre and post intervention.

However, it is important to also consider the original research hypothesis and the theoretical framework used, to review whether the actual biofeedback intervention itself may have caused the physiological changes in people with ASD.

7.4.7 *Theoretical framework*

Polyvagal theory which was used to develop the research hypothesis, led to predictions regarding a change in HRV indices over time, based on the assumption that participants would be able to use HRV biofeedback to regulate their ANS.

Thus, establishing resonant frequency breathing would increase 'respiratory sinus arrhythmia', help to activate the '*social engagement system'* (Porges 2009) and cause subsequent reductions in anxiety. The initial plan to use the resonant frequency (RF) breathing protocol which is argued to increase HRV (Lehrer 2000) using a multisensory biofeedback system was not employed. It was therefore not possible to determine if all participants were actually breathing at their resonant frequency on the portable home trainer devices used in this study.

Reports obtained from both participants and carers did indicate reductions in anxiety which may be related to the use of the HRV biofeedback intervention. However, whether any underlying regulation of ANS function or any activation of the '*social engagement system'* occurred remains uncertain and a number of other variables may have also influenced the changes in anxiety.

A new theoretical framework to explain and interpret HRV using an approach called '*Neurovisceral integration across a continuum of time'* may help to explain some of the findings in this study (Kemp *et al*. 2017). This framework, outlined in Chapter 2, emphasises the complex and dynamic series of systems which are regulated by the vagus nerve. Thus, HRV indices represent the state functioning of the vagus nerve and the overall regulation of these systems, at the particular time of measurement.

This theoretical approach advocates a more complex approach to interpretation of HRV, which can change as a result of multiple internal and external factors. Thus, the importance of rigorously accounting for and controlling all factors which may influence HRV becomes increasingly apparent, for any accurate interpretation of these indices within a research framework to take place.

7.5 Integration of study findings

> *"Anyone who isn't confused, really doesn't understand the situation"* (Bryan 1969, p.14).

This study involved multiple methods of data collection from both participants and carers and there is a danger of confusion and 'not being able to see the wood for the trees' in any such study. Whilst statistical tests on group data were carried out in this study, all results involved analysis on a small sample size with two different devices being used with participants. Thus, all statistical results are interpreted cautiously and require replication before any conclusions regarding the efficacy of HRV biofeedback can be made.

Demographic findings indicated that this was likely to be a representative sample of people with ASD, who exhibited a profile of difficulties which may increase their risk of future health difficulties.

Results showed that the equipment used for the assessment was reported as relatively easy to use with few problems noted. With regard to the proof of concept question *'can people with ASD use HRV biofeedback devices'* usability ratings for both devices were above average. However direct reports showed underlying differences, with the majority of participant using the finger sensor device reporting some degree of problem with its use. Several participant's reporting difficulties with use of this device showed increased anxiety, which may have been caused by the intervention. Findings overall suggest that it is possible for people with ASD to use HRV biofeedback devices although use of devices employing ear sensors may be preferable.

With regard to whether these devices did '*help to reduce anxiety in people with ASD'* direct reports from participants and their carers suggest a possible reduction in anxiety and meltdowns in some participants which may be related to use of the intervention.

Information obtained from questionnaire reports and debriefing reports showed concordance, with participants reporting decreases in anxiety on questionnaires, also giving debriefing reports of signs such as '*feeling calm'*. However participant reports and HRV indices were more varied, with some participants showing changes in the direction predicted by the research hypothesis on questionnaire reports, but not on HRV indices. It is notable that many other studies have not shown a clear concordance between questionnaire reports and measures of HRV and further research into the mechanisms behind HRV biofeedback has been advocated (Wheat 2010).

A study has been published which was not available for the current literature review reporting on combined use of HRV biofeedback and neurofeedback using a professional biofeedback system in 15 people with ASD aged between 6-18 years (Goodman *et al.* 2018). This study represents the first published study using the RF breathing protocol in people with ASD (Lehrer 2000; 2013). It is of note that participants in this study were excluded if they were not able to tolerate the electrodes and equipment used and were also excluded if they could not establish RF breathing (Goodman *et al.* 2018, p 12). Results were reported to suggest that HRV biofeedback either alone or in combination with neurofeedback, '*may improve behavioural features of ASD*' (Goodman *et al.* 2018, p 9).

New theoretical approaches may help to guide future research by highlighting the complexity of systems indexed by HRV data, and the need to take into account a wide range of variable when measuring, analysing and interpreting HRV. In addition, the availability of further normative reference values for HRV, and the development of guidelines for the assessment analysis and reporting of HRV data, in psychiatric populations should enable increased rigour in future research studies.

Determining the exact underlying mechanism of HRV biofeedback is beyond the limits of this study, however, the study findings do add further information regarding the use of small scale HRV biofeedback devices in this new population. The mechanism of effect in HRV biofeedback may not actually be related to resonant frequency breathing and further assessment of the reasons for changes reported as a result of this intervention are warranted.

More specifically it is argued that it has been important to include information from individual cases who became worse as a result of using biofeedback and that the information from these cases is as valuable as cases who improved as a result of biofeedback.

The differences and specific problems noted highlight a number of areas for future research to explore. For example, the finding of cold fingers in many participants was not a planned outcome part of the study protocol; however, this significantly affected the ability of some to use this type of device. This issue should be investigated further and may represent one reason for not using HRV biofeedback devices which use a finger sensor, particularly in this population. Once again it is important to remember that interventions designed for neurotypical populations may have different outcomes in people with ASD (Mottron 2017).

Further understanding the frequency and severity of the difficulties highlighted in this study could potentially help to uncover the mechanisms of effect in HRV biofeedback and may further highlight some of the physiological difficulties experienced by people with ASD.

7.6 Study strengths and contribution to knowledge

> *"Despite significant challenges it is possible to reduce cost and improve lives*" (Iemmi *et al.* 2017, p.10).

Recent reviews have highlighted the lack of funding for ASD, in comparison to other conditions, in addition to the high costs of meeting the needs of this increasing population (Buescher 2014; Iemmi *et al.* 2017). One key strength of this study was the testing of a new intervention in a population where there is high need, and where little research exists on areas that directly affect the individuals concerned (Pellicano and Charman 2014).

A further strength was the assessment of people with ASD by using direct reports from participants themselves in multiple formats, rather than simply focussing on carer reports. Research suggests that parent reports are not always congruent with direct reports from the person with ASD (Vasa 2014). Some research has also suggested that direct child reports correlate better with physiological measures of stress or anxiety than parent reports (Bitzika 2015). Thus, the combined use of text survey; questionnaires and debriefing reports from participants combined with carers adds strength to the validity of findings of both positive and negative effects.

The development of an assessment protocol for assessing HRV in young people with ASD can also be viewed as an additional strength. Despite limitations in the design of the study, results indicate that the type of assessment used was tolerated well by participants. Further adjustments should be made which would enable more detailed information to be gathered in this area, to add to the current literature on HRV in different populations.

Overall, the current study has contributed new knowledge on the early stage testing of a new intervention in people with ASD and provides a new data set of short term HRV recordings for this population.

Chapter 8. Recommendations

8.1 Overview

This study has contributed new information on the use of a home-based biofeedback intervention to manage anxiety in a vulnerable population. A number of important limitations to the current study have been reported in Chapter 7. Potential solutions to address the problems identified are now outlined.

This study was funded by the Public Health Agency of Northern Ireland and involved NHS staff and patients, and therefore early stage recommendations for future studies are outlined using a logic model, indicating how a larger scale study might practically operate within a health research framework.

8.2 Potential solutions to problems within current study

8.2.1 *Study design*

A number of additional changes to study design could be made in future studies, which could help to further elucidate the effects of this intervention. Thus, future studies could employ an 'active' control group and randomly assign participants to one of two different interventions. Studies which have tested HRV biofeedback have used alternative interventions such as meditation (van der Swan 2015); physical activity (Meier and Welch 2016), or 'sham biofeedback' as (Lehrer 1997). An important potential control intervention which could be employed in future studies assess would be to use breathing exercises only, without biofeedback. A study assessing HRV biofeedback for performance anxiety in musicians found that a short session of slow-paced breathing was as effective as HRV biofeedback (Wells 2012). Studies investigating longer term interventions could use a breathing pacer app for mobile smartphone use (such as 'E-Z Air' from www.bfe.org) which could assess and feedback paced breathing alone in comparison to HRV biofeedback.

Future studies could also consider employing case study design and methodology to assess the engagement of individual participants with this type of intervention.

8.2.2 *Recruitment and selection of sample*

A key limitation in this study was the small sample size. Future studies could, therefore, increase the age range for recruitment and allow for more varied methods of initiating contact with the research team such as leveraging social media, seeking recruitment support from voluntary sector organisations, or repeat contacting within NHS teams. This study did not attempt to recruit potential participants a second time after initial letters were sent, and it is possible that further contact calls could be considered in future studies.

Larger scale studies should collect further data on the characteristics of those who dropped out and record reasons for drop-out. This was collected in the current study however larger samples would enable statistical comparisons to assess whether this intervention was preferred by one particular group of participants.

Selection criteria in the current study did exclude medications such as beta blockers and tricyclic antidepressants known to affect HRV; however, some participants were taking other types of medication for treatment of anxiety or depression. Future larger scale studies could either include only those not taking medication, or separate participants into those who were taking prescribed medication and those who were medication free for further analysis.

8.2.3 *Equipment*

Estimates for appropriate sample size for any study depend upon the likely effect size for the primary outcome. This in turn depends upon accurate measurement with safe valid and reliable equipment. Professional multi sensor biofeedback assessment systems in clinic-based assessments could be employed when clients were attending therapy sessions, however, this could lead to increased anxiety in this population. Alternatively, a reduced lead system, such as the EASI-lead configuration, which has been shown to provide accurate 12-lead ECG reconstruction, using only 4 electrodes (Finlay *et al.* 2007; Guldenring *et al.* 2012), or a 24-hour home ambulatory recording device, using single lead ECG, could be employed. Based upon experience gained in this study, home-based recording may still be preferable for this population.

8.2.4 *Measures*

The current study used separate questionnaire measures for child and adult groups to assess anxiety and depression. Since the initial user review conducted in 2014, a new ASD specific anxiety questionnaire has been produced (Rodgers et al. 2016b). Interestingly this questionnaire asks for responses on some of the areas which were highlighted as triggers for anxiety in people with ASD in the interviews with carers in the current study. The development of this new ASD specific anxiety questionnaire may help future researchers understand and describe the symptoms experienced by people with ASD more accurately (Rodgers *et al.* 2016b).

A further issue, which could be addressed differently in future, is the reporting of information from carers. A systematic review of outcome measures has highlighted that there currently are few measures available for assessment of outcome of intervention trials in people with ASD (Brugha *et al.* 2015). The Autism Treatment Evaluation Checklist (ATEC) has been used to assess change (Berger 2011; Goodman *et al.*2018) and future studies could include use of this questionnaire to provide more quantified data on parent reports of change.

8.2.5 *Usage of biofeedback devices*

A further important area not fully addressed by this study is the need to accurately capture and record data from the biofeedback devices used by participants. The use of a large-scale biofeedback system (such as the NeXus-10®) enables detailed information on participant progress to be recorded during each training session, as adopted in a study by Goodman *et al.* (2018). Other studies employing small portable devices (e.g. HeartMath) permit recording of length of practice and level of coherence for later analysis (Whited 2014; Westlake 2015*).*

Potential solutions for future studies could be to either adopt the approach of (i) using large scale biofeedback monitoring systems which record information locally on a computer or (ii) to employ small portable biofeedback intervention devices and to transmit data from these to a secure cloud service. To comply with Governance regulations, these servers should be based in the UK.

8.2.6 *HRV assessment*

Despite attempts to standardise the HRV assessment process, several limitations are noted. One limitation in the assessment process was the variation in environments, due to the decision to undertake home based assessments.

Whilst attempts were made to standardise the assessment as much as possible each participant was assessed at home and thus in a different environment. Future studies should ensure factors such as bladder emptying; no prior caffeine intake; recording height and weight are taken into account. Adherence to GRAPH guidelines (Quintana 2016) would help to provide more standardised information on the assessment and analysis of HRV. Nevertheless, this study showed that home-based recording is achievable and preferred.

The importance of also analysing the respiration frequency of each participant to understand and interpret any changes in HRV has been emphasised (Weise *et al.* 1989: Billman 2015). Future studies could also use a respiration gauge, in conjunction with ECG, to obtain detailed information on both cardiac and respiration indices.

Future studies assessing the ANS profile of people with ASD could employ methods for carrying out more detailed physiological assessment, which use psychophysiological assessment equipment including peripheral temperature measurement and use of capnography to measure exhaled CO_2 (Khazan 2013). This would enable more accurate estimation of the physiological profile of people with ASD. However, this type of more complex assessment may well induce anxiety particularly in this population.

8.2.7 *Data analysis*

Finally, there is also potential for unconscious researcher bias in the collection and analysis of data. Further research involving collection and analysis of HRV data could resolve this problem by employing additional researchers to allow for blinding of both data inputting and data analysis, independent of data collection. Data analysis should also review further the demographic characteristics of both drop-outs and exclusions from the study.

8.3 Framework to guide future research

Program theory can be used to help to give a practical framework to explain the intent of a clinical intervention and to offer clear guidance on how it should be implemented in practice (Cooksy *et al.* 2001).

A logic model is frequently used as an illustration of a how a program theory should work (Rodgers 2008). Determining how the intervention should work in practice can also help to estimate the costs involved in setting up any larger scale study in the future. A logic model has therefore been outlined to illustrate inputs and activities needed to set up a future study employing an HRV biofeedback. The inputs required, and activities needed to assess outputs and outcomes of the study, are presented in Figure 8.1.

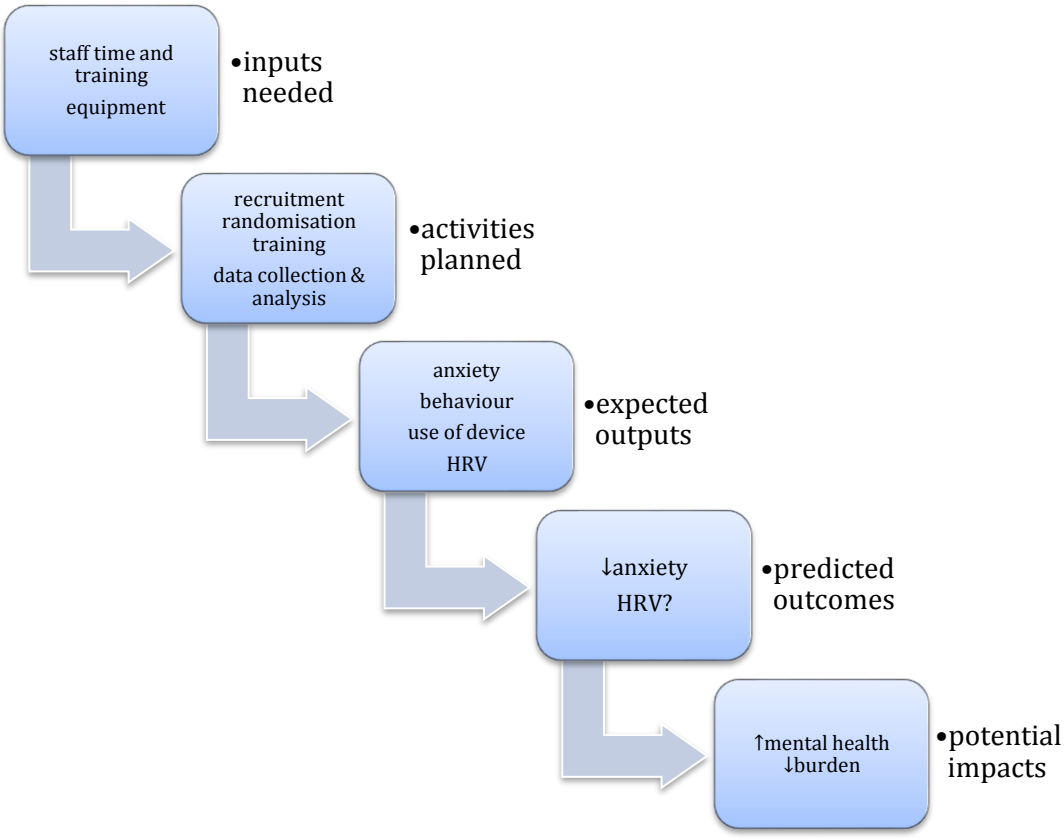


Figure 8.1 Illustration of a simple logic model to inform inputs and activities needed; outputs expected and predicted outcomes to assess a future intervention using HRV biofeedback.

8.3.1 *Inputs needed*

An initial assessment of the amount of time and the equipment needed involved should be carried out to determine costs of this intervention, both in terms of staff time and purchase of equipment needed. One of the potential challenges within any larger study will be to engage clinicians. The development of a detailed implementation plan agreed with key stakeholders will be essential to aid in the ongoing engagement of clinicians working within a complex health service framework (Joseph *et al.* 2011; NHS Improvement 2018). In addition, it will be important to monitor recruitment into the study and assess adherence to the intervention and levels of dropout (Moullin 2007; Moore *et al.* 2010).

8.3.2 *Activities planned*

Recruitment will be important as this will have a direct impact on the data collected and analysis of outcomes. The current study highlighted difficulties recruiting adults aged 18-24 and therefore inclusion of a wider age range for adults or inclusion of younger participants should be considered.

Pre-intervention assessment should involve ASD diagnostic profile assessment and possible psycho-physiological stress profiling to rule out hyperventilation and peripheral vasoconstriction prior to intervention. The actual HRV biofeedback intervention itself should involve either use of the Lehrer protocol (2013) using a professional clinic-based system or an alternative home trainer device that does not use finger sensors. Measurement of HRV over a 24-hour recording period may be more useful to further assess this variable. Strict adherence to an HRV assessment protocol for short term recordings should control for environmental factors that may cause changes in HRV.

During the intervention, repeat HRV assessment to monitor change over time should be conducted. Further expert advice on HRV analysis should be sought, or example using other forms of HRV analysis, such as Poincare plot indices (Rahman 2018). Regular monitoring of participants using ecological momentary assessment was seen as a strength of the current study and further use of this technique could be incorporated into future research.

The use of pre and post questionnaire for carers as well as participants will provide further standardised information on reports of behavioural change. To avoid bias, carers' data should be seen as supplementary, rather than as primary outcomes. The measurement of time spent using use of HRV biofeedback devices will be important to try to establish whether there are dose-response relationships when using these devices. Importantly, randomisation using an active control group will be needed to eliminate the effects of researcher training and user expectation of positive response.

8.3.3 *Outputs expected*

The outputs expected will be information on use of device; anxiety; behaviour and HRV indices. Quantitative data should therefore be collected on measures of participant resting state HRV and participant self-reports of anxiety. In addition, carers should be asked to provide both qualitative and quantitative information on any changes in participant behaviour before and after using the intervention. Data should be collected on usage and acceptability of the device over the period of the intervention, to assess dose-response relationships.

The views of participants, carers and also health care providers should be collected to obtain broader perspectives on the acceptability of the intervention, within a health service framework. Qualitative data from debriefing interviews and ratings will be important to provide information regarding the impact of this intervention from the perspectives of users and their carers, and health professionals.

8.3.4 *Outcomes predicted*

It is hypothesised that HRV biofeedback will be able to help people with ASD to reduce anxiety. The predicted outcomes are a reduction in participant anxiety. Secondary outcomes should detail signs of changes in participant behaviour observed by carers. The potential for HRV biofeedback to regulate underlying ANS dysfunction via establishment of resonant frequency breathing remains unclear. It is therefore important to further assess HRV in a more rigorously controlled manner with recording of additional confounding factors that may affect HRV to assess the extent to which participants can improve resting state HRV as a result of using HRV biofeedback.

8.3.5 *Potential Impact*

The potential impact of reducing levels of anxiety in people with ASD relates to both the individual and also to the impact on society. Thus, the potential impact of this type of intervention if shown to be effective would be improvements in mental health within the individual and reductions in burden to health service and society as a whole.

8.4 Additional areas for future research

Further investigation of the utility of a '*biofeedback stress profile*' assessment for people with ASD which had originally been planned for this study may be a useful area for future research. This would entail carrying out multimodal assessment of EMG; ECG; EDA; temperature and respiration in a more controlled clinic setting in a suitable number of participants to fully explore the associated physiology. Measurement of the physiological reactions of people with ASD could contribute to our understanding of this condition, and in addition may eventually represent an important method for assessment of the outcome of existing interventions such as CBT or medication. It is important to note that this type of assessment could also be used to assess traditional forms of treatment such as CBT or medication in other populations as well as people with ASD.

Further assessment of the risk factors for cardiac problems in people with ASD is viewed as another important area for further research. The sample of young people assessed in this study had similar characteristics to the wider population of people with ASD. High levels of anxiety and depression in conjunction with frequent use of medication; low levels of physical activity and possible underlying ANS differences may place people with ASD at increased risk of cardiovascular problems. Findings from this study suggest further investigation of potential cardiac difficulties in this population is warranted.

Finally, further attempts at teaching resonance frequency breathing to people with ASD could be attempted with additional use of a home trainer device for continued practice.

8.5 Conclusion

> *"The substantial direct and indirect economic effect of ASDs emphasizes the need to continue to search for effective interventions that make best use of scarce societal resources"* (Buescher *et al.*2014, p.721).

The high costs and continued lack of effective interventions to meet the needs of people with ASD have been emphasised in research reviews, as highlighted above.

The Lancet Global Mental Health Group (Horton 2007) recommended the introduction of innovative and easily accessible strategies for treating common mental health disorders such as anxiety and depression. A review of the cost of biofeedback treatment in clinical settings (Schneider 1987) found biofeedback to be cost effective on a number of measures such as reduced medication and clinical visits. Despite this, a review of complementary and alternative treatments by Kessler *et al.* (2001) indicated that biofeedback represented less than 2% of treatments reported for anxiety or depression.

HRV biofeedback has been argued to be an important adjunct to current interventions available for people with a range of conditions (Lehrer 2017). The use of technology has also been advocated as one possible solution to address the increasing burden of mental illness on society (Kazdin and Blase 2011).

Many people with ASD either do not want or cannot access mental health services and HRV biofeedback may represent a method for enabling people with ASD to reduce anxiety at home and utilise their existing skills more effectively. HRV biofeedback technology may represent one method of aiding or enhancing existing interventions for people with ASD.

However, for people with ASD future research is essential to further assess some of the questions raised by this study. Once again, the inherent problems trying to map existing interventions for neurotypicals onto people with ASD noted by Mottron (2017) are important to acknowledge. Anxiety management for people with ASD using HRV biofeedback offers potential but requires further research.

HRV biofeedback has been argued to combine a method of delivery, in area of interest, with the aim to intervene in an area of possible underlying dysfunction, in people with ASD.

Decisions were made several times in this study which compromised the overall study rigour as a result of ethical considerations. The equipoise that exists between strictness of research design, and ethical needs of participants, was swayed in favour of accommodating participant needs. This was felt to be necessary due to the exploratory nature of this research, and the high degree of vulnerability in this population. It is argued that the *intention to treat* principle (Newell 1992; Gupta 2011) which guided the study design and method of analysis enabled important information to be gathered which can inform future directions for research in this area.

A systematic review has highlighted the potential of biofeedback as a cost effective, non-pharmacological intervention (Schoenberg and David 2014). A further systematic review and meta-analysis has indicated efficacy of HRV biofeedback as an intervention for management of stress and anxiety across a range of populations (Goessl *et al.* 2017). Findings from this study suggest positive effects reported in both participants and their carers, and also a number of negative or inconclusive effects which should be investigated further.

In conclusion, HRV biofeedback has shown some promise as a potential low-cost pervasive intervention for people with ASD, however, the mechanism of effect remains unclear and further research is both important and warranted.

Finally, this study involved different groups of people with ASD and their carers, who proved to be active and interested participants, in both the development and the implementation of the study. Their enthusiasm showed that it is possible to carry out research with this vulnerable population.

> *"Sometimes it is the people no one can imagine anything of, who do the things no one can imagine."* (Moore 2014, The Imitation Game, p.116).

References

AAPB (2012) Abstracts of Papers Presented at the 43rd Annual Meeting of the Association for Applied Psychophysiology and Biofeedback. *Applied Psychophysiology and Biofeedback*, 37(4), 295–311.

Achenbach, T. M. (2009) *The Achenbach System of Empirically Based Assessment (ASEBA): Development, Findings, Theory, and Applications*. Available from: University of Vermont Research Center for Children, Youth, and Families. Burlington, VT, USA.

Achenbach, T. M., and Rescorla, L. A. (2001) *Manual for the ASEBA School-Age Forms and Profiles*. Available from: University of Vermont, Research Center for Children, Youth, and Families. Burlington, VT, USA.

Actiwave Cardio®. Available from: CamNtech Ltd. Upper Pendrill Court, Ermine Street North, Papworth Everard, CB23 3UY, Cambridge, UK.

Adolphs, R., Sears, L. and Piven, J. (2001) Abnormal processing of social information from faces in autism. *Journal of Cognitive Neuroscience*, 13(2), 232–240.

Aguinaga, N. J. (2006) An investigation of the effectiveness of computer-assisted biofeedback for students diagnosed as having autism spectrum disorder. Central Florida. Available at: http://library.ucf.edu/ [Accessed: 4th July 2013].

Alvares, G. A., Quintana, D. S., Kemp, A. H., Van Zwieten, A., Balleine, B. W., Hickie, I. B. and Guastella, A. J. (2013) Reduced heart rate variability in social anxiety disorder: Associations with gender and symptom severity. *PLoS ONE*, 8(7), 1–8.

American Psychiatric Association. (2013) *Diagnostic and Statistical Manual of mental disorders 5th edition (DSM-5®)*. American Psychiatric Publications.

Anderson, C. A., and Bushman, B. J. (2001) Effects of violent video games on aggressive behavior, aggressive cognition, aggressive affect, physiological arousal, and prosocial behavior: A meta-analytic review of the scientific literature. *Psychological science*, *12*(5), 353-359.

Anderson, C. A., Shibuya, A., Ihori, N., Swing, E. L., Bushman, B. J., Sakamoto, A., and Saleem, M. (2010) Violent video game effects on aggression, empathy, and prosocial behavior in Eastern and Western countries: A meta-analytic review. *Psychological bulletin*, *136*(2), 151.

Andrews, G., Goldberg, D. P., Krueger, R. F., Carpenter, W. T., Hyman, S. E., Sachdev, P., and Pine, D. S. (2009) Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity: Paper 1 of 7 of the thematic section: 'A proposal for a meta-structure for DSM-V and ICD-11'. *Psychological Medicine*, *39*(12), 1993-2000.

Angelone, A. and Coulter, N.A., (1964) Respiratory sinus arrhythmia: a frequency dependent phenomenon. *Journal of Applied Physiology*, (3), 479-482.

Aoki, Y., Yahata, N., Watanabe, T., Takano, Y., Kawakubo, Y., Kuwabara, H., Iwashiro, N., Natsubori, T., Inoue, H., Suga, M., Takao, H., Sasaki, H., Gonoi, W., Kunimatsu, A., Kasai, K. and Yamasue, H. (2014) Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain*, 137(11), 3073–3086.

Appelhans, B. M. and Luecken, L. J. (2006) Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*, 10(3), 229–240.

Arain, M., Campbell, M. J., Cooper, C. L. and Lancaster, G. A. (2010a) What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*, 10(67), 1–7.

Arch, J. J. and Ayers, C. R. (2013) Which treatment worked better for whom? Moderators of group cognitive behavioral therapy versus adapted mindfulness-based stress reduction for anxiety disorders. *Behaviour Research and Therapy*, 51(8), 434–442.

Atkins, D., Eccles, M., Flottorp, S., Guyatt, G. H., Henry, D., Hill, S., Liberati, A., O'Connell, D., Oxman, A. D., Phillips, B., Schünemann, H., Edejer, T. T.-T., Vist, G. E. and Williams, J. W. (2004) Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. *BMC Health Services Research*, 4(1), 38.

Austad, C., *in* Weir, K. (2016) Positive feedback. *Monitor on Psychology*, 47 (3), 52.

Autisitica (2015) *Autism and Mental Health: A guide to looking after your mind*. Available at: https://www.autistica.org.uk/downloads/files/Mental-health-autism-E-LEAFLET [Accessed: 27 September 2017].

Bacchini, H. F., Lopes, E. C., Marco Aurelio, M. A. G., Ferreira, J. O., Da Silva Neto, O. C., Da Rocha, A. F. and Talles Marcelo, T. M. G. (2015) Developing an affective point-of-care. 2014 *Proceedings IEEE Symposium on Computational Intelligence in Healthcare and e-Health*, 77–84.

Bagatell, N. (2010) From cure to community: Transforming notions of autism. *Ethos*, *38*(1), 33-55. Available at: https://doi.org/10.1111/j.1548-1352.2009.01080.x [Accessed: July 2012].

Bailey, J. J., Berson, A. S., Handelsman, H. and Hodges, M. (2001) Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. *Journal of the American College of Cardiology*, 38(7), 1902–1911.

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D. and Charman, T., (2006) Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: The special needs and autism project (SNAP). *The Lancet*, *368* (9531), 210-215.

Bal, E., Harden, E., Lamb, D., Van Hecke, A. V., Denver, J. W. and Porges, S. W. (2010) Emotion recognition in children with autism spectrum disorders: Relations to eye gaze and autonomic state. *Journal of Autism and Developmental Disorders*, 40 (3), 358–370.

Ballenger, J. C. (2000) Anxiety and depression: Optimizing treatments. *Primary Care Companion to the Journal of Clinical Psychiatry*, 2 (3), 71–79.

Balzarotti, S., Biassoni, F., Colombo, B. and Ciceri, M. R. (2017) Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. *Biological Psychology*, 130(April), 54–66.

Bandini, L. G., Gleason, J., Curtin, C., Lividini, K., Anderson, S. E., Cermak, S. A., Maslin, M. and Must, A. (2013) Comparison of physical activity between children with autism spectrum disorders and typically developing children. *Autism*, 17 (1), 44–54.

Bangor, A., Kortum, and Miller, J. (2009) Determining what individual SUS scores mean: Adding an adjective rating scale. *Journal of Usability Studies*, 4 (3), 114–123.

Baranowski, T., Blumberg, F., Buday, R., DeSmet, A., Fiellin, L. E., Green, C. S., Kato, M., Lu, A. S., Maloney, A. E., Mellecker, R., Morrill, B. A., Peng, W., Shegog, R., Simons, M., Staiano, A. E., Thompson, D. and Young, K. (2016) Games for health for children—current status and needed research. *Games for Health Journal*, 5 (1), 1–12.

Barlow, D. H. and Craske, M. G. (2006) *Mastery of Your Anxiety and Panic, Workbook*. 4th ed. New York NY: Oxford University Press.

Baron, M.G., Groden, J., and Lipsitt, L. (2006) *Stress and Coping in Autism*. New York, NY: Oxford University Press.

Baron-Cohen, S. (2002) The extreme male brain theory of autism. *Trends in Cognitive Sciences, 6* (6), 248-254.

Baron-Cohen, S. Scott, F.J., Allison, C., (2009) Prevalence of autism spectrum conditions: UK school-based population study. *British Journal of Psychiatry*, 194 (6), 500-509.

Baron-Cohen, S., Bowen, D. C., Holt, R. J., Allison, C., Auyeung, B., Lombardo, M. V., Smith, and Lai, M. C. (2015) The "reading the mind in the eyes" test: Complete absence of typical sex difference in 400 men and women with autism. *PLoS ONE*, 10 (8), 1–17.

Baron-Cohen, S., Leslie, A. M., and Frith, U. (1985) Does the autistic child have a "theory of mind?" *Cognition*, *21*(1), 37-46.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y. and Plumb, I. (2001) The "Reading the Mind in the Eyes Test" revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry*, 42 (2), 241–251.

Barrett, H. and Popovic, N. (2015) A meta-synthesis on the effects of combining heart rate variability biofeedback and positive emotion on workplace performance. *International Journal of Social Science Studies*, 3 (5), 61–68.

Baskin, S. M., Kirk, L., Lehrer, P.M. and Lubar, J. F. (2004) *Evidence-Based Practice in Biofeedback and Neurofeedback.* Wheatridge CA: AAPB Press.

Bassett, D. (2016) A literature review of heart rate variability in depressive and bipolar disorders. *Australian and New Zealand Journal of Psychiatry*, 50 (6), 511–519.

Basso, J. C. and Suzuki, W. A. (2017) The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: A review. *Brain Plasticity*, 2 (2), 127–152.

Beauchaine, T. P. and Thayer, J. F. (2014) Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology*, 98 (2), 338–350.

Beauchaine, T.P. (2015) Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current Opinion in Psychology*, 3, 43–47.

Beauchaine, T.P., Gatzke-Kopp, L. and Mead, H. K. (2007) Polyvagal Theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology*, 74 (2), 174–184.

Beck A.T. and Beck, J. S (2005) Beck Youth Inventories™ - Second edition for children and adolescents (BYI-II) manual and questionnaire forms. Available at: https://www.pearsonclinical.co.uk/ [Accessed 10th July 2013].

Beck Anxiety Inventory ® (1993) Manual and questionnaire forms. Available at: https://www.pearsonclinical.co.uk/[Accessed 11th July 2013].

Beck Depression Inventory-II ® (1996) Manual and questionnaire forms. Available at: https://www.pearsonclinical.co.uk/[Accessed 11th July 2013].

Beck, A. T., Epstein, N., Brown, G., and Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of consulting and clinical psychology*, *56*(6), 893.

Beck, J. G., Stanley, M. A., and Zebb, B. J. (1996) Characteristics of generalized anxiety disorder in older adults: a descriptive study. *Behaviour research and therapy*, *34*(3), 225-234.

Beckham, A. J., Greene, T. B. and Meltzer-Brody, S. (2013) A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. *Archives of Women's Mental Health*, 16(1), 59–65.

Bellido, A., Ruisoto, P., Beltran-Velasco, A. and Clemente-Suárez, V. J. (2018) State of the art on the use of portable digital devices to assess stress in humans. *Journal of Medical Systems*, 42(6) 100.

Bellini, S., (2004) Social skill deficits and anxiety in high functioning adolescents with autism spectrum disorders. *Focus on Autism and Other Developmental Disabilities*, 19 (2), 78-86.

Benarroch E., E., (1993) The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings*, 68, 10, 988-1001.

Benedetti, F. (2005) Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience*, 25(45), 10390-10402.

Benevides, T. W., and Lane, S. J., (2015) A review of cardiac autonomic measures: Considerations for examination of physiological response in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 45, 560-575.

Benn, R., Akiva, T., Arel, S., & Roeser, R. W. (2012) Mindfulness training effects for parents and educators of children with special needs. *Developmental Psychology*, 48(5), 1476.

