Measuring Prefrontal Cortex Response to Virtual Reality Exposure Therapy in Freely Moving Participants

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Abstract

Virtual Reality Exposure Therapy has demonstrated efficacy in the treatment of phobias; yet little is known about its underlying neural mechanisms. Neuroimaging studies have demonstrated that both traditional exposure therapy and virtual reality exposure therapy normalise brain activity within a prefrontal - amygdalar fear circuit after the treatment. However, the previous studies employed technologies that perhaps impact on ecological validity and naturalness of experience. Moreover, there are no studies investigating what is happening in the brain within a virtual reality session

This PhD takes a multidisciplinary approach and draws upon research areas of cognitive neuroscience, neuropsychology, and virtual reality. The approach is twofold - developmental and experimental. A key methodological objective was to maximise ecological validity by allowing freedom of movement and sight of one's own body. This was approached by combining wearable fNIRS within Immersive Projection Technology (IPT). The stimulus was adapted from a classic VR experiment - Pit Room. The scope of this PhD includes three experiments. The first pilot experiment tested the potential of combining the wearable Functional Near-Infrared Spectroscopy (fNIRS) device – NIRSport, with virtual reality (VR) display - CAVE-like Immersive Projection Technology (IPT) system – Octave. The aim was to test the feasibility of the protocol in terms of the design, integration of technology, and signal to noise ratio in the Pit Room study, which involved measuring brain response during exposure to heights in virtual reality. The study demonstrated that brain activity could be measured in IPT without a significant signal interference. Although there was no significant change in brain activity during exposure to virtual heights, the study found trends toward increased HbO in the prefrontal cortex. The second study investigated the brain activity indicative of fear inhibition and cognitive reappraisal within a single session of VRET in healthy controls. The heart rate was also measured as an indicator of emotional arousal (fear response) during the VRET session. 27 healthy volunteers were exposed to heights in virtual reality. Changes in oxygenated haemoglobin concentration in the prefrontal cortex were measured in three blocks using a wireless fNIRS, and heart rate was measured using a wireless psychophysiological monitor. Results revealed increased HbO concentration in the DLPFC and MPFC during exposure to the fear-evoking VR, consistent with fear inhibition and cognitive

reappraisal measured in previous neuroimaging studies that had not used VR. Within-session brain activity was measured at much higher temporal resolution than in previous studies. Consistent with previous studies, a trend showed an increase of brain activity in the DLPFC indicative of cognitive reappraisal at the beginning of the session. Then additionally the MPFC was activated consistent with fear inhibition. The heart rate showed a trend towards a gradual decrease within a session. The aim of the third study was to investigate the neural basis of VRET in an acrophobic population. In particular, the study focused on measuring functional brain activity associated with both within- and between-session learning. Psychophysiological monitoring was also employed to measure levels of emotional arousal within- and between sessions. 13 acrophobic volunteers took part in three-session VRET for a fear of heights. Changes in HbO in the prefrontal cortex were measured in three blocks to investigate within–session brain activity and across three sessions to investigate between-session inhibitory learning. Results demonstrated that phobic participants have decreased activity in the DLPFC and MPFC at the beginning, however, after three sessions of VRET, activity in these brain areas increased towards normal (measured in healthy controls). Although there was no within-session learning during the first and second session, the study found a significant increase in the DLPFC at the beginning of a session. During the second block, additionally, the MPFC was activated. The magnitude of brain activity in those regions was negatively correlated with the initial level of acrophobia. Due to the technical difficulties, no significant results were found in psychophysiological measures. However, subjective fear ratings decreased significantly within- and between sessions. Moreover, participants who felt more present demonstrated stronger results in brain activity at the end of VRET. This is the first project that investigated the neural correlates of fear inhibition and inhibitory learning by combining a VR display in which people can move around and see their body, with wearable neural imaging that gave a reasonable compromise between spatial and temporal resolution.

This project has an application in widening access to immersive neuroimaging across understanding, diagnosis, assessment, and treatment of, a range of mental disorders such as phobia, anxiety or post-traumatic stress disorder. An application that is receiving an interest in the clinical community is repeatable, direct and quantifiable

assessment within clinics, to diagnose, steer treatment and measure treatment outcome.

Abbreviations

BOLD Blood Oxygen-level Dependent

DLPFC Dorsolateral Prefrontal Cortex

EDA Electrodermal activity

EEG Electroencephalography

fMRI Functional Magnetic Resonance Imaging

fNIRS Functional Near-Infrared Spectroscopy

GSR Galvanic Skin Response

HAQ Height Anxiety Questionnaire

HbO Oxygenated Haemoglobin

HbR Deoxygenated Haemoglobin

HbT Total Haemoglobin

HMD Head-mounted Display

HR Heart Rate

HRF Hemodynamic Response Function

IPT Immersive Projection Technology

MPFC Medial Prefrontal Cortex

PET Positron Emission Tomography

PTSD Post Traumatic Stress Disorder

SMA Supplementary Motor Area

SNR Signal-to-noise ratio

SPM Statistical Parametric Mapping

SR Skin Resistance

SUDS Subjective Units of Distress Scale

tDCS Transcranial direct current stimulation

TMS Transcranial Magnetic Stimulation

VR Virtual Reality

VRET Virtual Reality Exposure Therapy

Chapter 1 Introduction

1. Introduction

This PhD takes a multidisciplinary approach and draws upon research areas of cognitive neuroscience, neuropsychology, and virtual reality. The approach is twofold - experimental and developmental.

The experimental approach of this PhD project aims to investigate the neural mechanisms underlying Virtual reality (VR) experience through the integration of a technology which bridges a gap between ecological validity and controllability. Understanding neural substrates of VR will not only aid the development of more efficient, controllable and ecologically valid research but also it will inform research on the field of VR and mental health, which has recently drawn the attention of many psychologists and clinicians. In particular, this project investigates neural substrates of inhibitory learning and cognitive reappraisal in Virtual Reality Exposure Therapy (VRET) in both healthy participants and patients with a moderate level of a specific phobia. Understanding how brain interacts with VR during therapy would guide and facilitate a therapeutic effect of the treatment.

The developmental approach of this PhD project aims to assess the integration of VR technology and brain imaging system and create VR simulation capable of triggering an emotional response, which resembles a response to real-life situations. For that reason, the ecological validity and naturalness of the response are essential factors in this project. They must be taken into account in order to ensure the generalisation of the VR experience to real-life situations. Therefore, this project introduces the integration of a portable wireless brain imaging module and a large VR space, in which people can freely move with others.

2. Research Problem

Previous studies measuring a physiological response to VR demonstrated that VR has the capability of triggering some level of anxiety even in non-phobic participants (Jang et al., 2002; Pugnetti et al., 2001; Wiederhold et al.,1998). For example, standing or moving near real or virtual heights, causes physiological reactions (Abelson & Curtis,

1989; Pugnetti et al., 2001). This property of VR has encouraged research implementing this technology in mental health care to assess, diagnose and treat a range of anxiety disorders (Bohil, Alicea, & Biocca, 2011). In order to use VR effectively as a treatment medium, there is a need to understand how VR exposure influences brain response. Unfortunately, neuroscience of VR is still in its infancy. Some studies have attempted to investigate the neural basis of VR experience using Functional Magnetic Resonance Imaging (fMRI) or Electroencephalography (EEG) (Pugnetti et al., 2001; Wiederhold & Wiederhold, 2008). Although fMRI provides the best method for acquiring brain images, it restricts natural movement by restraining a participant in a large, noisy cylinder-shaped tube. This may significantly impact on the naturalness of response and thus on performance or therapeutic outcome. Despite recent improvements in EEG systems which have become more feasible to use in terms of design and utility, combining EEG and VR could still be challenging due to its susceptibility to motion artifacts and signal interference (Usakli, 2010). Given these issues, there is a need to implement brain imaging technology which would facilitate more natural movement and response within VR.

On the other hand, there have been recent advances in VR technology, but these also suffer many drawbacks. For example, the most commonly used Head-mounted Display (HMD) may constrain natural locomotion and hides others from the view of a user. However, Immersive Projection Technology (IPT), or Cave-like (Cave Automatic Virtual Environment) systems may offer a promising solution. It immerses a user into a room-sized VR simulation which supports natural locomotion and interaction in the space without losing the sight of one's own body or presence of others. Therefore the amalgamation of wireless brain imaging and IPT could provide information about the neural response to the VR exposure in a more ecologically valid manner. Understanding the neural correlates of VR plays a crucial role in increasing the effectiveness of the treatment, particularly in VRET, which has attracted the attention of clinicians due to these advances in VR technology.

VRET has been used in the treatment of anxiety disorders, specific phobias or PTSD (Meyerbröker & Emmelkamp, 2010). Neuroimaging studies of anxiety disorders demonstrated that patients with anxiety, phobia and PTSD have functional and structural abnormalities within the prefrontal – amygdalar neural fear circuit and highlighted the

role of the Prefrontal Cortex (PFC) in pathological fear inhibition and cognitive reappraisal of emotions. Phobic patients show hypoactivation in the PFC which is inversely correlated with hyperactivation in the amygdala (Etkin & Wager, 2007). Therefore, the role of VRET is to restore the balance within the fear circuit.

The neural mechanisms underpinning traditional exposure therapy (ET) have been widely researched. Previous studies demonstrated that the PFC mediates processes of emotional regulation (Craske & Liao, 2012; Jovanovic & Norrholm, 2011; Quirk, Garcia, & González-Lima, 2006). It has been suggested that maladaptive patterns of emotional regulation are exhibited in anxiety, phobia or PTSD (Davidson et al., 2002). Emotional regulation model (Gross 1998) provides a theoretical framework for understanding mechanisms of exposure-based treatments. According to this model, two major strategies play a role in ET – cognitive reappraisal of emotions and fear inhibition (suppression). Systematic prolonged exposure to feared stimuli may enhance emotional regulation through adjustments cognitive reappraisal by reinterpretation of the meaning of a feared stimulus, and further - inhibition of a pathological response to this stimulus. VRET offers a medium that allows a systematic and prolonged exposure to fear-evoking stimuli while allowing controllability of the treatment (Powers et al., 2008). However, the temporal dynamics of emotional regulation and related neural activity within the fear circuit during VRET are yet to be understood. This project uses the wireless neuroimaging system – Functional Near-Infrared Spectroscopy (fNIRS) which allows for freedom of movement while the brain activity is recorded. However, fNIRS has a limited depth of penetration (Ferrari & Quaresima, 2012), which does not allow for recording brain activity from the amygdala, therefore this project focuses on the prefrontal part of the fear inhibitory circuit.

3. Research questions

This PhD project aims firstly to answer the question whether we can measure the PFC neural correlates of fear inhibition and reappraisal in VR while still maintaining the naturalness of the response and movement. Secondly, if so, what are the neural correlates of fear inhibition and reappraisal in healthy participants in VR with improved ecological validity? Do brains of patients with mental disorders respond to the fear-evoking virtual stimuli in the same manner as the healthy brain? Furthermore, can we use VR with

improved ecological validity to trigger inhibitory learning in patients with mental disorders and restore the balance in the fear circuit as measured through increased brain oxygenation in the PFC? If so, when does the change occur? Does inhibitory learning occur within a single VRET session or between multiple sessions? Finally, does the PFC inhibitory response correlate with other psychophysiological measures and subjective reports?