Berger, M. J. (2007) 'The efficacy of selected biofeedback techniques in mitigating symptoms associated with autism spectrum disorder. *Biofeedback*, 35(2), 62–68.

Berntson, G. G., Bigger, T.J., Eckberg, D. L., Grossman, P., Kaufmann, G., Malik, M., Nagaraja, H. N., Porges, S. W., Saul, J., Stone, H. and van der Molen, M. W. (1997) Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology*, 34 (6) 623–648.

Bettelheim, B. (1972). *The Empty Fortress*. New York: The Free Press.

Billman, G. E. (2011) Heart rate variability - A historical perspective. *Frontiers in Physiology*, 2 (November), 1–13.

Billman, G. E. (2013a) The effect of heart rate on the heart rate variability response to autonomic interventions. *Frontiers in Physiology*, 4 (August), 1–9.

Billman, G. E. (2013b) The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Frontiers in Physiology*, 4 (February), 1–5.

Billman, G. E., Huikur, H. V., Sacha, J. and Trimmel, K. (2015) An introduction to heart rate variability: methodological considerations and clinical applications. *Frontiers in Physiology*, 6(February), 1–3.

Bishop-Fitzpatrick, L., Minshew, N. J. and Eack, S. M. (2013) A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 43(3), 687–694.

Bitsika, V., Christopher, Sharpley, F. and Mills, R. (2016) Are sensory processing features associated with depressive symptoms in boys with an ASD? *Journal of Autism and Developmental Disorders*, 46, 242–252.

Bitsika, V., Sharpley, C. F. and Mills, R. (2016a) Disagreement between mothers' and their sons with an ASD on ratings of sensory features. *Research in Autism Spectrum Disorders*, 22, 10–19.

Bitsika, V., Sharpley, C. F., Andronicos, N. M., Agnew, L. L. and Mills, R. (2015) Which aspects of sensory features are associated with elevated cortisol concentrations in boys with an autism spectrum disorder? *Journal of Developmental and Physical Disability*, 27, 661–675.

Blase, K.L., van Dijke, A., Cluitmans, P. J. (2016) Efficacy of HRV-biofeedback as additional treatment of depression and PTSD 'Effectiviteit van hartritmevariabiliteitbiofeedback als aanvulling bij behandeling van depressie en posttraumatische stressstoornis. *Tijdschrift voor psychiatrie*, 58 (4), 292–300.

Blumenstein, B. and Orbach, I. (2014) Biofeedback for sport and performance enhancement. (May), 1–24. Oxford Handbooks online. Available at: http://www.oxfordhandbooks.com/view/10.1093/oxfordhb/9780199935291.001.0001/oxfordhb-9780199935291-e-001[Accessed April 2016].

Bodner, K. E., Beversdorf, D. Q., Saklayen, S. S. and Christ, S. E. (2012) Noradrenergic moderation of working memory impairments in adults with autism spectrum disorder. *Journal of the International Neuropsychological Society*, 18 (3), 556–564.

Bogdashina, O. (2014) Top 5 tips for autism professionals: Dr Olga Bogdashina on sensory difficulties. Available at: http://network.autism.org.uk/sites/default/files/ckfinder/files/ [Accessed: 12 December 2017].

Bogdashina, O. (2016) *Sensory Perceptual Issues in Autism and Asperger Syndrome: Different sensory experiences-different perceptual worlds*. London: Jessica Kingsley.

Bölte, S., Dziobek, I. and Poustka, F. (2009) Brief report: The level and nature of autistic intelligence revisited. *Journal of Autism and Developmental Disorders*, 39 (4), 678–682.

Bölte, S., Golan, O., Goodwin, M. S. and Zwaigenbaum, L. (2010) What can innovative technologies do for autism spectrum disorders? *Autism*, 14 (3), 155–159.

Bölte, S., Holtmann, M. and Poustka, F. (2008) The social communication questionnaire (SCQ) as a screener for autism spectrum disorders: Additional evidence and cross-cultural validity. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47 (6), 719–720.

Bolton, A. (1972) The anxious child. *British Medical Journal*, 3(5828), 690–692.

Borrione, L., Brunoni, A. R., Sampaio-Junior, B., Aparicio, L. M., Kemp, A. H., Benseñor, I., Lotufo, A. and Fraguas, R. (2018) Associations between symptoms of depression and heart rate variability: An exploratory study. *Psychiatry Research*, 262, 482–487.

Boulter, C., Freeston, M., South, M. and Rodgers, J. (2014) Intolerance of uncertainty as a framework for understanding anxiety in children and adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44 (6), 1391–1402.

Bovee, J.P., (1999) My experiences with autism and how it related to "Theory of Mind" - Part 1. *Advocate*, 32(5), 18-19. Available at : https://www.iidc.indiana.edu/pages/Should-We-Insist-on-Eye-Contact-with-People-who-have-Autism-Spectrum-Disorders [Accessed: 10th July 2013].

Bradley, R. T., Galvin, P., Atkinson, M. and Tomasino, D. (2012) Efficacy of an emotion self-regulation program for promoting development in preschool children. *Global Advances in Health and Medicine:* improving healthcare outcomes worldwide, 1(1), 36–50.

Bradley, R. T., McCraty, R., Atkinson, M., Arguelles, L., Rees, R. A., and Tomasino, D. (2007) *Reducing Test Anxiety and Improving Test Performance in America's Schools*. Boulder Creek CA: Institute of HeartMath Press.

Bradley, R. T., McCraty, R., Atkinson, M., Tomasino, D., Daugherty, A. and Arguelles, L. (2010) Emotion self-regulation, psychophysiological coherence, and test anxiety: Results from an experiment using electrophysiological measures. *Applied Psychophysiology Biofeedback*, 35(4), 261–283.

Braun, V., and Clarke, V. (2006) Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3, 77–101.

Brett, D., Warnell, F., McConachie, H. and Parr, J. R. (2016) Factors affecting age at ASD diagnosis in UK: No evidence that diagnosis age has decreased between 2004 and 2014. *Journal of Autism and Developmental Disorders*, 46 (6), 1974–1984.

Bridges, H. (2015) *ReframeyYour Thinking Around Autism. How the Polyvagal Theory and Brain Plasticity Help Us Make Sense of Autism.* London and Philadelphia: Jessica Kingsley.

Brooke, J. (1996). SUS-A quick and dirty usability scale. *Usability Evaluation in Industry*, *189* (194), 4-7.

Brotman, D. J., Golden, S. H. and Wittstein, I. S. (2007) The cardiovascular toll of stress. *The Lancet*, 370(9592), 1089–1100.

Brousselle, A., and Champagne, F. (2011) Program theory evaluation: Logic analysis. *Evaluation and Program Planning*, *34* (1), 69-78.

Bruggink, A., Huisman, S., Vuijk, R., Kraaij, V. and Garnefski, N. (2016) Cognitive emotion regulation, anxiety and depression in adults with autism spectrum disorder. *Research in Autism Spectrum Disorders*, 22, 34–44.

Brugha, T.S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., Bebbington, P, Jenkins, R. and Meltzer, H., (2011) Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of General Psychiatry*, *68* (5), 459-465.

Brunoni, A. R., Kemp, A. H., Dantas, E. M., Goulart, A. C., Nunes, M. A., Boggio, P S., Mill, J. G., Lotufo, A., Fregni, F. and Benseñor, I. M. (2013) Heart rate variability is a trait marker of major depressive disorder: Evidence from the sertraline vs electric current therapy to treat depression clinical study. *International Journal of Neuropsychopharmacology*, 16 (9), 1937–1949.

Bryan, W., (1969) *The Improbable Irish.* New York NY: Ace.

Buchhorn, R. (2014) Why are psychiatric disorders in children becoming more and more common? *International Journal of Emergency Mental Health*, 16(2), 322–325.

Buchhorn, R., Conzelmann, A., Willaschek, C., Störk, D., Taurines, R. and Renner, T. J. (2012) Heart rate variability and methylphenidate in children with ADHD. *Attention Deficit and Hyperactivity Disorders*, 4(2), 85–91.

Buescher, A. V. S., Cidav, Z., Knapp, M. and Mandell, D. S. (2014) Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatrics*, 168(8), 721–728.

Bujnakova, I., Ondrejka, I., Mestanik, M., Visnovcova, Z., Mestanikova, A., Hrtanek, I., Fleskova, D., Calkovska, A. and Tonhajzerova, I. (2016) Autism spectrum disorder is associated with autonomic underarousal. *Physiological. Research*, 65(5), 673–682.

Bulut, N. S., Würz, A., Yorguner Küpeli, N., Çarkaxhıu Bulut, G. and Sungur, M. Z. (2018) Heart rate variability response to affective pictures processed in and outside of conscious awareness: Three consecutive studies on emotional regulation. *International Journal of Psychophysiology*, 129, 18–30.

Buron, K.D. (2006) *When My Worries Get Too Big! A Relaxation Book for Children Who Live with Anxiety*. Shawnee Mission, KS: Autism Asperger Press.

Buron, K.D.and Curtis, M. (2003) *The Incredible 5-Point Scale*, Autism Asperger Publishing Company, Shawnee Mission, KA.

Caldwell, Y. T. and Steffen, P. R. (2018) Adding HRV biofeedback to psychotherapy increases heart rate variability and improves the treatment of major depressive disorder. *International Journal of Psychophysiology*, 131, 96-101.

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P, Spiegelhalter, D. and Tyrer, (2000a) Framework for design and evaluation of complex interventions to improve health. *BMJ*, 321, 694–696.

Canadian Agency for Drugs and Technology in Health (2017) *Neurofeedback and Biofeedback for Mood and Anxiety Disorders: A Review of Clinical Effectiveness and Guidelines. Rapid response report: summary with critical appraisal.* Ottawa Canada: CADTH. Available at: https://www.cadth.ca/neurofeedback-and-biofeedback-mood-and-anxiety-disorders-review-clinical-effectiveness-and-0 [Accessed: June 2018].

Carabotti, M., Scirocco, A., Maselli, M. A. and Severi, C. (2015) The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology*, 28(2), 203–209.

Carney, R. M. and Freedland, K. E. (2009) Depression and heart rate variability in patients with coronary heart disease. *Cleveland Clinic Journal of Medicine*, 76 (2), 13–17.

Case-Smith, J., Weaver, L. L., and Fristad, M. A. (2015) A systematic review of sensory processing interventions for children with autism spectrum disorders. *Autism*, *19*(2), 133-148.

Cepeda, F. X., Lapointe, M., Tan, C. O. and Andrew Taylor, J. (2018) Inconsistent relation of nonlinear heart rate variability indices to increasing vagal tone in healthy humans. *Autonomic Neuroscience: Basic and Clinical*, 213(January), 1–7.

Chalfant, A. M., Rapee, R. and Carroll, L. (2007) Treating anxiety disorders in children with high functioning autism spectrum disorders: A controlled trial. *Journal of Autism and Developmental Disorders*, 37, 1842–1857.

Chalfant, A.M. (2011. *Managing Anxiety in People with Autism: A Treatment Guide for Parents, Teachers and Mental Health Professionals*. Bethesda, MD: Woodbine House.

Chalmers, J. A., Heathers, J. A. J., Abbott, M. J., Kemp, A. H. and Quintana, D. S. (2016) Worry is associated with robust reductions in heart rate variability: a transdiagnostic study of anxiety psychopathology. *BMC Psychology*, 1–10.

Chalmers, J. A., Quintana, D. S., Abbott, M. J.-A. and Kemp, A. H. (2014) Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Frontiers in Psychiatry*, 5(July), 1–11.

Chandrasekhar, T. and Sikich, L. (2015) Challenges in the diagnosis and treatment of depression in autism spectrum disorders across the lifespan. *Dialogues in Clinical Neuroscience*, 17(2), 219–227.

Charman, T., Baird, G., Simonoff, E., Loucas, T., Chandler, S., Meldrum, D., and Pickles, A. (2007) Efficacy of three screening instruments in the identification of autistic-spectrum disorders. *The British Journal of Psychiatry*, *191* (6), 554-559.

Chen, X., Yang, R., Kuang, D., Zhang, L., Lv, R., Huang, X., Wu, F., Lao, G. and Ou, S. (2017) Heart rate variability in patients with major depression disorder during a clinical autonomic test. *Psychiatry Research*, 256.

Chenail, R. J. (2011) Learning to appraise the quality of qualitative research articles: A contextualized learning object for constructing knowledge. *The Qualitative Report*, 16(1), 236–248.

Cheshire, W. (2012) Highlights in clinical autonomic neuroscience: New insights into autonomic dysfunction in autism. *Autonomic Neuroscience*: *Basic and Clinical*, 171(1), 4–7.

Chittaro, L. and Sioni, R. (2014a) Affective computing vs. Affective placebo: Study of a biofeedback- controlled game for relaxation training. *International Journal of Human Computer Studies*, 72(8–9), 663–673.

Choi, K.-H., Kim, J., Kwon, O. S., Kim, M. J., Ryu, Y. H. and Park, J.-E. (2017) Is heart rate variability (HRV) an adequate tool for evaluating human emotions? – A focus on the use of the International Affective Picture System (IAPS)', *Psychiatry Research*, 251(February), 192–196.

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. A. and Geddes, J. R. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*, 1–10.

Clamor, A., Koenig, J., Thayer, J. F. and Lincoln, T. M. (2016) A randomized-controlled trial of heart rate variability biofeedback for psychotic symptoms. *Behaviour Research and Therapy*, 87, 207–215.

Climov, D., Lysy, C., Berteau, S., Dutrannois, J., Dereppe, H., Brohet, C. and Melin, J. (2014) Biofeedback on heart rate variability in cardiac rehabilitation: Practical feasibility and psycho-physiological effects. *Acta Cardiologica*, 69 (3) 299-307.

Coben, R. and Padolsky, I. (2016) Assessment-guided neurofeedback for autistic spectrum disorder. *Journal of Neurotherapy*, 11(1), 5–23.

Coben, R., Linden, M. and Myers, T. E. (2010) Neurofeedback for autistic spectrum disorder: A review of the literature. *Applied Psychophysiology Biofeedback*, 35(1), 83–105.

Cocks, K. and Torgerson, D. J. (2013) Sample size calculations for pilot randomized trials: a confidence interval approach. *Journal of Clinical Epidemiology*, 66, 197–201.

Cohen, H. and Benjamin, J. (2006) Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Autonomic Neuroscience*: *Basic and Clinical*, (128), 1–8.

Cohen, J., (1988) *Statistical Power Analysis for the Behavioral Sciences*. 2nd.edition Hillsdale NJ: Laurence Erlbaum.

Conde Pastor, M., Javier Menéndez, F., Sanz, M. T. and Vila Abad, E. (2008) The influence of respiration on biofeedback techniques. *Applied Psychophysiology Biofeedback*, 33(1), 49–54.

Cooksy, L. J., Gill, and Kelly, P. A. (2001) The program logic model as an integrative framework for a multimethod evaluation. *Evaluation and Program Planning*, 24(2), 119–128.

Cooper, K., Loades, M. E., and Russell, A. (2018) Adapting psychological therapies for autism. *Research in Autism Spectrum Disorders*, 43-50. https://doi.org/10.1016/j.rasd.2017.11.002 [accessed October 2018].

Cooper, T. M., McKinley, P. S., Seeman, T. E., Choo, T. H., Lee, S. and Sloan, R. (2015) Heart rate variability predicts levels of inflammatory markers: Evidence for the vagal anti-inflammatory pathway. *Brain, Behavior, and Immunity*, 49, 94-100.

Corbett, B. A., Mendoza, S., Wegelin, J. A., Carmean, V. and Levine, S. (2008) Variable cortisol circadian rhythms in children with autism and anticipatory stress. *Journal of Psychiatry and Neuroscience*, 33(3), 227–234.

Corder, K., Atkin, A. J., Bamber, D. J., Brage, S., Dunn, V. J., Ekelund, U., Owens, M., van Sluijs, E. M. F. and Goodyer, I. M. (2015) 'Revising on the run or studying on the sofa': Prospective associations between physical activity, sedentary behaviour, and exam results in British adolescents. *International Journal of Behavioral Nutrition and Physical Activity*, 12(1), 106.

Couto, B., Salles, A., Sedeño, L., Peradejordi, M., Barttfeld, P., Canales-Johnson, A., Dos Santos, Y. V., Huepe, D., Bekinschtein, T., Sigman, M., Favaloro, R., Manes, F. and Ibanez, A. (2013) 'The man who feels two hearts: The different pathways of interoception'. *Social Cognitive and Affective Neuroscience*, 9 (9), 1253–1260.

Craig, P., Dieppe, P, Macintyre, S., Michie, S., Nazareth, I. and Petticrew, M. (2008) Developing and evaluating complex interventions: the new Medical Research Council guidance revisiting the 2000 MRC framework. *BMJ*, 337(a1655), 1–6.

Crane, L., Chester, J. W., Goddard, L., Henry, L. A., and Hill, E. (2016) Experiences of autism diagnosis: A survey of over 1000 parents in the United Kingdom. *Autism, 20* (2), 153-162.

Crane, L., Goddard, L. and Pring, L. (2009) Sensory processing in adults with autism spectrum disorders. *Autism*, 13(3), 215–228.

Critchley, H. D. and Garfinkel, S. N. (2017) 'Interoception and emotion'. *Current Opinion in Psychology*, 17, 7–14.

Critchley, H. D. and Garfinkel, S. N. (2018) The influence of physiological signals on cognition. *Current Opinion in Behavioral Sciences*, 19, 13–18.

Critical Appraisal Skills Programme (2006) 'The Critical Skills Appraisal Programme', *Public Health Resource Unit*. Available at: http://www.cas [Accessed: 24 July 2017].

Critical Appraisal Skills Programme (2013) 'RCT Checklist', CASP checklists Oxford, 1–7. Available at: http://media.wix.com/ugd/dded87_40b9ff0bf53840478331915a8ed8b2fb.pdf [Accessed September 2014].

Critical Appraisal Skills Programme (2017a) 'CASP Literature Review Checklist', 1–4. Available at: http://media.wix.com/ugd/dded87_7e983a320087439e94533f4697aa109c.pdf [Accessed: 24 July 2017].

Crocetti, A., Masaraki, S., Merati, S., Menotti, R., Forti, S. and Aiello, G. (2010) 'Psychophysiological stress profile': A protocol to differentiate normal v's pathological subjects. *Activitas Nervosa Superior Rediviva*, 52 (4), 241–245.

Cryer, B. (2013) Coherence, care and inspiration: The power to heal organisations and ourselves. *Journal of Holistic Healthcare*, 10 (1), 29–33.

Cullins, S. W., Gevirtz, R. N., Poeltler, D. M., Cousins, L. M., Edward Harpin, R. and Muench, F. (2013) An exploratory analysis of the utility of adding cardiorespiratory biofeedback in the standard care of pregnancy-induced hypertension. *Applied Psychophysiology Biofeedback*, 38 (3), 161–170.

Cummins, R. A., and Lau, A. L. (2005) *Personal Wellbeing Index: Pre-school*. Burwood: Deakin University Press.

Daluwatte, C., Miles, J. H., Christ, S. E., Beversdorf, D. Q., Takahashi, T. N. and Yao, G. (2013) Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 43(8), 1910–1925.

Damiano, C. R., Mazefsky, C. A., White, S. W. and Dichter, G. S. (2014) Future directions for research in autism spectrum disorders. *Journal of Clinical Child and Adolescent Psychology*, 43(5), 828–843.

Daniels, A. M., and Mandell, D. S. (2014) Explaining differences in age at autism spectrum disorder diagnosis: A critical review. *Autism, 18* (5), 583-597.

Daniels, J., Schwartz, J. N., Voss, C., Haber, N., Fazel, A., Kline, A., Washington, P., Feinstein, C., Winograd, T. and Wall, D. (2018) Exploratory study examining the at-home feasibility of a wearable tool for social-affective learning in children with autism. *npj Digital Medicine*, 1(s32).

Dantas, E. Miranda, Kemp, A. H. and Andreao, R. V. (2018) Reference values for short-term resting-state heart rate variability in healthy adults: Results from the Brazilian longitudinal study of adult health - ELSA-Brasil study. *Psychophysiology*, 55 (6), e13052.

Darwin, C., (1872) The expression of the emotions in man and animals. *In:* Ekman, P. special edition (2009), *The Expression of the Emotions in Man and Animals.* London UK: Harper.

Datko, M., Pineda, J. A., and Müller, R. A. (2018) Positive effects of neurofeedback on autism symptoms correlate with brain activation during imitation and observation. *European Journal of Neuroscience*, 47(6), 579-591.

Davidson, J. (1992) Drug therapy of post-traumatic stress disorder. *The British Journal of Psychiatry*, 160(3), 309–314.

Davidson, J. R. (2006) Pharmacotherapy of social anxiety disorder: what does the evidence tell us? *The Journal of Clinical Psychiatry, 67*, 20-26.

Davidson, K. W., Mostofsky, E. and Whang, W. (2010) 'Don't worry, be happy': Positive affect and reduced 10-year incident coronary heart disease: The Canadian nova scotia health survey. *European Heart Journal*, 31(9), 1065–1070.

Davies, K. S. (2011) Formulating the evidence-based practice question: A review of the frameworks. *Evidence Based Library and Information Practice*, 6(2), 75–80.

Dawson, M., Soulières, I., Gernsbacher, M. A. and Mottron, L. (2007) The level and nature of intelligence. *Psychological science*, 18(8), 657–62.

de Boer, J. C., Adriani, P., van Houwelingen, J. W. and Geerts, A. (2016) Game maturity model for health care. *Games for Health Journal*, 5(2), 87–91.

de Bruin, E. I., Blom, R., Smit, F. M., van Steensel, F. J., and Bögels, S. M. (2015) MYmind: Mindfulness training for youngsters with autism spectrum disorders and their parents. *Autism*, *19*(8), 906-914.

de Bruin, E. I., van der Zwan, J. E. and Bögels, S. M. (2016) An RCT comparing daily mindfulness meditations, biofeedback exercises, and daily physical exercise on attention control, executive functioning, mindful awareness, self-compassion, and worrying in stressed young adults. *Mindfulness*, 7(5), 1182–1192.

de Vries, A. L. C., Noens, I. L. J., Cohen-Kettenis, P. T., Van Berckelaer-Onnes, I. A. and Doreleijers, T. A. (2010) Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40(8), 930–936.

Dean, M., Harwood, R., and Kasari, C. (2017) The art of camouflage: Gender differences in the social behaviors of girls and boys with autism spectrum disorder. *Autism, 21*(6), 678-689.

Del Pozo, J. M., Gevirtz, R. N., Scher, B. and Guarneri, E. (2004) Biofeedback treatment increases heart rate variability in patients with known coronary artery disease. *American Heart Journal*, 147(3).

Denver, J. W., Reed, S. F. and Porges, S. W. (2007) Methodological issues in the quantification of respiratory sinus arrhythmia. *Biological Psychology*, 74(2), 286–294.

Department for Education Northern Ireland DENI (2008) *Task Force Report on Autism*. Available at: www.deni.gov.uk/index/7special_educational_needs [Accessed July 2013].

Department for Health and Social Services (2011b) Physical activity guidelines for children and young people. Available at: https://www.nhs.uk/Livewell/fitness/Documents/children-and-young-people-5-18-years.pdf [Accessed: 5 December 2017].

Dern, S. and Sappok, T. (2016) Barriers to healthcare for people on the autism spectrum. *Advances in Autism*, 2(1), 2–11.

Di Palma, S. Tonacci A., Narzisi A., Domenici C., Pioggia G., Muratori F., Billeci L. (2017) Monitoring of autonomic response to socio-cognitive tasks during treatment in children with Autism Spectrum Disorders by wearable technologies: A feasibility study. *Computers in Biology and Medicine*, 85, 143–152.

Dijkers, M. (2013) Introducing GRADE: a systematic approach to rating evidence in systematic reviews and to guideline development'. e-newsletter: *Center on Knowledge Translation for Disability and Rehabilitation Research*, 1–9.

Dimsdale, J. E. (2008) Psychological stress and cardiovascular disease. *Journal of the American College of Cardiology*, 51(13), 1237–1246.

DiSantis, K. I., Birch, L. L., Davey, A., Serrano, E. L., Zhang, J., Bruton, Y. Fisher, J. O. (2013) 'Physical activity guidelines for adults (19-64 years). *Pediatrics*, 131(5), e1451-8.

Dove, D., Warren, Z., McPheeters, M. L., Lounds Taylor, J., Sathe, N. A., and Veenstra-VanderWeele, J. (2012) Medications for adolescents and young adults with autism spectrum disorders: A systematic review. *Pediatrics*, 130: 717–726.

Dubois, D., Ameis, S., Lai, M., Casanova, M., Desarkar, P. (2016) *International Journal of Developmental Neuroscience*, 52, 104–111.

Dugas, M. J., Gagnon, F., Ladouceur, R., and Freeston, M. H. (1998) Generalized anxiety disorder: A preliminary test of a conceptual model. *Behaviour research and therapy*, *36*(2), 215-226.

Dunn, W. (1994) Performance of typical children on the Sensory Profile: An item analysis. *American Journal of Occupational Therapy*, 48, 967-974.

Dunn, W. (1997a) The impact of sensory processing abilities on the daily lives of young children and their families: A conceptual model. *Infants and young children*, *9*, 23-35.

Dunn, W. (1999) *Sensory profile: User's manual*. San Antonio, TX: Psychological Corporation.

Dunn, W., Myles, B. S., and Orr, S. (2002) Sensory processing issues associated with Asperger syndrome: A preliminary investigation. *American Journal of Occupational Therapy*, *56* (1), 97-102.

Ebben, M. R., Kurbatov, V. and Pollak, C. (2009) Moderating laboratory adaptation with the use of a heart-rate variability biofeedback device (StressEraser®). *Applied Psychophysiology Biofeedback*, 34 (4), 245–249.

Eddie, D., Vaschillo, E., Vaschillo, B. and Lehrer, P. (2015) Heart rate variability biofeedback: Theoretical basis, delivery, and its potential for the treatment of substance use disorders. *Addiction Research and Theory*, 23(4), 266–272.

Edenfield, T. M. and Saeed, S. A. (2012) An update on mindfulness meditation as a self-help treatment for anxiety and depression. *Psychology Research and Behavior Management*, 5, 131–141.

Edmonds, W., Kennedy, T., Hughes, and Calzada, P. (2009) A single-participants' investigation of the effects of various biofeedback-assisted breathing patterns on heart rate variability: A practitioner's approach. *Biofeedback*, 37(4), 141–146.

Edmondson, D., Richardson, S., Fausett, J. K., Falzon, L., Howard, V. J. and Kronish, I. M. (2013) 'Prevalence of PTSD in survivors of stroke and transient ischemic attack: A meta-analytic review. *PLoS ONE*, 8(6), 4–9.

Ehlers, S., and Gillberg, C. (1993) The epidemiology of Asperger syndrome: A total population study. *Journal of Child Psychology and Psychiatry*, *34*(8), 1327-1350.

Eichenberg, C. and Schott, M. (2017) Serious games for psychotherapy: A systematic review. *Games for Health Journal*, 6(3), 127–135.

El Kaliouby P.R., Picard, R, Baron-Cohen, S., (2006) Affective computing and autism. *Annals of the New York Academy of Science*, *1093*, 228- 248.

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L. and Lancaster, G. A. (2016) 'CONSORT' 2010 statement: Extension to randomised pilot and feasibility trials. *BMJ*, 355(i5239), 1–29.

emWave2®; Available from: https://www.heartmath.co.uk/shop/ [Accessed July 2014].

Endow, J (7th February 2015 Blog) *Autistic Meltdown or Temper Tantrum*. Available at: http://www.judyendow.com/autistic-behavior/autistic-meltdown-or-temper-tantrum/[Accessed September 2016].

Ernst, G. (2017) Hidden signals-The history and methods of heart rate variability. *Frontiers in Public Health*, 5(October), 1–12.

Esch, B. E. and Carr, J. E. (2004) 'ecretin as a treatment for autism: A review of the evidence. *Journal of Autism and Developmental Disorders*, 34(5), 543–556.

Ewing, D. J., Campbell, I. W., and Clarke, B. F. (1976) Mortality in diabetic autonomic neuropathy. *The Lancet*, *307*(7960), 601-603.

Farber, B. A., and Lane, J. S. (2001) Positive regard. *Psychotherapy: Theory, Research, Practice, Training*, *38*(4), 390.

Farmer, C., Thurm, A. and Grant, P. (2013) Pharmacotherapy for the core symptoms in autistic disorder: Current status of the research. *Drugs*, 73(4), 303–314.

Farmer, G. D., Baron-Cohen, S. and Skylark, W. J. (2017) People with autism spectrum conditions make more consistent decisions. *Psychological Science*, 28 (8), 1067-1076.

Farr, W. (2010) Personalised technology for autism spectrum conditions is the future. *Journal of Assistive Technologies*, 4(1), 58–60.

Fava, M., Rush, A. J., Alpert, J. E., Balasubramani, G. K., Wisniewski, S. R., Carmin, C. N., Biggs, M. M., Zisook, S., Leuchter, A., Howland, R., Warden, D. and Trivedi, M. H. (2008) Difference in treatment outcome in outpatients with anxious versus nonanxious depression. *American Journal of Psychiatry*, 165(3), 342–351.

Favre, M. R., La Mendola, D., Meystre, J., Christodoulou, D., Cochrane, M., Markram, H. and Markram, K. (2015) Predictable enriched environment prevents development of hyperemotionality in the VPA rat model of autism. *Frontiers in Neuroscience*, 9(MAR), 1–14.

Felmingham, K. L., Stewart, L. F., Kemp, A. H. and Carr, A. R. (2016) The impact of high trait social anxiety on neural processing of facial emotion expressions in females. *Biological Psychology*, 117, 179–186.

Fergusson, D. (2002) Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ*, 325(7365), 652–654.

Field L., L., Edwards, S. D., Edwards, D. J. and Dean, S. E. (2018) Influence of HeartMath training programme on physiological and psychological variables. *Global Journal of Health Science*, 10(2), 126.

Field, S. S. (2015) How do genes and environment cause autism? *Austin Journal of Nutrition and Metabolism*, 2(2), 1017,1–3.

Figueredo, V. M. (2009) The time has come for physicians to take notice: The impact of psychosocial stressors on the heart. *American Journal of Medicine*, 122(8), 704–712.

Finlay, D. D., Nugent, C. D., Kellett, J. G., Donnelly, M. P., McCullagh, P. J., and Black, N. D. (2007) Synthesising the 12-lead electrocardiogram: Trends and challenges. *European Journal of Internal Medicine*, *18*(8), 566-570.

Fleming, B. Hurley, E., Goth (2015) *Choosing Autism Intervention.*, Pavilion Publishing Media: UK.

Fletcher-Watson, S. (2014) A targeted review of computer-assisted learning for people with autism spectrum disorder: Towards a consistent methodology. *Review Journal of Autism and Developmental Disorders*, 1(2), 87–100.

Fletcher-Watson, S., Adams, J., Brook, K., Charman, T., Crane, L., Cusack, J., Leekam, S., Milton, D., Parr, J. R. and Pellicano, E. (2018) Making the future together: Shaping autism research through meaningful participation. Available online at: https://www.ncbi.nlm.nih.gov/pubmed/30095277 [Accessed 2nd September 2018].

Folstein, S. and Rutter, M. (1977) Infantile autism: a genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry and allied disciplines*, 18(4), 297–321.

Fombonne, E. (1999) The epidemiology of autism: A review. *Psychological Medicine*, *29* (4), 769-786.

Fombonne, E. (2005) The changing epidemiology of autism. *Journal of Applied Research in Intellectual Disabilities*, 18(4), 281–294.

Fonoberova, M., Mezi, I., Buckman, J. F., Fonoberov, V. A., Mezi, A., Vaschillo, E. G., Mun, E.-Y., Vaschillo, B. and Bates, M. E. (2014) A computational physiology approach to personalized treatment models: the beneficial effects of slow breathing on the human cardiovascular system. *American Journal Physiology*: *Heart and Circulatory Physiology*, 307(7), H1073–H1091.

Foster, J. A. and McVey Neufeld, K. A. (2013) Gut-brain axis: How the microbiome influences anxiety and depression. *Trends in Neurosciences*, 36(5), 305–312.

Fox, S. I. (2006) *Human Physiology*, 9th Edition. New York: McGraw-Hill.

Francis, H. M., Fisher, A., Rushby, J. A. and McDonald, S. (2016) Reduced heart rate variability in chronic severe traumatic brain injury: Association with impaired emotional and social functioning, and potential for treatment using biofeedback. *Neuropsychological Rehabilitation*, 26(1), 103–125.

Francis, H. M., Penglis, K. M. and McDonald, S. (2016) Manipulation of heart rate variability can modify response to anger-inducing stimuli. *Social Neuroscience*, 11(5), 545–552.

Frank, D. L., Khorshid, L., Kiffer, J. F., Moravec, C. S. and McKee, M. G. (2010) Biofeedback in medicine: Who, when, why and how? *Mental Health in Family Medicine*, 7(2), 85–91.

Freitag, C. M., Jensen, K., Elsuni, L., Sachse, M., Herpertz-Dahlmann, B., Schulte-Rüther, M., Hänig, S., Gontard, A., Poustka, L., Schad-Hansjosten, T., Wenzl, C., Sinzig, J., Taurines, R., Geißler, J., Kieser, M. and Cholemkery, H. (2016) Group-based cognitive behavioural psychotherapy for children and adolescents with ASD: the randomized, multicentre, controlled SOSTA – net trial. *Journal of Child Psychology and Psychiatry*, 57 (5), 596-605.

Friedman, B. H. (2007) An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. *Biological Psychology*, 74(2), 185–199.

Friedrich, E. V. C., Sivanathan, A., Lim, T., Suttie, N., Louchart, S., Pillen, S. and Pineda, J. A. (2015) An effective neurofeedback intervention to improve social interactions in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 45(12), 4084–4100.

Friedrich, E. V. C., Suttie, N., Sivanathan, A., Lim, T., Louchart, S. and Pineda, J. A. (2014) Brain computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum. *Frontiers in Neuroengineering*, 7(July), 1–7.

Frith, U., and Happé, F. (1994) Autism: Beyond "theory of mind". *Cognition*, *50*(1-3), 115-132.

Fydrich, T., Dowdall, D., and Chambless, D. L. (1992) Reliability and validity of the Beck Anxiety Inventory. *Journal of Anxiety Disorders*, *6* (1), 55-61.

Gadow, K.D., Devincent, C.J., Pomeroy, J., and Azizan, A. (2005) Comparison of DSM-IV symptoms in elementary school-age children with PDD versus clinic and community samples. *Autism*, 9 (4), 392 – 415.

García-Berjillos, E., Aliño, M., Gadea, M., Espert, R. and Salvador, A. (2015) 'Efi cacia del neurofeedback para el tratamiento de los trastornos del espectro autista: Una revisión sistemática'. *Revista de Psicopatología y Psicología Clínica*, 20(202), 151–163.

Garfinkel, S. N., Tiley, C., O'Keeffe, S., Harrison, N. A., Seth, A. K. and Critchley, H. D. (2016) Discrepancies between dimensions of interoception in autism: Implications for emotion and anxiety. *Biological Psychology*, 114,117–126.

Geisler, F. C. M., Kubiak, T., Siewert, K. and Weber, H. (2013) Cardiac vagal tone is associated with social engagement and self-regulation. *Biological Psychology*, 93 (2), 279–286.

Geisler, F. C. M., Vennewald, N., Kubiak, T. and Weber, H. (2010) The impact of heart rate variability on subjective well-being is mediated by emotion regulation. *Personality and Individual Differences*, 49 (7), 723–728.

Geschwind, D. H. (2011) Genetics of autism spectrum disorders. *Trends in Cognitive Sciences, 15* (9), 409-416.

Gevirtz, R. (2013a) The nerve of that disease: The vagus nerve and cardiac rehabilitation. *Biofeedback*, 41(1), 32–38.

Gevirtz, R. (2013b) The promise of heart rate variability biofeedback: Evidence-based applications. *Biofeedback*, 41(3), 110–120.

Gevirtz, R. and Dalenberg, C. (2008a) Heart rate variability biofeedback in the treatment of trauma symptoms. *Applied Psychophysiology and Biofeedback*, 22(1), 22–23.

Ghaziuddin, M., Ghaziuddin, N. and Greden, J. (2002) Depression in persons with autism: Implications for research and clinical care. *Journal of Autism and Developmental Disorders*, 32(4), 299–306.

Ghazuddin, M (2005) *Mental Health Aspects of Autism and Asperger Syndrome.* London: Jessica Kingsley.

Gillberg, C., Billstedt, E., Sundh, V. and Gillberg, I. C. (2010) Mortality in autism: A prospective longitudinal community-based study. *Journal of Autism and Developmental Disorders*, 40(3), 352–357.

Gillespie-Lynch, K., Kapp, S. K., Shane-Simpson, C., Shane Smith, D. and Hutman, T. (2014) Intersections between the autism spectrum and the internet: Perceived benefits and preferred functions of computer-mediated communication. *Intellectual and Developmental Disabilities*, 52(6), 456–469.

Ginsberg, J. and Fogo, W. (2014) Perspectives on research on the use of heart rate variability biofeedback for combat-related posttraumatic stress disorder. *Biofeedback,* 42(4), 143–145.

Godlee, F., Smith, J., and Marcovitch, H. (2011) Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ*, 342:c7452.

Goelitz, J. and Lloyd, T. (2012) *Using emWave 2 ® technology for children with ADHD, An evidence-based intervention*. Available at: http://www.heartmath.com/wp-content/uploads/2014/04/adhd_4_10_2012.pdf [Accessed July 10th 2013].

Goessl, V. C., Curtiss, J. E. and Hofmann, S. G. (2017) The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychological Medicine*, 47 (15) 2578-2586.

Golan, O. and Baron-Cohen, S. (2006) Systemizing empathy: Teaching adults with Asperger syndrome or high-functioning autism to recognize complex emotions using interactive multimedia. *Development and Psychopathology*, 18(02), 591–617.

Golan, O., Baron-Cohen, S., Hill, J. J. and Golan, Y. (2006) The "Reading the Mind in Films" Task: Complex emotion recognition in adults with and without autism spectrum conditions. *Social Neuroscience,* 1(2), 111–123.

Goldsmith, T. and LeBlanc, L. (2004) Use of technology in interventions for children with autism. *Journal of Early and Intensive Behavior* 1(2), 166–178.

Goodman, M., Castro, N., Sloan, M., Sharma, R., Widdowson, M., Herrera, E. and Pineda, J. (2018) A neurovisceral approach to autism: Targeting self-regulation and core symptoms using neurofeedback and biofeedback. *NeuroRegulation*, 5(1), 9–29.

Goodwin, M. S., Groden, J., Velicer, W. F. and Diller, A. (2007) Brief report: Validating the Stress Survey Schedule for persons with autism and other developmental disabilities. *Focus on Autism and Other Developmental Disabilities*, 22(3), 183–189

Goodwin, M. S., Groden, J., Velicer, W. F., Lipsitt, L. P., Baron, M. G., Hofmann, S. G. and Groden, G. (2006) Cardiovascular arousal in individuals with autism. *Focus on Autism and Other Developmental Disabilities*, 21(2), 100–123.

Gorman, J. M. and Sloan, R. (2000) Heart rate variability in depressive and anxiety disorders. *American Heart Journal*, 140(4), S77–S83.

Gotink, R. A., Meijboom, R., Vernooij, M. W., Smits, M. and Hunink, M. G. M. (2016) 8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice: A systematic review. *Brain and Cognition*, 108, 32–41.

Gould, J., and Ashton-Smith, J. (2011) Missed diagnosis or misdiagnosis? Girls and women on the autism spectrum. *Good Autism Practice (GAP), 12* (1), 34-41.

Grandin T., (2010) *Temple Grandin and Autism: An MSNBC interview with Joan Raymond*. Available at: https://jezebel.com/5462363/a-bunch-of-social-yak-yaks-temple-grandin-and-autism [Accessed 4th September 2014].

Grandin T., (2011) *An Inside view of Autism*. Available at: https://www.autism.com/advocacy_grandin [Accessed 4th September 2014].

Grandin, T. (2006) *Thinking in pictures: And other reports from my life with autism*. New York NY: Vintage Press.

Grandin, T. *in* Bennie, M., (22 February 2016 Blog) *Stimming the good and bad of anxious behaviours*. Available at: https://autismawarenesscentre.com/stimming-the-good-and-bad-of-anxious-behaviours/ [Accessed 6th September 2017].

Grandin, T., (2015) The way I see it: A personal look at autism and asperger's. *Autism Asperger's Digest*: Arlington TX: Future Horizons Press.

Grandin, T., and Panek, R. (2014) *The Autistic Brain: Helping different kinds of minds succeed*. Boston, MA: Houghton Mifflin Harcourt.

Graneheim, U. H. and Lundman, B. (2004) Qualitative content analysis in nursing research: Concepts, procedures and measures to achieve trustworthiness. *Nurse Education Today*, 24 (2), 105–112.

Graneheim, U. H., Lindgren, B. M. and Lundman, B. (2017) Methodological challenges in qualitative content analysis: A discussion paper. *Nurse Education Today*, 56, 29–34.

Granovetter, M. (2013) Let's talk therapy: Treatments for children with autism. *The Lancet*, 382(9894), 753.

Gray, C. (1994) *Comic Strip Conversations*. Future Horizons: Arlington TX.

Graziano, P. and Derefinko, K. (2013) Cardiac vagal control and children's adaptive functioning: A meta-analysis. *Biological Psychology*, 94 (1), 22–37.

Green, S. A. and Ben-Sasson, A. (2010) Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: Is there a causal relationship? *Journal of Autism and Developmental Disorders*, 40(12), 1495–1504.

Gringras P, Gamble C, J (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo-controlled trial. *BMJ*,345: e6664.

Groden, J., Goodwin, M. S., Baron, M. G., Groden, G., Velicer, W. F., Lipsitt, L. P., ... and Plummer, B. (2005) Assessing cardiovascular responses to stressors in individuals with autism spectrum disorders. *Focus on Autism and Other Developmental Disabilities*, *20* (4), 244-252.

Gross, M. J., Shearer, D. A., Bringer, J. D., Hall, R., Cook, C. J. and Kilduff, L. (2016) Abbreviated resonant frequency training to augment heart rate variability and enhance on-demand emotional egulation in elite sport support staff. *Applied Psychophysiology Biofeedback*, 41(3), 263–274.

Grossman, P. (1993) Respiratory sinus arrhythmia, cardiac vagal tone, and respiration. *Psychophysiology*, 30, 486–495.

Grossman, P. and Taylor, E. W. (2007) Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology*, 74, 263–285.

Grossman, P., Karemaker, J. and Wieling, W. (1991) Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: The need for respiratory control. *Psychophysiology*, 28, 201–216.

Grühn, D. and Scheibe, S. (2008) Age-related differences in valence and arousal ratings of pictures from the International Affective Picture System (IAPS): Do ratings become more extreme with age? *Behavior Research Methods*, 40(2), 512–521.

Grynszpan, O., Weiss, P. L. (Tamar), Perez-Diaz, F. and Gal, E. (2014) Innovative technology-based interventions for autism spectrum disorders: A meta-analysis. *Autism*, 18(4), 346–361.

Guldenring, D., Finlay, D. D., Nelwan, S.P., Nugent, C. D., Donnelly, M.P., and Bond, R. R. (2012) Estimation performance of a reduced lead system during continuous 12-lead ECG ST-segment monitoring. *Journal of Electrocardiology*, *45*(6), 604-608.

Gupta, S. K. (2011) Intention-to-treat concept: a review. *Perspectives in Clinical Research*, *2*(3), 109.

Haensel, A., Mills, P. J., Nelesen, R. A., Ziegler, M. G. and Dimsdale, J. E. (2008) The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. *Psychoneuroendocrinology*, 33(10),1305–1312.

Hamilton, J. L. and Alloy, L. B. (2016) Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research. *Clinical Psychology Review*, 50, 67–79.

Hampton, J. R. (2013) *The ECG Made Easy*. Elsevier Health Sciences.

Hastings, P. D., Nuselovici, J. N., Utendale, W. T., Coutya, J., McShane, K. E. and Sullivan, C. (2008) 'Applying the polyvagal theory to children's emotion regulation: Social context, socialization, and adjustment', *Biological Psychology*, 79(3), 299–306.

Hayano J, Yasuma F, Okada A, (1996) Respiratory sinus arrhythmia: a phenomenon improving pulmonary gas exchange and circulatory efficiency. *Circulation*, 94,842–847.

Hazen, E.P., Stornelli, J. L., O'Rourke, J. a, Koesterer, K. and McDougle, C. J. (2014) Sensory symptoms in autism spectrum disorders. *Harvard Review of Psychiatry*, 22(2), 112–24.

HeartMath Institute (2015) '*Science of the Heart - Volume 2'*.Available at: https://www.heartmath.org/resources/videos/science-of-the-heart/ [Accessed 12th December 2016].

HeartMath LLC, Boulder Creek, California; USA. https://www.heartmath.com/about/ [Accessed 11th July 2013].

Heathers, J. A. (2014) Everything Hertz: methodological issues in short-term frequency-domain HRV. *Frontiers in physiology*, *5*, 177.

Heathers, J. A. J. (2013) Smartphone-enabled pulse rate variability: An alternative methodology for the collection of heart rate variability in psychophysiological research. *International Journal of Psychophysiology*, 89(3), 297–304.

Hedman, E., Miller, L., Schoen, S. and Nielsen, D. (2012) Measuring autonomic arousal during therapy. *Proceedings of 8th International Design and Emotion Conference*: London, 11–14.

Heilman, K. J., and Porges, S. W. (2007) Accuracy of the LifeShirt®(Vivometrics) in the detection of cardiac rhythms. *Biological psychology*, *75*(3), 300-305.

Heilman, K. J., Bal, E. (2007) Respiratory sinus arrhythmia and tympanic membrane compliance predict spontaneous eye gaze behaviors in young children. *Developmental Psychobiology*, (May), 531–542.

Heilman, K. J., Handelman, M., Lewis, G., and Porges, S. W. (2008) Accuracy of the StressEraser® in the detection of cardiac rhythms. *Applied Psychophysiology and Biofeedback*, *33*(2), 83-89.

Henriques, G., Keffer, S., Abrahamson, C. and Horst, S. J. (2011) Exploring the effectiveness of a computer-based heart rate variability biofeedback program in reducing anxiety in college students. *Applied Psychophysiology and Biofeedback*, 36(2), 101–112.

Hickok, G. (2009) Eight problems for the mirror neuron theory of action: Understanding in monkeys and humans. *Journal of Cognitive Neuroscience*., 21(7), 1229–1243.

Hill, E. L. (2004). Executive dysfunction in autism. *Trends in Cognitive Sciences, 8* (1), 26-32.

Hillebrand, S., Gast, K. B., De Mutsert, R., Swenne, C. A., Jukema, J. W., Middeldorp, S., Rosendaal, F. R. and Dekkers, O. M. (2013) Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: Meta-analysis and dose-response meta-regression. *Europace*, 15(5), 742–749.

Hillier, A. J., Fish, T., Siegel, J. H. and Beversdorf, D. Q. (2011) Social and vocational skills training reduces self-reported anxiety and depression among young adults on the autism spectrum. *Journal of Developmental and Physical Disabilities*, 23(3), 267–276.

Hillier, A., Galizzi, M. and Ferrante, K. (2017) Healthcare experiences of young adults with autism spectrum disorder. *Advances in Autism*, 3(4), 206–219.

Hirstein, W., Iversen, P. and Ramachandran, V. S. (2001) Autonomic responses of autistic children to people and objects *Proceedings of the Royal Society B: Biological Sciences*, 268(1479), 1883–1888.

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P. and Bölte, S. (2016) Premature mortality in autism spectrum disorder. *British Journal of Psychiatry*, 208(3), 232–238.

Hoen, P. W., Whooley, M. A., Martens, E. J., Na, B., van Melle, J. and de Jonge, P. (2010) Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease. *Journal of the American College of Cardiology*, 56(11), 838–844.

Hoffmann, A., Ettinger, U., Reyes del Paso, G. A. and Duschek, S. (2017) Executive function and cardiac autonomic regulation in depressive disorders. *Brain and Cognition*, 118(April), 108–117.

Hofmann S.G, Sawyer A.T, Witt A.A, Oh D. (2010) The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology*,78 (2),169–183.

Hollander, E. (2013) Social synchrony and oxytocin: From behavior to genes to therapeutics. *American Journal of Psychiatry*, 170, 1086–1089.

Hollocks, M.J., Howlin, P., Papadopoulos A.S., Khondoker, M. and Simonoff E., (2014) Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. *Psychoneuroendocrinology*, 46, 32-45.

Holtmann, M., Steiner, S., Hohmann, S., Poustka, L., Banaschewski, T., and Bölte, S. (2011) Neurofeedback in autism spectrum disorders. *Developmental Medicine and Child Neurology, 53*(11), 986-993.

Holzman, J. B. and Bridgett, D. J. (2017) Heart rate variability indices as bio-markers of top-down self-regulatory mechanisms: A meta-analytic review. *Neuroscience and Biobehavioral Reviews*, 74, 233–255.

Hon, E. H. (1963) The classification of fetal heart rate (I). A working classification. *Obstetrics and Gynaecology*, *22* (2), 137-146.

Horton, R. (2007) Launching a new movement for mental health. *The Lancet*, *370* (9590), 806.

Hovland, A., Pallesen, S., Hammar, Å., Hansen, A. L., Thayer, J. F., Tarvainen, M. and Nordhus, I. H. (2012) The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. *International Journal of Psychophysiology*, 86(3), 269–275.

Howlin, P. (2000) Outcome in adult life for more able individuals with Autism or Asperger Syndrome. *Autism*, 4 (1), 63–83.

Howlin, P., Magiati, I., and Charman, T., (2009) Systematic review of early intensive behavioral interventions for children with autism. *American Journal on Intellectual and Developmental Disabilities*, 114 (1) 23-41.

Huang, C., Gevirtz, R. N., Onton, J. and Criado, J. R. (2018) Investigation of vagal afferent functioning using the heartbeat event related potential. *International Journal of Psychophysiology*, 131, 113-123.

Hubert, B. E., Wicker, B., Monfardini, E. and Deruelle, C. (2009) Electrodermal reactivity to emotion processing in adults with autistic spectrum disorders. *Autism*, 13 (1), 9–19.

Hughes, P. A. (2008) Instrumentation for Heart Rate Variability Biofeedback: The NeXus System. *Biofeedback*, *36* (1) 10-13.

Huikuri, H. V, Mäkikallio, T., Airaksinen, K. E. J., Mitrani, R., Castellanos, A. and Myerburg, R. J. (1999) Measurement of heart rate variability: a clinical tool or a research toy? *Journal of the American College of Cardiology*, 34 (7), 1878–1883.

Hwang, Y.-S., Kearney, P., Klieve, H., Lang, W., & Roberts, J. (2015) Cultivating mind: Mindfulness interventions for children with Autism Spectrum Disorder and problem behaviours, and their mothers. *Journal of Child and Family Studies*, 24(10), 3093-3106.

Iemmi, V., Knapp, M., and Ragan, I. (2017) *The Autism Dividend: Reaping the Rewards of Better Investment.* London, UK: London School of Economics and Political Science. Available at: http://nationalautismproject.org.uk/wp-content/uploads/2017/01/autism-dividend-report.pdf [Accessed December 2017].

Inner Balance™. Available from: https://www.heartmath.co.uk/shop/ [Accessed July 2014].

Jaarsma, P. and Welin, S. (2012) Autism as a natural human variation: Reflections on the claims of the neurodiversity movement. *Health Care Analysis*, 20 (1), 20–30.

Jackson, L., (2002) *Freaks, Geeks and Aspergers Syndrome: A User Guide to Adolescence*. London UK: Jessica Kingsley.

Jandackova, V. K., Scholes, S., Britton, A. and Steptoe, A. (2016) Are changes in heart rate variability in middle-aged and older people normative or caused by pathological conditions? Findings from a large population-based longitudinal cohort study. *Journal of the American Heart Association*, 5(2), 1–14.

Jarczok, M. N., Jarczok, M., Mauss, D., Koenig, J., Li, J., Herr, R. M. and Thayer, J. F. (2013) Autonomic nervous system activity and workplace stressors — A systematic review. *Neuroscience and Biobehavioral Reviews*, 37 (8), 1810–1823.

Jitlina, K., Zumbo, B., Mirenda, P, Ford, L., Bennett, T., Georgiades, S., Waddell, C., Smith, I. M., Volden, J., Duku, E., Zwaigenbaum, L., Szatmari, P., Vaillancourt, T. and Elsabbagh, M. (2017) Psychometric properties of the Spence Children's Anxiety Scale: Parent report in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 47(12), 3847–3856.

Johnson, C., Burke, C., Brinkman, S. and Wade, T. (2017) A randomized controlled evaluation of a secondary school mindfulness program for early adolescents: Do we have the recipe right yet? *Behaviour Research and Therapy*, 99, 37–46.

Jones, L., Hastings, R. P., Totsika, V., Keane, L., & Rhule, N. (2014) Child behavior problems and parental well-being in families of children with autism: The mediating role of mindfulness and acceptance. *American Journal on Intellectual and Developmental Disabilities*, 119(2), 171-185.

Joseph, V., West, R. M., Shickle, D., Keen, J., and Clamp, S. (2011) Key challenges in the development and implementation of telehealth projects. *Journal of Telemedicine and Telecare*, 17(2), 71-77.

Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG. (1992) Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *American Journal of Psychiatry*, 149, 936–943.

Kabat-Zinn, J. (1982) An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*, 4(1), 33-47.

Kalinowski, A., and Humphreys, K. (2016) Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. *Addiction*, *111* (7), 1293-1298.

Kamen, P. W., Krum, H. and Tonkin, A. M. (1996) Poincaré plot of heart rate variability allows quantitative display of parasympathetic nervous activity in humans. *Clinical Science*, 91(2), 201–8.

Kanne, S. M., Mazurek, M. O., Sikora, D., Bellando, J., Branum-Martin, L., Handen, B., Katz, T., Freedman, B., Powell, M. and Warren, Z. (2014) The autism impact measure (AIM): Initial development of a new tool for treatment outcome measurement. *Journal of Autism and Developmental Disorders*, 44(1), 168–179.

Kanner, L. (1943) Autistic disturbances of affective contact. *Nervous Child*, *2*, 217-250.

Kapp, S. K., Gillespie-Lynch, K., Sherman, L. E. and Hutman, T. (2013) Deficit, difference, or both? Autism and neurodiversity. *Developmental psychology*, 49 (1), 59–71.

Karavidas, M. (2008) Heart rate variability biofeedback for major depression. *Biofeedback*, 36 (1), 18–21.

Karavidas, M.K., Lehrer, M., Vaschillo, E., Vaschillo, B., Marin, H., Buyske, S., Malinovsky, L., Radvanski, D., Hassett, A., (2007) Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Applied Psychophysiology and Biofeedback*, 32, 19-30.

Kazdin, A. E., and Blase, S. L. (2011) Rebooting psychotherapy research and practice to reduce the burden of mental illness. *Perspectives on psychological science*, *6* (1), 21-37.

Keenan-Mount, R., Albrecht, N. J., & Waters, L. (2016) Mindfulness-based approaches for young people with autism spectrum disorder and their caregivers: Do these approaches hold benefits for teachers? *Australian Journal of Teacher Education*, 41(6), 5.

Kemp, A. H. and Quintana, D. S. (2013) The relationship between mental and physical health: Insights from the study of heart rate variability. *International Journal of Psychophysiology*, 89(3), 288–296.

Kemp, A. H., Brunoni, A. R., Santos, I. S., Nunes, M. A., Dantas, E. M., De Figueiredo, R. C., Pereira, A. C., Ribeiro, A. L., Mill, J. G., Andreão, R. V., Thayer, J. F., Benseñor, I. M. and Lotufo, P.A. (2014) Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: An ELSA-Brasil cohort baseline study. *American Journal of Psychiatry*, 171(12),1328–1334.

Kemp, A. H., Koenig, J. and Thayer, J. F. (2017a) From psychological moments to mortality: A multidisciplinary synthesis on heart rate variability spanning the continuum of time. *Neuroscience and Biobehavioral Reviews*, 83, 547–567.

Kemp, A. H., López, S. R., Passos, V. M. A., Bittencourt, M. S., Dantas, E. M., Mill, J. G., Ribeiro, A. L., Thayer, J. F., Bensenor, I. M. and Lotufo, P. A. (2016) Insulin resistance and carotid intima-media thickness mediate the association between resting-state heart rate variability and executive function: A path modelling study. *Biological Psychology*, 117, 216–224.

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K. and Gatt, J. M. (2010) Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry*, 67(11), 1067–1074.

Kemp, A. H., Quintana, D. S., Kuhnert, R. L., Griffiths, K., Hickie, I. B., and Guastella, A. J. (2012) Oxytocin increases heart rate variability in humans at rest: implications for social approach-related motivation and capacity for social engagement. *PLoS One*, *7*(8), e44014.

Kemp, A. H., Quintana, D. S., Quinn, C. R., Hopkinson, P. and Harris, A. W. F. (2014) Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: Implications for future morbidity and mortality. *Frontiers in Psychology*, 5(NOV),1387.

Keng, S. L., Smoski, M. J. and Robins, C. J. (2011) Effects of mindfulness on psychological health: A review of empirical studies. *Clinical Psychology Review*, 31(6), 1041–1056.

Kennedy, J. J. and Pretorius, M. (2008) Integrating a portable biofeedback device into call centre environments to reduce employee stress: Results from two pilot studies. *Journal of Workplace Behavioral Health*, 23(3), 295–307.

Kennedy, L. and Parker, S. H. (2018) Biofeedback as a stress management tool: a systematic review. *Cognition, Technology and Work*. 1-30.

Kerns, C. M., Kendall, P. C., Zickgraf, H., Franklin, M. E., Miller, J. and Herrington, J. (2015) Not to be overshadowed or overlooked: Functional impairments associated with comorbid anxiety disorders in youth with ASD. *Behavior Therapy*, 46 (1), 29–39.

Kerns, C.M., Kendall, P. Berry, L., Souders, M.C., Franklin, M.E., Schultz, R.T., (2014) Traditional and atypical presentations of anxiety in youth with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 44, 2851-2861.

Kessler, R. and Glasgow, R. E. (2011) A proposal to speed translation of healthcare research into practice: Dramatic change is needed. *American Journal of Preventive Medicine*, 40(6), 637–644.

Kessler, R. C., Soukup, J., Davis, R. B., Foster, D. F., Wilkey, S. A., Van Rompay, M. I., and Eisenberg, D. M. (2001) The use of complementary and alternative therapies to treat anxiety and depression in the United States. *American Journal of Psychiatry*, *158*(2), 289-294.

Khazan, I. Z. (2013) *The Clinical Handbook of Biofeedback: A step-by-step guide for training and practice with mindfulness*. Chichester UK: John Wiley and Sons.

Kientz, M.A. and Dunn, W., (1997) A comparison of the performance of children with and without autism on the Sensory Profile. *American Journal of Occupational Therapy, 51*(7), 530-537.

Kim, H.-G., Cheon, E.-J., Bai, D.-S., Lee, Y. H. and Koo, B.-H. (2018b) Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry Investigation*, 15(3), 235–245.

Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., and Song, D. H. (2011) Prevalence of autism spectrum disorders in a total population sample. *American Journal of Psychiatry*, *168*(9), 904-912.

Kleen, M. and Reitsma, B. (2011) Appliance of heart rate variability biofeedback in acceptance and commitment therapy: A pilot study. *Journal of Neurotherapy*, 15(2), 170–181.

Kleiger, R. E. (1995) Heart rate variability and mortality and sudden death post infarction. *Journal of Cardiovascular Electrophysiology*, *6* (5), 365-367.

Klusek, J., Roberts, J.E., Losh, M. (2015) 'Cardiac autonomic regulation in autism syndrome: A Review', *Psychological Bulletin*, 141(1), 141–175.

Knapp, M., Romeo, R., and Beecham, J. (2009) Economic cost of autism in the UK. *Autism*, *13* (3), 317-336.

Knott, F., Dunlop, A. W. and Mackay, T. (2006) Living with ASD: How do children and their parents assess their difficulties with social interaction and understanding? *Autism*, 10(6), 609–617.

Koenig, J. and Thayer, J. F. (2016) Sex differences in healthy human heart rate variability: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, 64, 288–310.

Koenig, J., Kemp, A. H., Beauchaine, T.P., Thayer, J. F. and Kaess, M. (2016) Depression and resting state heart rate variability in children and adolescents - A systematic review and meta-analysis. *Clinical Psychology Review*, 46, 136–150.

Koenig, J., Rash, J. A., Campbell, T. S., Thayer, J. F. and Kaess, M. (2017) A meta-analysis on sex differences in resting-state vagal activity in children and adolescents. *Frontiers in Physiology*, 8(AUG), 582.

Koenig, J., Williams, D.P., Kemp, A. H. and Thayer, J. F. (2016) Vagally mediated heart rate variability in headache patients-a systematic review and meta-analysis. *Cephalalgia*, 36(3), 265–278.

Koh, C. E., Young, C. J., Young, J. M. and Solomon, M. J. (2008) Systematic review of randomized controlled trials of the effectiveness of biofeedback for pelvic floor dysfunction. *British Journal of Surgery*, 95(9), 1079–1087.

Kotozaki, Y., Takeuchi, H., Sekiguchi, A., Yamamoto, Y. and Shinada, T. (2014a) Biofeedback-based training for stress management in daily hassles: an intervention study. *Brain and Behaviour*, 4(4), 566–579.

Kouijzer, M. E. J., van Schie, H. T., Gerrits, B. J. L., Buitelaar, J. K. and de Moor, J. M. H. (2013) Is EEG-biofeedback an effective treatment in autism spectrum disorders? A randomized controlled trial. *Applied Psychophysiology and Biofeedback*, 38(1), 17–28.

Krasnikov, G. V., Tyurina, M. Y., Tankanag, A. V., Piskunova, G. M. and Chemeris, N. K. (2013) Analysis of heart rate variability and skin blood flow oscillations under deep controlled breathing. *Respiratory Physiology and Neurobiology*, 185(3), 562–570.

Kreibig, S. D. (2010) Autonomic nervous system activity in emotion: A review. *Biological Psychology*, 84(3), 394–421.

Krivonogova, E. (2013) Non-communicable disease epidemic: epidemiology in action (EuroEpi 2013 and NordicEpi 2013): Aarhus, Denmark 11 to 14 August 2013. *European Journal of Epidemiology*, 28 (1).130.

Krygier, J. R., Heathers, J. A. J., Shahrestani, S., Abbott, M., Gross, J. J. and Kemp, A. H. (2013) Mindfulness meditation, well-being, and heart rate variability: A preliminary investigation into the impact of intensive vipassana meditation. *International Journal of Psychophysiology*, 89 (3), 305–313.

Kushki, A., Brian, J., Dupuis, A. and Anagnostou, E. (2014) Functional autonomic nervous system profile in children with autism spectrum disorder. *Molecular Autism*, 5, 39.

Kushki, A., Drumm, E., Pla Mobarak, M., Tanel, N., Dupuis, A., Chau, T. and Anagnostou, E. (2013) Investigating the autonomic nervous system response to anxiety in children with autism spectrum disorders. *PLoS ONE*, 8(4), e59730.

Kuss, O., Schumann, B., Kluttig, A., Greiser, K. H. and Haerting, J. (2008) Time domain parameters can be estimated with less statistical error than frequency domain parameters in the analysis of heart rate variability. *Journal of Electrocardiology*, 41(4), 287–291.

La Rovere, M. T., Pinna, G. D., Maestri, R., Mortara, A., Capomolla, S., Febo, O., Ferrari, R., Franchini, M., Gnemmi, M., Opasich, C., Riccardi, P G., Traversi, E. and Cobelli, F. (2003) Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*, 107(4), 565–570.

La Vaque, T. J., Hammond, D. C., Trudeau, D., Monastra, V., Perry, J., Lehrer, P., and Sherman, R. (2002) Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological evaluations. *Applied Psychophysiology and Biofeedback*, 27, 273–281.

Lai, M.-C., Lombardo, M. V and Baron-Cohen, S. (2014) Autism. *The Lancet*, 383(9920), 896–910.

Lancaster, G. (2004) Planning complex interventions using pilot and feasibility studies: what is good practice? *Centre for Excellence in Teaching and Learning*. Available at: http://www.uhbristol.nhs.uk/media/2517305/glancaster_talk_pilot [Accessed: 2nd July 2013].

Lancaster, G., Lancaster, G. A., Dodd, S. and Williamson, P. R. (2004) Design and analysis of pilot studies: recommendations for good practice. *Journal of Evaluation in Clinical Practice*, 10(2), 307–312.

Lande, R. G., Williams, L. B., Francis, J. L., Gragnani, C. and Morin, M. L. (2010) Efficacy of biofeedback for post-traumatic stress disorder. *Complementary Therapies in Medicine*, 18(6), 256–259.

Lane, R. D., McRae, K., Reiman, E. M., Chen, K., Ahern, G. L. and Thayer, J. F. (2009) Neural correlates of heart rate variability during emotion. *NeuroImage*, 44(1), 213–222.

Lang, P. J. (2014) 'Emotion's response patterns: The brain and the autonomic nervous system', *Emotion Review*, 6(2), 93–99.

Lang, P. J., Bradley, M. M. and Cuthbert, B. N. (1997) 'International Affective Picture System' (IAPS): Technical Manual and Affective Ratings. *NIMH Center for the Study of Emotion and Attention.* Gainsville FL: University of Florida.

Lang, P. J., McTeague, L. M. and Bradley, M. M. (2014) Pathological anxiety and function/dysfunction in the brain's fear/defense circuitry. *Restorative Neurology and Neuroscience*, 32(1), 63–77.

Lang, P.J., Bradley, M.M. and Cuthbert, B.N., (1998) Emotion and motivation: measuring affective perception. *Journal of Clinical Neurophysiology*, *15*(5), 397-408.

Lavalley, M. (2003) 'Intent-to-treat' analysis of randomized clinical trials. Available at: http://people.bu.edu/mlava/ [Accessed: April 2014].

LaVaque, T.J., Hammond, D.C., Trudeau, D., Monastra, V., Perry, J., Lehrer, P., Matheson, D., and Sherman, R. (2002) Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological evaluations. *Applied Psychophysiology and Biofeedback, 27*(4), 273-281. Copublished in *Journal of Neurotherapy, 6*(4), 11-23.

Lehrer P.M., Irvin, C.G., Lu, S-E. Scardella, A., (2018) Heart rate variability biofeedback does not substitute for asthma controller medication. *Applied Psychophysiology and Biofeedback*, 43, 57-73.

Lehrer, P. M. and Gevirtz, R. (2014) Heart rate variability biofeedback: How and why does it work? *Frontiers in Psychology*, 5(JUL), 756.

Lehrer, P. M., Vaschillo, E. and Vaschillo, B. (2000) Resonant frequency biofeedback training to increase cardiac variability: Rationale and manual for training. *Applied Psychophysiology Biofeedback*, 25(3), 177–191.

Lehrer, P. M., Vaschillo, E., Vaschillo, B., Lu, S.-E., Scardella, A., Siddique, M. and Habib, R. H. (2004) Biofeedback treatment for asthma. *Chest*, 126(2), 352–61.

Lehrer, P. (2013a) How does heart rate variability biofeedback work? Resonance, the baroreflex, and other mechanisms. *Biofeedback*, 41(1), 26–31.

Lehrer, P. (2017. Biofeedback: An important but often-ignored ingredient in psychotherapy. *Policy Insights from the Behavioral and Brain Sciences*, 4(1), 57-63.

Lehrer, P. and Vaschillo, E. (2006) Heart rate variability biofeedback: Effects of age on heart rate variability and baroreflex. *Chest*, 129(2), 278–284.

Lehrer, P. and Vaschillo, E. (2008) The future of heart rate variability biofeedback. *Biofeedback*, 36(1), 11–14.

Lehrer, P., Carr, R. E., Smetankine, A., Vaschillo, E., Peper, E., Porges, S., and Hochron, S. (1997) Respiratory sinus arrhythmia versus neck/trapezius EMG and incentive inspirometry biofeedback for asthma: A pilot study. *Applied Psychophysiology and Biofeedback*, *22*(2), 95-109.

Lehrer, P., Eddie, D. (2013) Dynamic processes in regulation and some implications for biofeedback and biobehavioral interventions. *Applied Psychophysiology and Biofeedback*, 38(2), 143–155.

Lehrer, P., Smetankin, A. and Potapova, T. (2000) Respiratory sinus arrhythmia biofeedback therapy for asthma: A report of 20 unmedicated pediatric cases using the Smetankin method. *Applied Psychophysiology and Biofeedback*, 25(3), 193–199.

Lehrer, P., Vaschillo, B., Zucker, T., Graves, J., Katsamanis, M., Aviles, M. and Wamboldt, F. (2013) Protocol for heart rate variability biofeedback training. *Biofeedback*, 41(3), 98–109.