4. Scope

This PhD assesses the combination of cutting-edge technology to facilitate the naturalness of response and movement in VR. The project attempts to measure fear inhibition response and reappraisal to the virtual threat involving exposure to highs, while maintaining the freedom of movement through employing the brain imaging system – fNIRS NIRSport, and large immersive projection technology (IPT) – Octave. NIRSport is a wearable, portable, non-invasive, multichannel neuroimaging tool for measuring hemodynamic response in the brain.

This project employed a classic VR experimental scenario that features the Pit Room – an arousal–inducing VR simulation involving exposure to heights. The scenario was originally used by the group of Mel Slater (Slater, Usoh, & Steed, 1995; Usoh et al., 1999), and then replicated by the other research groups in presence studies, which investigated a subjective feeling of "being-there" in VR environment, and its impact on perception, emotion and behaviour (Cleworth, Horslen, & Carpenter, 2012; Khanna, Yu, Mortensen, & Slater, 2006; Phillips, Interrante, & Kaeding, 2012; Zimmons, Panter, & Ph, 2003). Meehan first demonstrated that the Pit Room simulation triggers a physiological response in healthy participants (Meehan et al., 2002). This project employs the Pit Room simulation in order to measure neural correlates of fear inhibition and reappraisal when participants experience virtual heights. The objective of the pilot study was to test the feasibility of the protocol in terms of the design, integration of technology and signal-to-noise ratio. The objective of the second study was to measure the neural correlates of fear inhibition in healthy participants when they experience the virtual height. The objective of the third study was to measure neural correlates of fear inhibition and inhibitory learning in participants with a fear of heights across multiple VRET sessions.

5. Contribution

This PhD has both methodological and theoretical contributions. Methodological contributions will inform the neuroscientific and VR community about the potential and advantages of combining wireless neuroimaging and large VR systems to bridge the crucial gap between ecological validity and controllability of the design.

The theoretical contributions will inform neuroscience and the VR field about brain response to VR, particularly the neural mechanisms indicative of fear inhibitory response and reappraisal in VR that lies “at the heart” of VRET for anxiety disorders, specific phobias and PTSD. Previous studies demonstrated that VR is capable of triggering an inhibitory response within the PFC. This project will aim to reaffirm those results using methods which potentially are more ecologically valid. Moreover, this project will provide an insight into what is happening in the PFC within and between VRET sessions. This has several applications in mental health improving treatment, diagnosis and management of many mental disorders related to the impairment of inhibitory function such as phobias, anxiety, PTSD or addictions.

The amalgamation of these two technologies will open the door to more ecologically valid and controllable studies investigating brain response to virtual stimuli that require reasonable spatial and temporal resolution of brain images, without reducing the naturalness of experience thorough overly constraining movement or losing sight of one's own body.

Chapter 2 Background

1. Aim and overview of the chapter

The aim of this chapter is to present general prerequisite information essential to understanding the main body of this thesis and how this information relates to the research problem. This PhD utilises evidence from several disciplines, therefore this chapter focuses on the description of the theoretical framework, core concepts, historical developments and breakthroughs, from the field of virtual reality, neuroimaging and virtual reality exposure therapy. The Venn diagram (Figure 1) conceptualises the relationship between these disciplines, and where they overlap. Because the scope of those disciplines is broad, this background chapter focuses on key publications and concepts relevant to the field and examines how they relate to one another. More detailed literature surveys and critical evaluation of the neuroscience of VRET will be presented in the next chapter.

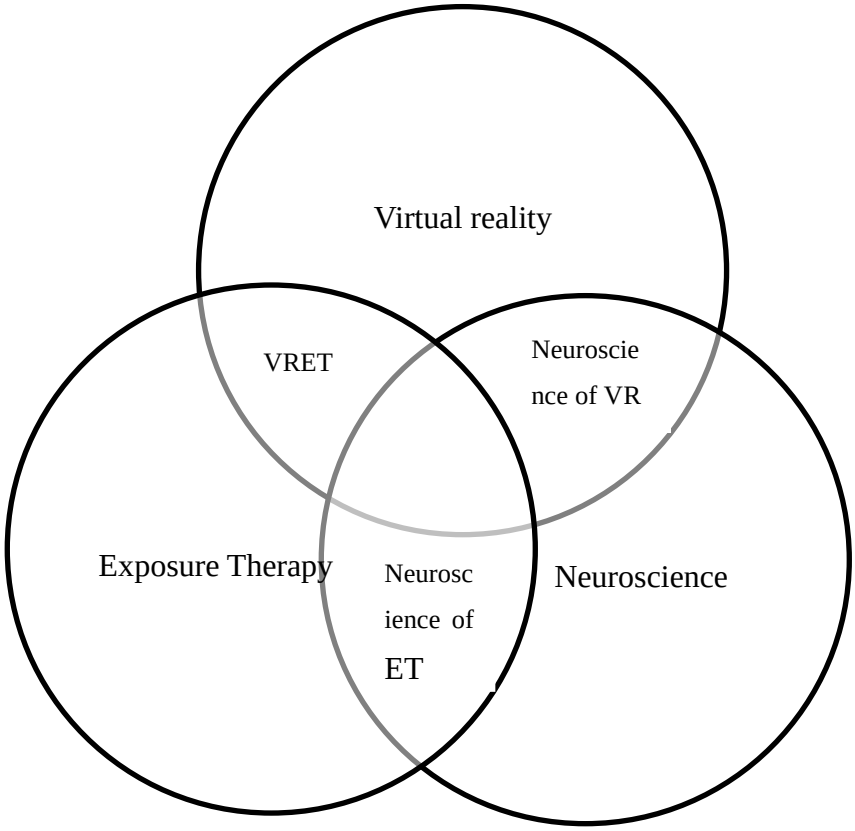

Figure 1 Venn Diagram demonstrating the scope of this thesis – split and overlap between related disciplines

Section 2 of this chapter describes the current state of research in neuroimaging and VR technology and advantages of combining them for research and therapy. Then the history of combining VR and neuroimaging is briefly presented. Next, the section describes current challenges in merging VR and brain imaging techniques. Section 3 describes the advantages of employing wireless brain imaging technology within VR. Section 4 describes wireless fNIRS and presents previous studies which combined fNIRS with VR and describes how this combination facilitates the naturalness of the response. Section 5 describes the importance of ecological validity and naturalness of the response in research and therapy and how VR technology offers the potential for the creation of ecologically valid protocols for research and therapy. Section 6 describes virtual reality exposure therapy as one of the most promising applications for VR in mental health. The section introduces the concept of VRET, history, theoretical framework, and application, focusing on VRET for acrophobia because of the scope of this PhD. Next, is a description of the advantages, importance and potential of combining VRET with physiological monitoring and neuroimaging. The last section (7) describes the role of the prefrontal cortex in fear inhibition and exposure therapy. The next chapter – Systematic Review, provides a more detailed literature survey on the neuroscience of VRET, which is more specific to the research question addressed by this thesis.

2. Combining brain imaging with virtual reality

Emerging technological advances in neuroimaging and Virtual Reality (VR) offer unprecedented opportunities for researchers and clinicians to design new tools and applications in both research and therapy.

Over the past few years, VR technology has become more powerful and affordable. The last few years have brought rapid technological advances and a new generation of low-cost, compact and lightweight devices such as Oculus Rift (https://www.oculus.com/en-us/rift/), Sony PSVR (https://www.playstation.com/en-gb/explore/playstation-vr/), HTC Vive VR(http://www.htcvr.com/), Razer OSVR (http://www.razerzone.com/osvr), Durovis Dive (https://www.durovis.com/), as well as mobile VR systems, such as Samsung Gear VR (https://www.oculus.com/en-us/gear-vr/) or Google Daydream (https://vr.google.com/daydream/), as well as simple low-cost VR cardboard mounts, such as Google Cardboard (https://www.google.co.uk /get/cardboard/) or “I Am Cardboard VR” (http://www.imcardboard.com/).

Augmented Reality (AR) technology is expected to hit the market in 2018 with the Google Glass (https://www.google.co.uk/intl/en/glass/start/), Magic Leap (https://www.magicleap.com/) or HoloLens (https://www.microsoft.com/microsoft-hololens/en-us). VR has had a very good reception in many fields such as gaming, science, medicine, military, education or therapy. According to Goldman Sachs, the Wall Street Journal, Digi-Capital, and Piper Jaffray, by the year 2020 the VR/AR market will achieve $150 billion of revenue, disrupting the current mobile market, and overtaking smartphones, tablets, laptops, gaming consoles, TV and PCs (http://www.digi-capital.com/reports/#augmented-virtual-reality).

The new generation of VR systems is becoming more affordable and accessible for customers, both at the clinics and at patients' homes, beginning a technological revolution in mental health, by allowing treatment in more ecologically valid conditions (Slater & Sanchez-Vives, 2016). This is because VR technology provides tools for the creation of dynamic, multimodal and emotionally engaging simulations, which might closely resemble real-life situations and thus enhance more naturalistic responses, which might transfer to the real world performance (Parsons, 2015; Riva, 2005). Therefore, psychotherapy experts forecast that VR therapy would be one of the major approaches in the future mental health care (Norcross, Pfund, & Prochaska, 2013). Furthermore, the study conducted by Garcia-Palacios et al., (2001) demonstrated that 80% of participants with a specific phobia would choose VRET over traditional in-vivo and imaginal exposure therapy, which indicates a significant shift in healthcare towards technological advances.

On the other hand, brain imaging technologies are also gaining more importance in both research and therapy, providing improved spatial and temporal resolution of structural and functional brain images. Neuroimaging allows for the investigation of brain areas and networks involved in a range of cognitive processes as well as being useful for the understanding and diagnosis of neural and mental disorders or assessing treatment outcome. Physiological brain imaging methods allow for the measurement of cerebral blood flow and metabolic processes which provide insight into regional brain function (Raichle & Mintun, 2006). The most commonly used methods in cognitive neuroscience are Positron Emission Tomography (PET), Functional Magnetic Resonance Imaging (fMRI) and Electroencephalography (EEG) (Horwitz, Friston, & Taylor, 2000).

PET was introduced in the 70s and it allowed for measuring task-evoked brain activity by measuring radiation from the positrons emitted by radioactive tracers administered to the subject (Nutt, 2002). Magnetic Resonance Imaging (MRI) was introduced in the 80s and is currently considered the primary brain imaging technique in both neuroscience and medicine. Functional MRI (fMRI) uses MRI signal changes in order to measure functional brain activity by using a blood-oxygen-level-dependent (BOLD) signal (Huettel, Song, & McCarthy, 2004). Both PET and fMRI measure neural and vascular blood flow. Another type of neuroimaging focuses on measuring electrophysiological activity in the brain. EEG is the oldest brain imaging method which was discovered in 1924. It records electrical activity from the brain by placing electrodes on the scalp (Niedermeyer & Silva, 2004).