Lehrer, P. (2013b) History of heart rate variability biofeedback research: A personal and scientific voyage. *Biofeedback*, 41(3), 88–97.

Lehrer, P. (2003) Applied psychophysiology: Beyond the boundaries of biofeedback. *Applied Psychophysiology and Biofeedback*, 28(4), 291–304.

Lemaire, J. B., Wallace, J. E., Lewin, A. M., de Grood, J. and Schaefer, J. (2011) The effect of a biofeedback-based stress management tool on physician stress: A randomized controlled clinical trial. *Open Medicine*, 5(4), 154–165.

Levati, S., Campbell, P., Frost, R., Dougall, N., Wells, M., Donaldson, C. and Hagen, S. (2016) Optimisation of complex health interventions prior to a randomised controlled trial: a scoping review of strategies used. *Pilot and Feasibility Studies*, 2(17), 1–17

Levine, J. C., Fleming, R., Piedmont, J. I., Cain, S. M. and Chen, W. J. (2016) Heart rate variability and generalized anxiety disorder during laboratory-induced worry and aversive imagery. *Journal of Affective Disorders*, 205, 207–215.

Levinson, M. (2007) The Autism–epilepsy connection. *Epilepsia*, *48* (9):33-35.

Levy, A., and Perry, A. (2011) Outcomes in adolescents and adults with autism: A review of the literature. *Research in Autism Spectrum Disorders*, *5*(4), 1271-1282.

Levy, S. E., Mandell, D. S. and Schultz, R. T. (2009) Autism. *The Lancet*, 374(9701), 1627–1638.

Lewin, S., Glenton, C. and Oxman, A. D. (2009) Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ*, 339, b3496–b3496.

Lewis, G. F., Furman, S. A., McCool, M. F. and Porges, S. W. (2012) Statistical strategies to quantify respiratory sinus arrhythmia: Are commonly used metrics equivalent? *Biological Psychology*, 89(2), 349–364.

Lewis, J. R. and Sauro, J. (2009) The factor structure of the System Usability Scale. In: Kurosu M. (eds.) *Human Centered Design, Lecture notes in Computer Science*, 5619, 94-103.

Leyfer, O. T., Folstein, S. E., Bacalman, S., Davis, N. O., Dinh, E., Morgan, J., Tager-Flusberg, H. and Lainhart, J. E. (2006) Comorbid psychiatric disorders in children with autism: Interview development and rates of disorders. *Journal of Autism and Developmental Disorders*, 36(7), 849–861.

Li, X., Zhang, T., Song, L.-, Zhang, Y., Zhang, G.-G., Xing, C.-X. and Chen, H. (2015) Effects of heart rate variability biofeedback therapy on patients with poststroke depression: A case study. *Chinese Medical Journal*, 128(18), 2542.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. A. and Clarke, M. (2009) The PRISMA Statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLOS Medicine*, 6(7), 1–28.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. A., Clarke, M., Devereaux, P. J., Kleijnen, J. and Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*, 62(10), e1-34.

Liddell, B. J., Kemp, A. H., Steel, Z., Nickerson, A., Bryant, R. A., Tam, N., Tay, A. K. and Silove, D. (2016) Heart rate variability and the relationship between trauma exposure age, and psychopathology in a post-conflict setting. *BMC Psychiatry*, 16(1), 1–10.

Lin, I. M., Tai, L. Y. and Fan, S. Y. (2014) Breathing at a rate of 5.5 breaths per minute with equal inhalation-to-exhalation ratio increases heart rate variability. *International Journal of Psychophysiology*, 91(3), 206–211.

Lin, I.-M., Fan, S.-Y., Lu, H.-C., Lin, T.-H., Chu, C.-S., Kuo, H.-F., Lee, C.-S. and Lu, Y.-H. (2015) Randomized controlled trial of heart rate variability biofeedback in cardiac autonomic and hostility among patients with coronary artery disease. *Behaviour Research and Therapy*, 70, 38–46.

Lin, S. L., Huang, C. Y., Shiu, S. and Yeh, S. H. (2015) Effects of yoga on stress, stress adaption, and heart rate variability among mental health professionals - A randomized controlled trial. *Worldviews on Evidence-Based Nursing*, 12(4).

Lipsky, D. (2011) *From Anxiety to Meltdown*: *How Individuals on the Autistic Spectrum Deal with Anxiety, Experience Meltdowns, Manifest Tantrums, and How You Can Intervene Effectively*. Philadelphia, PA: Jessica Kingsley.

Lischke, A., Lemke, D., Neubert, J., Hamm, A. O. and Lotze, M. (2017) Inter-individual differences in heart rate variability are associated with inter-individual differences in mind-reading. *Scientific Reports*, 7(1), 1–7.

Lischke, A., Pahnke, R., Mau-Moeller, A., Behrens, M., Grabe, H. J., Freyberger, H. J., Hamm, A. O. and Weippert, M. (2018) Inter-individual differences in heart rate variability are associated with inter-individual differences in empathy and alexithymia. *Frontiers in Psychology*, 9(February), 1–9.

Lloyd, A., Brett, D. and Wesnes, K. (2010) Coherence training in children with attention-deficit hyperactivity disorder: cognitive functions and behavioral changes. *Alternative Therapies in Health and Medicine*, 16(4), 34–42.

Lobel, A., Engels, R. C. M. E., Stone, L. L., Burk, W. J. and Granic, I. (2017) Video gaming and children's psychosocial wellbeing: A longitudinal study. *Journal of Youth and Adolescence*, 46(4), 884–897.

Lofthouse, N., Hendren, R, Hurt, E. Arnold, E. and Butter E, (2012) *Autism Research and Treatment*, Article ID: 870391, 1-22.

Lombardi, F., Huikuri, H., Schmidt, G., and Malik, M. (2018) Short-term heart rate variability: easy to measure, difficult to interpret. *Heart Rhythm*, 15 (10), 1559-1560. [Accessed online 2nd September 2018].

Lord C. Rutter M., (2001) Autism Diagnostic Observation Schedule Available from; https://www.hogrefe.co.uk/shop/autism-diagnostic-observation-schedule-2nd-edition.html [Accessed: 24 July 2013].

Lord, C., and Jones, R. M. (2012) Annual Research Review: Re-thinking the classification of autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *53*(5), 490-509.

Lotter, V. (1966) Epidemiology of autistic conditions in young children - 1. Prevalence. *Social Psychiatry*, 1(3), 124–135.

Louwerse, A., Tulen, J. H. M., van der Geest, J. N., van der Ende, J., Verhulst, F. C. and Greaves-Lord, K. (2014) Autonomic responses to social and nonsocial pictures in adolescents with autism spectrum disorder. *Autism Research*, 7(1), 17–27.

Lucena, F. (2011) Statistical coding and decoding of heartbeat intervals. *PLoS ONE*, 6(6), 1–13.

Lugnegård, T., Hallerbäck, M. U., and Gillberg, C. (2011) Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Research in Developmental Disabilities*, *32*(5), 1910-1917.

Lydon, S., Healy, O., Reed, P., Mulhern, T., Hughes, B. M. and Goodwin, M. S. (2014) A systematic review of physiological reactivity to stimuli in autism. *Developmental Neurorehabilitation*, 8423(September), 1–21.

MacKinnon, S., Gevirtz, R., McCraty, R. and Brown, M. (2013) Utilizing heartbeat evoked potentials to identify cardiac regulation of vagal afferents during emotion and resonant breathing. *Applied Psychophysiology Biofeedback*, 38(4) 241-255.

Madders, T. (2010) '*You Need to Know', National Autistic Society* s, 1–31. Available at: http://www.autism.org.uk/get-involved/campaign/successes/reports/you-need-to-know.aspx. [Accessed: September 2011].

Maddox, B., Miyazaki, Y., and White S. W. (2017) Long-term effects of CBT on social impairment in adolescents with ASD. *Journal of Autism and Developmental Disorders* 47, 3872–3882.

Magiati, I., Lerh, J. W., Hollocks, M. J., Uljarevic, M., Rodgers, J., McConachie, H., Ozsivadjian, A., South, M., Van Hecke, A., Hardan, A., Libove, R., Leekam, S. and Simonoff, E. (2017) The measurement properties of the spence children's anxiety scale-parent version in a large international pooled sample of young people with autism spectrum disorder. *Autism Research*, 10(10), 1629–1652.

Maglione, M. A., Gans, D., Das, L., Timbie, J. and Kasari, C. (2012) Nonmedical interventions for children with ASD: Recommended guidelines and further research needs. *Pediatrics*, 130(Supplement), S169–S178.

Malik, M. and Camm, A. J. (1993) Components of heart rate variability - what they really mean and what we really measure. *The American Journal of Cardiology*, 72(11), 821–822.

Malik, M., Bigger, J., Camm, A. and Kleiger, R. (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *European Heart Journal*, *17*, 354–381.

Markram, H. (2007) 'The intense world syndrome' – an alternative hypothesis for autism. *Frontiers in Neuroscience*, 1(1), 77–96.

Mather, M. and Thayer, J. F. (2018) How heart rate variability affects emotion regulation brain networks. *Current Opinion in Behavioral Sciences*, 19, 98–104.

Matson, J. L. and Cervantes, P. E. (2014) Commonly studied comorbid psychopathologies among persons with autism spectrum disorder. *Research in Developmental Disabilities*, 35(5), 952–962.

Matson, J. L., Benavidez, D. A., Compton, L. S., Paclawskyj, T., and Baglio, C. (1996) Behavioral treatment of autistic persons: A review of research from 1980 to the present. *Research in Developmental Disabilities*, *17*(6), 433-465.

Matsushima, K., Matsubayashi, J., Toichi, M., Funabiki, Y., Kato, T., Awaya, T. and Kato, T. (2016) Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum disorders. *Research in Autism Spectrum Disorders*, 25, 37–46.

Matto D. (2013) The added advantage of the psychophysiological stress profile. *Psychophysiology Today* 8 (1) 5-9.

Mazefsky, C. A., Herrington, J., Siegel, M., Scarpa, A., Maddox, B. B., Scahill, L. and White, S. W. (2013) The role of emotion regulation in autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(e1527–5418) 679–688.

Mazurek, M. O., Handen, B. L., Wodka, E. L., Nowinski, L., Butter, E., and Engelhardt, C. R. (2014). Age at first autism spectrum disorder diagnosis: The role of birth cohort, demographic factors, and clinical features. *Journal of Developmental and Behavioral Pediatrics*, *35*(9), 561-569.

Mazzone, L., Ruta, L. and Reale, L. (2012) Psychiatric comorbidities in Asperger syndrome and high functioning autism: diagnostic challenges. *Annals of General Psychiatry*, 11(1), 16.

McCambridge, J., Witton, J. and Elbourne, D. R. (2014) Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects. *Journal of Clinical Epidemiology*, 67 (3), 267–277.

McCoy, K.M., Westlake, G. Zucker, S.H. DiGangi, S. A. (2014) Evaluation of a biofeedback intervention in college students diagnosed with an autism spectrum disorder. *Journal of the Division of Autism and Developmental Disorders (DADD)*, 1(1), 121–135.

McCraty, R. (2005) Enhancing emotional, social, and academic learning with heart rhythm coherence feedback. *Biofeedback*, 33(4)130–134.

McCraty, R. (2007) HRV: From depletion to renewal: Positive emotions and heart rhythm coherence feedback. *Psychophysiology*, 36 (1), 30–34.

McCraty, R. (2017) New frontiers in heart rate variability and social coherence research: techniques, technologies, and implications for improving group dynamics and outcomes. *Frontiers in Public Health*, 5(October), 1–13.

McCraty, R. and Atkinson, M. (2012) Resilience training program reduces physiological and psychological stress in police officers. *Global Advances in Health and Medicine*, 1(5), 44–66.

McCraty, R. and Shaffer, F. (2015) Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Global Advances in Health and Medicine*, 4 (1), 6–61.

McCraty, R. and Zayas, M. A. (2014) Cardiac coherence, self-regulation, autonomic stability and psychosocial well-being. *Frontiers in Psychology*, 5, 1–13.

McCraty, R., and Childre, D. (2010) Coherence: bridging personal, social, and global health. *Alternative Therapies in Health and Medicine*, *16* (4), 10-24.

McCraty, R., Atkinson, M., and Bradley, R. T. (2004) Electrophysiological evidence of intuition: Part 1. The surprising role of the heart. *The Journal of Alternative and Complementary Medicine*, *10* (1), 133-143.

McCraty, R., Atkinson, M., Stolc, V., Alabdulgader, A., Vainoras, A. and Ragulskis, M. (2017) Synchronization of human autonomic nervous system rhythms with geomagnetic activity in human subjects. *International Journal of Environmental Research and Public Health*, 14 (7), 770.

McCraty, R., Atkinson, M., Tiller, W. A., Rein, G. and Watkins, A. D. (1995) The effects of emotions on short-term power spectrum analysis of heart rate variability. *The American Journal of Cardiology*, 76(14), 1089–1093.

McCraty, R., Atkinson, M., Tomasino, D. and Bradley, R. T. (2009) The coherent heart: Heart-brain interactions, psychophysiological coherence, and the emergence of system-wide order. *Integral Review*, 5(2), 10–115.

McDonnell, A., McCreadie, M., Mills, R., Deveau, R., Anker, R. and Hayden, J. (2015) The role of physiological arousal in the management of challenging behaviours in individuals with autistic spectrum disorders. *Research in Developmental Disabilities*, 36, 311–322.

Mcgoey, T., Root, Z., Bruner, M. W. and Law, B. (2016) Evaluation of physical activity interventions in children via the reach, efficacy/effectiveness, adoption, implementation, and maintenance (RE-AIM) framework: A systematic review of randomized and non-randomized trials. *Preventive Medicine*, 82, 8–19.

McKee, M. G. (2008) Biofeedback: An overview in the context of heart-brain medicine. *Cleveland Clinic Journal of Medicine*, 75(2), 31–34.

McManis, M. H., Bradley, M. M., Berg, W. K., Cuthbert, B. N. and Lang, P. J. (2001) Emotional reactions in children: Verbal, physiological, and behavioral responses to affective pictures. *Psychophysiology*, 38(2), 222–231.

McPartland, J. C., Webb, S. J., Keehn, B., and Dawson, G. (2011) Patterns of visual attention to faces and objects in autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *41*(2), 148-157.

McPheeters, M.L., Warren Z., Sathe N., (2011) A systematic review of medical treatments for children with autism spectrum disorders. *Pediatric*s,127(5) 1312-1321.

McSweeney, L., Araújo-Soares, V., Rapley, T. and Adamson, A. (2017) A feasibility study with process evaluation of a preschool intervention to improve child and family lifestyle behaviours. *BMC Public Health*, 17(1), 248.

Meckley, A. (2013) Balancing unbalanced breathing: The clinical use of capnographic biofeedback. *Biofeedback*, 41(4), 183–187.

Medical Research Council (2000) A framework for development and evaluation of RCTs for complex interventions to improve health: MRC. Available at: https://www.mrc.ac.uk/documents/pdf/rcts-for-complex-interventions-to-improve-health/[Accessed: 24 July 2014].

Medical Research Council (2010) Review of Mental Health Research - Report of the Strategic Review Group 2010. Available at: https://www.mrc.ac.uk/documents/pdf/mrc-mental-health-research-report-2010/ [Accessed: 19 October 2017].

Medical Research Council (2010) Review of Mental Health Research - Report of the Strategic Review Group 2010. Available at: https://www.mrc.ac.uk/documents/pdf/mrc-review-of-mental-health-research-2010/ [Accessed: 24 July 2014].

Medical Research Council (2016) MRC Delivery Plan. Available at: https://www.mrc.ac.uk/publications/browse/mrc-delivery-plan-2016-2020/ [Accessed: 19 October 2017].

Medical Research Council (2017) Strategy for lifelong mental health: Research leading science for better health. Available at: https://www.mrc.ac.uk/documents/pdf/strategy-for-lifelong-mental-health-research/ [Accessed: 19 October 2017].

Meier, N. F. and Welch, A. S. (2016b) Walking versus biofeedback: a comparison of acute interventions for stressed students. *Anxiety, Stress and Coping*, 29(5), 463–478.

Meijer, A., Conradi, H. J., Bos, E. H., Anselmino, M., Carney, R. M., Denollet, J., Doyle, F., Freedland, K. E., Grace, S. L., Hosseini, S. H., Lane, D. A., Pilote, L., Parakh, K., Rafanelli, C., Sato, H., Steeds, R.P., Welin, C. and De Jonge, (2013) Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: Individual patient data meta-analysis. *British Journal of Psychiatry*, 203(2), 90–102.

Michels, N., Clays, E., De Buyzere, M., Huybrechts, I., Marild, S., Vanaelst, B., De Henauw, S. and Sioen, I. (2013) Determinants and reference values of short-term heart rate variability in children. *European Journal of Applied Physiology*, 113(6), 1477–1488.

Mikels, J. A., Fredrickson, B. L., Larkin, G. R., Lindberg, C. M., Maglio, S. J. and Reuter-Lorenz, P. A. (2005) Emotional category data on images from the international affective picture system. *Behavior Research Methods*, 37(4), 626–630.

Mills, R. (2017) *Stress, Autism and Research: An interview with Richard Mills'*. Available at: http://network.autism.org.uk/sites/default/files/ckfinder/files/ [Accessed: 12 December 2017].

Ming, X., Bain, J.M., Smith, D., Brimacombe, M., Gold Von-Simson, G., Axelrod, F.B., (2011) Assessing autonomic dysfunction symptoms in children: Pilot study. *Journal of Child Neurology*, 26, 420-427.

Ming, X., Julu, P. O. O., Brimacombe, M., Connor, S. and Daniels, M. L. (2005) Reduced cardiac parasympathetic activity in children with autism. *Brain and Development*, 27(7), 509–516.

Ming, X., Patel, R., Kang, V., Chokroverty, S. and Julu, P. O. (2016) Respiratory and autonomic dysfunction in children with autism spectrum disorders. *Brain and Development*, 38(2), 225–232.

Mintz, J. (2013) Additional key factors mediating the use of a mobile technology tool designed to develop social and life skills in children with autism spectrum disorders: Evaluation of the 2nd HANDS prototype. *Computers and Education, 63*, 17-27.

Miu, A. C., Heilman, R. M. and Miclea, M. (2009) Reduced heart rate variability and vagal tone in anxiety: Trait versus state, and the effects of autogenic training. *Autonomic Neuroscience: Basic and Clinical*, 145(1–2), 99–103.

Mockford, C., Staniszewska, S., Griffiths, F. and Herron-Marx, S. (2012) The impact of patient and public involvement on UK NHS health care: a systematic review. *International Journal for Quality in Health Care*, 24(1), 28–38. Available at: http://dx.doi.org/10.1093/intqhc/mzr066. [Accessed: June 2017].

Moher, D; Liberati, A; Tetzlaff, J. and Altman, D. (2010) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Preferred Reporting Items for Systematic reviews and Meta-Analyses', *British Medical Journal* (Overseas and Retired Doctors Edition), 8, b2535.

Montano, N., Porta, A., Cogliati, C., Costantino, G., Tobaldini, E., Casali, K. R. and Iellamo, F. (2009) Heart rate variability explored in the frequency domain: A tool to investigate the link between heart and behavior. *Neuroscience and Biobehavioral Reviews*, 33(2), 71–80.

Montaque, I., Dallos, R., and McKenzie, B. (2018) "It feels like something difficult is coming back to haunt me": An exploration of 'meltdowns' associated with autistic spectrum disorder from a parental perspective. *Clinical Child Psychology and Psychiatry, 23*(1), 125-139.

Montgomery, J., Banner, M., Burls, A., Caney, S., Farsides, B., Gallagher, A., Gill, R., Greenfield, A., Haimes, E., Hughes, J., Jackson, R., Laurie, G., Lawrence, D., Lewens, T., Leyser, O. and Lucassen, A. (2015) *Children and Clinical Research: Ethical Issues.* Available at: http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf. [Accessed: 2nd July 2014].

Moore, G. (2014) *The Imitation Game.* Screen play. New York: The Weinstein Company.

Moore, G., Audrey, S., Barker, M., Bond, L., Bonell, C., Hardeman, W., Moore, L., O'Cathain, A., Tinati, T., Wight, D. and Baird, J. (2010) *Process evaluation of complex interventions UK Medical Research Council (MRC) guidance.* Available at: https://www.mrc.ac.uk/documents/pdf/mrc-phsrn-process-evaluation-guidance-final/ [Accessed January 2014].

Moravec, C. S. and McKee, M. G. (2013) Psychophysiologic remodelling of the failing human heart. *Biofeedback*, 41(1), 7–12.

Moravec, Christine S; McKee, M. G. (2010) Abstract 9: Multidisciplinary research in biofeedback. *Cleveland Clinic Journal of Medicine*, 77, supplement 3; S85a.

Moree, B.N. and Davis III, T.E., (2010) Cognitive-behavioral therapy for anxiety in children diagnosed with autism spectrum disorders: Modification trends. *Research in Autism Spectrum Disorders*, 4 (3), 346 – 354.

Morgan, S.M., Mora, J. A. (2017) Effect of heart rate variability biofeedback on sport performance, a systematic review. *Applied Psychophysiology and Biofeedback*, 42 (3), 235-245.

Morris, S. B. and DeShon, R. (2002) Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychological Methods*, 7(1), 105–125.

Moseley, D. S., Tonge, B. J., Brereton, A. V and Einfeld, S. L. (2011) Psychiatric comorbidity in adolescents and young adults with autism. *Journal of Mental Health Research in Intellectual Disabilities*, 4(4), 29–243.

Moss, D. (2008a) Special issue: The emergent science and practice of heart rate variability biofeedback. *Biofeedback*, 36(1),1–4.

Moss, D. (2008b) Special Issue: The psychophysiology of respiration and the effects of breath training. *Biofeedback*, 36(2), 43–44.

Moss, D. and Shaffer, F. (2017) The application of heart rate variability biofeedback to medical and mental health disorders. *Biofeedback*, 45(1), 2–8.

Moss, D., Lagos, L. and Shaffer, F. (2013) 'Don't add or miss a beat': A special issue on current evidence and current practice in heart rate variability biofeedback. *Biofeedback*, 41(3), 83–84.

Mottron, L. (2017) Should we change targets and methods of early intervention in autism, in favor of a strengths-based education? *European Child and Adolescent Psychiatry*, 1–11.

Moullin, M. (2007) Performance measurement definitions: Linking performance measurement and organisational excellence. *International Journal of Health Care Quality Assurance*, 20, 3, 181-183.

Mouridsen, S. E., Brønnum-Hansen, H., Rich, B., and Isager, T. (2008) Mortality and causes of death in autism spectrum disorders: an update. *Autism*, *12*(4), 403-414.

Mouridsen, S. E., Rich, B., and Isager, T. (2011) A longitudinal study of epilepsy and other central nervous system diseases in individuals with and without a history of infantile autism. *Brain and Development*, *33*(5), 361-366.

Mulder, L. J. M. (1992) Measurement and analysis-methods of heart-rate and respiration for use in applied environments. *Biological Psychology*, 34(2–3), 205–236.

Munoz, M. L., Van Roon, A., Riese, H., Thio, C., Oostenbroek, E., Westrik, I., De Geus, E. J. C., Gansevoort, R., Lefrandt, J., Nolte, I. M. and Snieder, H. (2015) Validity of ultra-short recordings for heart rate variability measurements. *PLoS ONE*, 10(9), 1–15.

Murray, D., Lesser, P. M. (1999) *Autism and Computing*. Available at: www.autismandcomputing.org.uk [Accessed April 2011].

Nabi, H., Hall, M., Koskenvuo, M., Singh-Manoux, A., Oksanen, T., Suominen, S., Kivimäki, M. and Vahtera, J. (2010) Psychological and somatic symptoms of anxiety and risk of coronary heart disease: The health and social support prospective cohort study. *Biological Psychiatry*, 67(4), 378–385.

Narayanan, A., White, C. A., Saklayen, S., Scaduto, M. J., Carpenter, A. L., Abduljalil, A., and Beversdorf, D. Q. (2010) Effect of propranolol on functional connectivity in autism spectrum disorder-a pilot study. *Brain imaging and behavior*, *4*(2), 189-197.

National Autistic Society, (2010) *What is Autism?* Available at: www.autism.org.uk [Accessed May 2011].

National Autistic Society, (2016) *Autism Meltdowns* Available at https://www.autism.org.uk/about/behaviour/meltdowns.aspx [Accessed: April 2017].

National Institute for Health and Care Excellence (August 2013) Autism: The management and support of children and young people on the autism spectrum. *NICE Clinical Guideline 170*, www.guidance.nice.org.uk/cg170 [Accessed 21st May 2014].

National Institute for Health and Care Excellence (June 2012). Autism: The management and support of adults on the autism spectrum, *NICE Clinical Guideline 142*, www.guidance.nice.org.uk/cg142[Accessed 21st May 2014].

Nelwan, S.P, Kors, J. A., Meij, S. H., Van Bemmel, J. H. and Simoons, M. L. (2004) Reconstruction of the 12-lead electrocardiogram from reduced lead sets. *Journal of Electrocardiology*, 37(1), 11–18.

Nestoriuc, Y., Martin, A., Rief, W. and Andrasik, F. (2008) Biofeedback treatment for headache disorders: A comprehensive efficacy review. *Applied Psychophysiology and Biofeedback*, 33(3), 125–140.

Newell, D. J. (1992) Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology*, *21*(5), 837-841.

Newman, J. B. (2013) Heart Disease: From psychosocial to pathophysiological to treatment with biofeedback - An overview. *Biofeedback*, 41(1), 39–42.

Nexus-10 Mark II® Professional biofeedback monitoring system. Available from *Mind Media B.V*. Herten; Netherlands, and at: https://www.mindmedia.com/en/products/nexus-10-mkii/

NHS Improvement. Online library of quality, service improvement and redesign tools: Project management: an overview. Available at: https://improvement.nhs.uk/documents/2147/project-management-overview.pdf [accessed February 2018].

Nolan, R. P., Jong, P., Barry-Bianchi, S. M., Tanaka, T. H., and Floras, J. S. (2008) Effects of drug, biobehavioral and exercise therapies on heart rate variability in coronary artery disease: A systematic review. *European Journal of Cardiovascular Prevention and Rehabilitation*, *15*(4), 386-396.

Nolan, R.P., Floras, J. S., Harvey, P. J., Kamath, M. V., Picton, P. E., Chessex, C., Hiscock, N., Powell, J., Catt, M., Hendrick, H., Talbot, D. and Chen, M. H. (2010) Behavioral neurocardiac training in hypertension: A randomized, controlled trial. *Hypertension*, 55(4), 1033–1039.

Nolan, R.P., Kamath, M. V, Floras, J. S., Stanley, J., Pang, C., Picton, and Young, Q. R. (2005) Heart rate variability biofeedback as a behavioral neurocardiac intervention to enhance vagal heart rate control. *American Heart Journal*, 149(6).

Nunan, D., Sandercock, G. R. H. and Brodie, D. A. (2010) A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *PACE - Pacing and Clinical Electrophysiology*, 33(11), 1407–1417.

O 'Cathain, A., Hoddinott, P., Lewin, S., Thomas, K. J., Young, B., Adamson, J., Jansen, Y. J., Mills, N., Moore, G. and Donovan, J. L. (2015) Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot and Feasibility Studies*, 1(32), 1–13

O'Rourke, M. A., Stokes, S., Regina, F., Susko, K., Hendry, W., Anderson, A., Sofge, J., Ginsberg, J. and Burch, J. (2017) Heart rate variability (HRV) training for symptom control in cancer survivors. *Journal of Clinical Oncology*. 35(5suppl), 148–148.

Oberleitner, R., Ball, J., Gillette, D., Naseef, R., and Stamm, B. H. (2006) Technologies to lessen the distress of autism. *Journal of Aggression, Maltreatment and Trauma*, *12*(1-2), 221-242.

Oberman, L. M., and Ramachandran, V. S. (2007) The simulating social mind: the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychological Bulletin*, 133(2), 310.

Oberman, L. M., Hubbard, E. M., Mccleery, J.P., Altschuler, E. L., Ramachandran, V. S. and Pineda, J. A. (2005) EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Cognitive Brain Research* 24 (2), 190–198.

Oberman, L. M., Winkielman, P.and Ramachandran, V. S. (2009) Slow echo: Facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. *Developmental Science*, 12(4), 510–520.

Ospina, M. B., Seida, J. K., Clark, B., Karkhaneh, M., Hartling, L., Tjosvold, L., and Smith, V. (2008) Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. *PloS one*, *3* (11), e3755.

Oxman, A., Cook, D. and Guyatt, G. (1994) Critical appraisal checklist for a systematic review. Study design: Systematic review, with or without meta-analysis. Adapted from: Critical Appraisal Skills Programme (CASP), Public Health Resource Unit', Department of General Practice, University Glasgow, 1–4. Available at: http://www.gla.ac.uk/media/media_64047 [Accessed: 24 July 2016].

Ozonoff, S., Pennington, B. F., and Rogers, S. J. (1991) Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *Journal of Child Psychology and Psychiatry*, *32*(7), 1081-1105.

Ozsivadjian, A. and Knott, F. (2011) Anxiety problems in young people with autism spectrum disorder: A case series. *Clinical Child Psychology and Psychiatry*, 16(2), 203–214.

Ozsivadjian, A., Hibberd, C., and Hollocks, M. J. (2014) Brief report: the use of self-report measures in young people with autism spectrum disorder to access symptoms of anxiety, depression and negative thoughts. *Journal of Autism and Developmental Disorders*, *44* (4), 969-974.

Page, A. S., Cooper, A. R., Griew, P. and Jago, R. (2010) Children's screen viewing is related to psychological difficulties irrespective of physical activity. *Pediatrics.* 126(5), e1011-1017.

Papadakis, M., Sharma, S., Cox, S., Sheppard, M. N., Panoulas, V. F. and Behr, E. R. (2009) The magnitude of sudden cardiac death in the young: A death certificate-based review in England and Wales. *Europace*, 11(10), 1353–1358.

Park, G., and Thayer, J. F. (2014) From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. *Frontiers in Psychology*, *5*, 278.

Pastor, M. C., Bradley, M. M., Lw, A., Versace, F., Molt, J. and Lang, P. J. (2008) Affective picture perception: Emotion, context, and the late positive potential. *Brain Research*, 1189(1), 145–151

Patriquin, M. A., Scarpa, A., Friedman, B. H. and Porges, S. W. (2013) Respiratory sinus arrhythmia: A marker for positive social functioning and receptive language skills in children with autism spectrum disorders. *Developmental Psychobiology*, 55(2), 101–112.

Patron, E., Benvenuti, S. M., Favretto, G., Valfre, C., Bonfa, C., Gasparotto, R., and Palomba, D. (2013) Biofeedback assisted control of respiratory sinus arrhythmia as a biobehavioral intervention for depressive symptoms in patients after cardiac surgery: a preliminary study. *Applied Psychophysiology and Biofeedback*, *38*(1), 1-9.

Peira, N., Fredrikson, M. and Pourtois, G. (2014) Controlling the emotional heart: Heart rate biofeedback improves cardiac control during emotional reactions. *International Journal of Psychophysiology*, 91(3), 225–231.

Pellicano, E. (2007) Links between theory of mind and executive function in young children with autism: Clues to developmental primacy. *Developmental Psychology*, *43*(4), 974.

Pellicano, E., Dinsmore, A., and Charman, T. (2014) What should autism research focus upon? Community views and priorities from the United Kingdom. *Autism*, *18*(7), 756-770.

Pellicano, E., Dinsmore, A., and Charman, T. (2014) Views on researcher-community engagement in autism research in the United Kingdom: a mixed-methods study. *PLoS One*, *9*(10), e109946.

Pellicano, L., Dinsmore, A., and Charman, T. (2013) *A Future Made Together: Shaping autism research in the UK*. Institute of Education, University of London. Available at: http://discovery.ucl.ac.uk/10017703/ [Accessed 10th September 2014]

Pelton, M. K. and Cassidy, S. A. (2017) Are autistic traits associated with suicidality? A test of the interpersonal-psychological theory of suicide in a non-clinical young adult sample. *Autism Research*, 10(11), 1891–1904.

Penzlin, A. I., Barlinn, K., Illigens, B. M. W., Weidner, K., Siepmann, M. and Siepmann, T. (2017) Effect of short-term heart rate variability biofeedback on long-term abstinence in alcohol dependent patients - a one-year follow-up. *BMC Psychiatry*, 17(1), 1–8.

Penzlin, A. I., Siepmann, T., Illigens, M.B., Weidner, K. and Siepmann, M. (2015) Heart rate variability biofeedback in patients with alcohol dependence: a randomized controlled study. *Neuropsychiatric Disease and Treatment*, 11, 2619–2627.

Peper, E., Booiman, A., Lin, I.-M., Harvey, R. and Mitose, J. (2016) Abdominal SEMG feedback for diaphragmatic breathing: A methodological note. *Biofeedback*, 44 (1), 42–49.

Peper, E., Booiman, A., Tallard, M. and Takebayashi, N. (2010) Surface electromyographic biofeedback to optimize performance in daily life: Improving physical fitness and health at the worksite. *Japanese Journal of Biofeedback Research*, 37(1), 19–28.

Peper, E., Harvey, R., Takabayashi, N. and Hughes, P. (2009) How to do clinical biofeedback in psychosomatic medicine. *Japanese Journal of Biofeedback Research*, 36(2), 1–16.

Peper, E., Nemoto, S., Lin, I.-M. and Harvey, R. (2015) 'Seeing is believing': Biofeedback as a tool to enhance motivation for cognitive therapy. *Biofeedback*, 43(4), 168–172.

Peper, E., Tylova, H., Gibney, K., H., Harvey, R., Combatalade, D., (2008) *Biofeedback Mastery. An Experiential Teaching and Self-Training Manual*. Wheat Ridge, CO: AAPB.

Pereira, T., Almeida, P. R., Cunha, J. S. and Aguiar, A. (2017) Heart rate variability metrics for fine-grained stress level assessment. *Computer Methods and Programs in Biomedicine*, 148, 71–80.

Petrowski, K., Wichmann, S., Siepmann, T., Wintermann, G.-B., Bornstein, S. R. and Siepmann, M. (2017) Effects of mental stress induction on heart rate variability in patients with panic disorder. *Applied Psychophysiology and Biofeedback*, 42(2), 1–1.

Petrowski, K., Wintermann, G.-B. and Siepmann, M. (2012) Cortisol response to repeated psychosocial stress. *Applied Psychophysiology and Biofeedback*, 37, 103–107.

Pfeiffer, E. A. (2004) Sensory modulation and affective disorders in children and adolescents with Asperger syndrome. *American Journal of Occupational Therapy*, 64 (7–B), 3231.

Phillips, K. L., Schieve, L. A., Visser, S., Boulet, S., Sharma, A. J., Kogan, M. D., and Yeargin-Allsopp, M. (2014) Prevalence and impact of unhealthy weight in a national sample of US adolescents with autism and other learning and behavioral disabilities. *Maternal and Child Health Journal*, *18*(8), 1964-1975.

Picard, R. W. (2009) Future affective technology for autism and emotion communication. *Philosophical Transactions of the Royal Society: Biological Sciences*, 364(1535), 3575–3584.

Pickett, J., Xiu, E., Tuchman, R., Dawson, G. and Lajonchere, C. (2011) Mortality in individuals with autism, with and without epilepsy. *Journal of Child Neurology*, 26(8), 932–939.

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C. and Malige, A. (2016) Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. *Biological Psychiatry*, 79(8), 657–666.

Porges, S. W. (1986) Respiratory sinus arrhythmia: Physiological basis, quantitative methods, and clinical implications. In Grossman, P. Janssen K.H.L., Vaitl D. (eds) *Cardiorespiratory and Cardiosomatic Psychophysiology*. NATO ASI series, 114, 105-115 Boston, MA: Springer.

Porges, S. W. (1995) Cardiac vagal tone: a physiological index of stress. *Neuroscience and Biobehavioral Reviews*, *19*(2), 225-233.

Porges, S. W. (2001) The polyvagal theory: Phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology*, 42(2) 123–146.

Porges, S. W. (2003) Social engagement and attachment. *Annals of the New York Academy of Sciences*, 1008, 31–47.

Porges, S. W. (2007) The Polyvagal Perspective. *Biological Psychology*, 74(2), 116–143.

Porges, S. W. (2009) The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleveland Clinic Journal of Medicine*, *76*(2), S86.

Porges, S. W. and Byrne, E. a (1992) Research methods for measurement of heart rate and respiration', Special Issue: Cardiorespiratory measures and their role in studies of performance. *Biological Psychology*, 34(2–3), 93–130.

Porges, S. W., Macellaio, M., Stanfill, S. D., McCue, K., Lewis, G. F., Harden, E. R., Handelman, M., Denver, J., Bazhenova, O. V. and Heilman, K. J. (2013) Respiratory sinus arrhythmia and auditory processing in autism: Modifiable deficits of an integrated social engagement system? *International Journal of Psychophysiology*, 88(3), 261–270.

Porges, S.W. (1995) Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology*, *32*,301-318.

Porges, S.W. (2006) Asserting the role of biobehavioral sciences in translational research: the behavioral neurobiology revolution. *Developmental Psychopathology*, *18*, 923-933.

Porges, S.W., (2011) *The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation*. New York NY: Norton.

Posadzki, P., Kuzdzal, A., Lee, M. S. and Ernst, E. (2015) Yoga for heart rate variability: A systematic review and meta-analysis of randomized clinical trials. *Applied Psychophysiology and Biofeedback*, 40(3), 239–249.

Postorino, V., Fatta, L. M., Sanges, V., Giovagnoli, G., De Peppo, L., Vicari, S. and Mazzone, L. (2016) Intellectual disability in autism spectrum disorder: Investigation of prevalence in an Italian sample of children and adolescents. *Research in Developmental Disabilities*, 48, 193–201.

Power, E.M., (2016) *Evaluating the Effectiveness of Biofeedback in Improving Emotional Regulation for a Student with Autism Spectrum Disorder*. (Doctoral dissertation, The Chicago School of Professional Psychology. ProQuest Information and Learning; US. No. 10085662.

Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M. R., and Rahman, A. (2007) No health without mental health. *The Lancet*, *370*(9590), 859-877.

Prinsloo, G. E., Derman, W. E., Lambert, M. I. and Rauch, H. G. L. (2013) The effect of a single episode of short duration heart rate variability biofeedback on measures of anxiety and relaxation states. *International Journal of Stress Management*, 20(4), 391–411.

Prinsloo, G. E., Derman, W. E., Lambert, M. I., & Rauch, H. G. L. (2013) The effect of a single session of short duration biofeedback-induced deep breathing on measures of heart rate variability during laboratory-induced cognitive stress: A pilot study. *Applied Psychophysiology and Biofeedback*, 38, 81-90.

Prinsloo, G. E., Rauch, H. G. L., Lambert, M. I., Muench, F., Noakes, T. D. and Derman, W. E. (2011) The effect of short duration heart rate variability (HRV) biofeedback on cognitive performance during laboratory induced cognitive stress. *Applied Cognitive Psychology*, 801, 792–801.

ProComp Infinity ™. Available from*: Thought Technology Ltd*. 2180 Belgrave Avenue, Montreal, QC H4A 2L8 Canada and at: http://www.thoughttechnology.com/

Quintana, D. S. and Heathers, J. A. J. (2014) Considerations in the assessment of heart rate variability in biobehavioral research. *Frontiers in Psychology*, 5(Jul) 1–10.

Quintana, D. S., Elstad, M., Kaufmann, T., Brandt, C. L., Haatveit, B., Haram, M., Nerhus, M., Westlye, L. T. and Andreassen, O. A. (2016) Resting-state high-frequency heart rate variability is related to respiratory frequency in individuals with severe mental illness but not healthy controls. S*cientific reports*, Nature publishing group, 1–8.

Quintana, D., Alvares, G. and Heathers, J. (2016) Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. *Translational Psychiatry*, 6(e803), 1–10.

Quintana, D.S. Guastella, A.J., Outhred, T. Hickie, I. B., Kemp, A. H., (2012) Heart rate variability is associated with emotion recognition: direct evidence for a relationship between the autonomic nervous system and social cognition. *International Journal of Psychophysiology*, 86, 168-172.

Rahman, S., Habel, M., and Contrada, R. J. (2018) Poincaré plot indices as measures of sympathetic cardiac regulation: Responses to psychological stress and associations with pre-ejection period. *International Journal of Psychophysiology*, Available online at: https://www.sciencedirect.com/science/article/abs/pii/S0167876018300564?via%3Dihub [Accessed 4th September 2018].

Rainville, P., Bechara, A., Naqvi, N., and Damasio, A. R. (2006) Basic emotions are associated with distinct patterns of cardiorespiratory activity. *International Journal of Psychophysiology*, *61*(1), 5-18.

Ratanasiripong, P, Ratanasiripong, N. and Kathalae, D. (2012) Biofeedback intervention for stress and anxiety among nursing students: A randomized controlled trial. *ISRN Nursing*, 2012, 1–5.

Ratanasiripong, P., Sverduk, K., Hayashino, D. and Prince, J. (2010) Setting up the next generation biofeedback program for stress and anxiety management for college students: A simple and cost-effective approach. *College Student Journal*, 97–100.

Ratanasiripong, P., Sverduk, K., Prince, J. and Hayashino, D. (2012) Biofeedback and counseling for stress and anxiety among college students. *Journal of College Student Development*, 53(5), 742–749.

Reaven, J. (2011) The treatment of anxiety symptoms in youth with high-functioning autism spectrum disorders: Developmental considerations for parents. *Brain research*, *1380*, 255-263.

Reid, A., Nihon, S., Thompson, L. and Thompson, M. (2013) The effects of heart rate variability training on sensorimotor rhythm: A pilot study. *Journal of Neurotherapy*, 17(1),43–48.

Reiner, R. (2008) Integrating a portable biofeedback device into clinical practice for patients with anxiety disorders: Results of a pilot study. *Applied Psychophysiology and Biofeedback*, 33(1), 55–61.

Remington, A. and Fairnie, J. (2017) A sound advantage: Increased auditory capacity in autism. *Cognition*, 166, 459–465.

Research Autism survey (2016)Available at http://researchautism.net/about-us-research-autism/beating-stress-in-autism/beating-stress-autism-survey-results [Accessed November 2016].

Reyes del Paso, G. A., Langewitz, W., Mulder, L. J. M., van Roon, A. and Duschek, S. (2013) The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology*, 50(5), 477–487.

Reyes, F. J. (2014) Implementing heart rate variability biofeedback groups for veterans with posttraumatic stress disorder. *Biofeedback*, 42(4), 137–142.

Reynard, A., Gevirtz, R., Berlow, R., Brown, M. and Boutelle, K. (2011) Heart rate variability as a marker of self-regulation. *Applied Psychophysiology and Biofeedback*, 36(3), 209–215.

Richa, S., Fahed, M., Khoury, E., and Mishara, B. (2014) Suicide in autism spectrum disorders. *Archives of Suicide Research*, *18*(4), 327-339.

Richardson W.S, Wilson M.C, Nishikawa J, Hayward R.S. (1995) The well-built clinical question: a key to evidence-based decisions. *American College of Physicians Journal Club*. Nov–Dec;123(3): A12–3.

Rimland, B., and Edelson, S. M. (1999) *Autism Treatment Evaluation Checklist (ATEC).* San Diego, CA: Autism Research Institute.

Ritterfeld, U., Cody, M., and Vorderer, P. eds. (2009) *Serious Games: Mechanisms and Effects*. Routledge.

Rockliff, H., Gilbert, P., McEwan, K., Lightman, S., and Glover, D. (2008) A pilot exploration of heart rate variability and salivary cortisol responses to compassion-focused imagery. *Clinical Neuropsychiatry*, *5*(3), 132-139.

Rodgers, J., Wigham, S., McConachie, H., Freeston, M., Honey, E. and Parr, J. R. (2016) Development of the anxiety scale for children with autism spectrum disorder (ASC-ASD). *Autism Research*, 9(11), 1205–1215.

Rodgers, P. J. (2008) Using programme theory to evaluate complicated and complex aspects of interventions. *Evaluation*, 14(1), 29–48.

Russell, A. J., Murphy, C. M., Wilson, E., Gillan, N., Brown, C., Robertson, D. M., Craig, M. C., Deeley, Q., Zinkstok, J., Johnston, K., McAlonan, G. M., Spain, D. and Murphy, D. G. M. (2015) The mental health of individuals referred for assessment of autism spectrum disorder in adulthood: A clinic report. *Autism*, 20(5) 623–627.

Rutgers, A. H., Bakermans-Kranenburg, M. J., Van Ijzendoorn, M. H. and Van Berckelaer-Onnes, I. A. (2004) Autism and attachment: a meta-analytic review. *Journal of Child Psychology and Psychiatry*, 45(6), 1123–1134.

Rutter, M., Bailey A., and Lord, C., (2003) Social Communication Questionnaire. Available from; https://www.hogrefe.co.uk/shop/social-communication-questionnaire-85199.html [Accessed July 2014].

Sahakian, B. J., Malloch, G. and Kennard, C. (2010) A UK strategy for mental health and wellbeing. *The Lancet*, 375(9729), 1854–1855.

Sammito, S. and Böckelmann, I. (2016) Reference values for time- and frequency-domain heart rate variability measures. *Heart Rhythm*, 13(6) 1309-1316.

Santhirasegaram, L. (2011) A book finally written: Case study of effective intervention five years' post closed head injury. *Journal of Neurotherapy*, 15(4) ,441-443.

Sasaki, K. and Maruyama, R. (2014) Consciously controlled breathing decreases the high-frequency component of heart rate variability by inhibiting cardiac parasympathetic nerve activity. *The Tohoku Journal of Experimental Medicine*, 233(3), 155–163.

Sasson, N. J., Faso, D. J., Nugent, J., Lovell, S., Kennedy, D. and Grossman, R. B. (2017) Neurotypical peers are less willing to interact with those with autism based on thin slice judgments. *Scientific Reports.* Nature Publishing Group. Available at: http://www.nature.com/srep/2017/170201/srep40700/full/srep40700.html, [Accessed 1st February 2017].

Saunders, S., Cummins, F., Darby, G. M. and Donnell, D. M. (2013) *Stress Reduction through Computer Games utilizing EDR*, Available at: http://dublinhumangivens.ie/wp-content/uploads/2012/07/Stress-Reduction-through-Computer-Games-utilising-EDR-PIpdf. [Accessed 1st July 2014].

Sauro, J. (2011) *A Practical Guide to the System Usability Scale: Background, Benchmarks and Best Practices*. Denver, CO: Measuring Usability LLC.

Scarpa, A. and Reyes, N. (2011) Improving emotion regulation with CBT in young children with high functioning autism spectrum disorders, a pilot study. *Behavioural and Cognitive Psychotherapy*, 2011, 39, 495–500.

Schanen, N. C. (2006) Epigenetics of autism spectrum disorders. *Human Molecular Genetics*, 15(SUPPL. 2), 138–150.

Schardt, C., Adams, M. B., Owens, T., Keitz, S. and Fontelo, P. (2007) Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Medical informatics and decision making*, 7,16.

Schauder, K. B. and Bennetto, L. (2016) Toward an interdisciplinary understanding of sensory dysfunction in autism spectrum disorder: An integration of the neural and symptom literatures. *Frontiers in Neuroscience*, 10(JUN), 1–18.

Schneider, C. J. (1987) Cost effectiveness of biofeedback and behavioral medicine treatments: A review of the literature. *Biofeedback and Self-Regulation*, *12*(2), 71-92.

Schoenberg, P. L. A. and David, A. S. (2014) 'Biofeedback for psychiatric disorders: A systematic review', *Applied Psychophysiology and Biofeedback*, 39(2), 109–135.

Schreibman, L., Dawson, G., Stahmer, A. C., Landa, R., Rogers, S. J., McGee, G. G., Kasari, C., Ingersoll, B., Kaiser, A. P., Bruinsma, Y., McNerney, E., Wetherby, A. and Halladay, A. (2015) Naturalistic developmental behavioral interventions: Empirically validated treatments for autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 45(8), 2411–2428.

Schubert, C., Lambertz, M., Nelesen, R. A., Bardwell, W., Choi, J. B. and Dimsdale, J. E. (2009) Effects of stress on heart rate complexity-A comparison between short-term and chronic stress. *Biological Psychology*, 80(3), 325–332.

Schulz, K. F., Altman, D. G., and Moher, D. (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Medicine*, *8*(1), 18.

Schwartz, M., and Andrasik, F. (Eds.) (2003) *Biofeedback: A Practitioner's Guide* (3rd ed.). New York NY: The Guilford Press.

Schwartz, M.S. and Andrasik F. (2016) *Biofeedback: A Practitioner's Guide* (4th ed.). New York NY: The Guilford Press.

Scolnick, B., Mostofsky, D. I. and Keane, R. J. (2014) Pilot study employing heart rate variability biofeedback training to decrease anxiety in patients with eating disorders. *Journal of Eating Disorders*, 2(1), 17.

Selles, R. R. and Storch, E. A. (2013) Translation of anxiety treatment to youth with autism spectrum disorders. *Journal of Child and Family Studies*, 22(3), 405–413.

Selles, R. R., Arnold, E. B., Phares, V., Lewin, A. B., Murphy, T. K. and Storch, E. A. (2015) 'Cognitive-behavioral therapy for anxiety in youth with an autism spectrum disorder: A follow-up study', *Autism*, 19(5), 613–621.

Seppälä, S., Laitinen, T., Tarvainen, M.P.P, Tompuri, T., Veijalainen, A., Savonen, K. and Lakka, T. (2014) Normal values for heart rate variability parameters in children 6-8 years of age: The PANIC Study. *Clinical Physiology and Functional Imaging*, 34(4), 290–296.

Shader T. M. Gatzke-Kopp, L.M. Crowell, S.E. Reid, J. Thayer, J. Vasey M.W., Webster-Stratton, C. Bell, Z. and Beauchaine, T. P. (2017) Quantifying respiratory sinus arrhythmia: Effects of mis specifying breathing frequencies across development. *Development and Psychopathology*, 30, 351.

Shaffer, F. and Combatalade, D. C. (2013) 'Don't add or miss a beat': A guide to cleaner heart rate variability recordings. *Biofeedback*, 41(3), 121–130.

Shaffer, F. and Ginsberg, J. (2017) An overview of heart rate variability: Metrics and norms. *Frontiers in Public Health*, 5(September), 1–17.

Shaffer, F. and Venner, J. (2013) Heart rate variability anatomy and physiology. *Biofeedback*, 41(1), 13–25.

Shaffer, F., Crawford, J. and Moss, D. (2013) BCIA launches a heart rate variability biofeedback certificate of completion. *Biofeedback*, 41(1), 4–6.

Shaffer, F., McCraty, R. and Zerr, C. L. (2014) 'A healthy heart is not a metronome': an integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, 5(September), 1–19.

Shahrestani, S., Stewart, E. M., Quintana, D. S., Hickie, I. B. and Guastella, A. J. (2014) Heart rate variability during social interactions in children with and without psychopathology: A meta-analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 55(9) 981-989.

Shahrestani, S., Stewart, E. M., Quintana, D. S., Hickie, I. B. and Guastella, A. J. (2015) Heart rate variability during adolescent and adult social interactions: A meta-analysis. *Biological Psychology*, 105, 43–50.

Sharpley, C. F., Bitsika, V., Agnew, L. L. and Andronicos, N. M. (2015) Eight-month test-retest agreement in morning salivary cortisol, self- and parent-rated anxiety in boys with an Autism Spectrum Disorder. *Physiology and Behavior*, 151, 207-212.

Sharry, J., McDermott, M. and Condron, J. (2003) 'Relax to win': Treating children with anxiety problems with a biofeedback video game. *Eisteach*, (2), 22–26.

Siegel, M. and Beaulieu, A. A (2012) Psychotropic medications in children with autism spectrum disorders: A systematic review and synthesis for evidence-based practice. *Journal of Autism and Developmental Disorders* 42:1592–1605.

Siepmann, M., Hennig, U.-D., Timo, S., Nitzsche, K., Mü Ck-Weymann, M., Petrowski, K. and Weidner, K. (2014) The effects of heart rate variability biofeedback in patients with preterm labour. *Applied Psychophysiology and Biofeedback*, 39, 27–35.

Siepmann, M., Volkan, A., Ae, A., Unterdörfer, J., Katja, A., A, and Mueck-Weymann, M. (2008) A pilot study on the effects of heart rate variability biofeedback in patients with depression and in healthy subjects. *Applied Psychophysiology and Biofeedback*, 33, 195–201.

Siever, D. (2005) History of biofeedback: The Hershel Toomin story. *Biofeedback*, 36, (2), 74-81.

Silver, M. and Oakes, P. (2001) Evaluation of a new computer intervention to teach people with autism or asperger syndrome to recognize and predict emotions in others. *Autism*, 5(3), 299–316.

Sim, J. and Lewis, M. (2012) The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of Clinical Epidemiology*, 65, 301–308.

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., and Baird, G., (2008) Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47 (8), 921-929.

Simpson, J., and Weiner, E. S. (1989). *Oxford English Dictionary*. Available online at: http://www.oed.com/ [Accessed 6th March 2018].

Simpson, R. L. (2005) Evidence-based practices and students with autism spectrum disorders. *Focus on Autism and Other Developmental Disabilities* Fall, 20(3), 140–149.

Singer, D. H. (2010) High heart rate variability, marker of healthy longevity. *American Journal of Cardiology*, 106(6), 910.

Singh, N. N., Lancioni, G. E., Manikam, R., Winton, A. S., Singh, A. N., Singh, J., & Singh, A. D. (2011) A mindfulness-based strategy for self-management of aggressive behavior in adolescents with autism. *Research in Autism Spectrum Disorders*, 5(3), 1153-1158.

Sivaratnam, C. S., Newman, L. K., Tonge, B. J. and Rinehart, N. J. (2015) Attachment and emotion processing in children with autism spectrum disorders: Neurobiological, neuroendocrine, and neurocognitive considerations. *Review Journal of Autism and Developmental Disorders*, 2(2), 222–242.

Smith, C. (2015) *Emotional Wellbeing and Mental Health in Young People with ASD*. Available at: http://network.autism.org.uk/sites/default/files/ckfinder/files [Accessed March 2017].

Sofronoff, K. Attwood, T. and Hinton, S., (2005) A randomised controlled trial of a CBT intervention for anxiety in children with Asperger's syndrome. *Journal of Child Psychology and Psychiatry*, 46, 1152-1160.

Song, N., Liu, J., Proctor, M. and Yu, J. (2015) Right and left vagus nerves regulate breathing by multiplicative interaction. *Respiratory Physiology and Neurobiology*. Elsevier B.V., 219, 25–29.

Song, R., Lui, J., and Kong, X., (2016) Autonomic dysfunction and autism: Subtypes and clinical perspectives. *North American Journal of Medicine and Science*, 9(4), 172-180.

South, M. and Rodgers, J. (2017) Sensory, emotional and cognitive contributions to anxiety in autism spectrum disorders. *Frontiers in Human Neuroscience*, 11(January), 1–7.

Spain, D., Harwood, J., Mendez, L. and Happé, M. A. (2017) Cognitive behaviour therapy for social anxiety in autism spectrum disorder: a systematic review. *Advances in Autism*, 3(1), 34–46.

Spek, A. A., van Ham, N. C. and Nyklíček, I. (2013) Mindfulness-based therapy in adults with an autism spectrum disorder: A randomized controlled trial. *Research in Developmental Disabilities*, 34(1), 246–253.

Spielberger, C. D. (1983) *Manual for the State-Trait Anxiety Inventory (STAI)* self-evaluation questionnaire. Palo Alto CA: Consulting Psychologists Press.

Stamatakis, E., Hamer, M. and Dunstan, D. W. (2011) Screen-based entertainment time, all-cause mortality, and cardiovascular events: Population-based study with ongoing mortality and hospital events follow-up. *Journal of the American College of Cardiology*, 57(3), 292–299.

State, M. W., and Levitt, P. (2011) The conundrums of understanding genetic risks for autism spectrum disorders. *Nature Neuroscience*, *14*(12), 1499.

Steer, R. A., Kumar, G., Beck, J. S., and Beck, A. T. (2001) Evidence for the construct validities of the Beck Youth Inventories with child psychiatric outpatients. *Psychological Reports*, *89*(3), 559-565.

Steffen, P. R., Austin, T., DeBarros, A. and Brown, T. (2017) The impact of resonance frequency breathing on measures of heart rate variability, blood pressure, and mood. *Frontiers in Public Health*, 5(August), 6–11.

Stein, P. and Kleiger, R. (1999) Insights from the study of heart rate variability. *Annual Review of Medicine*, 50, 249–261.

Stein, P. K., and Reddy, A. (2005) Non-linear heart rate variability and risk stratification in cardiovascular disease. *Indian Pacing and Electrophysiology Journal*, *5*(3), 210.

Steiner, N. J., Frenette, E., Hynes, C., Pisarik, E., Tomasetti, K., Perrin, E. C. and Rene, K. (2014) A pilot feasibility study of neurofeedback for children with autism. *Applied Psychophysiology and Biofeedback*, 39, 99–107.

Steptoe, A. and Brydon, L. (2009) Emotional triggering of cardiac events. *Neuroscience and Biobehavioral Reviews*, 33(2), 63–70.

Sterling, L., Dawson, G., Estes, A. and Greenson, J. (2008) Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 38(6), 1011–1018.

Stern, M. J., Guiles, R. A. F. and Gevirtz, R. (2014) HRV biofeedback for pediatric irritable bowel syndrome and functional abdominal pain: A clinical replication series. *Applied Psychophysiology Biofeedback*, 39(3–4), 287–291.

Stewart, M. E., Barnard, L., Pearson, J., Hasan, R. and O'Brien, G. (2006b) Presentation of depression in autism and Asperger syndrome. *Autism*, 10(1), 103–116.

StressEraser®: Helicor Ltd.; New York. (device now unavailable).

Striefel, S. (2008) Ethical aspects of heart rate variability biofeedback. *Biofeedback*, 36(1), 5–8.

Stuart, R., (2000) Should we insist on eye contact with people who have autism spectrum disorders? *The Reporter*, 5(3), 7-12.

Sugarman, L. I., Garrison, B. L. and Williford, K. L. (2013) 'Symptoms as solutions': Hypnosis and biofeedback for autonomic regulation in autism spectrum disorders. *American Journal of Clinical Hypnosis*, 56(2), 152–173.

Swan, M. (2009) Emerging patient-driven health care models: An examination of health social networks, consumer personalized medicine and quantified self-tracking. *International Journal of Environmental Research and Public Health*, 6(2), 492–525.

Tan, G., Shaffer, F., Lyle, R., and Teo, I. (2016) *Evidence-based Practice in Biofeedback and Neurofeedback*, 3rd edition. Wheat Ridge, CO: AAPB Press.

Tan, G., Wang, and Ginsberg, J. (2013) Heart rate variability and posttraumatic stress disorder. *Biofeedback*, 41(3), 131–135.

Tarvainen, M. (2016) Kubios HRV (ver.3.0.2) users guide, Available at: www.kubios.com/support@kubios.com[Accessed June 21st, 2017].

Tarvainen, M. P. P., Niskanen, J.P., Lipponen, J. A., Ranta-aho, O. and Karjalainen, A. (2014) Kubios HRV - Heart rate variability analysis software. *Computer Methods and Programs in Biomedicine*, 113(1), 210–220.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation*, 93, 1043-1065.

Tawakol, A., Ishai, A., Takx, R. A., Figueroa, A. L., Ali, A., Kaiser, Y., Truong, Q. A., Solomon, C. J., Calcagno, C., Mani, V., Tang, C. Y., Mulder, W. J., Murrough, J. W., Hoffmann, U., Nahrendorf, M., Shin, L. M., Fayad, Z. A. and Pitman, R. K. (2017) Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *The Lancet*, 389(10071), 834–845.

Taylor, B., Jick, H., and MacLaughlin, D. (2013) Prevalence and incidence rates of autism in the UK: time trend from 2004–2010 in children aged 8 years. *BMJ open*, *3*(10), e003219.

Taylor, L. E., Swerdfeger, A. L. and Eslick, G. D. (2014) Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. *Vaccine*, 32(29), 3623–3629.

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., Robson, R., Thabane, M., Giangregorio, L. and Goldsmith, C. H. (2010) A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology*, 10(1), 1–10.

Thayer, J. F. and Brosschot, J. F. (2005) Psychosomatics and psychopathology: Looking up and down from the brain. *Psychoneuroendocrinology*, 30(10), 1050–1058.

Thayer, J. F. and Lane, R. D. (2007) The role of vagal function in the risk for cardiovascular disease and mortality. *Biological Psychology*, 74(2), 224–242.

Thayer, J. F. and Lane, R. D. (2009) Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience and Biobehavioral Reviews*, 33(2), 81–88.

Thayer, J. F., and Lane, R. D. (2000) A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, *61*(3), 201-216.

Thayer, J. F., and Lane, R. D. (2007) The role of vagal function in the risk for cardiovascular disease and mortality. *Biological psychology*, *74*(2), 224-242.

Thayer, J. F., and Sternberg, E. (2006) Beyond heart rate variability. *Annals of the New York Academy of Sciences*, *1088*(1), 361-372.

Thayer, J. F., Hansen, A. L., Saus-Rose, E. and Johnsen, B. H. (2009) Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine*, 37(2), 141–153.

Thayer, J. F., Yamamoto, S. S. and Brosschot, J. F. (2010) The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, 141(2), 122–131.

The Critical Skills Appraisal Programme (2006) The critical skills appraisal programme: making sense of evidence. Public Health Resource Unit, England., 1–3. Available at: http://www.casp-uk.net/ [Accessed: 21 December 2017].

Thibault, R. T., Veissière, S., Olson, J. A. and Raz, A. (2018) Treating ADHD with suggestion. *Neurofeedback and Placebo Therapeutics*, 1–14.

Thomas, B. H., Ciliska, D., Dobbins, M. and Micucci, S. (1998) Quality assessment tool for quantitive studies. *Effective Public Health Practice Project'*, 1–4. Available at: http://www.nccmt.ca/registry/resource/pdf/14.pdf [Accessed: 9 August 2017].

Thompson M. and Thompson, L. (2011) Setting up for success with asperger's and autistic spectrum disorder. *Journal of Neurotherapy*, 15(4), 426-427.

Thompson M., Thompson L., Reid A. and Santhirasegaram, L. (2011) Neural networks: An exploration of functions influenced by neurofeedback. *Journal of Neurotherapy*, 15(4), 447-448.

Thompson, L., Thompson, M. and Reid, A. (2010a) Functional neuroanatomy and the rationale for using EEG biofeedback for clients with Asperger's syndrome. *Applied Psychophysiology Biofeedback*, 35(1), 39–61

Thompson, L., Thompson, M. and Reid, A. (2010b) Neurofeedback outcomes in clients with Asperger's Syndrome. *Applied Psychophysiology Biofeedback*, 35(1), 63–81.

Thomson, L. *in* Weir, K. (2016) Positive feedback. *Monitor on Psychology*, 47 (3), 51-55.

Thrum A., (2012) The importance of autism research. *Dialogues in Clinical Neuroscience* 14 (3) 219-222.

Thurber, M. R., Bodenhamer-Davis, E., Johnson, M., Chesky, K. and Chandler, C. K. (2010) Effects of heart rate variability coherence biofeedback training and emotional management techniques to decrease music performance anxiety. *Biofeedback*, 38(1), 28–40.

Thurston, R. C., Rewak, M. and Kubzansky, L. D. (2013) An anxious heart: Anxiety and the onset of cardiovascular diseases. *Progress in Cardiovascular Diseases*, 55(5), 524–537.

Toichi, M. and Kamio, Y. (2003) Paradoxical autonomic response to mental tasks in autism. *Journal of Autism and Developmental Disorders*, 33(4), 417–426.

Tomchek, S. D. and Dunn, W. (2007) Sensory processing in children with and without autism: A comparative study using the short sensory profile. *American Journal of Occupational Therapy*, 61(2), 190–200.

Tong, A., Sainsbury, P. and Craig, J. (2007) Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal of Quality in Health Care*, 19(6), 349–357.

Torrado, J. C., Gomez, J., and Montoro, G. (2017) Emotional self-regulation of individuals with autism spectrum disorders: Smartwatches for monitoring and interaction. *Sensors* (Basel, Switzerland), 17(6), 1359.

Tsai, H. J., Kuo, T. B. J., Lee, G. S. and Yang, C. C. H. (2015) Efficacy of paced breathing for insomnia: Enhances vagal activity and improves sleep quality. *Psychophysiology*, 52(3).

Tsuji, H., Larson, M. G., Venditti, F. J., Manders, E. S., Evans, J. C., Feldman, C. L., and Levy, D. (1996) Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study. *Circulation*, *94*(11), 2850-2855.

Tully, P. J., Cosh, S. M., and Baune, B. T. (2013) A review of the effects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. *Psychology, Health and Medicine*, *18*(6), 627-644.

U.S. Department of Health and Human Services (2012) Prevalence of autism spectrum disorders – autism and developmental disabilities monitoring network, 14 sites, United States. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR)*, 61, 3, March 30. Available at: https://www.cdc.gov/mmwr/pdf/ss/ss6103.pdf [Accessed 10th July 2013].

UK Chief Medical Officer (2011) '*Physical activity for children and young people'*. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/541231/CYP infographic.[Accessed: 5 December 2017].

UK Chief Medical Officer (January 2016). *'Alcohol Guidelines Review'*: Summary of the Proposed New Guidelines, Available at: https://www.gov.uk/government/consultations/health-risks-from-alcohol-new-guidelines.[Accessed: 5 December 2017].

Uljarevic, M. and Hamilton, A. (2013) Recognition of emotions in autism: A formal meta-analysis. *Journal of Autism and Developmental Disorders*, 43, 1517–1526.

Uljarević, M., Lane, A., Kelly, A. and Leekam, S. (2016) Sensory subtypes and anxiety in older children and adolescents with autism spectrum disorder. *Autism Research*, 9 1073–1078.

Umetani, K., Singer, D. H., McCraty, R. and Atkinson, M. (1998) Twenty-four-hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *Journal of the American College of Cardiology*, 31(3), 593–601.

Ung, D., Selles, R., Small, B. J. and Storch, E. A. (2015) A systematic review and meta-analysis of cognitive-behavioral therapy for anxiety in youth with high-functioning autism spectrum disorders. *Child Psychiatry and Human Development*, 46, 533–547.

Uno, Y., Uchiyama, T., Kurosawa, M., Aleksic, B. and Ozaki, N. (2015) Early exposure to the combined measles-mumps-rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder. *Vaccine*,33 (21), 2511–2516.

Usui, H. and Nishida, Y. (2017) The very low-frequency band of heart rate variability represents the slow recovery component after a mental stress task. *PLoS ONE*, 12(8) e0182611. Available at: https://doi.org/10.1371/journal.pone.0182611 [Accessed April 2018].

Uusitalo, A. L. T., Laitinen, T., Väisänen, S. B., Länsimies, E. and Rauramaa, R. (2004) Physical training and heart rate and blood pressure variability: a 5-yr randomized trial. *American Journal of Physiology. Heart and Circulatory Physiology*, 286(5), H1821–H1826.

van der Zwan, J.E., de Vente, W., Huizink, A.C., Bögels, S.M. and de Bruin, E.I., (2015) Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. *Applied Psychophysiology and Biofeedback*, *40* (4), 257-268.

van Diest, I., Verstappen, K., Aubert, A. E., Widjaja, D., Vansteenwegen, D. and Vlemincx, E. (2014) Inhalation/exhalation ratio modulates the effect of slow breathing on heart rate variability and relaxation. *Applied Psychophysiology and Biofeedback*, 39(3–4), 71–180.

van Dixhoorn, J. (2008) Whole-body breathing. *Psychophysiology*, 36(2), 54–58.

van Dixhoorn, J., and Duivenvoorden, H. J. (1985) Efficacy of Nijmegen questionnaire in recognition of the hyperventilation syndrome. *Journal of Psychosomatic Research*, *29*(2), 199-206.

van Doorn P. (1983). Een vragenlijst voor hyperventilatieklachten. *De Psycholoog* 18: 513-517.

van Hecke A. Vaughan., Lebow, J., Bal, E. (2009) Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child Development*, 80, (4), 1118-1133.

van Steensel, F. J. A. and Heeman, E. J. (2017) Anxiety levels in children with autism spectrum disorder: A meta-analysis. *Journal of Child and Family Studies*. Springer US, 26(7), 1753–1767.

van Steensel, F. J. A., Bögels, S. M. and Perrin, S. (2011) Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis. *Clinical Child Family Psychology Review*, 14, 302–317.

van Steensel, F. J., Dirksen, C. D., and Bögels, S. M. (2013) A cost of illness study of children with high-functioning autism spectrum disorders and comorbid anxiety disorders as compared to clinically anxious and typically developing children. *Journal of Autism and Developmental Disorders*, *43*(12), 2878-2890.

van Zyl, L. T., Hasegawa, T. and Nagata, K. (2008) Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. *Biopsychosocial Medicine*, 2(1), 12.