Functional Near-Infrared Spectroscopy (fNIRS) is a relatively new tool for measuring the hemodynamic response from the brain using near-infrared light. It was discovered in 1992 and the first single-channel fNIRS experiment was published in 1993 (Yoko Hoshi & Tamura, 1993). The first multichannel fNIRS system, which allowed for measuring neural activity from multiple brain regions, was introduced in 1994 by Hitachi (Maki et al., 1995). The first commercial multichannel fNIRS system was released in 2000 by Hitachi (Ferrari & Quaresima, 2012) and the first wireless fNIRS was introduced in 2009 (Atsumori et al., 2009). With these improvements, the field of functional brain imaging has become rapid-growing, offering unprecedented opportunities for multidisciplinary research providing a powerful tool to investigate neural correlates of cognitive functions in a variety of contexts and experimental settings (Riva, 1998).

Combining VR and brain imaging offers a route for bridging the gap between ecological validity and controllability of the research design (Rey & Alcañiz, 2010). Within VR neuroscientists can recreate scenarios, which on the one hand allow for the triggering of naturalistic responses, and on the other hand are highly controllable and repeatable. Human brains evolved “being-in-the-world” (Heidegger, 1962), navigating and acting in 3d space, moving around and interacting with objects. Previous studies on presence in VR demonstrated that the lack of movement, multisensory cues and active interaction with the environment has a negative impact on task performance (Basdogan, Ho, Srinivasan, & Slater, 2000; Kober, Kurzmann, & Neuper, 2012; Ravassard et al., 2013).

VR offers tools for the recreation of such familiar and naturalistic interactions, tricking the brain into operating in a 'reality', which resembles its natural environment (Bohil et al., 2011; Hoffman, Richards, Coda, Richards, & Sharar, 2003) and triggering naturalistic response (Meehan, 2002; 2007). Moreover, VR allows for the creation of scenarios that would be difficult or unsafe to create in the real world, such as simulations of the battlefield (Rothbaum et al., 1999), heights (Meehan et al., 2002), or fire (Cha et al., 2012).

Concurrently, VR can benefit from neuroscience. Current advances in neuroimaging can offer VR researchers a tool for optimising and designing more compelling and efficient virtual environments. Structural characteristic and functional brain activity should be taken into account when attempting to provide more realistic experiences in VR and in the verification of its ecological validity (Bohil et al., 2011). Understanding how the human brain interacts with VR can help to establish a foundation for developing simulations, which are designed directly for the optimisation of natural brain response.

VR was combined for the first time with brain imaging by Aguirre et al. in 1996. The authors combined fMRI and the virtual 3D maze displayed on a desktop screen within the fMRI scanner to investigate topographical learning in humans (Aguirre, et al., 1996). However, the standard fMRI screen may break a sense of presence (a feeling of being immersed into a VR environment) due to its limited field of view. Therefore some researchers started using a magnet-friendly fiberoptic custom display to deliver high resolution, wide field of view stereographic stimuli during a fMRI scan (Hoffman et al., 2003). The system was later assessed in a study on presence. Despite being constrained in the fMRI scanner, participants reported a high illusion of presence. The authors demonstrated that the custom display system did not interfere with the brain images with regard to levels of noise and image distortion (Hoffman et al., 2003).

Unfortunately combining fMRI with HMDs is more problematic than using standard VR displays within a scanner. Most HMDs are not magnet-compatible because they contain ferromagnetic components, which would interact with the magnetic field generated by MRI scanner. Moreover, HMDs emit electromagnetic waves, which distort brain images and introduce a noise to the data. Therefore some researchers started developing magnet-friendly HMDs. Campbell et al., (2009) used fMRI compatible HMD

in a case study involving a planning task. The participant was exposed to two VR scenarios – a virtual city (spatial planning task) and a virtual Tower of London (non-spatial planning task). The result of the study showed an increased activity in the prefrontal and parietal regions indicative of spatial planning, however, the activity was higher during the Tower of London task. The study demonstrated that brain activity is modulated by the ecological validity of a task, which could be improved by employing VR. Although the single-subject study is not sufficient for the statistical power in fMRI studies, authors demonstrated the potential of using HMDs in fMRI scanner as an ecologically valid stimulus delivery medium for neuroscientific research. Another group used the fMRI-friendly custom HMD system combined with a 'data glove', which is a device that resembles a regular glove containing sensors that can measure the hand's movements and transform them into an input for VR interactions. Devices were made using non-conducting and non-magnetizing materials. The system was designed in order to deliver mirror-therapy for phantom limb pain (Bach, Schmitz, & Maaß, 2010). A mirror therapy is the type of treatment for phantom limb pain in which a mirror is used to create a visual illusion of movement of the affected limb (Ramachandran & Rodgers-Ramachandran, 1996). Another study later assessed the system in an experiment involving Illusory Hand Ownership. In the rubber hand illusion, illusory ownership occurs when participant's own hand is placed out of view and the rubber hand, which is placed in a position of the real hand, receives a synchronous visual and tactile stimulation. This might cause an illusion of the attribution of the rubbers hand to a participant's body (Botvinick & Cohen, 1998). Prior to the experiment, two participants were tested if they are susceptible to the classical rubber hand illusion using self-report (Botvinick & Cohen, 1998). Afterwards, there were classified as either highly susceptible or low susceptible to the illusion. Then they were placed in the fMRI scanner and underwent the virtual hand illusion experiment. Their right hand was placed under the blanket, which was covering their body, and the left hand was placed on the blanket. The pneumatic device which was delivering the tactile stimulation (giving a sensation of a light touch) to the hand, was placed on the dorsal side of the participants' index finger. This set up corresponded to the positioning of the virtual arms that they viewed in the HMD. The tactile stimulation was presented synchronously with VR simulation displaying moving objects (rods) touching the virtual hand. The data glove allowed for delivery of visuotactile stimulation. After the experiment, the participants were asked to rate their sense of illusory ownership for the virtual hand. The highly susceptible participant reported a high sense of illusory

ownership, whilst the low susceptibility participant reported a low level of sense of illusory ownership. The data analysis revealed different patterns of activation for both conditions. Both participants showed increased activity in the occipital cortex and premotor areas, which have been shown to be activated during the classical rubber hand illusion (Ehrsson, Spence, & Passingham, 2004). However, the highly susceptible participant additionally showed increased activity in the secondary somatosensory cortex and cerebellum, which were shown to be activated during the observation and experience of touch in the space which is occupied by one's own hand (Bach et al., 2012; Keysers et al., 2004). The sample size in the study was too small to make a valid scientific conclusion, however, the study showed the potential of the method of combining fMRI with the magnet-friendly HMD and the data glove.

The potential of combining EEG with HMDs was assessed in a study conducted in 1998 by Bayliss and Ballard. The authors performed the analysis in the frequency domain in order to assess the effect of VR equipment on EEG data. The recordings were acquired while performing the same visual task in the HMD combined with the ISCAN eye tracker and on the standard PC display. The results of the study demonstrated that the noise level from the HMD combined with the eye tracker was comparable to the noise generated by the PC screen. In fact, the PC screen added more noise to the data than VR, validating the feasibility of the design. However, the authors reported that the HMD pressed and displaced electrodes (Bayliss & Ballard, 1998).

Many other studies in the past few years have combined neuroimaging techniques with HMDs or immersive display VR systems in studies investigating human navigation and driving behaviour (Calhoun et al., 2002; Carvalho, Pearlson, Astur, & Calhoun, 2006; Hartley, Maguire, Spiers, & Burgess, 2003; Maguire, 1998; Spiers & Maguire, 2006b, 2006a, 2007b; Walter et al., 2001), social interaction (King, Blair, Mitchell, Dolan, & Burgess, 2006; Pelphrey, Viola, & McCarthy, 2004; Schilbach et al., 2006), spatial memory (Burgess, Maguire, Spiers, & O'Keefe, 2001; King, Hartley, Spiers, Maguire, & Burgess, 2005), violent behaviour (Mathiak & Weber, 2006; Weber, Ritterfeld, & Mathiak, 2006), and emotion (Baumgartner & Valko, 2006), or presence (Bouchard et al., 2010, 2012; Kober et al., 2012).

Most of these studies employed fMRI or Electroencephalography EEG. The first one offers a high spatial resolution (1 mm^3) while the second offers a better temporal

resolution (~ 1 ms). However, lying within a huge and noisy fMRI scanner restricts freedom of movement and could evoke anxiety by restraining a participant in a big noisy cylinder-shaped machine (Irani et al., 2007). Moreover, because of its bulky and stationary nature, fMRI can be difficult to implement in studies, which involve natural movement. This has recently encouraged some researchers to develop portable and compact brain imaging methods. Furthermore, there is a trend emerging in the brain imaging field with research looking to establish whether the results obtained from stationary brain scanners are consistent with the results obtained from portable scanners, showing a good correlation between fMRI data and portable fNIRS and EEG (Muthalib et al., 2013).

3. Combining wearable neuroimaging with virtual reality

Recently improvements in neuroimaging equipment have been made, making brain imaging more compact, and providing wireless and portable equipment, which could be light and comfortable enough to be worn by a participant without inducing excessive discomfort of fatigue. Besides a few clinical and research versions of wearable EEG systems introduced in a past few years, there are already commercially available dry-electrodes EEG systems on the market such as Emotiv Epoc (http://emotiv.com/) or NeuroSky MindWave (http://neurosky.com/), mainly designed for gaming and neurofeedback. This breakthrough technology offers great potential for VR researchers to combine wearable brain imaging with VR. Török et al., (2014) combined wireless EEG with CAVE VR systems in which people can more freely move. The aim of the study was to measure the amount of noise and the signal interference from the EEG and VR systems while the participant was walking, standing or sitting. The authors concluded that although the signal-to-noise ratio was good, still they recommended a careful measurement of the noise when combining EEG and VR (Török et al., 2014).

However, one of the most challenging disadvantages of EEG is its susceptibility to motion artifacts and electronic signal interference. Many VR peripheral devices such as tracking systems, projectors, displays, cables, plugs, switches, and magnetic fields emit a lot of electromagnetic low-frequency noise in the range of 1-120 Hz.

fNIRS provides a compromise between the spatial resolution of fMRI and the temporal resolution of EEG within VR (Ferrari & Quaresima, 2012; Piper et al., 2014).

Specifically, it is hoped that it will allow natural movement while providing a clear, less noisy, signal with minimised motion artifacts and electrical signal interference. The better spatial resolution of fNIRS relative to EEG allows for better accuracy in identifying brain regions activated by the particular cognitive task. On the other hand, the better temporal resolution (reflected in higher sampling rate) of fNIRS in comparison to fMRI, allows a better understanding of the temporal brain activity, and in some cases better statistical analysis power regarding changes in the shape of the hemodynamic response function (Irani et al., 2007; Piper et al., 2014; Tak & Ye, 2014). Some researchers have already used wireless fNIRS in order to investigate brain activity in the real world during walking (Nieuwhof et al., 2012) or cycling (Piper et al., 2014).