Vasa, R. A., Carroll, L. M., Nozzolillo, A. A., Mahajan, R., Mazurek, M. O., Bennett, A. E., Wink, L. K. and Bernal, M. (2014) A systematic review of treatments for anxiety in youth with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(12), 3215–3229.

Vasa, R. A., Mazurek, M. O., Mahajan, R., Bennett, A. E., Bernal, M.P., Nozzolillo, A. A., Arnold, L. E. and Coury, D. L. (2016) Assessment and treatment of anxiety in youth with autism spectrum disorders. *Pediatrics*, 137(Supplement), S115–S123.

Vaschillo, B. (2000) Resonant frequency biofeedback training to increase cardiac varaibility: Rational and manual for training. *Applied Psychophysiology and Biofeedback*, 25, 177–191.

Vaschillo, E. G., Vaschillo, B. and Lehrer, P. M. (2006) Characteristics of resonance in heart rate variability stimulated by biofeedback. *Applied Psychophysiology and Biofeedback*, 31(2), 129–142.

Verschuere, B., Brandsen, T. and Pestoff, V. (2012) Co-production: The state of the art in research and the future agenda. *Voluntas: International Journal of Voluntary and Non-profit Organizations*, *23*(4), 1083-1101.

Villani, D., Carissoli, C., Triberti, S., Marchetti, A., Gilli, G. and Riva, G. (2018) Videogames for emotion regulation: A systematic review. *Games for Health Journal*, 7(2), 85-99.

Virnes, M., Kärnä, E. and Vellonen, V. (2015) Review of research on children with autism spectrum disorder and the use of technology. *Journal of Special Education Technology*, 30(1), 13–27.

von Rosenberg, W., Chanwimalueang, T., Adjei, T., Jaffer, U., Goverdovsky, V. and Mandic, D. (2017) Resolving ambiguities in the LF/HF ratio: LF-HF scatter plots for the categorization of mental and physical stress from HRV. *Frontiers in Physiology*, 8(JUN), 1–12.

Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., and Valentine, A. (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet*, 351 (9103), 637-641.

Walters, S., Loades, M. and Russell, A. (2016) A systematic review of effective modifications to cognitive behavioural therapy for young people with autism spectrum disorders. *Review Journal of Autism and Developmental Disorders*, 3(2), 137–153.

Wang, Y., Hensley, M.K. Tasman, A. (2016) Heart rate variability and skin conductance during repetitive TMS course in children with autism. *Applied Psychophysiology and Biofeedback*, 41, 47–60.

Watts, S. J. Rodgers. J. Riby, D. (2016) A systematic review of the evidence for hyporesponsivity in ASD. *Review Journal of Autism and Developmental Disorders*, 3, 286-301.

Wazen, G. L. L., Gregório, M. L., Kemp, A. H. and Godoy, M. F. (2018) Heart rate variability in patients with bipolar disorder: From mania to euthymia. *Journal of Psychiatric Research*, 99(January), 33–38.

Weatherall, M. (1999) Biofeedback or pelvic floor muscle exercises for female genuine stress incontinence: A meta-analysis of trials identified in a systematic review. *BJU International*, 83(9), 1015–1016.

Weeks, D. L., Whitney, A. A., Tindall, A. G. and Carter, G. T. (2015) Pilot randomized trial comparing intersession scheduling of biofeedback results to individuals with chronic pain: Influence on psychologic function and pain intensity. *American Journal of Physical Medicine and Rehabilitation*, 94(10), 869–878.

Weise, F., and Heydenreich, F. (1989) Effects of modified respiratory rhythm on heart rate variability during active orthostatic load. *Biomedica Biochimica Acta*, *48*(8), 549-556.

Welch, P. (1967). The use of fast fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. *IEEE Transactions on Audio and Electroacoustics*, *15*(2), 70-73.

Wells, R., Outhred, T., Heathers, J. A. J., Quintana, D. S. and Kemp, A. H. (2012) 'Matter over mind': A randomised-controlled trial of single-session biofeedback training on performance anxiety and heart rate variability in musicians. *PLoS ONE*, 7(10) e46597.

Westlake, G. (2013) *Evaluation of a Biofeedback Intervention in College Students Diagnosed with Autism Spectrum Disorders* (Doctoral dissertation, Arizona State University). ProQuest Information and Learning; US. No. 3595257.

Weston, L. Hodgekins, J. Langdon, P. E. (2016) Effectiveness of cognitive behavioural therapy with people who have autistic spectrum disorders: A systematic review and meta-analysis. *Clinical Psychology Review*, 49,41-54.

Wheat, A. L. and Larkin, K. T. (2010) Biofeedback of heart rate variability and related physiology: A critical review. *Applied Psychophysiology and Biofeedback*, 35(3), 229–242.

White, S. W., Schry, A. R., Miyazaki, Y., Ollendick, T. H., and Scahill, L. (2015) Effects of verbal ability and severity of autism on anxiety in adolescents with ASD: One-year follow-up after cognitive behavioral therapy. *Journal of Clinical Child and Adolescent Psychology*, *44*(5), 839-845.

Whited, A., Larkin, K. T. and Whited, M. (2014) Effectiveness of emWave2® biofeedback in improving heart rate variability reactivity to and recovery from stress. *Applied Psychophysiology and Biofeedback*, 39(2), 75–88.

Whooley, M. A. (2006) Depression and cardiovascular disease: Healing the broken-hearted. *Journal of the American Medical Association*, 295(24), 2874–2881.

Wigham, S. and Mcconachie, H. (2014) Systematic review of the properties of tools used to measure outcomes in anxiety intervention studies for children with autism spectrum disorders. *PLoS ONE*, 9(1), 1–17.

Williams, K., Wray, J. A. and Wheeler, D. M. (2012) Intravenous secretin for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*, (4) CD003495.

Wilson, S. T., Chesin, M., Fertuck, E., Keilp, J., Brodsky, B., Mann, J. J., Sönmez, C. C., Benjamin-Phillips, C. and Stanley, B. (2016) Heart rate variability and suicidal behavior. *Psychiatry Research*, 240 241-247.

Windthorst, P., Mazurak, N., Kuske, M., Hipp, A., Giel, K. E., Enck, P., and Teufel, M. (2017) Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: an exploratory pilot study. *Journal of Psychosomatic Research*, *93*, 6-13.

Wing, L. (1981a) Asperger's syndrome: a clinical account. *Psychological Medicine*, *11*(1), 115-129.

Wong, C., Odom, S. L., Hume, K. A., Cox, A. W., Fettig, A., Kucharczyk, S., Brock, M. E., Plavnick, J. B., Fleury, V. and Schultz, T. R. (2015) Evidence-based practices for children, youth, and young adults with autism spectrum disorder: A Comprehensive Review. *Journal of Autism and Developmental Disorders*, 45, 1951–1966.

Wood, J. J., Drahota, A., Sze, K., Har, K., Chiu, A., and Langer, D. A. (2009) Cognitive behavioral therapy for anxiety in children with autism spectrum disorders: A randomized, controlled trial. *Journal of Child Psychology and Psychiatry*, 50, 224–234.

Wood, J.J. and Gadow, K. D. (2010) Exploring the nature and function of anxiety in youth with autistic spectrum disorders. *Clinical Psychology Science and Practice*, 17, (4), 281-292.

Yasuma, F. Hayano, J. (2004) Respiratory sinus arrhythmia: Why does the heartbeat synchronize with breathing? *Chest*, 125(2), 683–690.

Young, H. and Benton, D. (2015) We should be using nonlinear indices when relating heart-rate dynamics to cognition and mood. *Scientific Reports*, Nature Publishing group, 5, 16619.

Yu, L. C., Lin, I. M., Fan, S. Y., Chien, C. L. and Lin, T. H. (2018) One-year cardiovascular prognosis of the randomized, controlled, short-term heart rate variability biofeedback among patients with coronary artery disease. *International Journal of Behavioral Medicine*, 1–12.

Yucha, C. B. (2002) Problems inherent in assessing biofeedback efficacy studies. *Applied Psychophysiology and Biofeedback*, 27(1), 99–106.

Yucha, C. B. (2004) '*Evidenced Based Biofeedback': Evidence-Based Practice in Biofeedback and Neurofeedback*. Wheat Ridge, CO: AAPB Press.

Yucha, C., and Montgomery, D. (2008) *Evidence-based Practice in Biofeedback and Neurofeedback*. Wheat Ridge, CO: AAPB Press.

Zucker, T.L., Samuelson, K.W., Meunch, F., (2009) The effects of respiratory sinus arrhythmia biofeedback on heart rate variability and posttraumatic stress disorder: A pilot study. *Applied Psychophysiology and Biofeedback*, 34, 135-143.

Appendices

Appendix I: Ethical Approval

Phase 1 Ethical approval 20th January 2015.

UNIVERSITY OF ULSTER **RESEARCH GOVERNANCE**

RG3 Filter Committee Report Form

Project Title	Exploring the use of heart rate variability biofeedback
Chief Investigator	Prof George Kernohan
Filter Committee	Nursing and Health Research

This form should be completed by Filter Committees for all research project applications in categories A to D (*for categories A, B, and D the University's own application form – RG1a and RG1b – will have been submitted; for category C, the national, or ORECNI, application form will have been submitted).

Where substantial changes are required the Filter Committee should return an application to the Chief Investigator for clarification/amendment; the Filter Committee can reject an application if it is thought to be unethical, inappropriate, incomplete or not valid/viable.

Only when satisfied that its requirements have been met in full and any amendments are complete, the Filter Committee should make one of the following recommendations:

The research proposal is complete, of an appropriate standard and is in

- category A and the study may proceed* [x]
- category B and the study must be submitted to the University's Research Ethics Committee** Please indicate briefly the reason(s) for this categorisation [ ]
- category C and the study must be submitted to ORECNI along with the necessary supporting materials from the Research Governance Section*** [ ]
- category D and the study must be submitted to the University's Research Ethics Committee** [ ]

Signed: [signature] Date: 20/1/2015

Filter Committee Member

*The application form and this assessment should now be returned to the Chief Investigator. The Filter Committee should retain a copy of the complete set of forms.

** The application form and this assessment should now be returned to the Chief Investigator so that he/she can submit the application to the UUREC via the Research Governance section. The Filter Committee should retain a copy of the complete set of forms for their own records.

*** The application form and this assessment should now be returned to the Chief Investigator so that he/she can prepare for application to a NRES/ORECNI committee. The Filter Committee should retain a copy of the complete set of forms for their own records.

For all categories, details of the application and review outcome should be minuted using the agreed format and forwarded to the Research Governance section

Version 3 (10/07) 1

Phase 2: Provisional ethical approval 18th December 2015

HSC Business Services Organisation

Office for Research Ethics Committees Northern Ireland (ORECNI)

Customer Care & Performance Directorate
Office Suite 3
Lisburn Square House
Haslem's Lane
Lisburn
Co. Antrim BT28 1TW
Tel:+44 (0) 28 9260 3107
www.orecni.hscni.net
HSC REC A

18 December 2015

Professor George Kernohan
Professor of Health Research
University of Ulster
Room 12I21, Jordanstown Campus
NEWTOWNABBEY
BT37 0QB

Dear Professor Kernohan

Study Title:	**An Investigation into the Use of Heart Rate Variability Biofeedback in People with Autistic Spectrum Disorder**
REC reference:	**15/NI/0255**
IRAS project ID:	**139122**

The Research Ethics Committee reviewed the above application at the meeting held on 15 December 2015. Thank you for attending to discuss the application with Dr Helen Coulter and Dr Mark Donnelly.

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

The Committee would be content to give a favourable opinion of the application, subject to receiving a complete response to a request for the following information:

1. Please provide a written assurance that the StressEraser device has not been withdrawn because of safety concerns.
2. The Committee agreed that some changes are required to the participant information documents.

Participant Invite letter

- It is unclear who this is aimed at, the adult participant, the child participant or the carer. The language could be more lay friendly and "Southeastern trust" should read South Eastern HSC Trust.

Participant Information Sheet and Consent Forms

- It was agreed that there should be separate Information Sheets and Consent Forms for the 13-17 year age group and the 18-24 year age group which should be appropriate for the

Phase 2: Final ethical approval 22nd January 2016

Ulster University
Shore Road
Newtownabbey
County Antrim
BT37 0QB
Northern Ireland
T: +44 (0)28 9036 6552/6518/6629
F: +44 (0)28 9036 6479
ulster.ac.uk

Our Ref: NC:GOV

22 January 2016

Professor G Kernohan
Room 12L21
School of Nursing
Ulster University
Jordanstown Campus

Dear Professor Kernohan

Research Governance Reference Number: 15/0118
ORECNI Reference Number: 15/NI/0255
Study Title: An investigation into the use of heart rate variability biofeedback in people with Autistic Spectrum Disorder

The Research Governance section has been advised that the above application has been given a favourable ethical opinion by an HSC/NHS ethics committee. Once you have gained permission from the Trust(s) involved, the research can proceed.

Please note the additional documentation relating to research governance and indemnity matters, including the requirements placed upon you as Chief Investigator.

1. **Please complete and return the Chief Investigator Statement of Compliance prior to commencing the study and keep a copy for your file.**

2. **Please retain all other documents.**

Further details of the University's policy along with guidance notes, procedures, terms of reference and forms are available at the following web address:

http://research.ulster.ac.uk/office/rofficeeg.html

If you need any further information or clarification of any points, please do not hesitate to contact me.

Yours sincerely

Nick Curry
Senior Administrative Officer
Research Governance
028 9036 6629
n.curry@ulster.ac.uk

Research & Innovation

Phase 2: NHS Ethical approval SEHCT governance 5th February 2016

South Eastern Health and Social Care Trust

Professor George Kernohan
Professor of Health Research
University of Ulster
Room 12121 Jordanstown Campus
Newtownabbey
BT37 0QB

05 February 2016 **Our Ref:** SET/15/43

Dear Professor Kernohan

Study Title: **An Investigation into the Use of Heart Rate Variability Biofeedback in People with Autistic Spectrum Disorder**

HSC Trust Ref: SET/15/43 (Please quote this number in all future correspondence)
IRAS Ref: 139122

I am pleased to advise that the South Eastern H&SC Trust has given Research Governance Permission for the above project to commence. Permission is granted for the duration of the project to 20 July 2017

The following documents have been approved for use in the project:

Document	Version	Date
Protocol	2	24/09/15
Letters of Invitation to Participant {Participant Invitation Letter [Child aged 13-17 years and carer]}	2	17/01/16
Letters of Invitation to Participant {Participant Invitation Letter [Adults with Autistic Spectrum Disorder]}	2	17/01/16
Other: [Non-validated Questionnaire – Case Report Form]	2	17/01/16
Participant Consent Form [Consent Form Adult with Autistic Spectrum Disorder]	2	17/01/16
Participant Consent Form [Consent Form Carer of Child aged 13-17]	2	17/01/16
Participant Consent Form [Consent Form Carer Nominated by Adult with Autistic Spectrum Disorder]	2	17/01/16
Participant Information Sheet {PIS} [Participant Information Sheet Version 2 {Child aged 13-17 years}]	2	17/01/16
Participant Information Sheet {PIS} [Participant Information Sheet Version 2	2	17/01/16

Research & Development Office 1st Floor, Home 3, Ulster Hospital, Dundonald, Belfast BT16 1RH
Tel: 028 9055 3101 Email: paul.carlin@setrust.hscni.net

Phase 2: Research governance start date 21st March 2016

Ulster University
Shore Road
Newtownabbey
County Antrim
BT37 0QB
Northern Ireland
T: +44 (0)28 9036 6552/6518/6629
F: +44 (0)28 9036 6479
ulster.ac.uk

ULSTER UNIVERSITY **RESEARCH GOVERNANCE**

Chief Investigator Statement of Compliance

To be returned following receipt of a favourable ethical opinion and/or HSC Trust permission and prior to commencement of the study

Name of CI: Professor G Kernohan
Ulster Research Governance Study Ref: 15/0118
ORECNI Study Ref: 15/NI/0255
Study title: An investigation into the use of heart rate varibility biofeedback in people with Autistic Spectrum Disorder

Collaborating HSC/NHS organization: SEHSCT

I understand that Ulster University has agreed to act as sponsor/co-sponsor or equivalent for the above study and that this places certain obligations upon me as Chief Investigator.

These are:

- to adhere to the research ethics, governance and other appropriate policies of the University and any HSC/NHS organisation involved in the study
- to conduct the study in full compliance with the approved protocol
- to report any adverse events as required by the University and HSC/NHS procedures
- to provide interim and final reports on the progress and outcomes of the study
- to seek advance permission for any amendments or extensions to the study
- where appropriate to register the study on a publicly accessible database

I agree to the above and confirm that:

- the host HSC/NHS organisation (where applicable) is aware of and supports this study
- a favourable ethical opinion has been obtained (where applicable) and the study will commence on

  date: 21 March 2016

  and end on

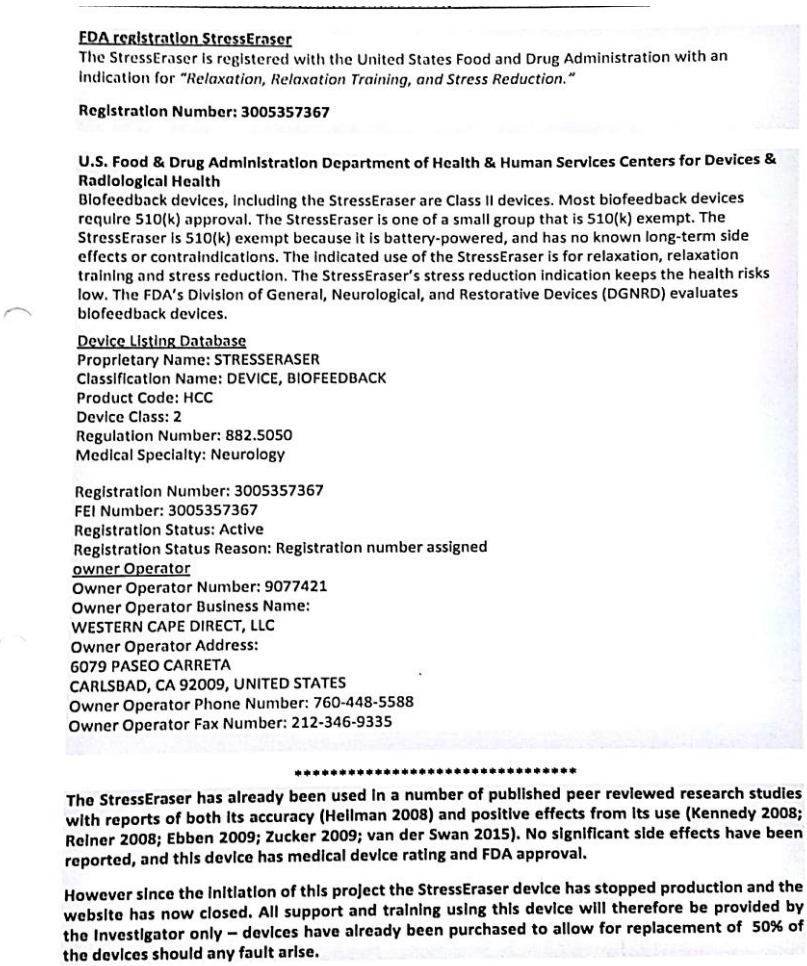
  date: 20 July 2017

Signed: George Kernohan Date: 2 Feb 2016
(Chief Investigator)

Research & Innovation

Appendix II: Biofeedback Equipment

StressEraser safety information



FDA registration StressEraser
The StressEraser is registered with the United States Food and Drug Administration with an indication for *"Relaxation, Relaxation Training, and Stress Reduction."*

Registration Number: 3005357367

U.S. Food & Drug Administration Department of Health & Human Services Centers for Devices & Radiological Health
Biofeedback devices, including the StressEraser are Class II devices. Most biofeedback devices require 510(k) approval. The StressEraser is one of a small group that is 510(k) exempt. The StressEraser is 510(k) exempt because it is battery-powered, and has no known long-term side effects or contraindications. The indicated use of the StressEraser is for relaxation, relaxation training and stress reduction. The StressEraser's stress reduction indication keeps the health risks low. The FDA's Division of General, Neurological, and Restorative Devices (DGNRD) evaluates biofeedback devices.

Device Listing Database
Proprietary Name: STRESSERASER
Classification Name: DEVICE, BIOFEEDBACK
Product Code: HCC
Device Class: 2
Regulation Number: 882.5050
Medical Specialty: Neurology

Registration Number: 3005357367
FEI Number: 3005357367
Registration Status: Active
Registration Status Reason: Registration number assigned
owner Operator
Owner Operator Number: 9077421
Owner Operator Business Name:
WESTERN CAPE DIRECT, LLC
Owner Operator Address:
6079 PASEO CARRETA
CARLSBAD, CA 92009, UNITED STATES
Owner Operator Phone Number: 760-448-5588
Owner Operator Fax Number: 212-346-9335

****

The StressEraser has already been used in a number of published peer reviewed research studies with reports of both its accuracy (Heilman 2008) and positive effects from its use (Kennedy 2008; Reiner 2008; Ebben 2009; Zucker 2009; van der Swan 2015). No significant side effects have been reported, and this device has medical device rating and FDA approval.

However since the initiation of this project the StressEraser device has stopped production and the website has now closed. All support and training using this device will therefore be provided by the investigator only – devices have already been purchased to allow for replacement of 50% of the devices should any fault arise.

The StressEraser is registered with the United States Food and Drug Administration with an indication for *"Relaxation, Relaxation Training, and Stress Reduction."* Registration Number: 3005357367

StressEraser training guidelines

All devices have been used according to manufacturer's instructions using existing training manuals accompanying the device and, on the links, listed below.

https://www.youtube.com/watch?v=G9DyXtwTETM

https://www.youtube.com/watch?v=0oSfKN-Cl2Uandt=30s

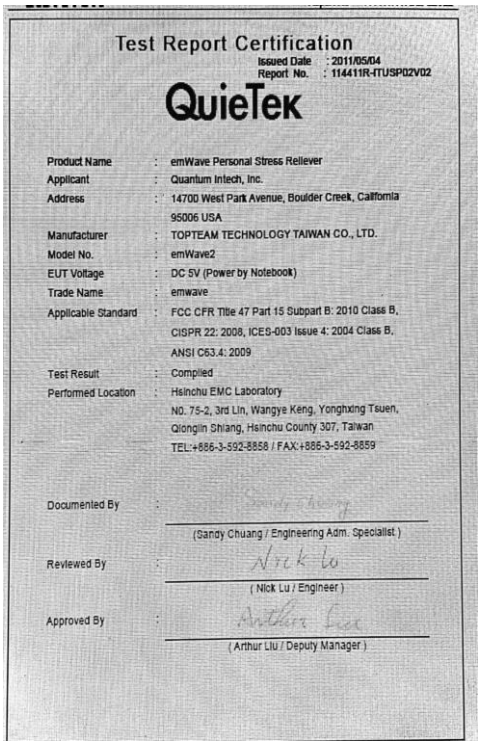
https://www.youtube.com/watch?v=HXdAmP4D_i0

Inner Balance and emWave2 safety information

The Inner balance and emWave 2® devices have been issued with a declaration of conformity as outlined below. The Inner Balance and emWave2 products are not registered as medical devices.

They are described as *'educational devices designed for relaxation'.*

Declaration of conformity – Quantum Intech Inc.



Test Report Certification

Issued Date : 2011/05/04
Report No. : 114411R-ITUSP02V02

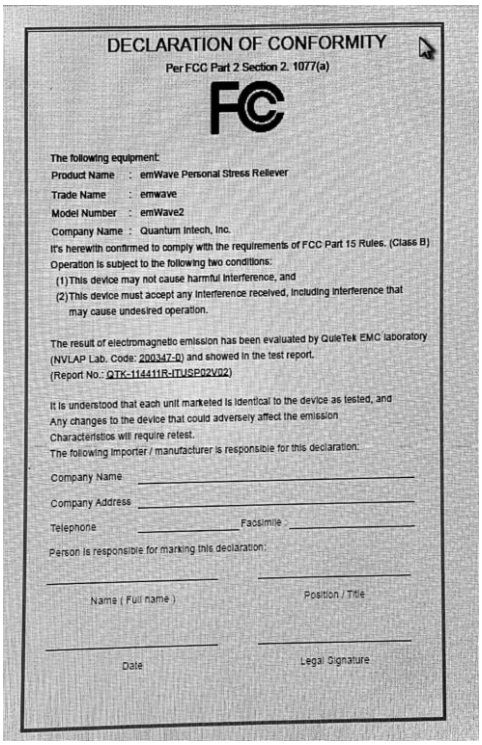
QuieTek

Product Name	:	emWave Personal Stress Reliever
Applicant	:	Quantum Intech, Inc.
Address	:	14700 West Park Avenue, Boulder Creek, California 95006 USA
Manufacturer	:	TOPTEAM TECHNOLOGY TAIWAN CO., LTD.
Model No.	:	emWave2
EUT Voltage	:	DC 5V (Power by Notebook)
Trade Name	:	emwave
Applicable Standard	:	FCC CFR Title 47 Part 15 Subpart B: 2010 Class B, CISPR 22: 2008, ICES-003 Issue 4: 2004 Class B, ANSI C63.4: 2009
Test Result	:	Complied
Performed Location	:	Hsinchu EMC Laboratory No. 75-2, 3rd Lin, Wangye Keng, Yonghxing Tsuen, Qionglin Shiang, Hsinchu County 307, Taiwan TEL:+886-3-592-8858 / FAX:+886-3-592-8859

Documented By : _____ (Sandy Chuang / Engineering Adm. Specialist)

Reviewed By : Nick Lu _____ (Nick Lu / Engineer)

Approved By : Arthur Liu _____ (Arthur Liu / Deputy Manager)



DECLARATION OF CONFORMITY

Per FCC Part 2 Section 2. 1077(a)

FC

The following equipment:

Product Name : emWave Personal Stress Reliever
Trade Name : emwave
Model Number : emWave2
Company Name : Quantum Intech, Inc.

It's herewith confirmed to comply with the requirements of FCC Part 15 Rules. (Class B)
Operation is subject to the following two conditions:
(1) This device may not cause harmful interference, and
(2) This device must accept any interference received, including interference that may cause undesired operation.

The result of electromagnetic emission has been evaluated by QuieTek EMC laboratory (NVLAP Lab. Code: 200347-0) and showed in the test report.
(Report No.: QTK-114411R-ITUSP02V02)

It is understood that each unit marketed is identical to the device as tested, and Any changes to the device that could adversely affect the emission Characteristics will require retest.
The following importer / manufacturer is responsible for this declaration:

Company Name _____
Company Address _____
Telephone _____ Facsimile _____
Person is responsible for marking this declaration:

Name (Full name) _____ Position / Title _____

Date _____ Legal Signature _____

HeartMath is a registered trademark of the Institute of HeartMath. Inner balance and emWave2® are trademarks of Quantum Intech, Inc.

HeartMath training guidelines

All devices have been used according to manufacturer's instructions using existing training manuals accompanying the device and, on the links, listed below.

https://www.heartmath.com/heartmath-technology-free-training/

http://www.heartmath.com/emWave 2-training-videos/

Appendix II: ECG Equipment

ECG assessment equipment – Actiwave Cardio

Actiwave cardio	**Supplier**
The Actiwave Cardio is an ultra-miniature single channel ECG waveform recorder. The very small size allows for continuous monitoring in a wide range of patients and applications.	www.camntech.com 
Docking station	Available from
At the end of the recording, the Cardio is removed from the electrodes and placed on a dock connected to a PC. The Actiwave control software transfers data from the recorder to the PC via the dock and USB cable.	CamNtech Ltd, Upper Pendrill Court, Ermine street North, Papworth Everard, Cambridge CB233UY www.camntech.com 
Cardio prep pads	Available from
Skin should be lightly exfoliated using Cardio prep to remove any existing dead skin, sweat and sebum	Unomedical, stock 2121m Cardiac services 6 Wildflower way Boucher Road Belfast BT12 6TA 

Gel Electrodes	Available from	
The Actiwave Cardio attaches to the chest using standard ECG electrodes with 4mm male snap connectors (e.g. Cleartrace gel electrodes).	Cardiac services 6wildflower way Boucher Road Belfast BT12 6TA	

ECG equipment safety information – Actiwave Cardio

Actiwave Cardio Regulatory Information

Medical Devices Directive (EU)

CamNtech operates a certified Quality Management System in compliance with relevant Directives and Standards. The following list provides details of QMS and regulatory compliance with links to certificates and/or regulatory listings.

ISO13485 UKAS:

CamNtech has been audited by the Notified Body SGS UK Ltd and certified as meeting the requirements of ISO13485:2003 and EN ISO13485:2012 (UKAS).


Certificate GB14/91368

SGS

CamNtech Ltd

Upper Pendrill Court, Ermine Street North, Papworth Everard, Cambridge, CB23 3UY, UK

has been assessed and certified as meeting the requirements of

ISO 13485:2003
EN ISO 13485:2012

For the following activities

Design, development, manufacture and distribution of ambulatory devices for the recording of heart rate, ECG, EEG, EMG, Physical Activity and Patient Recorded Outcome and related software

This certificate is valid from 01 May 2014 until 01 May 2017 and remains valid subject to satisfactory surveillance audits. Re certification audit due before 14 March 2017. Issued 1. Certified since 01 May 2014

Authorised by

SGS United Kingdom Ltd Systems & Services Certification Rossmore Business Park Ellesmere Port Cheshire CH65 3EN UK t +44 (0)151 350 6600 f +44 (0)151 350 6600 www.sgs.com

SGS 13485-2 0612

Page 1 of 1

UKAS MANAGEMENT SYSTEMS 005

SGS SGS SGS

ECG assessment equipment safety information – Actiwave Cardio

The Actiwave is a Class 2a Medical Device conforming to the essential safety and health requirements and provisions of EC Council Directives93/42/EEC, Annex V.

CamNtech Ltd has been assessed and certified as meeting the requirements of the above directive by SGS United Kingdom Ltd, Notified body number 0120 (Certificate numberGB06/67703).


EC Certificate Production Quality Assurance System: Certificate GB06/67703

The management system of

CamNtech Ltd

Upper Pendrill Court, Ermine Street North, Papworth Everard, Cambridge, CB23 3UY, UK

has been assessed and certified as meeting the requirements of

Directive 93/42/EEC
on medical devices, Annex V

For the following products

Actiheart Heart Rate Monitor, Actiwave ECG, EEG and EMG waveform recorder and related analysis software.

For placing on the market of Class IIb or Class III devices covered by this certificate, an EC Type Examination Certificate according to Annex III is required.

This certificate is valid from 01 May 2014 until 01 May 2019 and remains valid subject to satisfactory surveillance audits.
Re certification audit due before 14 March 2017
Issue 7, Certified since 10 March 2006

Certification is based on reports numbered GB/PC 211183

Authorised by

SGS United Kingdom Ltd, Notified Body 0120

SGS CE 13 0311

Page 1 of 1

Assessment Equipment safety information– *Actiwave Cardio*

FDA 510(k) Clearance (USA)

CamNtech has submitted the required documentation to the United States Food and Drug Administration (FDA) under the 510(k) program. Each device has been found to be substantially equivalent to predicate devices in terms of Indications for use, design and safety. Each device has been cleared by the FDA to be marketed as a medical device in the USA with the following 510(k) numbers:

Device	Class (US FDA)	510(k) n
Actiwave cardio	2	K052

Manufacturer

CamNtech Ltd, Upper Pendrill Court, Papworth Everard, Cambridgeshire, CB233UY, UK

Tel: 01480 831223 Fax: 01480 831733

email:t echnical@camntech.co.uk Web: www.camntech.com

Procedure for skin preparation and attachment of sensors

Procedure for skin preparation and attachment of sensors for ECG assessment – *Actiwave cardio*

The skin should simply be cleaned with warm water and soap.
Alcohol is not recommended as this can potentially cause skin irritation. Shaving is also not recommended unless this is done several days before application. Participants with hair on the chest area who are keen to participate will be advised to use the alternative Nexus equipment.

Skin should be lightly exfoliated using Cardio prep to remove any existing dead skin, sweat and sebum (e.g. Uno medical, stock code 2121m)
Electrode pads should then be applied to the sternum area of the chest (e.g. Cleartrace electrodes)

The first pad should be placed onto the centre of the chest and the Cardio unit attached onto it.
Then the second pad is attached to the other clip on the Cardio unit and connecting cable is used to position the second electrode, so the two pads are aligned horizontally –
two different positions are suitable depending on the participant's preference (see figure 2 below for one example of positioning).

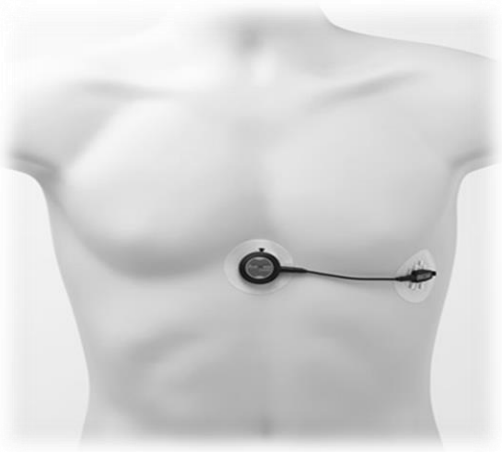
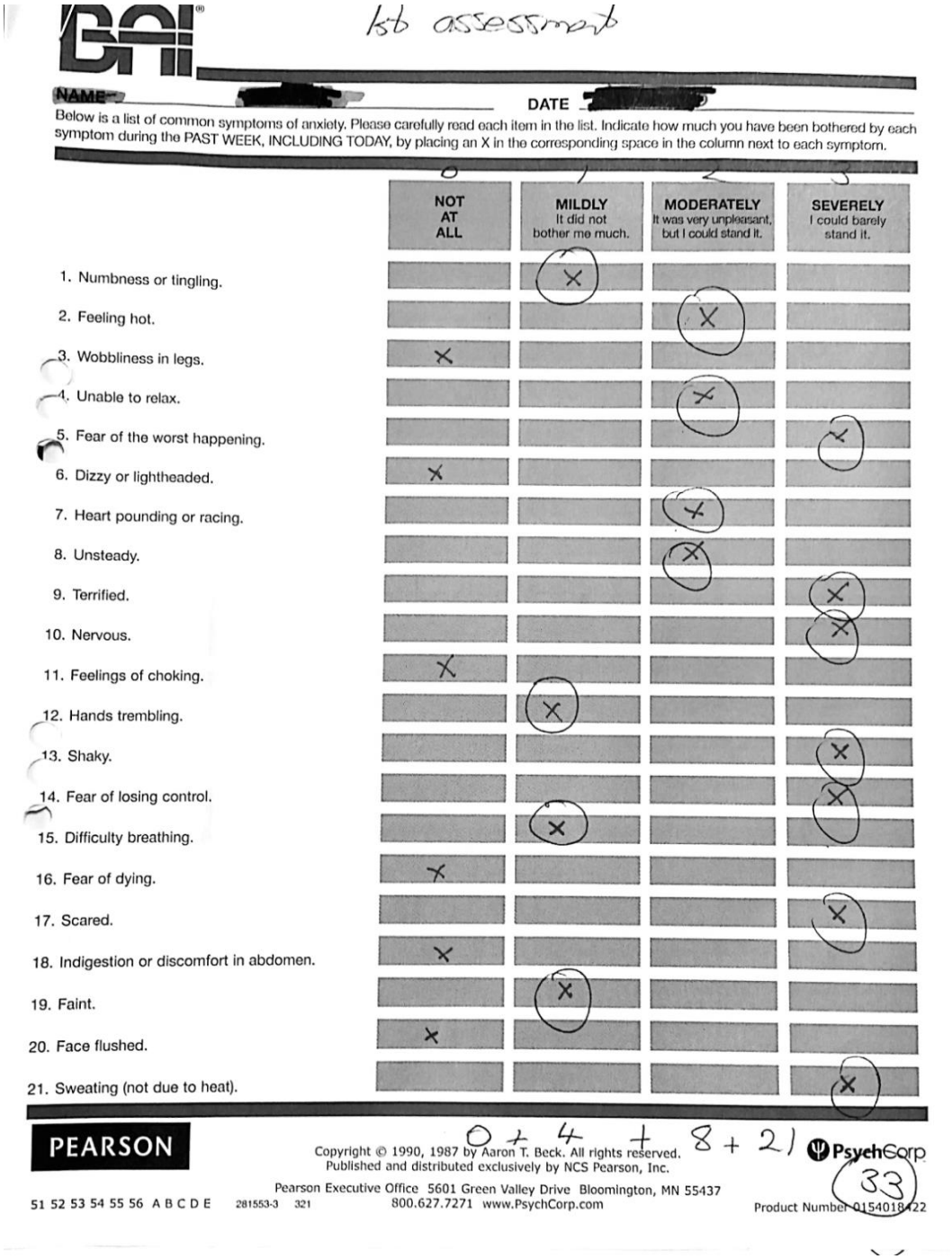


Figure 2: Actiwave cardio – placement

Appendix III: Anonymised samples of Measures

Beck Anxiety Inventory



BAI

kb assessment

NAME [redacted] DATE [redacted]

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each symptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	0 NOT AT ALL	1 MILDLY It did not bother me much.	2 MODERATELY It was very unpleasant, but I could stand it.	3 SEVERELY I could barely stand it.
1. Numbness or tingling.		X		
2. Feeling hot.			X	
3. Wobbliness in legs.	X			
4. Unable to relax.			X	
5. Fear of the worst happening.				X
6. Dizzy or lightheaded.	X			
7. Heart pounding or racing.			X	
8. Unsteady.			X	
9. Terrified.				X
10. Nervous.				X
11. Feelings of choking.	X			
12. Hands trembling.		X		
13. Shaky.				X
14. Fear of losing control.				X
15. Difficulty breathing.		X		
16. Fear of dying.	X			
17. Scared.				X
18. Indigestion or discomfort in abdomen.	X			
19. Faint.		X		
20. Face flushed.	X			
21. Sweating (not due to heat).				X

0 + 4 + 8 + 21

33

PEARSON

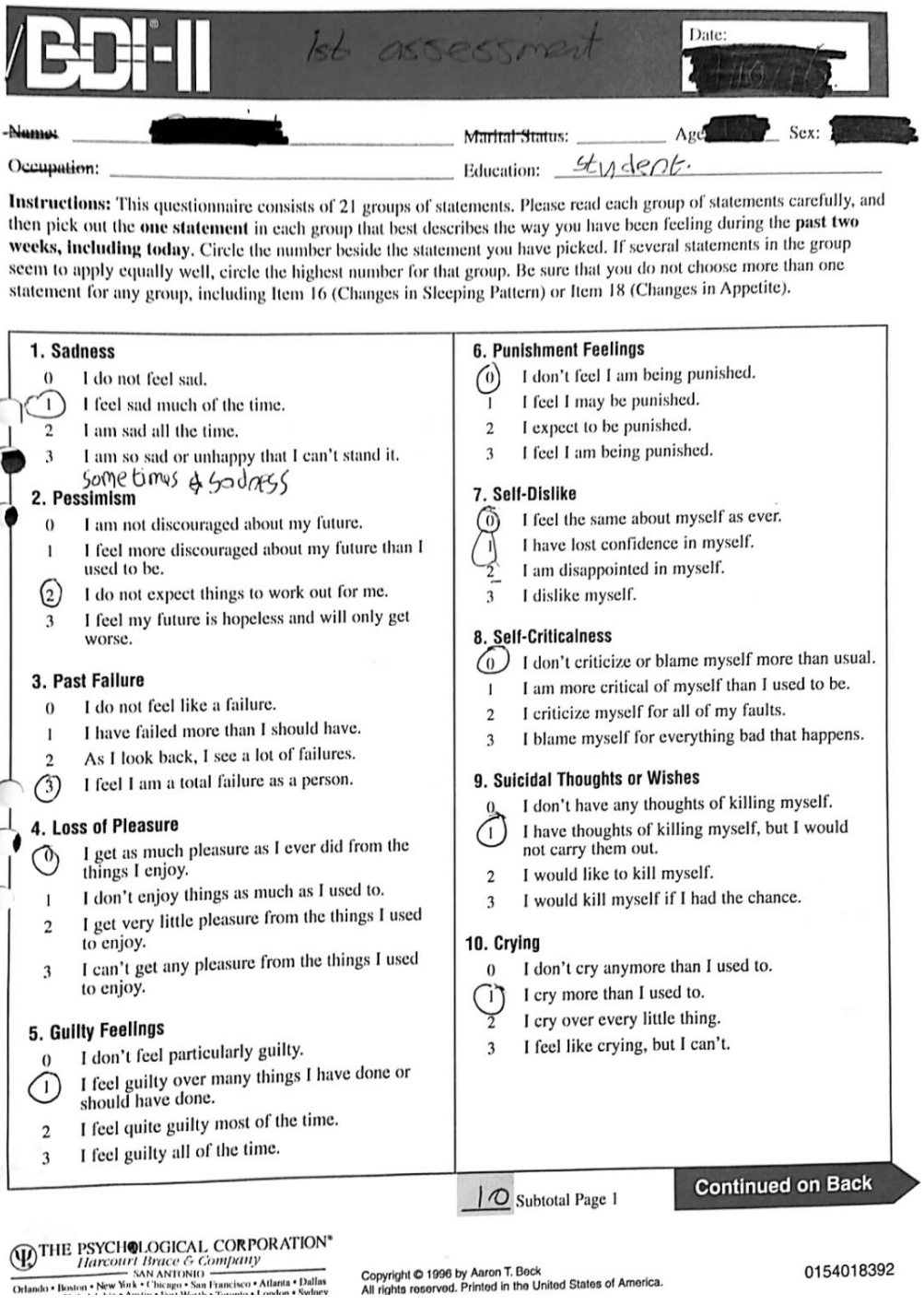
Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437
800.627.7271 www.PsychCorp.com

51 52 53 54 55 56 A B C D E 281553-3 321

PsychCorp

Product Number 0154018422

Beck Depression Inventory-II



BDI-II 1st assessment Date: [redacted]

Name: [redacted] Marital Status: _____ Age [redacted] Sex: [redacted]

Occupation: _____ Education: student.

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
0 I do not feel sad.
(1) I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.
sometimes I sadness

2. Pessimism
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
(2) I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
(3) I feel I am a total failure as a person.

4. Loss of Pleasure
(0) I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0 I don't feel particularly guilty.
(1) I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings
(0) I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike
(0) I feel the same about myself as ever.
(1) I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness
(0) I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0 I don't have any thoughts of killing myself.
(1) I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don't cry anymore than I used to.
(1) I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

10 Subtotal Page 1

Continued on Back

THE PSYCHOLOGICAL CORPORATION
Harcourt Brace & Company
SAN ANTONIO
Orlando • Boston • New York • Chicago • San Francisco • Atlanta • Dallas

0154018392

Beck Youth Inventory-II

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the one word (Never, Sometimes, Often, or Always) that tells about you best, especially in the last two weeks. THERE ARE NO RIGHT OR WRONG ANSWERS.

		0	1	2	3
1.	I worry someone might hurt me at school.	Never	Sometimes	Often	Always
2.	My dreams scare me.	Never	Sometimes	Often	Always
3.	I worry when I am at school.	Never	Sometimes	Often	Always
4.	I think about scary things.	Never	Sometimes	Often	Always
5.	I worry people might tease me.	Never	Sometimes	Often	Always
6.	I am afraid that I will make mistakes.	Never	Sometimes	Often	Always
7.	I get nervous.	Never	Sometimes	Often	Always
8.	I am afraid I might get hurt.	Never	Sometimes	Often	Always
9.	I worry I might get bad grades.	Never	Sometimes	Often	Always
10.	I worry about the future.	Never	Sometimes	Often	Always
11.	My hands shake.	Never	Sometimes	Often	Always
12.	I worry I might go crazy.	Never	Sometimes	Often	Always
13.	I worry people might get mad at me.	Never	Sometimes	Often	Always
14.	I worry I might lose control.	Never	Sometimes	Often	Always
15.	I worry.	Never	Sometimes	Often	Always
16.	I have problems sleeping.	Never	Sometimes	Often	Always
17.	My heart pounds.	Never	Sometimes	Often	Always
18.	I get shaky.	Never	Sometimes	Often	Always
19.	I am afraid that something bad might happen to me.	Never	Sometimes	Often	Always
20.	I am afraid that I might get sick.	Never	Sometimes	Often	Always

11 14 BAI-Y Total RS 25

3

Social Communication Questionnaire – reported by carer

[redacted] CARER
INITIAL ASD review

1. Is she/he now able to talk using short phrases or sentences? If *no*, skip to question 8.	(yes)	no
2. Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	(yes)	no
3. Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up)?	(yes)	no
4. Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	(yes)	no
5. Has she/he ever got her/his pronouns mixed up (e.g., saying *you* or *she/he* for *I*)?	(yes)	no
6. Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying *hot rain* for *steam*)?	(yes)	no
7. Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again?	yes	(no)
8. Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through?	yes	(no)
9. Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	(yes)	no
10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?	(yes)	no
11. Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)?	(yes)	no
12. Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended?	yes	(no)
13. Has she/he ever had any special interests that were *unusual* in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains, dinosaurs)?	(yes)	no
14. Has she/he ever seemed to be *unusually* interested in the sight, feel, sound, taste, or smell of things or people?	(yes)	no
15. Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	(yes)	no
16. Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	yes	(no)
17. Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	(yes)	(no)
18. Has she/he ever had any objects (*other* than a soft toy or comfort blanket) that she/he *had* to carry around?	yes	(no)
19. Does she/he have any particular friends or a best friend?	yes	(no)

LIFETIME

Social Communication Questionnaire (SCQ)

AutoScore™ Form

Michael Rutter, M.D., F.R.S., Anthony Bailey, M.D., Sibel Kazak Berument, Ph.D., Catherine Lord, Ph.D., and Andrew Pickles, Ph.D.

Published by
WESTERN PSYCHOLOGICAL SERVICES
wps 12031 Wilshire Boulevard Los Angeles, CA 90025-1251
Publishers and Distributors

[redacted]
Name of Subject

[redacted]
Date of Birth

Date of Interview

Chronological Age [redacted]

Name of Respondent

Relation to Subject

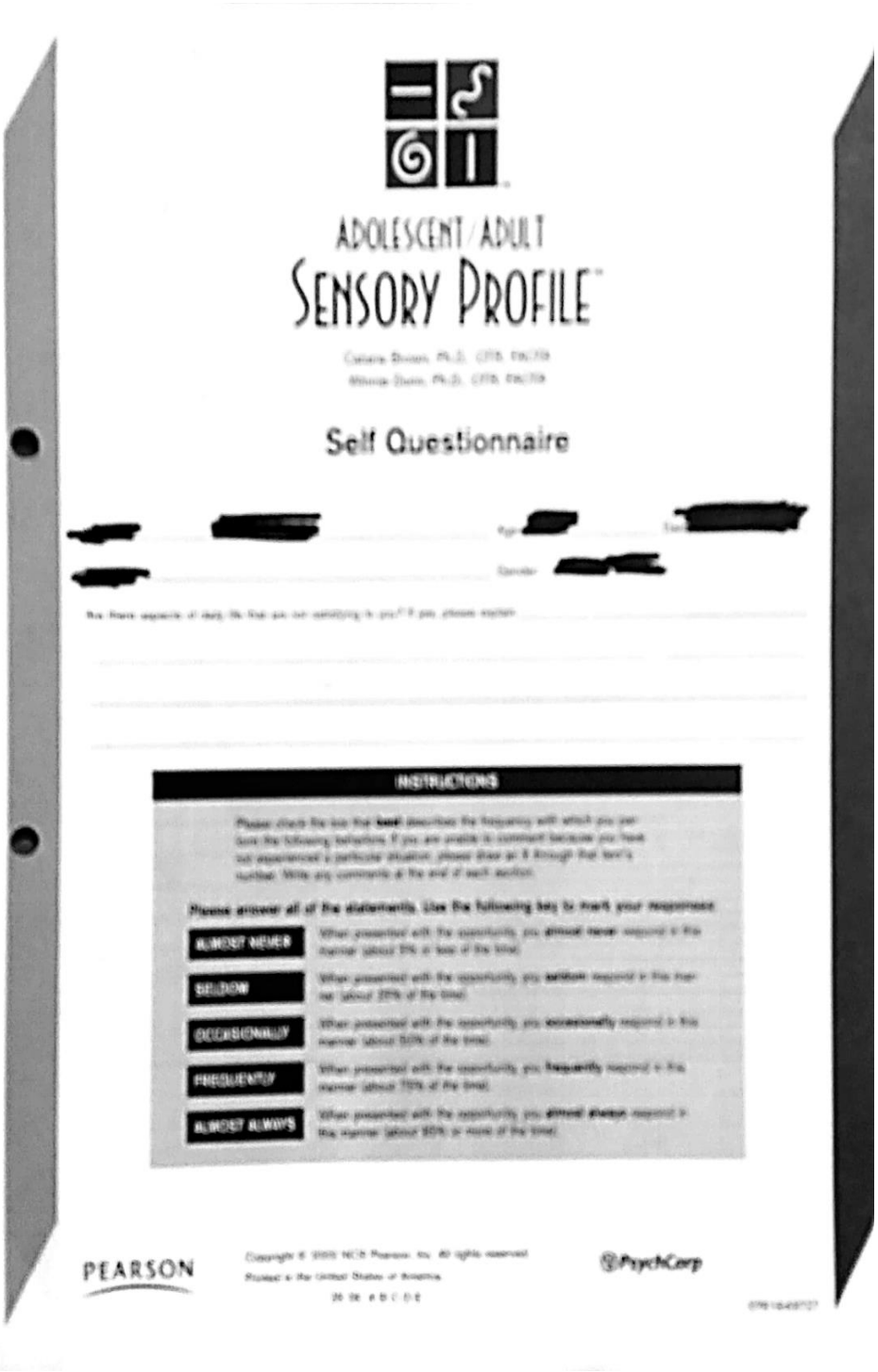
Clinician Name

School/Clinic

Directions

Thank you for taking the time to complete this questionnaire. Please answer each question by circling *yes* or *no*. A few questions ask about several related types of behavior; please circle *yes* if *any* of these behaviors have ever been present. Although you may be uncertain about whether some behaviors were ever present or not, please answer *yes* or *no* to every question on the basis of what you think.

Adolescent / Adult Sensory profile – carer and participant



ADOLESCENT/ADULT

SENSORY PROFILE™

Self Questionnaire

INSTRUCTIONS

ALMOST NEVER

SELDOM

OCCASIONALLY

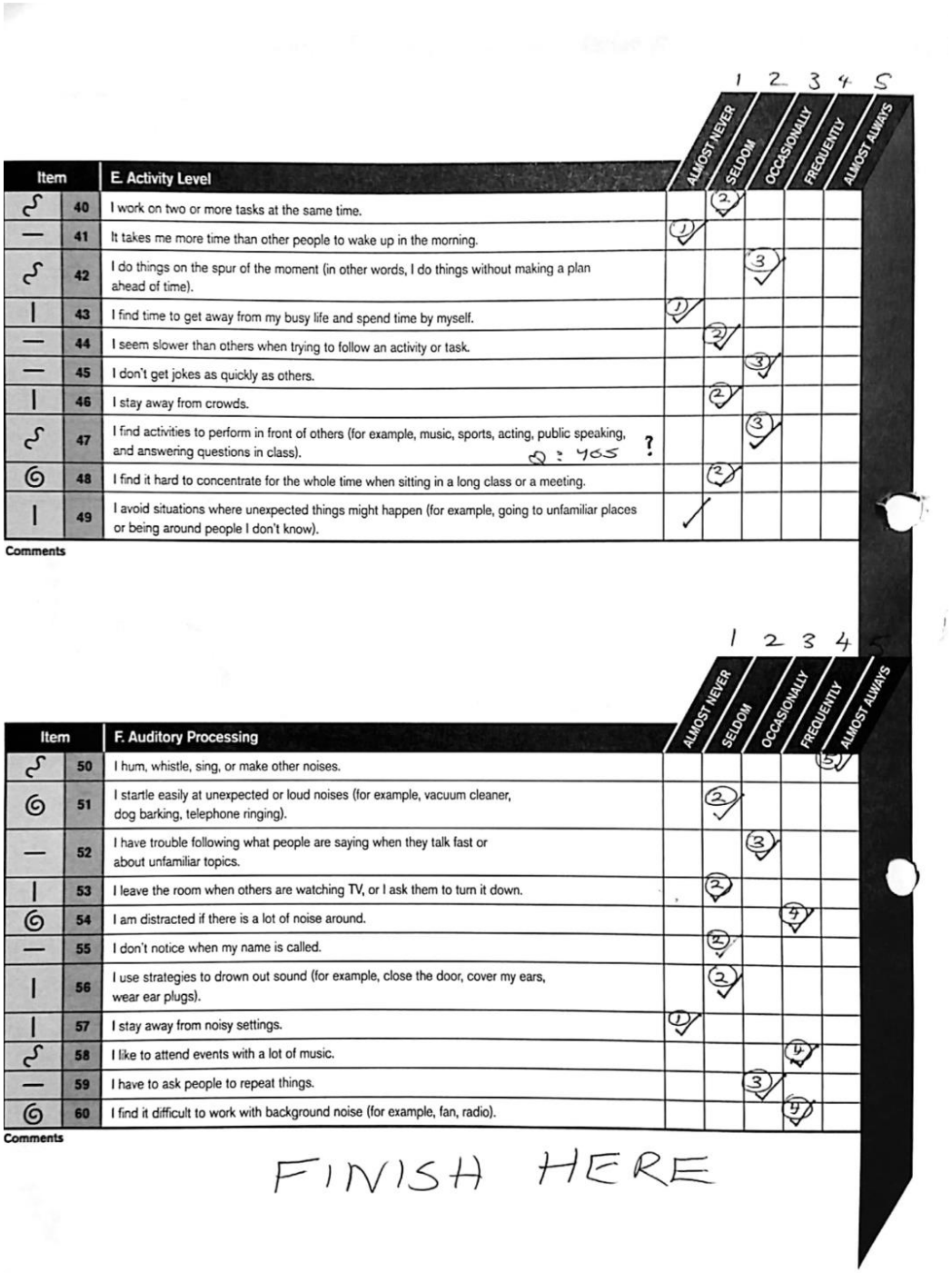
FREQUENTLY

ALMOST ALWAYS

PEARSON

PsychCorp

Adolescent / Adult Sensory profile



Item		E. Activity Level	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	40	I work on two or more tasks at the same time.		2			
	41	It takes me more time than other people to wake up in the morning.	1				
	42	I do things on the spur of the moment (in other words, I do things without making a plan ahead of time).			3		
	43	I find time to get away from my busy life and spend time by myself.	1				
	44	I seem slower than others when trying to follow an activity or task.		2			
	45	I don't get jokes as quickly as others.			3		
	46	I stay away from crowds.		2			
	47	I find activities to perform in front of others (for example, music, sports, acting, public speaking, and answering questions in class). Q: 405 ?			3		
	48	I find it hard to concentrate for the whole time when sitting in a long class or a meeting.		2			
	49	I avoid situations where unexpected things might happen (for example, going to unfamiliar places or being around people I don't know).	✓				

Comments

Item		F. Auditory Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	50	I hum, whistle, sing, or make other noises.					5
	51	I startle easily at unexpected or loud noises (for example, vacuum cleaner, dog barking, telephone ringing).		2			
	52	I have trouble following what people are saying when they talk fast or about unfamiliar topics.			3		
	53	I leave the room when others are watching TV, or I ask them to turn it down.		2			
	54	I am distracted if there is a lot of noise around.				4	
	55	I don't notice when my name is called.		2			
	56	I use strategies to drown out sound (for example, close the door, cover my ears, wear ear plugs).		2			
	57	I stay away from noisy settings.	1				
	58	I like to attend events with a lot of music.				4	
	59	I have to ask people to repeat things.			3		
	60	I find it difficult to work with background noise (for example, fan, radio).				4	

Comments

FINISH HERE

4

Nijmegen questionnaire – sample

Patient Name: [redacted] 3 Date: Today

ASSESSMENT MODULE: NIJMEGEN QUESTIONNAIRE

Please circle the score that best describes the frequency with which you experienced the symptoms listed.

Symptom	Never	Seldom	Sometimes	Often	Very Often
Chest Pain	0	(1)	2	3	4
Feeling tense	0	1	2	(3)	4
Blurred Vision	(0)	1	2	3	4
Dizziness	(0)	1	2	3	4
Confusion or loss of touch with reality	0	1	(2)	3	4
Fast or deep breathing	0	1	(2)	3	4
Shortness of breath	0	(1)	2	3	4
Tightness across chest	0	1	(2)	3	4
Bloated sensation in stomach	(0)	1	2	3	4
Tingling in fingers and hands	(0)	1	2	3	4
Difficulty in breathing or taking a deep breath	(0)	1	2	3	4
Stiffness or cramps in fingers and hands	0	(1)	2	3	4
Tightness around the mouth	(0)	1	2	3	4
Cold hands or feet	(0)	1	2	3	4
Palpitations in the chest	0	(1)	2	3	4
Anxiety	0	1	2	(3)	4
		(4)	(4)	(3)	(16)

Total Points: _____

N.B cold fingers + tremor noted etc.

Progress report via survey monkey

How are your stress levels today?

- ❑ no stress
- ❑ slight stress
- ❑ moderate stress
- ❑ very stressed
- ❑ totally stressed

If you are stressed do you know what is making you stressed?

- ❑ School problem
- ❑ Work problem
- ❑ Home problem
- ❑ Relationship problem
- ❑ Other reason I am stressed _____
- ❑ Don't know why I am stressed

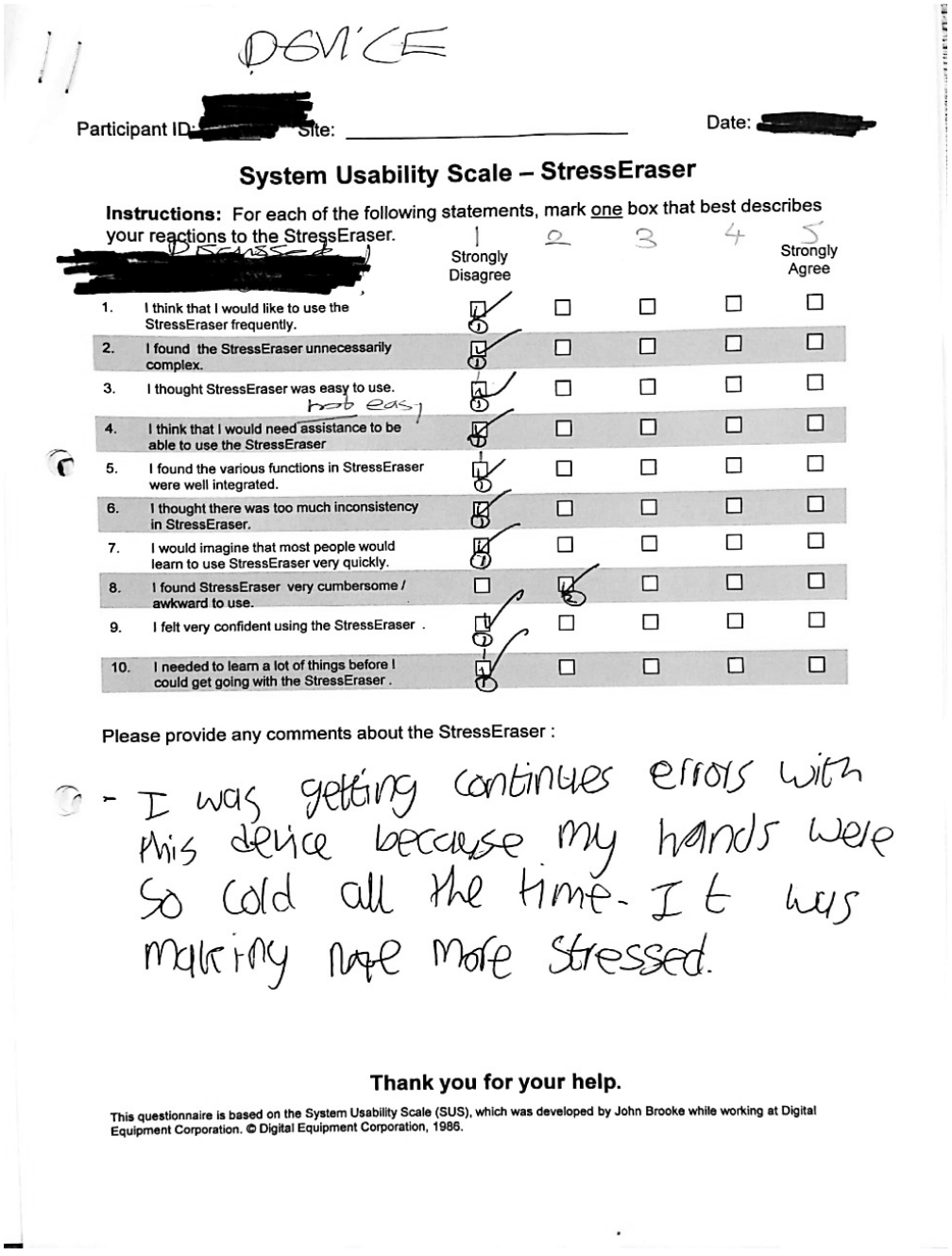
Did you use your biofeedback device today?

- ❑ Didn't use it
  I didn't use it because _____
- ❑ Used it and it helped
- ❑ Used it and didn't help

How long did you use your device for?

- ❑ Less than 5minutes
- ❑ 5-10 minutes
- ❑ More than 10 minutes

System Usability Scale – sample of StressEraser report



DEVICE

Participant ID: [redacted] Site: _____ Date: [redacted]

System Usability Scale – StressEraser

Instructions: For each of the following statements, mark one box that best describes your reactions to the StressEraser.

[redacted]

		1 Strongly Disagree	2	3	4	5 Strongly Agree
1.	I think that I would like to use the StressEraser frequently.	☑	☐	☐	☐	☐
2.	I found the StressEraser unnecessarily complex.	☑	☐	☐	☐	☐
3.	I thought StressEraser was easy to use. (not easy)	☑	☐	☐	☐	☐
4.	I think that I would need assistance to be able to use the StressEraser	☑	☐	☐	☐	☐
5.	I found the various functions in StressEraser were well integrated.	☑	☐	☐	☐	☐
6.	I thought there was too much inconsistency in StressEraser.	☑	☐	☐	☐	☐
7.	I would imagine that most people would learn to use StressEraser very quickly.	☑	☐	☐	☐	☐
8.	I found StressEraser very cumbersome / awkward to use.	☐	☑	☐	☐	☐
9.	I felt very confident using the StressEraser .	☑	☐	☐	☐	☐
10.	I needed to learn a lot of things before I could get going with the StressEraser .	☑	☐	☐	☐	☐

Please provide any comments about the StressEraser :

- I was getting continues errors with this device because my hands were so cold all the time. It was making me more stressed.

Thank you for your help.

This questionnaire is based on the System Usability Scale (SUS), which was developed by John Brooke while working at Digital Equipment Corporation. © Digital Equipment Corporation, 1986.

System Usability Scale – sample of Inner balance report

DEVICES.

Participant ID: [redacted] Site: _____ Date: [redacted]/12

System Usability Scale

Instructions: For each of the following statements, mark one box that best describes your reactions to **Inner Balance**

		1 Strongly Disagree	2	3	4	5 Strongly Agree
1.	I think that I would like to use Inner Balance frequently.	☐	☐	☐	☑ (4)	☐
2.	I found I Balance unnecessarily complex.	☑ (1)	☐	☐	☐	☐
3.	I thought Inner Balance was easy to use.	☐	☐	☐	☑ (4)	☐
4.	I think that I would need assistance to be able to use Inner Balance	☑ (1)	☐	☐	☐	☐
5.	I found the various functions of Inner Balance were well integrated.	☐	☐	☐	☐	☑ (3)
6.	I thought there was too much inconsistency in the Inner Balance	☑ (1)	☐	☐	☐	☐
7.	I would imagine that most people would learn to use Inner Balance very quickly.	☐	☐	☐	☐	☑ (5)
8.	I found Inner Balance very cumbersome / awkward to use.	☑ (1)	☐	☐	☐	☐
9.	I felt very confident using Inner Balance	☐	☐	☑ (3)	☐	☐
10.	I needed to learn a lot of things before I could get going with Inner Balance	☑ (1)	☐	☐	☐	☐

Please provide any comments about **Inner Balance**

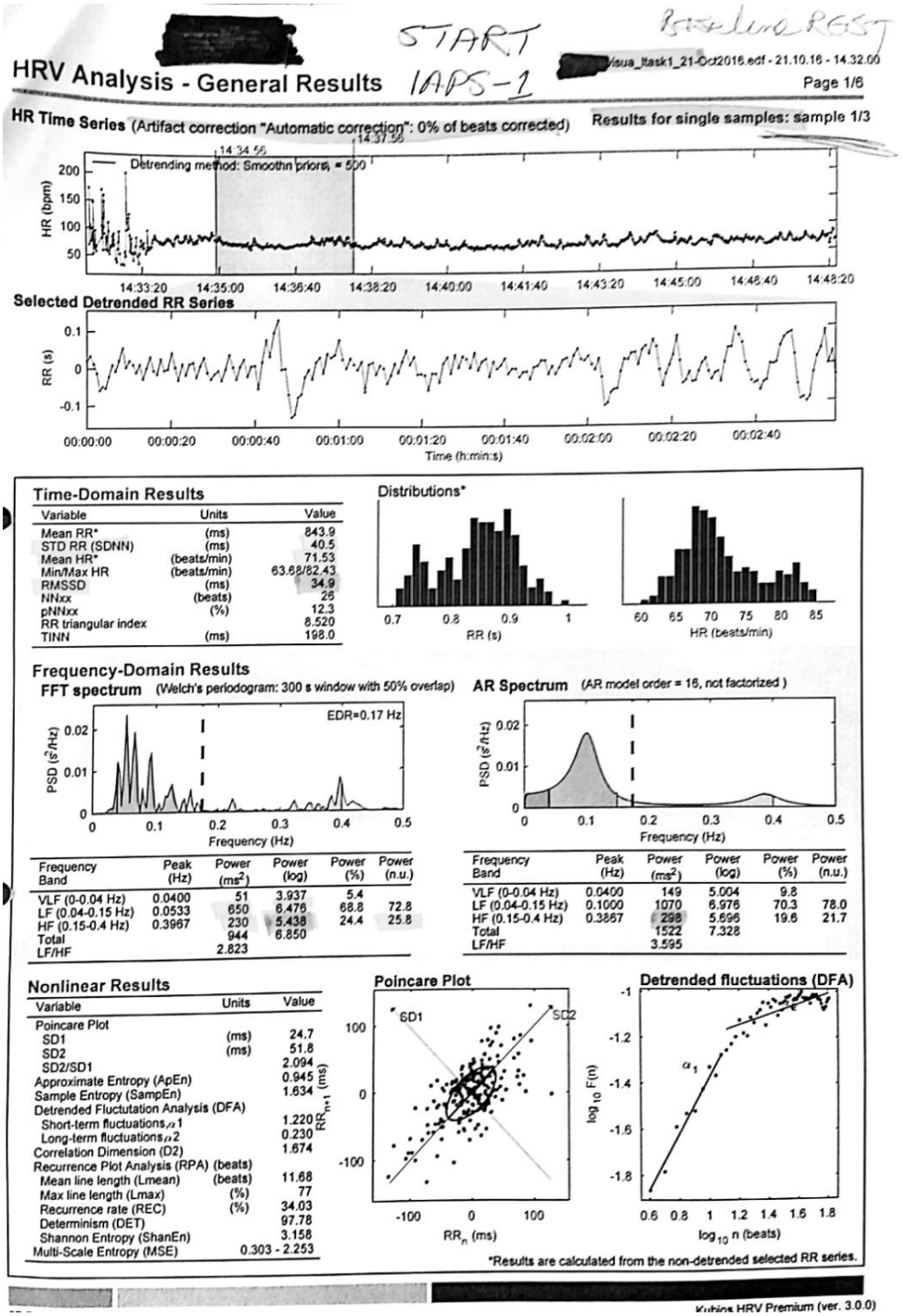
[redacted]

1	2	3	4	5	6	7	8	9	10
4	1	4	1	3	1	5	1	3	1

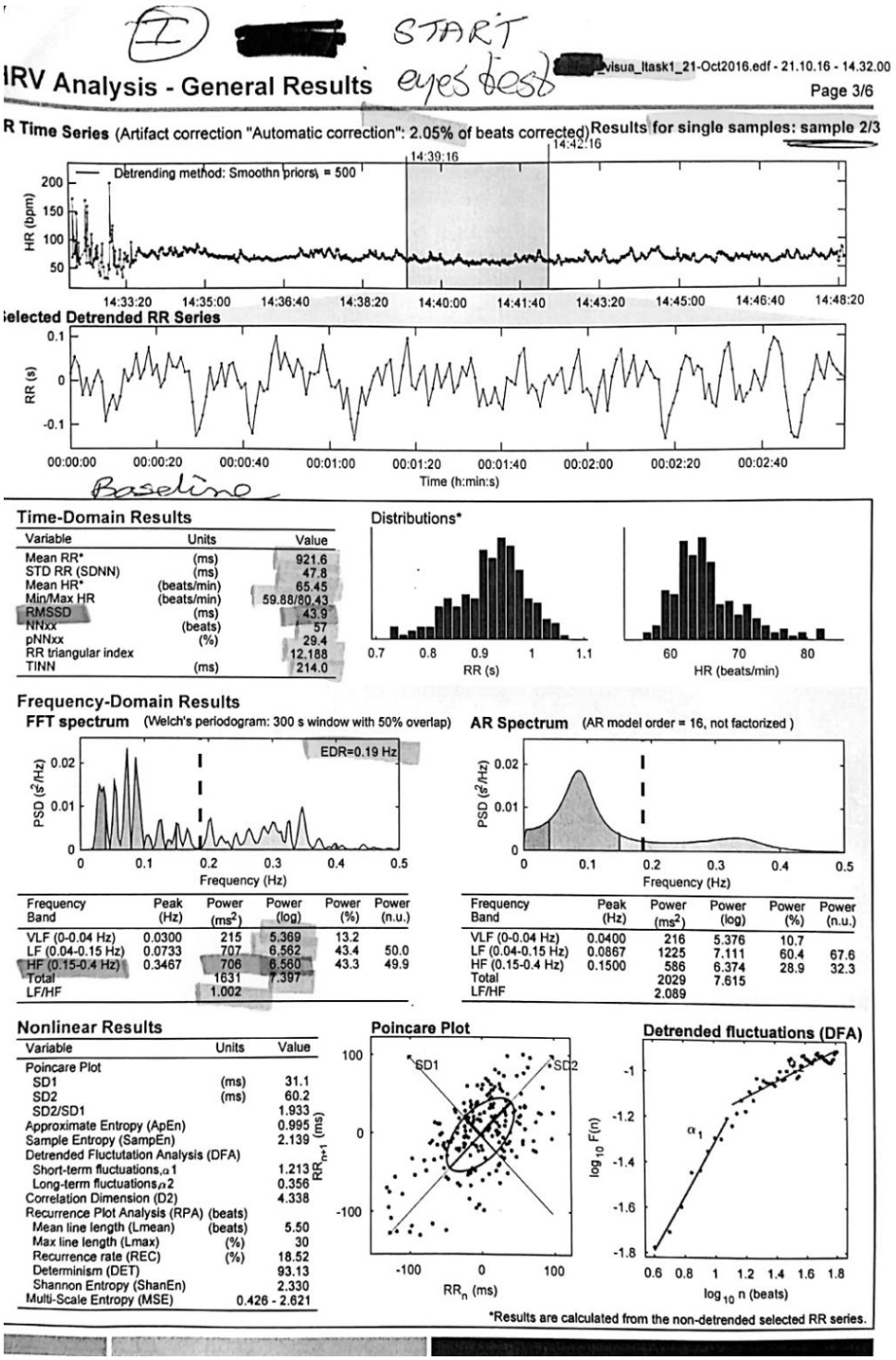
Thank you for your help.