4. Combining Functional Near-Infrared Spectroscopy (fNIRS) with VR

fNIRS was tested in combination with VR first time by Holper et al., (2010). They used fNIRS as a tool for monitoring virtual sensory-motor rehabilitative training, demonstrating its feasibility, efficacy, and compatibility with VR technology. The experiment involved execution, imitation, observation and motor imagery of a grasping task performed by a virtual limb. The experiment involved two groups – "unilateral" (N = 15) which performed the task using one hand, with data recorded from left hemisphere, and "bilateral" (N = 8), who performed the task using both hands, with data recorded from both hemispheres. Both groups performed a task in front of a custom table VR display. Each participant was asked to place hands on the VR table system. The image on the display showed virtual arms in the same orientation and position as the arm of the participant. The experiment consisted of four experimental conditions – passive observation, observation and motor imagery, motor imagery, and imitation. The results of the experiment suggested that in the unilateral group there were significant HbO concentration changes for motor imagery and imitation. The bilateral group showed significant HbO concentration changes for within-condition observation, as well as between-conditions with lower HbO during observation compared to imitation. In the bilateral group, the imitation task using the non-dominant hand resulted in larger HbO changes in both hemispheres as compared to the unilateral group. The experiment demonstrated firstly that VR can evoke activity in the brain during observation, motor, and imagination-based tasks performed in VR. Secondly, that this activity can be

measured by fNIRS in VR. This was the first study that demonstrated the neurorehabilitative potential of combining VR with fNIRS and the system can activate and measure the action-observation brain areas (Holper et al., 2010) consistent with previous fMRI studies (Filimon, Nelson, Hagler, & Sereno, 2007). Sergalia et al., (2011) assessed a potential combination of fNIRS and HMDs. In order to ensure a correct placement of fNIRS optodes on the scalp, the authors used a custom modified HMD helmet. The experiment recruited eight healthy participants and involved the line bisection task in a virtual room. During the experiment, participants were sat in the virtual room in front of the white panel displaying horizontal lines. The task involved bisecting the displayed lines by moving a red dot through the manipulation of a Nintendo Wii controller from two different distances – 60cm and 120cm. Although there were no significant results related to the contrast between conditions, the study found a significant increase of HbO with respect to the baseline, confirming the feasibility of using fNIRS in combination with HMDs without causing a discomfort to the participants and problems with optodes displacement during data acquisition (Seraglia et al., 2011). Another study by Moro et al. published in 2014 used fNIRS in combination with a semi-immersive VR environment using the swing balance task. The participants were asked to stand on the force platform which measured the centre of mass, while watching a virtual representation of themselves on the virtual swing board. The task involved maintaining a balance on the virtual swing board susceptible to external destabilising forward and backward perturbations. The result demonstrated an increased HbO in the prefrontal cortex while participants were performing the swing balance task. The study demonstrated the potential of using the technology in neurorehabilitation assessment and training for balance control, preventing a risk of fall associated with several elderly conditions, movement disorders, stroke, or Parkinson's disease (Moro, Bisconti, & Muthalib, 2014). The same group, at the beginning of 2016, published another study, which involved a semi-immersive VR environment combined with fNIRS for a visuomotor task adopted in neurorehabilitation of upper limb motor function. The authors updated their system by adding a 3D hand-tracking device, which is commercially available on the market – LEAP Motion (https://www.leapmotion.com/). The participants performed four different VR hand movements with the purpose of following a virtual sphere over a virtual path while the brain activity was recorded. This was the first study, which demonstrated the potential for combining VR, fNIRS and the Leap Motion hand tracking system in research. The system could have future applications in upper-limb neurorehabilitation,

assessment of neuroplasticity following motor rehabilitation, or as a safe and comfortable medium to provide feedback for patients and therapists during treatment (Moro et al., 2016).

In summary, the aforementioned studies significantly improved ecological validity of the experimental design by using fNIRS within VR environments and demonstrated this combination has a potential to facilitate movement. Locomotion in virtual reality might facilitate naturalness of the response and enhance presence (Slater et al., 1995).

5. Ecological validity and naturalness of the response

Ecological validity is defined as "the degree to which results obtained in controlled experimental conditions are related to those obtained in naturalistic environments" (Tupper & Cicerone, 1990). Regarding VR, ecological validity is characterised by the level of realism and naturalness of the simulation (Gorini, Capideville, De Leo, Mantovani & Riva, 2011).

The naturalness of the experience has been proven to have an impact on the participant's performance during the experimental session, but also on the outcome of a therapy (Rizzo et al., 2004). According to the embodied cognition theory, the human brain has evolved to control and optimise cognition and behaviour while acting in a dynamic environment, therefore the human mind and cognition should not be understood in isolation, but in the context of its relationship to a physical body that acts in the world and interacts with objects (Borghi & Cimatti, 2010). The embodied cognition theory was inspired by the ecological psychology of James Gibson (1979), which viewed perception in terms of affordances. On the ground of this theory, affordances are potential "offers" or possibilities for interactions with the environment and objects. Affordances do not capture abstract physical attributes of objects, but rather their functional properties and possibilities for actions that can be taken with them. These affordances are perceived by organisms and driving their actions, for example, a chair is to sit on it, food is to eat it, water is to drink it etc. Therefore according to the ecological psychology, perception and action are interlinked, "so we must perceive in order to move, but we must also move in order to perceive", and therefore to learn about objects, we must use them (Gibson, 1979). According to the embodied cognition theory, cognition and perception are closely linked to goal-directed action, active exploration, and interaction with the environment (Borghi

& Cimatti, 2010; Wilson, 2002). VR technology embodies users into a dynamic 3D virtual environment that allows a real-time interaction and might be perceived as near to reality, therefore it offers a possibility as a medium to investigate cognitive functions in action (Riva, 2005). Most of our knowledge about human brain response has been acquired from laboratory experiments that involved exposure to artificial, simplified, abstracted and isolated stimuli in artificial settings. Most studies in cognitive neuroscience tend to explain cognitive functions by decomposing them into detached cognitive modalities such as: visual, auditory or motor tasks, however, this approach does not resemble real-life experience where we use all of our cognitive modalities as one cognitive stream which provides us with a coherent multisensory perception and interaction in the real word (Keetels & Vroomen, 2012; Spence & Squire, 2003). Moreover, traditional neuroimaging studies very often lack naturalistic temporal resolution. It is common practice in neuroscience to arrange static isolated stimuli in either blocked or event related designs usually 10-60 seconds in duration (Amaro & Barker, 2006). This approach, however, may significantly impact on the naturalness of response which can violate ecological validity and does not reflect how the brain would respond in the real world, which is a complex, dynamic, and seldom organised in blocks or events with a few seconds duration (Spiers & Maguire, 2007).

Recently there is an increasing trend in neuroscience to move from investigating brain response in seclusion within artificially controlled laboratory settings to investigating these functions within a more natural real-life performance (Felsen & Dan, 2005). This approach, however, implies several challenges. Neuroscientists attempt to investigate how the human brain processes information in the natural environment, but the complexity of the natural environment could impact on the controllability of the research by confounding experimental variables. Therefore some studies have used films in order to investigate brain response to natural scenes (Bartels & Zeki, 2004; Moran et al., 2004). Nevertheless, passive watching of films does not entirely resemble real-life situations which involve active interactions with people, objects, and the environment.

VR technology offers a potential for designing scenarios in which a participant can interact with the environment or others as in real-life and move freely around the space in a natural manner. The VR environment can be manipulated and controlled by the researcher or by the user and it is updated in real time through interaction (Azuma, 1997). However, different immersion methods influence in different ways the naturalness of an

experience. Head-mounted Displays (HMD) are commonly used in research or therapy. One of the disadvantages of HMDs is that it hides others or a therapist from the view of the user. Moreover, it restricts natural locomotion usually using a controller such as a joystick or a mouse to control the movement. This impacts negatively on VR ecological validity but also can cause cybersickness (Slater et al., 1995). Cybersickness is a condition that may occur in response to the use of virtual environments. It is believed that it might be associated with perceived motion in a VR as a result of sensory conflict between sensory systems: visual, vestibular and proprioceptive (Kim, Kim, Kim, Ko, & Kim, 2005). CAVE (CAVE Automatic Virtual Environment) systems and Immersive Projection Technology (IPT), immerse a user into a room-sized VR simulation which supports natural locomotion and interaction in the space without losing the sight of one's own body or the presence of others (Cruz-Neira et al., 1993). This property of CAVE-like VR systems has particular potential as a therapeutic medium in clinical sciences, where the co-presence of a therapist plays a crucial role during the treatment session, in particular in VRET.

6. Virtual Reality Exposure Therapy (VRET)

Virtual Reality Exposure Therapy (VRET) may integrate 3D computer graphics, body tracking devices, visual displays, auditory, olfactory and other sensory input devices to immerse a user into a computer-generated interactive virtual environment (Brooks, 1999; Riva, 2009). VRET is an extension of Exposure Therapy (ET) which is a type of cognitive-behavioural therapy (CBT) commonly used in the treatment of anxiety disorders, specific phobias or PTSD. The aim of CBT approaches (including ET and VRET) is to challenge and change maladaptive thoughts beliefs and behaviours by improving emotional regulation (Butler, Chapman, Forman, & Beck, 2006). To date, VRET is the most common application of VR in the clinical sciences and it has been widely used in the treatment of a variety of anxiety disorders, specific phobia, addictions and PTSD (McCann et al., 2014).

6.1.Advantages and disadvantages of VRET

ET has demonstrated efficacy in many randomised controlled trials including treatment of PTSD (Foa et al., 2005), Obsessive Compulsive Disorder (OCD) (Whittal,

Robichaud, Thordarson, & McLean, 2008), Panic Disorder (PD) (Gloster et al., 2011), social phobia – fear of social situations (Clark et al., 2006), as well as meta-analysises (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Ougrin, 2011). The treatment procedure attempts to reduce symptoms by confronting the patient with anxiogenic stimuli (Foa et al., 1986). Traditionally ET could be delivered in vivo – when the patient encounters an anxiogenic stimulus directly or can be imaginary - when a patient is guided by the therapist through an imaginary scenario which contains anxiogenic stimuli which must be confronted, whilst repeating the narrative verbally as descriptions of a patient's fear-evoking or traumatic memories and feelings (Rothbaum & Schwartz, 2002). Although the efficiency of in vivo and imaginal ET has been confirmed in several studies (Rauch et al., 2012; Rothbaum & Schwartz, 2002) some patients are unwilling or unable to effectively engage emotionally during an imaginal exposure, failing to visualise and recall the feared stimuli, which is a fundamental problem, especially in phobias and PTSD, as avoidance of anxiogenic cues and reminders of the trauma is one of the key symptoms (Rizzo et al, 2007). Studies on psychotherapy suggest that the inability to emotionally engage during exposure is a crucial predictor of negative treatment outcomes (Jaycox et al., 1998). According to emotional processing theory (described in section 6.2), an optimal engagement is necessary for the fear structure activation, which then allows for modification of its pathological elements trough corrective learning, reflected in the reduction of anxiety symptoms after the treatment (Foa et al., 1986). Recent advancements in VR simulation technology provide a tool that could facilitate exposure for avoidant participants helping them to maintain optimal engagement by using various multisensory stimuli (Rothbaum, Rizzo, & Difede, 2010).