This questionnaire is based on the System Usability Scale (SUS), which was developed by John Brooke while working at Digital Equipment Corporation. © Digital Equipment Corporation, 1986.

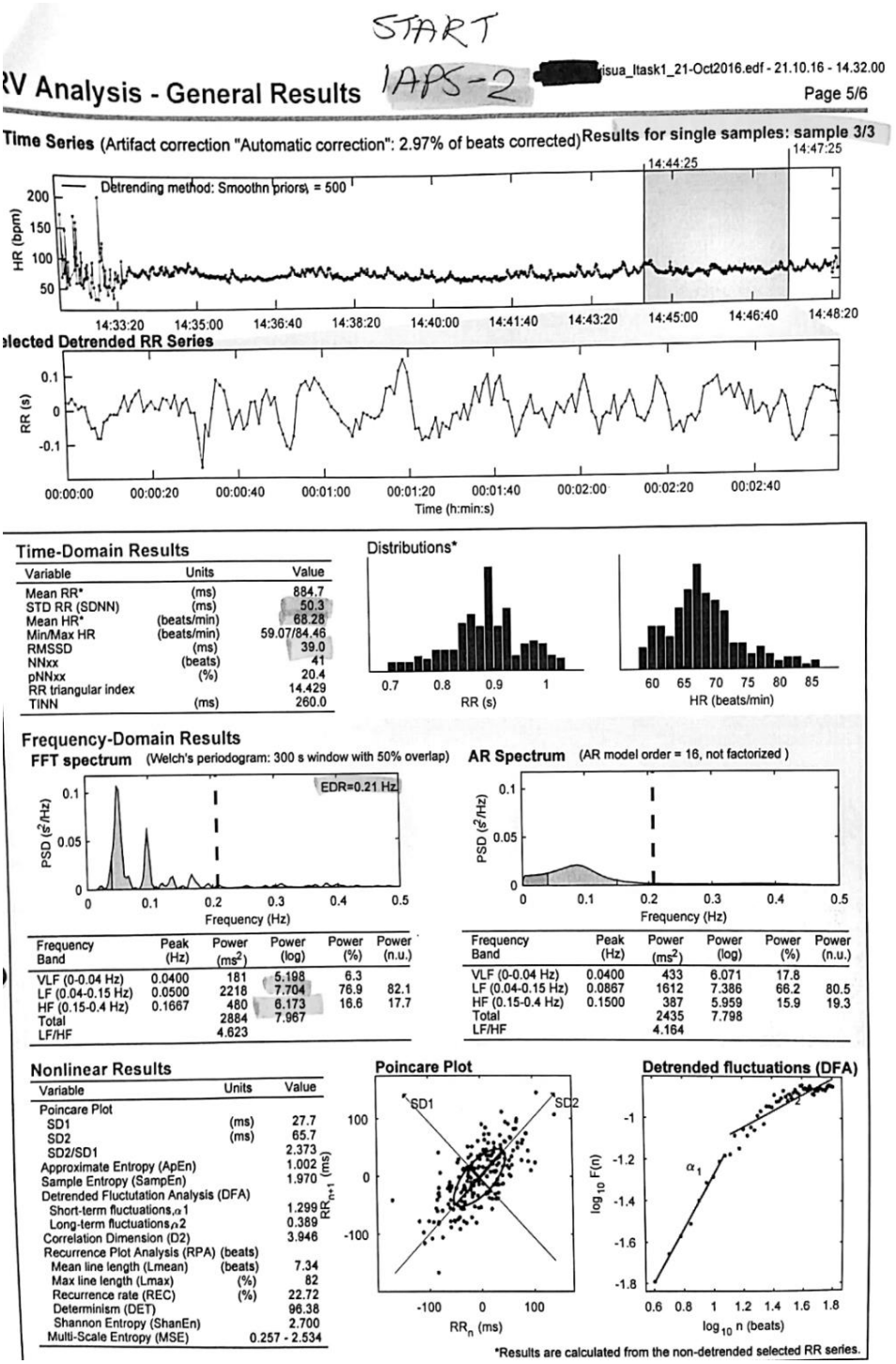
HRV Measurement – sample of baseline recording



HRV Measurement – sample of Mind in Eyes Test



HRV Measurement – sample of recovery task



International Affective Picture System (IAPS)– list of images used

International affective picture system	Image numbers
Initial baseline measurement IAPS-1	5200
	5210
	5260
	5301
	5501
	5594
	5600
	5631
	5660
	5665
Final recovery task IAPS-2	5700
	5720
	5725
	5726
	5750
	5800
	5825
	5890
	5982
	5991

HRV assessment using Three-Part Visual task – Timings for analysis

Visual task		Timing	
Section	Type of task	Start slide	Finish slide
1.	IAPS-1	3	14
2.	MIND IN EYES task	17	31
3.	IAPS-2	34	45

Participant debriefing– sample of StressEraser report

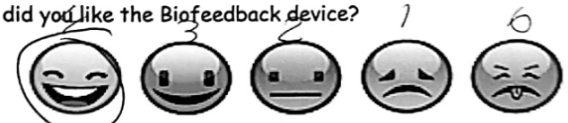
[redacted]

Debriefing report form

Participant PIN [redacted] Date of report [redacted]

I want to know what you thought about the study.

How much did you like the Biofeedback device?



absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

When I am stressed or anxious it helps me to calm down or relax.

What did you not like about the biofeedback device?

N/A

If the Biofeedback device was difficult to use what would help others use one in the future?

The videos would be helpful for anyone who is starting

Participant debriefing – sample of StressEraser report

Debriefing report form

Participant PIN [redacted] Date of report [redacted]/17

SE

I want to know what you thought about the study.

How much did you like the Biofeedback device?

absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

It was very easy and quick to use.

What did you not like about the biofeedback device?

it wasn't very modern, sometimes it was hard to turn the light on when using it, found it sometimes difficult to control my heartrate when I was anxious when using the device.

If the Biofeedback device was difficult to use what would help others use one in the future?

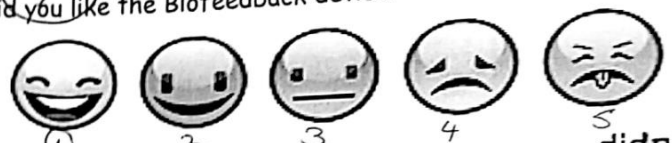
~~A tutorial on how to use it without the light turning off also~~ A fix to the timeout/dark resetting, and how to turn the on screen light on without the entire device resetting.

Participant debriefing – sample of StressEraser report

I want to know what you thought about the study.

How much did you like the Biofeedback device?

4



What was good about the biofeedback device?

It helped me get to sleep everytime I used it.

What did you not like about the biofeedback device?

Nothing everything was fine.

If the Biofeedback device was difficult to use what would help others use one in the future?

Try online there is multiple videos about it to help.

Participant debriefing – sample of Inner Balance report

Debriefing report form

Participant PIN [redacted] Date of report _____

I want to know what you thought about the study.

How much did you like the Biofeedback device?

absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

It was easy to use and was very easy to focus while using it.

What did you not like about the biofeedback device?

If the Biofeedback device was difficult to use what would help others use one in the future?

A small video tutorial on how to use the device when you download the app

Participant debriefing – sample of Inner Balance report

Debriefing report form

Participant PIN [redacted] Date of report [redacted]17

I want to know what you thought about the study. INNER BALANCE

How much did you like the Biofeedback device?

4

absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

It showed my heart rate at the end of the session and gave it a rating out of 4 stars.

What did you not like about the biofeedback device?

Waiting

If the Biofeedback device was difficult to use what would help others use one in the future?

If they watched video on how to operate it and how it works

Participant debriefing – sample of Inner Balance report

Debriefing report form

Participant PIN [redacted] Date of report [redacted]

I want to know what you thought about the study.

How much did you like the Biofeedback device?

absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

Easy to use and looked like a pair of ipod earphones, so was comfortable using in public - e.g. library.

What did you not like about the biofeedback device?

Earclip kept slipping. Might have affected readings.

If the Biofeedback device was difficult to use what would help others use one in the future?

N/A.

Carer debriefing – sample of StressEraser report

Debriefing report form

Participant PIN [redacted] Date of report _____

I want to know what you thought about the study.

How much did you like the Biofeedback device?

absolutely loved it! ✓ didn't love it at all

What was good about the biofeedback device?

Loved the 'idea' of it but in practice my [redacted] didn't use it enough to get any benefit. [redacted] was introduced to it at a stressful time. Feel he would have benefited more if started at a less stressful /holiday time.

What did you not like about the biofeedback device?

Nothing

If the Biofeedback device was difficult to use what would help others use one in the future?

[redacted] found it easy to use. Now that exams are over and hopefully life is less stressful I will encourage him to get into the habit of using it so that he is used to it when he needs it most.

Carer debriefing – sample of Inner Balance report

CARER

Debriefing report form

rticipant PIN [redacted] Date of report _____

want to know what you thought about the study. [redacted]

ow much did you like the Biofeedback device?

absolutely loved it! ⟷ didn't love it at all

What was good about the biofeedback device?

Easy to understand + use
Good because it is visual + sound
can be controlled.
Discrete

What did you not like about the biofeedback device?

Nothing!

If the Biofeedback device was difficult to use what would help others use one in the future?

No Difficulty.

Appendix IV: Procedure

Participant invitation letter

Participant Invite
Carers of Young People with Autistic Spectrum Disorder aged 13-17 years.

Dear Parent/guardian, Date January 2017

My name is Dr Helen Coulter. I am a consultant clinical psychologist working for South Eastern Health and Social Care Trust. I am also carrying out research at Ulster University.

I want to try to find ways of helping people with autistic spectrum disorder manage stress.

I would like to invite you and your child to participate in my research study which is titled *"An Investigation into the use of Heart Rate Variability Biofeedback in people with Autistic spectrum disorder".*

This research is aimed at helping people with Autistic Spectrum Disorder manage stress by using technology to help teach slow controlled breathing and increase levels of relaxation.

All the assessment & training will be provided by me in your own home. I will visit you and your child at home 5 times over a period of 12 weeks – over this time it will involve

- ✓ *Training for your child in the use of a biofeedback device which will be provided by me in your own home (I will do this over two separate home visits to make sure your child is happy using the device – your child can also keep the device at the end of the project if they wish).*
- ✓ *Your child sending me short reports on their progress each day (this can be by text, email or in writing - we can decide which is the best way to do this if you & your child decide to take part).*
- ✓ *Questionnaires checking your child's levels of anxiety & depression and assessments of their heart rate for 15 minutes using ECG sensors (this will happen 3 times, at the beginning, middle and at the end of the study).*
- ✓ *In addition, I will ask you for further information, about your child's stress levels and life in interviews at the beginning and at the end of the study.*

To participate in the study your child must be aged between 13-17 years and must have a confirmed diagnosis of autistic spectrum disorder and no major learning disability. In addition your child must not have a heart condition or skin problems like severe eczema / psoriasis.

If you don't want to take part in this research study that's ok. You don't have to contact me and your child will still get the same treatment from South Eastern Health & Social Care trust.

If you are interested, or if you would simply like to know more about the study and about biofeedback devices, please read the enclosed information and watch the video clips about the project with your child. Please contact me if you can't download the information videos or if you have any more questions. I have enclosed further participant information for you in this pack.

Yours sincerely,

Participant information sheet – sample pages

Participant Information Sheet 13 - 17 years

Biofeedback to help manage stress in people with Autistic Spectrum Disorder

Hello

My name is Dr Helen Coulter.
I am a Consultant Clinical Psychologist.
I work with people with Autistic Spectrum Disorder.

Here is a picture of me.

I work in the Health service.

HSC South Eastern Health and Social Care Trust

I am also doing research at University.

Ulster University

1

Participant information sheet

I am doing a study.

A study is a way of finding things out.

Do you want to be in the study?

This information leaflet tells you all about the study.
It helps you to decide if you want to be in the study or not.

This is what I want to find out

I want to help people with Autistic Spectrum Disorder manage their stress levels.

- I will be giving people technology devices.
- The devices help people to relax by showing them how to slow down their breathing and heart rate.
- They show you how well you are doing by giving you information about your breathing and heart rate.
- The devices are called **Biofeedback** devices - because they give you feedback about your biological reactions - that is why the word bio is used beside feedback.
- These devices work by checking how your heart is working by measuring the blood flow from either your finger tip or your earlobe.

2

Participant exclusion criteria form

Exclusion criteria	If yes EXCLUDE from study
Non-English speaker	
Learning Disability (IQ< 70)? (Check understanding)	
Psychosis /active suicidal ideation? (Check understanding)	
Eczema / psoriasis?	
Immunosuppressing condition? (Check understanding)	
Narcotics / Beta blockers / BZ? (Check understanding)	
Cardiac condition / pacemaker?	
Drug / alcohol addiction?	

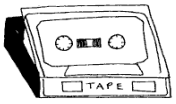
Participant assent form

I have read the information leaflet about the study.
I understand what will happen.
I had a chance to ask questions about it.
I am happy for Helen to ask my carer more information about me and let my doctor know I am taking part.

I agree to be in the study.

YES ☐  NO ☐ 

I say that it is OK for Helen to record my heart rate with my carer present whilst I look at a series of pictures.

YES ☐ NO ☐ 

If I start the study and then later on want to stop being in the study, I can do this whenever I want to.

I can tell Helen at any time if I do not want to be in the study.

Helen will write and record what I say and what I do but no one will know it was me.

I can phone Helen if I want to know more about the study.
Helen's phone number is 028 91510190.

_____ _____
My signature Date

_____ _____
Helen's signature Date

Client confidential information form

Participant information

Name

DOB

Telephone (mobile)

Telephone (home / work)

Address

Emergency contact name

Emergency contact telephone

GP information

Name

Address

Telephone

Key worker information

Team Adult ASD / Child ASD/ CAMHS / Other

Telephone Address

Demographic information form

Information about yourself		**Information about your lifestyle**	
Gender	Male	Activity level	< 1hour per week
	Female		1-3hrs per week
	Other		>3hrs per week
Age	13-17	Smoking	Yes / no
	18-24	Drugs	Yes / no
		Sleep difficulty	Yes / no
Education	Grammar school	Alcohol intake	
	Secondary school		
	University / College		< 14units per week
	NEET		
			>14units per week
Employm	School		
	College /university		
	Employed		
	Unemployed		
ASD diagnosis			
MH diagnosis	Anxiety	Medication	
	Depression		
	Other		

Technology information form

Technology and internet access	
Does participant have Internet access	Yes / no
Have participants and carers accessed web links	Yes / no
How will participant complete reports	Email / smartphone (check no cost) / written reports
Does participant have iPad available for Inner Balance	iPad / no iPad
Participant level of expertise using technology	Expert / advanced / intermediate / beginner / unskilled
Type of technology accessed	Gaming /video and TV / texting / social media / email / phone call / other
Frequency of use	
Problems with technology	

Interview and assessment protocol

RESEARCHER SCRIPT FOR INITIAL HOME INTERVIEW v2

WELCOME

"Good morning / afternoon. First of all I would like to thank you for agreeing to participate in this interview and I look forward to hearing your contributions. My name is Dr Helen Coulter and I am a Consultant Clinical Psychologist working in SEtrust. I am carrying out research at Ulster University and would like to look at new ways of helping people with autism manage stress and anxiety by using biofeedback technology."

The researcher will read out the following reminder about confidentiality:

"If you do decide to take part in the study, I will let your <GP / keyworker > know you are involved and will also let them know when you have finished. The information you give in interviews, questionnaires and clinic recordings will remain confidential and will not be sent to your GP. If, however you tell me about something that puts either yourself or others in danger then I will have to let others know about this – however I will always tell you / your carer if I have to do this"

CARER INPUT

"An important part of this research study is that I would like with your permission to ask both you and your carer information about yourself and your stress levels – I would also like to ask your carer to be present whilst you have your heart rate recorded – please let me know now if you have any concerns or questions about this"

DEMOGRAPHIC INFORMATION FORM

Researcher now completes demographic information form and confirms eligibility

REVIEW OF EQUIPMENT

Researcher now shows and demonstrates use of equipment to be used in both home training and assessment to both participant and carer.

"I am now going to show you the equipment that will be used both in the clinic assessment and at home – you can try it out and ask me any questions"

OFFER OF FURTHER TIME

"If you wish we can now go ahead with the assessment – however if you would like more time to think about everything or to talk to someone else you can say so now. You can contact me again if you decide later on that you do want to take part in the study"

CONSENT

The researcher will ensure that the participant and carer have read and reviewed the participant information sheet and assent / consent form

"I want to check that you have read the Participant information sheet and assent / consent forms and ask if you have any further questions"

"Are you now happy to sign the written assent / consent form?"

Researcher now checks written consent / assent forms signed

DEMOGRAPHIC INFORMATION and QUESTIONNAIRES

Researcher now completes and questionnaires with participants and carer.

*"I am now going to ask you / your carer some questions which will enable me to complete a short contact details form. After this I will give you a **3**-digit PIN code which will then be the only identification we use on all the questionnaires and recordings. Your name will only be on your consent form and the initial contact form, but I will store these separately in a locked filing cabinet at Ulster University".*

PARTICIPANT PHYSIOLOGICAL ASSESSMENT

"I am now going to ask you to complete the physiological assessment of your heart rate. The sensors will stay on whilst you look at some images on the computer. Once attached the sensors should feel comfortable but please do tell me if you do experience any discomfort. The whole assessment will take about 15 minutes."

Researcher attaches sensors to participant and begins recording (carer present)

Researcher asks participant to watch PowerPoint presentation on laptop and records time on pc for start of 15-minute visual task

REMOVAL OF SENSORS

"The physiological assessment is now finished, and I would now like to remove the sensors".

PARTICIPANT QUESTIONNAIRES

I would now like you to complete some questionnaires. This will take about 15 minutes.

CARER REPORT ON PARTICIPANT STRESS PROFILE

"I now want to ask your carer how they feel you react to stress and how often you become stressed – everyone reacts in their own unique way – so I want to find out what your specific reactions are"

1. *"Can you tell me how (Participant) reacts when they are stressed?"*
2. *"What are the triggers for (Participants) stress reactions (meltdowns)?"*
3. *"How often does (Participant) show stress reactions (meltdowns)?"*
4. *"What do you think helps (Participant) to manage their stress levels?"*
5. *"What are the main obstacles preventing (Participant) manage their stress levels?"*

RANDOMISATION

"We can now open the sealed envelope to see which type of device you will be getting and whether you will be starting immediately or waiting 6 weeks before you get the device".

Researcher now gives sealed envelope to participant / carer to open

FURTHER DATES FOR TRAINING

"I would now like to agree dates for the home training sessions so that I can come back to teach you how to use the biofeedback device. We can also arrange the dates for the other two visits at the mid-point and at the end of the study."

Researcher now agrees dates for further assessment and training sessions.

SUMMARY AND CONCLUSION

"Finally, I would like to give you details of the support services available should you wish to access them – these include 24-hour support helplines should you need to talk to someone when other services are unavailable". "Do you have any further questions?"

Researcher offers Support helpline information sheet to both participant and carer.

Researcher offers 'thank you'

The duration of the Home interview will be approximately 120 minutes.

This schedule will be repeated for the mid-point interview

(except for consent and appt planning)**.**

Support Helpline form

Participant & Carer Support Helpline

GP OUT OF HOURS Telephone	
North Down & Ards area	(028) 9182 2344
Lisburn & Down area	(028) 9260 2204

BANGOR & NORTH DOWN SAMARITANS	
Telephone local branch:	02891 46 46 46
National telephone:	116 123
Email Samaritans:	jo@samaritans.org
Address	92 Dufferin Avenue Bangor BT20 3AD

LIFELINE NI	
Telephone	0808 808 8000
Further information from	www.lifelinehelpline.info/faq
	www.mindingyourhead.info

CHILDLINE	
Telephone	0800 1111
Further information from	www.childline.org.uk

National Autistic Society

Advice for people with autism spectrum disorders and their families and carers.

Autism Helpline

Tel:	0808 800 4104 (open 10.00am-4.00pm, Monday-Friday)
Text:	07903 200 200
Minicom service:	0845 070 4003
Email enquiry service:	visit www.autism.org.uk/enquiry and complete the online form

The Autism Helpline provides impartial, confidential information, advice and support for people with autism spectrum disorders their families and carers.

Appendix V: Direct Reports

PHASE 1 NHS and Voluntary sector expert reports

Evaluation of design; participant information; measures; equipment; procedure and risks by NHS and voluntary sector experts (n=6).

Area of study	Problems highlighted	Changes made as a result
Study design	*"waiting 12 weeks seems too long - people may drop out or just go and buy the device"*	Reduce time to 6 weeks for waiting list group. Intervention to remain 12 weeks
	"Many people with autism have poor insight into their levels of stress and their triggers for stress" *"need to involve carers in pre- and post-interviews"* *"Carer interview needed even in high ability ASD adults".*	Include carer interview for all participants. If adult participant, then also request consent to include interview from trusted adult. Carers viewpoint essential for both groups.
	"Significant level of sensory sensitivities seen in many people with autism which may affect use of this technology"	Inclusion of an additional sensory profile questionnaire to monitor progress of those participants with sensory difficulties.
Participant information	*"Need to have photos and video clips to explain both assessment process and the intervention."* *"Words confusing for people with autism"*	Include photos of researcher using equipment in written PIS. Include video format. Include training videos from existing device materials
	"People with autism take a literal approach to information and will be distracted by any inconsistencies in pictures in PIS leaflet"	Consistency of visual images used in PIS and consent important – use identical photos of researcher using equipment
Measures	*"Autism Stress Survey Schedule; Achenbach and STAI too long confusing – 'use simpler scales' 'include sensory check'* *"measure depression as well as anxiety – both linked"* *"Carers will want to talk about problems and any changes in an interview rather than a questionnaire - may get more information"*	Use Beck questionnaires. Include Sensory Profile questionnaire Use standard interview with carers
	"Use technology to aid reporting of symptoms - this is less stressful and increases compliance"	Use online progress reporting via text / email rather than using written reporting materials.

Dates of meetings with ASD professional experts: 27th June; 9th July; 2nd Sept; 10th November 2014; 15th June 2015

PHASE 1 NHS and Voluntary sector expert reports

Evaluation of design; participant information; measures; equipment; procedure and risks with NHS and voluntary sector experts (n=6), showing problems highlighted and changes made to final study.

Area of study	Problems highlighted	Changes to pilot study made as a result
Equipment	*"No studies like this on ASD – need to collect information on potential problems with devices" "Good rationale – visual, portable, and uses technology" "Devices not specifically licensed for use in children – however high need for support in young people with ASD"*	Use devices already trialled in research in non ASD populations. Ensure devices have FDA approval / CE mark Use with teenagers and young adults – ensure assent as well as consent Do not use with younger children or learning disability
	"Need to have early success or could cause increased anxiety"	
	"Be aware of those with significant sensory issues – they will be unlikely to cope with the assessment process"	Carry out sensory profile screening at beginning of study. Review of all equipment with participant at home prior to consent
	"Physiological assessment task may trigger high anxiety"	Simplify physiological assessment task, sensors and equipment used
	"Sensor attachment may trigger high anxiety "	
Procedure	*"The clinic assessment seems too stressful for people with autism"*	Remove clinic assessment.
	"Unlikely to recruit or will induce anxiety in those already recruited"	Consider having physiological assessment completed at home using standardised procedure.
	"significant anxieties experienced by this client group attending unfamiliar clinic settings".	
	"Training needs to include more visual material and fewer written instructions	Use video clips as well as written user guides. Simplify guidelines.
Risks	*"Use technology to check progress"*	Ensure carer / trusted adult present during home visits Have lone worker protocol
	"People with ASD may form strong attachment to researcher and want continual follow up or alternately may become aggressive during visits"	Have clear debriefing plan / offer limited follow up service or information on other services.

Dates of meetings with ASD professional experts: 27th June; 9th July; 2nd Sept; 10th November 2014; 15th June 2015

PHASE 1 ASD adult reports

Evaluation of design; participant information; measures; equipment; procedure and risks by ASD adult groups (n=15) showing problems highlighted and changes made to final study.

Area of study	Problems highlighted	Changes to pilot study made as a result
Study design	*Will not want to wait 12 weeks to get device*	Reduce waiting time for control group
Participant information (Visual strength in ASD)	*"Include more pictures" "Pictures should be specific and accurate" "Need pictures of researcher rather than someone you will not actually meet" "Visual information good – no need for long discussion"*	Include pictures of researcher using equipment instead of generic photos.
Measures (short and simple)	*"use simpler scales"* *"prefer to text or email" (rather than telephone or interview)* *"don't want to be recorded"* *"tick boxes or write a few words"*	Use Beck depression and anxiety questionnaires Use text messaging service to check progress
Equipment (Sensory sensitivity)	*"Velcro and wires (on Nexus assessment equipment) too stressful for some with sensory issues" "Too many wires"*	Allow potential participants to see and try out equipment at home prior to consent. Consider alternative assessment equipment.
(Training)	*"Training video good for device" "Can show me how stressed I am …can show others"*	Training videos – biofeedback devices
Procedure (Clinic assessment)	*"Clinic assessment (physiological assessment with sensors) may cause high anxiety"* *"Would be better at home"*	Remove assessment in clinic. Physiological assessment to be completed at home using standardised procedure
Risks	*"Need to be able to work it or else will get more stressed"*	Clear training to ensure success - offer follow up if needed

Dates of workshops with ASD user groups: 2nd April 2014; 20th March 2015

PHASE 1Undergraduate student reports

Evaluation of psychophysiological assessment procedure using Nexus-10 Mark II biofeedback system with undergraduate students (n=9).

Area of study	Problems highlighted	Changes to pilot study made as a result
Physiological assessment task	*Number of tasks confusing.* *IAPS task "too long"* *IAPS questionnaire "confusing" and could not be completed*	Simplify assessment by reducing number of visual image tasks. questionnaire removed from study
Sensor attachment	*Wires and straps may upset some people – may be a problem for people with sensory issues.*	Final decision on type of equipment to be made after 2nd ASD user group review Consider using wireless equipment
Sensors	*Explain more about what each sensor will record.*	Increase explanation regarding types of sensors and what each one measures
Assessment equipment	*"Too many wires" in Nexus assessment equipment*	Consider using wireless equipment
	"Can't complete questionnaires if sensors on fingers or arms"	Complete questionnaires separately from physiological assessment OR use wireless equipment
	"Arms can feel a bit wet"	Use different electrodes to attach to sensors Sensitive skin wipes can also be provided for cleaning any residue from sensors at end of procedure for participants if needed
Data recording	Unusual heart rate recordings.	Review with Cardiac physiologist and consultant Cardiologist. Check equipment and data collection procedure Consider different equipment

*Dates of clinic assessments with undergraduates: 12th ,19th and 25th February; 5th March 2015

PHASE 2 Problems reported by participants at debriefing

PROBLEMS REPORTED BY PARTICIPANTS
- first device made me more stressed / getting errors because my hands so cold
- I found no issue with the device
- nothing
- nothing everything was fine
- earclip kept slipping
- didn't like the way it wouldn't access my finger/ kept having errors especially if very stressed/ didn't work if extreme stress too difficult to use
- problems switching on and off sound / date and time reset on device / if very stressed dont remember to use it
- not very modern/ hard to turn the light on at night/ difficult to control heart rate when very anxious / date and time resetting / not practicing all the time
- none
- hard to get smooth waves / didn't practice it / couldn't get a lot of points /didn't use it when stressed
- doesn't work if fingers are cold / sticky pads painful when removing / its harder to get smooth waves if stressed but I was able to do it
- NOT REPORTED
- need to set precise times for practice / hard to get sensor to stay on ear / hard to get pulse
- awkward on the finger and on the ear / don't want to practice
- NOT REPORTED
- struggled to obtain points and it caused me a bit of stress to get points / found it difficult to get points
- hard to remember to practice / would be better if on phone / couldn't use first one errors as cold fingers /sunlight caused errors
- hard to remember to use it everyday
- time consuming /just didn't feel it really helped / didn't use it much
- a lot to learn / assessment too long / not using device now

PHASE 2 Benefits reported by participants at debriefing

BENEFITS REPORTED BY PARTICIPANTS
- used after difficult / stressful day and helped / helped when people were annoying me/ helps me calm down and relax
- the information presented was calming / it allowed for me to collect my thoughts
- easy to use / very easy to focus when using it / video tutorial useful
- it helped me sleep every time I used it / there are lots of videos online / it helped with my problems / use it every day / will continue to use
- easy to use /comfortable/look like earphones so comfortable using it in public
- efficent and quick / most useful at night / good for mild-moderate stress / liked it / helped easy to use
- visuals good / if stressed used it and helped / helps get to sleep at night / used same breathing but without device when in bed as don't want to get up / will continue
- it was easy and quick to use / helps to wind down at night/use to get to sleep
- showed my heart rate / it gave me a rating / video tutorial useful / has helped me control anxiety
- easy to use/ easy to carry and store
- helped me control my breathing / video tutorial / I can see what I am doing / it has given me breathing techniques that I can use / helped me calm down
- NOT REPORTED
- made it clear and easy to control my breathing /made me more relaxed / infromation clear also
- I felt better
- NOT REPORTED
- excellent and simple to use / showed me more about breathing and stress
- it helped me be happier /use at night / would use again
- its easy to use / it helped with breathing slowly/
- easy to understand / its easy to use/seem to be accurate
- breathing better now / have used breathing without the device / might use another device if on android

PHASE 2 Problems reported by carers at debriefing

CARER	PROBLEMS REPORTED
-	no negative reports
-	had no difficulties
-	finding time to fit into routine
-	none
-	none
-	didn't help when very upset possibly required too much concentration
-	not always immediately available when stressed / prompts to use it would be good
-	none
-	too many introduction pages in manual - this increased anxiety
-	started at stressful time - would have benefitted more if started at less stressful time / didn't use it enough to get any benefit
-	cold fingers and could not get a reading / bulky
-	NO REPORTS
-	finding time to do it
-	P wouldn't use it - no point in continuing / didn't practice
-	if sweating couldnt use it / kept stopping
-	P felt self conscious using it in public /
-	P didn't use it enough / was useful but stopped using it / behaviour better but not sure if due to device / couldn't use first device
-	hard to remember to use it every day
-	not compatible with android devices
-	nothing its very simple / hard to know how much practiced / not using now

PHASE 2 Benefits reported by carers at debriefing

CARER BENEFITS REPORTED
- easy to understand and use / good because visual / sound can be controlled / P was given control
- enabled P to focus and be still / encouraged techniques to help self regulate
- good on the phone / could take it everywhere /helped P calm down before going to college
- really helped with confidence
- real benefits in helping develop awareness of physical symtoms/increased ability to identify patterns as they developed /increased ability to anticipate and take greater control managing anxiety
- a particularly satisfying fidget toy / helped for mild stress
- understood how to use it/ felt valued / special because just for P/ portable / easy to access / easy to understand / less stimming
- can use any time or place without anyone being aware of it / easy to use on a regular basis / can see results and get record of effects
- very visual / instant feedback / easy to understand / P could monitor own progress / could recognise symptoms of early stress / especially good at decreasing stress for exams / better at socialising and teacher has noticed also / more smiles and eye contact
- good idea / easy to use
- portable / fun / easy to use /recent holiday increased anxiety travelling and it helped / especially good at helping to wind down at night and to get through difficult situations / gives P control / visual feedback good / helped with panic attacks
- really helped P get hold of anxiety before it escalated into full meltdown / have no doubt P was able to complete exams because of this
- seemed good
- helped P relax
- being able to see effect of your breathing / helpful learn how to control breathing when anxious /easy to use / increased awareness of stress and effect on body / have learnt useful technique for future
- easy to use / couldn't fault it /
- easy to use / very useful during exams / practiced before going in for exams /helped to decrease anxiety and increase focus / will use again
- good to diffuse situation if P upset / easy to use
- giving more control to person directly / visual / something to concentrate on / simple to use