VRET for anxiety disorders gradually immerses participants in dynamic fear-relevant environments in which the dose of stimuli and its emotional content can be accurately controlled by the clinician according to the individual needs of each participant. The fear network can be activated without demanding that the participant actively endeavours to access the experience through effortful memory retrieval (Rothbaum et al., 1995; 2006). Through gradual contact to virtual trauma-related cues, VRET elicits fear-related responses in a safe context which allows the participant to interact with virtual scenarios in the same manner as with the real environment (Riva & Gamberini, 2000).

VRET offers many advantages over traditional exposure therapy, especially for PTSD military veterans, as it allows the clinician to create war-related stimuli, which are rarely encountered in safe settings out of the battlefield. Moreover, VRET offers a resolution for avoidant participants, who tend to avoid dealing with the feared stimuli and who could be afraid or ashamed performing a therapy in vivo, which usually is performed in public places such as in case of social phobia or fear of flying (Emmelkamp & Krijn, 2002). Therefore, VRET provides an advantage over traditional therapy when the time and environment are limited and difficult to control, or that may put the participant at risk if delivered in vivo. Furthermore, virtual reality exposure therapy allows for better experimental methodology and design as it improves protocol standardisation, duration and type of stimuli delivered (Rizzo, Difede, & Rothbaum, 2013). In VRET participants can experience and act in simulation in a more natural manner as if it was real. This phenomenon is associated with the concept of presence, defined as a subjective sense of being "there"(Slater & Wilbur, 1997). Presence has been considered playing an important role in VRET, which leads to the experience of anxiety, which is necessary for a successful treatment (Krijn et al., 2004) (described in more details in the next section).

Despite the recent technological advancements in VRET, it still suffers many flaws, particularly regarding stimuli delivery for vulnerable participants. Wearing head-mounted displays can make a participant feel isolated from the environment and from the therapist, which can trigger excessive anxiety, particularly in PTSD patients. Therefore, using Cave-like systems allows a therapist to be present together with a patient in virtual space and controlling virtual exposure as well as the patient's response.

6.2. The theoretical framework of Exposure Therapy and Virtual Reality Exposure Therapy

A few theoretical models have been proposed to explain the mechanisms of ET and its virtual extension, such as: emotional processing theory (Foa & Kozak, 1986), conditional learning (Milad, Rosenbaum, & Simon, 2014), inhibitory learning (Craske & Kircanski, 2008) and cognitive reappraisal (Gross, 1998; Ochsner & Gross, 2005).

Emotional Processing Theory

Foa and Kozak (1986) in their emotional processing theory proposed a theoretical framework for understanding anxiety disorders and the emotional processing of fear during ET. On the basis of the emotional processing theory, anxiety, phobias or PTSD involve morbid fear structures which cause pathological fear responses and can be formatted in memory as a result of a traumatic event. Those fear structures are activated when information represented in these structures is encountered. The morbid fear structures comprise a set of pathological information about feared stimuli, response, and its meaning. Therefore, fear reduction requires altering the associations between stimulus representations of feared stimuli and associated pathological representations of threat. In acrophobia such a fear structure consists of three components: information about the stimulus – height (standing on a balcony); response – elevated heart rate; and meaning – "I am going to fall and die". According to the emotional processing theory, efficient therapy protocol requires emotional processing and activation of the maladaptive fear structures in order to modify their pathological elements and their meaning and incorporate new safety information so that the aversive stimuli does not trigger fear responses anymore. This is achieved by direct confrontation with feared stimuli, which activates the fear structure, for example in acrophobia treatment – standing on a balcony. The fear-relevant information must also contain elements that are incompatible with those stored in the pathological fear structure, for example, the absence of the expected harm - standing on a balcony and not falling down. This process then leads to cognitive reprocessing of pathological meanings, which results in a reduction of anxiety symptoms. The reprocessing occurs through learning of new responses, and an incorporation of the new corrective nonpathological information, or formation of a new non-fear structure that replaces the old one, as the result of habituation (Foa et al., 1986). Habituation is a learning process which leads to a reduction in the strength of the emotional response (desensitisation) to the stimulus following repeated exposure to the given stimulus (Rankin et al., 2009). The activation of fear structures and habituation can be measured by subjective reports (such as Subjective Units of Distress SUDS, which measure the subjective intensity of distress), behavioural observations (body language or facial expressions indicative of fear response, such as looking away or towards the threat, slow walking etc.) and physiological responses (in heart rate, skin conductance, skin temperature, which indicate psychophysiological arousal) or neural monitoring (brain

activity in the prefrontal-amygdalar fear circuit). In exposure therapy, we can distinguish within-session habituation (WSH) and between-session habituation (BSH). WSH is a short-term learning reflected in a gradual decrease in emotional response to the feared stimulus, measured as a difference between initial fear response (first trial) and end fear response (last trial) within a single session of exposure. BSH is a form of the long-term learning process which results in a change in meaning (risk of harm, valence) of the feared stimulus. BSH could be measured as a difference between the last response of the previous exposure therapy session and the first response of the following exposure session. A difference between the first trial of the first session and the last trial of the last session, if measured as an indication of overall BSH at the end of the treatment reflected in the reduction of anxiety levels (Kozak et al., 1988). Many studies have examined emotional processing theory in empirical studies, however, the results are mixed. While some studies found that WSH habituation as measured by a drop in subjective fear ratings is correlated with a BSH and thus with a treatment outcome (Pitman et al., 1996; Van Minnen & Hagenaars, 2002), others have shown no evidence for WSH effect during ET (Baker et al., 2010; Meuret, Seidel, Rosenfield, Hofmann, & Rosenfield, 2012). Therefore, more studies are needed to investigate WSH and BSH in exposure-based treatments. The neural basis of BHS and WHS are described in section 9.

Moreover, some studies on fear conditioning have demonstrated that extinction learning does not erase old fear associations, but rather results in new inhibitory associations which exist along old ones (Bouton, 2000; Craske & Kircanski, 2008). Inhibitory learning model that draws from extinction learning provides an alternative theoretical framework for understanding anxiety disorders and exposure therapy.

Inhibition and Inhibitory learning model

Inhibition is characterised by an ability to delay, withhold or withdraw from inappropriate responses and allows for a transition to behaviour more relevant to the goal or circumstances (Barkley, 1997). Inhibition of a fear response is the ability to discriminate between danger and safety signals and suppress fear responses in the presence of safety cues and it involves suppression or reduction of irrelevant emotional responses (Jovanovic, Kazama, Bachevalier, & Davis, 2012). Craske and colleagues explain exposure therapy in terms of inhibitory learning which was derived from the classical conditioning and extinction theory (Craske et al., 2008). Within this

approach, fear acquisition (fear conditioning) is related to learning the association between a neutral - conditioned stimulus (CS), with an aversive unconditioned stimulus – (US). After repeated pairings, the US becomes a conditioned stimulus (CS) inducing an expectation of US and therefore anxiety. The repeated exposure to the CS in the absence of US results in a gradual reduction of anxiety - extinction, that leads to learning that the stimulus is not dangerous, and therefore modulation perception of the CS (Craske, Liao, & Vervliet, 2012; Lissek & van Meurs, 2014; Wolpe, 1968). Unlike in habituation-based models such as emotional processing, according to inhibitory learning model, associations between CS and US are not erased during extinction, but they are inhibited by the new CS-US non-threat inhibitory associations developed during inhibitory learning. Therefore, following successful exposure treatment and extinction learning, the fear-evoking stimulus has two meanings: the original excitatory (i.e., fear-based) meaning and the inhibitory ("safety-based") meaning. Thus, even if fear decreases following exposure therapy, the original excitatory meaning is retained in memory and it may be recovered under some circumstances such as a change in context (renewal), the passage of time (spontaneous recovery), and reacquisition of the original association caused by adverse events after extinction (Bouton, 2002). Consequently, even after successful exposure treatment up to 50–60% patients show to some degree return of fear (relapse of fear that has previously declined) at follow-up assessments (Craske & Kircanski, 2008; Jacoby & Abramowitz, 2016; Rachman, 1989). Therefore, a few strategies have been proposed in order to enhance inhibitory learning (Craske et al., 2014). Firstly, fear extinction appears to depend on the context in which inhibitory learning occurred (Maren, Phan, & Liberzon, 2013). Therefore, context can either activate the old fear structure, or the new fear structure. One main implication of the inhibitory learning model is that the treatment should occur in multiple contexts to enhance extinction and the probability that the new nonpathological fear structure will be activated instead of the old pathological fear structure. Authors also recommend variability in duration, frequency and intensity of exposure session, as well as variability in exposure stimuli and safety signals (Craske et al., 2014; 2015). VRET offers tools to enhance inhibitory learning due to its flexibility and controllability (advantages of VRET described in section 6.1).

Between-session extinction is associated with inhibitory long-term learning and is mediated by modifications and reassessment in 'meaning' of the potentially

threatening stimuli, or lower probability of harm as well as the lower negativity of the stimulus (Craske et al., 2012). Previous studies have demonstrated that greater between-session habituation, as measured by Subjective Units of Distress (SUDS) is correlated with the decrease of symptoms in ET (Rauch, Foa, Furr, & Filip, 2004). On the other hand, within-session habituation or decline in SUDS, over the course of an individual session, could be a predictor of positive response to ET (Van Minnen & Hagenaars, 2002). However, some studies show no evidence for within-session habituation effects during ET (Baker et al., 2010), which might suggest that habituation during ET requires some consolidation time or neuroplasticity (Quirk & Mueller, 2008).

According to the emotional regulation (ER) model proposed by Gross (1998) inhibition of fear (called expressive suppression in the ER model) is often proceeded by cognitive reappraisal.

Cognitive Reappraisal of Emotions

Cognitive reappraisal, which is a type of emotional regulation process, provides another complementary framework for understanding exposure-based treatments. Emotional regulation is an ability to control or modify emotions, as well as their physiological and behavioural components that can occur automatically (without attentional resources, for example, habits - regulatory strategies acquired during childhood) or intentionally (for example people might deliberately attend to information, situations or people that maximise good emotions and avoid those that can evoke negative emotions) (Gross, 1998). Cognitive reappraisal is a method for intentional explicit emotion regulation, which involves using cognitive strategies (thoughts) in order to alter and reinterpret the emotional significance of the stimulus and as a result modification of its emotional impact (Gross, 1998). While inhibition could be an automatic and passive process, cognitive reappraisal requires attentional resources and effortful employment of cognitive strategies (Hartley & Phelps, 2010). Therefore, emotional reappraisal is a goal-oriented strategy, which is most commonly used to reduce negative emotions and increase positive emotions (Ochsner & Gross, 2005). There are two main strategies used during reappraisal process – reinterpretation and distancing. Reinterpretation involves changing the subjective interpretation of a stimulus to decrease emotion by asserting an alternative meaning, for example when

viewing negative pictures of patients in the hospital, one might think that patients will feel better after the treatment. Distancing involves changing a personal psychological connection to a stimulus by shifting conceptual or spatiotemporal third-person perspective from a stimulus, for example, when viewing negative event pictures, one can imagine that it happened long ago or far away (Ochsner & Gross, 2005; Trope & Liberman, 2010).

As a result, cognitive reappraisal down-regulates emotional experience leading to the control of the negative emotional response (Ochsner, Bunge, Gross, & Gabrieli, 2002) and subsequently to inhibition (Goldin, McRae, Ramel, & Gross, 2008).

Unlike inhibition (suppression), which could be automatic, cognitive reappraisal requires active engagement and effort of the participant to alter a meaning of the stimulus to change emotions through executive control process (Hartley & Phelps, 2010). Moreover, according to Grosses' process model of emotion regulation (1998), cognitive reappraisal and inhibition strategies occur at different time-points during the emotional response process, and they are categorised as two different classes of emotional regulation strategies. Thus, cognitive reappraisal is an antecedent-focused emotional regulation strategy, which occurs early in the process before the activation of emotional response expression and change in behaviour and physiological reactions. It might, therefore, change the temporal process of the emotional response before it was fully unfolded. On the other hand, inhibition expressive suppression (inhibition) is a response-focused emotional regulation strategy that occurs later when an emotion has already unfolded and after the behavioural and physiological responses have been generated (Gross, 1998; Sheppes & Gross, 2011).

Some studies suggested that cognitive reappraisal might facilitate extinction learning and therefore maximise exposure therapy. For example in the study conducted by Delgado et al., (2008) participants who were conditioned to either yellow or blue square using electric shocks were asked either just to attend to their emotions or use cognitive reappraisal by imagining calm images during the electric shock. The results revealed that participants who were using cognitive reappraisal strategy had decreased skin conductance, which was indicative with decreased arousal. Another study obtained similar results, showing that cognitive reappraisal has better and durable

effects on fear extinction 24 hours after conditioning session (Shurick et al., 2012). Blechert et al., (2015) used the same procedure using social stimuli (images of social situations) as conditioned and unconditioned stimuli. The result revealed that using reappraisal during fear extinction learning significantly reduced conditioned negative valence of the unconditioned stimuli. The outcome of those studies could imply that reappraisal might have an important role in ET facilitating extinction learning during treatment of anxiety disorders.

Effective regulation of emotion is essential for both our mental and physical wellbeing. The lack of inhibitory function and cognitive reappraisal have both been linked to many mental disorders, such as anxiety, phobias, PTSD, substance abuse, antisocial personality disorder, borderline personality disorder, bipolar disorder, ADHD and impulsivity (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001).

The flexibility and usability of VRET technology bring unprecedented opportunities to create a variety of situations or cues, which are not available in traditional therapies and therefore facilitate the efficacy of emotional regulation such as inhibitory learning and cognitive reappraisal.

6.3. Efficacy of VRET

To date there have been several qualitative reviews (Botella et al., 2004; Gerardi et al., 2010; Glantz et al., 2003; Goncalves et al., 2012; Hodges et al., 2001; Krijn et al., 2004; Meyerbröker & Emmelkamp, 2010; Riva, 2005) and four quantitative meta-analyses (described below) published which reviewed the literature regarding the efficacy of VRET for anxiety disorders and specific phobias and three for PTSD. Evidence suggested that VRET was superior to the control group and at least equally effective as in vivo exposure or other CBT-based approaches. This part focuses only on meta-analyses because they constitute the most reliable approach in assessing the evidence and efficacy of the treatment in clinical sciences (Conn et al., 2012).

The meta-analysis performed by Powers and Emmelkamp (2008) assessed 13 studies comparing VRET to in-vivo and a control condition (wait list). The random effects analysis performed by the authors demonstrated a large mean effect size for VRET in comparison to the control condition (Cohen's d = 1.11) as assessed with self-report measures. Moreover, they demonstrated that in vivo therapy was not significantly more

effective than VRET and there was a trend showing greater efficacy of VRET over in vivo treatment (Cohen's d = 0.35) (Powers & Emmelkamp, 2008). Another meta-analysis conducted by Parsons and Rizzo (2008) focused on clinical and non-clinical populations. Twenty-one studies met inclusion criteria and they used only data from before and after VRET. The overall pre- and post-treatment effect size was d = 0.95 (Parsons & Rizzo, 2008). Opris et al., (2012) assessed 23 studies that compared VRET for anxiety disorders such as specific phobias and PTSD, with an evidence-based intervention from randomized-controlled trails. The analysis showed an overall effect size of d = 1.12 for VRET compared with wait-list conditions as measured with self-reports. Furthermore, there was no overall difference between VRET and CBT at post-treatment (k = 15) and at 3–6 months follow-up (k = 7) on self-report measures. The authors also reviewed the outcome of studies comparing VRET with CBT on behavioural assessments. The analysis included 8 studies at post-treatment and four studies at follow-up. They reported an overall effect size of d = − 0.03 and d = 0.24. These results indicated that there was not a difference between VRET and CBT on behavioural assessments. Moreover, they concluded that there was no difference between VRET and CBT, showing that VRET is as effective as traditional evidence-based interventions (Opriş et al., 2012). The recent meta-analysis performed by Morina et al., (2015) assessed whether VRET treatment effects can be transferred to real-life situations. They included fourteen clinical trials which employed VRET for treatment of specific phobias. They compared the efficacy of VRET to CBT, placebo and waitlist controls on behavioural assessment. Authors reported that the analysis demonstrated that patients undergoing VRET did significantly better on behavioural assessments after VRET treatment than before. There was an effect size of the Hedges' g = 1.23. Moreover, patients who received VRET performed better on behavioural assessments at post-treatment than patients who were assigned to the wait list, with the effect size g = 1.41. Results of behavioural assessment comparing VRET with in vivo approaches at post-treatment and at follow-up showed no significant differences in effect size (g = − 0.09 and 0.53). The analysis demonstrated that effect sizes of behavioural measurement were similar to self-report measures. The findings demonstrate that VRET can produce a significant post-treatment behavioural change in real-life situations such as approaching a real spider after treatment of arachnophobia or taking a flight after the treatment of fear of flying. Authors concluded that the result of the meta-analysis supports the hypothesis that the VRET effects as for patients with anxiety disorders can be transferred over to real-life situations.

In summary, all the evidence obtained for the meta-analyses performed up to date suggest that VRET is superior to the wait list conditions and as effective as traditional treatments for anxiety disorders.

6.4. History of VRET

Virtual Reality Exposure Therapy (VRET) was introduced for the first time by Rothbaum and colleagues (1996) for treatment of fear of flying in a small case study (Rothbaum & Hodges, 1996). Since then, VRET has been significantly developed, and its efficacy has been verified in several controlled studies as a treatment for anxiety disorders such as: fears of flying (Maltby, Kirsch, Mayers, & Allen, 2002; Rothbaum, Hodges, Smith, Lee, & Price, 2000; Rothbaum et al., 2006), agoraphobia (Malbos, Rapee, & Kavakli, 2012), spider phobia (Garcia-Palacios & Hoffman, 2002), social anxiety (Klinger et al., 2005), fear of flying (Rothbaum et al., 2000), panic disorder (Botella et al., 2007) as well as a functional skill training and motor rehabilitation for post-stroke or traumatic brain injury (TBI) patients (Cuthbert et al., 2014; Lloréns, Noé, Colomer, & Alcañiz, 2014).

VRET for PTSD was first developed and used at the Georgia Tech and Emory University. PTSD is a type of anxiety disorder, which may develop after being involved in, or witnessing, traumatic events such as assault, natural disaster, vehicle accident or war (Rothbaum et al., 1999). A virtual Vietnam scenario was developed for Vietnam veterans diagnosed with PTSD which resulted in a promising case study of a 50-years old Vietnam veteran with PTSD (Rothbaum et al., 1999), which was followed by the first open clinical trial to treat 10 Vietnam veterans in 2001. After 16 sessions of VRET involving virtual Vietnam, participants reported a reduction of PTSD symptoms from 15% to 67% (Rothbaum & Hodges, 2001). Another open trial using VRET for PTSD was conducted by Ready and colleagues (2006). The study used the same virtual Vietnam simulation. The study demonstrated that VRET lead to a significant reduction of PTSD symptoms compared to the pre-treatment baseline, moreover the result was maintained on the 3- and 6-month follow-up assessments (Ready & Pollack, 2006). The study did not involve any control group, therefore the next study was conducted comparing the virtual Vietnam simulation to person-centred therapy, but the study did not yield any significant results (Ready, Gerardi, Backscheider, Mascaro, & Rothbaum, 2010). Roy et al., (2010) employed fMRI in order to investigate the effect of VRET for PTSD using the simulation

of virtual Afghanistan on brain function in the first randomised controlled trial (RTC). 29 Afghanistan war veterans (15 with PTSD and traumatic brain injury (TBI), 9 PTSD, 1 TBI, and 4 controls) were recruited. From 15 PTSD participants, they were randomised – 7 to VRET treatment or traditional ET. From 15 PTSD participants, 8 completed the treatment and 6 dropped out. Participants received 12 sessions of VRET or ET. The environment consisted of virtual Afghanistan simulations such as walking on the market or driving a Humvee. Although there was no statistical difference between VRET and ET treatments, the after-treatment fMRI scan showed functional changes in the brain. Participants who completed the treatment demonstrated decreased activity in the amygdala and increased activity in the prefrontal cortex. Another RTC was conducted on 20 active duty soldiers from Iraq and Afghanistan. 10 of these participants were randomly assigned to the VRET group and 10 to traditional a treatment (Prolonged Exposure, Cognitive Processing Therapy, Eye Movement Desensitisation and Reprocessing, or group therapy). Participants from all treatment groups showed a significant reduction in PTSD symptoms, although there was no significant difference between them (McLay et al., 2011). The biggest RTC using VRET for PTSD involved active-duty soldiers from Afghanistan and Iraq randomly assigned to 3 groups - VRET – 52, ET 51 (ET) or WAIT 53. The simulation involved scenarios such as walking on the market or driving a Humvee in Afghanistan or Iraq. Unfortunately, there was a big drop out - 44% from VRET group and 41% from ET group dropped out. The results of the study did not prove the efficacy of VRET, moreover, participants who underwent ET treatment showed a bigger drop in PTSD symptoms than those who underwent VRET (Reger et al., 2016). In summary, the evidence regarding the efficacy of VRET for PTSD is mixed, therefore more studies are needed in order to investigate its efficacy.

Recently there has been a rapid increase in the establishment of clinics, centres and psychological or psychiatry services delivering VRET as a treatment for many mental disorders. The Virtually Better is a private centre that delivers VRET treatment for a range of specific phobias, addictions or PTSD (http://www.virtuallybetter.com/). The Virtual Reality Medical Centre (VRMC) with two centres – in San Diego and Los Angeles, was established by Brenda Wiederhold. VRMC uses VRET in treatment for anxiety disorders and PTSD (http://www.vrphobia.com/). Another one - The Interactive Media Institute (IMI) is a non-profit organisation using advanced technologies in the treatment of a wide range of health issues. In Europe, there is an ongoing international project - Virtual

Environment in Clinical Psychology (VEPSY), involving top European researchers in VRET such as Giuseppe Riva, Mariano Alcañiz and Cristina Botella. The aim of the project is the integration of VR technology in clinical assessment and treatment, in particular, mental disorders such as anxiety disorders; male impotence and premature ejaculation; and obesity, bulimia, and binge-eating disorders (Riva et al., 2001).

6.5. VRET for fear of heights (acrophobia)

Acrophobia is classified as a specific phobia according to the ICD – 10 (F40.241, Word Health Organization, International Classification of Disease). Specific phobia is characterised as a "strong, irrational fear of something that poses little or no actual danger". The most common symptoms of a specific phobia are panic, fear, rapid heartbeat, shortness of breath, trembling, or a strong desire to avoid or get away when encountered with the feared stimuli. A fear of heights is the most common type of specific phobia, affecting about 5% of the population (Kapfhammer et al., 2015). Although a majority of people have an inherited disposition to avoid heights as a healthy functional and adaptive wariness necessary to survival (Marks & Nesse, 1994), in some people it can develop into acrophobia. Individuals with acrophobia experience unrealistic or excessive fear while being high off the ground such as on a balcony, ladder, bridge, walking upstairs or taking a lift. Avoidance is one of the hallmarks of a fear of heights, therefore people who suffer this would try to avoid situations and places involving heights, such as taking certain jobs, renting a flat located in a high building, attending events or doing jobs that might be far from the ground, which significantly impacts on the quality of life. There are two major approaches explaining the origins of acrophobia. Foa and Kozak proposed an associative explanation of the phobia as a disorder that develops following a traumatic experience involving heights (Foa & Kozak, 1986). However, not all acrophobic individuals have a history of traumatic experiences involving heights, therefore some researchers proposed non-associative factors influencing the development of acrophobia. Davey (1997) argued that acrophobia develops as a result of cognitive biases in some people who have inherited vulnerabilities for increased interpretation of internal bodily sensations that are related to movement in height-related situations as threatening.

Coelho and Wallis (2010) proposed an alternative understanding according to which acrophobia is associated with the abnormalities in control of balance and visual

perception of movement and somatosensory sensations. Healthy people use the visual, vestibular and somatosensory systems to learn how to move in height-related situations (Adolph, 2008). However, in some individuals fear of heights might develop due to an intersensory conflict between vision, somatosensory and vestibular senses. This conflict may occur in situations when the vestibular and somatosensory systems detect a body shift which is not detected by the visual system because the visual distance to nearest objects is too large. This mismatch of senses and perception could be due to motion parallax (Coelho & Wallis, 2010). Motion parallax is associated with observer head movement and is defined as a depth cue in which objects, which are closer in the field of view move faster than objects, which are further in the field of view (Gibson et al., 1959). Increasing postural sway (movement of the centre of mass in a standing position) could be a strategy to resolve this intersensory conflict, but the bigger the distance between the visual cues and eyes, the bigger the postural sway due to the reduced or lack of depth cues and motion parallax (Brandt, Arnold, Bles, & Kapteyn, 1980; Whitney et al., 2005). Above about 3 meters postural sway might become impaired causing fear of falling (Bles, Kapteyn, Brandt, & Arnold, 1980; T Brandt et al., 1980; Thomas Brandt, Grill, Strupp, & Huppert, 2018). Therefore it was proposed that fear of heights could be related to vertigo: a warning signal created by the loss of postural control when the distance between the observer and visible stationary objects becomes too large (Coelho & Wallis, 2010).

VRET for acrophobia was first introduced for clinical use by Rothbaum et al. in 1995 in a case study. The study recruited an undergraduate male student with a fear of heights to undergo VRET twice weekly for 3 weeks. Wearing the HMD, the subject was exposed to height in the virtual elevator. During the exposure, SUDS were obtained every 5 minutes. The subject was able to control the dose of exposure by pressing the button and progressing from floor 0 to 48. The authors reported reduced self-reported anxiety (SUDS) and avoidance of heights scores (HAQ) after VRET (Rothbaum et al., 1995). The same year the authors conducted the first controlled study, which involved 20 undergraduate students with a fear of heights. Students were randomly assigned either to the VRET or to the wait list. Over 8 weeks participants were exposed to the series of simulations including 3 footbridges above the water, 4 balconies, and the glass elevator. The efficacy of VRET was assessed using self-reported anxiety and avoidance of heights. The results of the study demonstrated that VRET produced significantly lower scores in all the self-reported measures than the wait-list group (Rothbaum et al., 1995).

Another study investigated the relationship between levels of anxiety and presence in VRET for acrophobia. Regenbrecht et al., (1998) in the presence study asked the healthy participant to walk on the virtual bridges which were 8 meters in order to perform a task. After the experiment, subjects completed the developed presence questionnaire, height anxiety questionnaire, and height avoidance questionnaire. The results of the experiment demonstrated that the presence score was positively correlated with the reported fear in VR demonstrating that the level of presence and immersion might influence the magnitude of emotional response in VR.

The first between-subject controlled study which directly compared VRET for acrophobia with exposure in vivo was conducted by Emmelkamp et al., (2002). The virtual simulation created for this study very closely resembled real-life locations used in the experiment – a shopping mall, the fire escape, and the roof garden of the University building. Thirty-three acrophobic participants assigned randomly either to the VRET or in vivo group were asked to use escalators, walking upstairs while looking down at the ground level in both treatment conditions. The exposure in both conditions was performed with the assistance of a therapist who encouraged the patient to progress to the higher level when the fear diminished. During the treatment, participants had to rate their anxiety level using SUDs every few minutes, and they were assessed with the Acrophobia Questionnaire (AQ) (Cohen, 1977), the Attitude Towards Heights Questionnaire (ATHQ)(Abelson & Curtis, 1989) and the Behavioural Avoidance Test (BAT)(Geen, 1987). The authors reported that VRET treatment was effective as the exposure in vivo, and the treatment effects were maintained in the six-months following assessment.

Krin et al., (2004) first compared the efficacy of VRET for the treatment of acrophobia in two VR systems – HMDs and CAVEs. Thirty-seven participants were randomly assigned to one of three groups: the first a VRET group using an HMD, the second a VRET group using a CAVE system, and the third a waiting control group. Both VRET groups received three weekly 1.5 h sessions of VRET for acrophobia for 4 weeks. The treatment protocol involved four VR simulations used in gradual order - a shopping mall with four floors, a fire escape with six floors in an open space, a roof garden on a building, and a virtual building site with eight floors. After the treatment, all participants were assessed for the fear of height using subjective reports. Also, a follow-up was held 6 months after treatment. Unfortunately, 10 participants dropped out from the study. The remaining participants were assessed using questionnaires. The study demonstrated that

VRET was superior to waitlist controls on anxiety score and avoidance and attitudes towards heights. No differences in efficacy were found between VRET delivered in CAVEs and using HMDs. All the results remained stable up to the 6-month follow-up (Krijn et al., 2004). Another study performed by Juan and Perez in 2009 which compared HMDs and CAVEs in 25 healthy participants, found a significant difference between HMDs and CAVEs. Participants were asked to walk into the room in which the floor dropped away and the walls rose up creating a falling sensation. The result demonstrated the superiority of the CAVE system in evoking higher levels of anxiety as well as presence as measured by questionnaires (Juan & Pérez, 2009). Both studies used pre-consumer HMDs. It is therefore possible that employing a new generation of VR systems would provide different results, however, to date, there are no peer-reviewed studies published comparing a new generation of consumer HMDs to CAVE VR.

Some researchers have used physiological monitoring during VRET for acrophobia (Diemer, Lohkamp, Mühlberger, & Zwanzger, 2016; Simeonov, Hsiao, Dotson, & Ammons, 2005; Wilhelm et al., 2005) arguing that it will provide more objective methods to assess the emotional state of patients, and therefore improve the progress of a treatment.

7. Combining VRET with physiological monitoring

Although many studies have investigated objective physiological correlates of arousal as an index of presence in VR (Meehan, 2007), physiological indicators of anxiety have not been established well enough regarding VRET treatment. With only a few studies published so far, the results are mixed.

According to emotional processing theory, physiological arousal plays a crucial role in exposure therapy as it indicates the activation of maladaptive fear structures which can then be modified by the treatment strategy (Foa & Kozak, 1986). Application of physiological monitoring in VRET allows for the measuring of an index of fear structure activation, which is necessary in exposure therapy for learning to occur (Foa & Kozak, 1986). It can help determine the level of arousal during the exposure - whether it is too low or too high and can help to assess whether a patient is ready to progress toward the next level of fear intensity. It can also be used to evaluate if successful learning has occurred and the patient has been desensitised (Gaggioli et al., 2014; Lang, 1977; Wiederhold et al., 2002). Physiological correlates of in vivo exposure therapy have been

previously reported using heart rate or skin conductance measures in treatment of agoraphobia (Holden & Barlow, 1986), driving phobia (Alpers et al., 2005), claustrophobia (Alpers & Sell, 2008), flying phobia (Wilhelm & Roth, 1998), obsessive-compulsive disorder (Grayson et al., 1986) or animal phobia (Nesse et al., 1985). These studies demonstrated that measuring HR could be a promising approach to measuring the level of fear. When phobic participants were exposed to fear-eliciting cues during treatment, the HR increased significantly indicating an increased arousal, in comparison to neutral cues (Emmelkamp & Felten, 1985). However, so far in VRET, the majority of studies have relied on the patient's subjective self-reports, such as Subjective Units Of Distress (SUDs), in order to assess levels of anxiety experienced during virtual exposure (Krijn et al., 2004). According to Wiederhold and colleagues, physiological monitoring offers a better tool for an objective assessment of participant's level of anxiety in VRET. The authors demonstrated that VRET combined with physiological monitoring results in lower relapse rates in follow up analysis for fear of flying due to the better insight into patient's inner state and level of arousal than VRET alone (Wiederhold et al., 2002). So far a few studies have applied physiological monitoring in VRET studies on disorders such as fear of flying (Wiederhold et al., 2002), acrophobia (Wilhelm et al., 2005), social anxiety (Slater et al., 2006), and PTSD (Popovic et al, 2006).

Regarding acrophobia, VRET studies have focused on measuring physiological response in acrophobic and healthy participants. Wilhelm et al., (2005) recruited 9 low-anxious and 11 high-anxious participants with a fear of heights. Using HMDs all participants were immersed into the virtual elevator with an open cabin platform attached to the metal tower. The experimenter controlled the movement raising or lowering the platform in 7 steps. During the experiment, participants rated their level of fear on a scale from 0 to 11. Continuous HR and skin conductance level (SCL) physiological recording were measured. After the experiment, participants were assessed for levels of presence in VR. The result of the study found significant increases of HR and SCL in the high-anxious group as well as healthy participants. Moreover, physiological parameters differed between groups for SCL, however not for HR. The authors, in comparing results to previous in vivo studies which used physiological monitoring, concluded that SCL, but not HR, was a reliable physiological measure of anxiety in VR (Wilhelm et al., 2005). Similarly, the study conducted on healthy participants by Simeonov et al. (2005) found a significant increase in SCL, but not in HR, during VRET height exposure, but both

SCL and HR were significantly elevated during in vivo height exposure. This study did not involve participants with a fear of heights, therefore, it was not clear to what extent VRET was capable of triggering a psychophysiological response in patients with acrophobia.

On the other hand, the recent study performed by Diemer et al., (2016) which involved a bigger sample and both phobic and non-phobic participants, showed the effect of physiological response during VRET. The authors exposed 40 acrophobic participants and 40 healthy controls to virtual height and assessed subjective fear ratings and physiological measures (HR, SCL and salivary cortisol). The measures were obtained during baseline and during a VR challenge, which involved standing on a roof, 13.9 meters above ground, looking down into the street and then looking straight ahead five times each. For data analysis, the authors compared between patients and controls and between baseline and VR challenge. Fear subjective ratings differed significantly between baseline and VR height challenge but in the patients, the difference was bigger. Physiological indicators of fear - HR and SCL increased significantly during the VR challenge, however, the arousal was similar in patients and controls. Moreover, the salivary cortisol levels in patients and controls did not differ significantly. Further post-hoc analysis revealed a stronger HR increase when looking down in patients than in controls. Regarding the presence questionnaire, the correlation with physiological measures was found only in patients (Diemer et al., 2016).

In summary, the evidence for the impact of VRET on physiological monitoring is mixed and therefore it is difficult to draw any conclusion. While some studies found that heart rate during VRET increases when participants were exposed to virtual heights, others failed to replicate those results.

Some researchers argue that changes in physiological parameters during the treatment do not necessarily indicate the learning effect (Baker et al., 2010; Craske, 2015). Moreover, it is difficult to infer the emotional state of the participant based on the index of physiological arousal. Some researchers demonstrated that the “novelty effect” significantly triggers the physiological response (Meehan, 2007). This project proposes using neuroimaging methods in VRET in order to measure the neural basis of fear inhibition and learning as a primary measure, and psychological monitoring to measure arousal during VRET as a secondary measure.

8. Combining VRET with neuroimaging

Although physiological changes during VRET have been already investigated by some researchers, understanding the neural basis of VRET is still in its infancy. Combining VRET with neuroimaging would aid in tailoring more efficient interventions by providing a method to evaluate treatment effects and confirm their ecological validity, as well as potential benefits or directions in research and clinical application. Unfortunately, VRET studies do not employ brain imaging methods in order to measure brain response. Most researchers use questionnaires such as Subjective Units of Distress (SUDS), in order to measure arousal and extinction learning during VRET session. These, however, are subjective measurements, which do not necessarily accurately reflect the factual state of a patient's mind. Yet, it is very difficult for a therapist to access patient's factual state of mind whilst relying only on observation and verbal communication with a patient. Verbal feedback from the patient often does not accurately reflect the actual state of the patient's mind due to its subjective nature. Moreover, in extreme situations, a patient may disattach from the reality either due to a lack of emotional engagement in exposure or due to extreme anxiety if the simulation is too intense. Therefore there is a need to employ objective neural measures of the patients level of arousal during VRET. Employing brain imaging methods in VRET may help a therapist to deliver more effective treatment, but it can also help to evaluate the technology used and treatment protocol effects, as well as provide a method to confirm their ecological validity, and any potential benefits or directions in research and clinical application. Moreover, neuroimaging could be implemented within VRET for real-time neurofeedback (Pfurtscheller & Leeb, 2011). This approach holds great potential, particularly in the treatment of neurological and psychiatric disorders (Holper et al., 2010). Applying neurofeedback in psychotherapy allows a therapist to monitor how a patient responds to the treatment and adjust the progress of the treatment to the patient's state of the mind (Schoenberg & David, 2014).

The full systematic review on the neural basis of VRET is presented in Chapter 3.

9. Role of the Prefrontal Cortex (PFC) in emotional regulation (reappraisal and inhibition) and Exposure Therapy (ET)

Previous neuroimaging studies on animals and humans identified the fear circuit which consists of the PFC and the amygdala (Shin & Liberzon, 2009). This PhD project

focuses on the prefrontal part of the fear circuit. In human neuroscience the PFC is usually divided into three main subregions:

- Medial PFC which consists of BA (Brodmann Area) 24, 25, 32 and 10.BA 10 is the foremost located brain region in the prefrontal cortex. In the literature the neuroanatomical nomenclature for this brain area vary, being labelled as the ventromedial prefrontal cortex, frontopolar prefrontal cortex, lateral frontopolar cortex or anterior prefrontal cortex (Burgess 2007). The medial PFC plays a role in the top-down regulation of a fear response, suppression of fear response when the threat is no longer present, attention to the emotional states of the self and others, and the guidance of response selection by emotional states (Davidson et al., 2002; Siddiqui et al., 2008).
- Orbitofrontal PFC consists of BA 11, 12, 13 and 47. It plays a role in the modulation of behavioural and automatic responses in fear-relevant situations (Davidson et al., 2002). Moreover, it plays a significant role in emotional-social behaviour and interactions (Siddiqui et al., 2008).
- Dorsolateral PFC consist of BA 9 and 46 (Cieslik et al., 2013). Dorsolateral functions relevant to fear regulation are believed to include involvement in working memory, response preparation, response selection, and top-down emotional regulation (Davidson, 2002). Emotional regulation can be modulated by the DLPFC using top-down executive control over emotional stimuli through processes of cognitive reappraisal, which is a psychological ability to assess the meaning of an emotional response through rationalising (Goldin et al., 2008).

A meta-analysis performed by Ipser (2013) on functional brain imaging of anxiety studies identified a role of the PFC, amygdala, right thalamus, left insula and cerebellum in specific phobia (Ipser, Singh, & Stein, 2013). The PFC plays a critical role in emotional regulation and fear inhibition. Neuroimaging connectivity studies showed that regions of the PFC have reciprocal connections with the amygdala, in particular, the medial PFC (MPFC) and orbitofrontal cortex have direct connections, and the dorsolateral prefrontal cortex (DLPFC) has indirect connections to the amygdala. Therefore prefrontal regions modulate amygdala activity via an inhibitory connection from regions of the prefrontal cortex which are activated during exposure to fear-evoking stimuli after extinction learning (Davidson, 2002; McGarry & Carter, 2016).

The neural bases of response inhibition in healthy participants have been widely investigated in neuroimaging studies. Those studies involved both motor and emotional inhibition. Approaches that examine brain activity during motor response inhibition usually implement tasks in fMRI scanner that involve a routine response, which requires effortful withdrawal or cancellation of the already initiated response when an occasional "stop" cue or instruction occurs. Two experimental paradigms that create withdrawal/cancellation responses are called the "Go/no-go task" (GNG) and the Stop Signal Task (SST), and these are commonly used in cognitive neuroscience. In this paradigm, participants are instructed to press a left or right button quickly in response to a "Go" cue. In randomly generated trials, a "Stop" cue is presented quickly, instructing the participant to inhibit the already planned response. The assumption is that having more "Go" than "Stop" trials involves responding rather than inhibiting the response, which leads to the development of a routine which can be later disrupted (Verbruggen & Logan, 2008). Aron and colleagues employed the Stop Signal Paradigm in order to investigate the neural bases of inhibition and demonstrated higher brain activity in the right prefrontal cortex during successful inhibition (Aron & Poldrack, 2006). Lesions in prefrontal regions result in an impaired ability to control motor inhibition (Hodgson et al., 2002).

The PFC also plays a crucial role in emotional inhibition and cognitive reappraisal of emotion. In particular, neuroimaging studies performed on healthy participants found increased activity in medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) during perception of fearful pictures (Lange et al., 2003), fearful faces (Nomura et al., 2004), emotional reappraisal (Ochsner et al., 2002), or suppressing negative mood during decision making (Beer, Knight, & D'Esposito, 2006). Moreover, studies found that increased activity in the DLPFC and MPFC has an inverse relationship with decreased amygdala activity in the regulation of emotions. Transcranial magnetic stimulation (TMS) studies demonstrated that the DLPFC plays a role in the recovery from anxiety (Balconi & Ferrari, 2013) and trauma (Karsen, Watts, & Holtzheimer, 2014). Boggio et a.l (2010) showed that repetitive TMS of the bilateral DLPFC reduces symptoms of PTSD, however, applying TMS on the right DLPFC has even better results, including at 3-months follow-up.

On the contrary, studies comparing patients with phobias, anxiety and PTSD with healthy controls demonstrated decreased activation in the DLPFC and the MPFC

inversely correlated with increased activity in the amygdala when exposed to anxiogenic stimuli, in those who suffered phobia, anxiety or PTSD (Duval, Javanbakht, & Liberzon, 2015; Etkin & Wager, 2007; Ipser, Singh, & Stein, 2013). The amygdala, which is a part of the limbic system, plays a crucial role in the detection of potentially threatening stimuli. A vast number of studies on rodents and humans have demonstrated that activity in the amygdala increases as a response to fear-relevant cues. Increased activity was found in the amygdala during viewing of negative pictures (Irwin et al., 1996), fearful faces (Morris et al., 1996) or aversive stimuli (Buechel et al.,1998). Conversely, in phobic patients, this amygdala activity is exaggerated due to abnormalities in the amygdala-prefrontal circuit (Rauch et al., 2003). Some researchers suggested that hypoactivation and hyperactivation in these areas may be associated with different symptom severity (Weber et al., 2013). Therefore patients who score high on symptom measurement scales in clinical assessment will show greater activity in the amygdala, and lower activity in prefrontal areas, which are correlated with symptom severity. Hypoactivation in the MPFC and DLPFC could indicate deficits in emotional regulation, while hyperactivation in the amygdala could indicate an abnormally exaggerated response to the threat (Duval et al., 2015). Therefore, modulation of the amygdala by the PFC could be one of the neural mechanisms which underlie the efficacy of ET and VRET in anxiety disorders, specific phobias and PTSD.

Despite evidence showing how ET changes the fear circuit, little is known about what is happening within the session (Åhs, Gingnell, Furmark, and Fredrikson, 2017). Within-session brain imaging would help therapists objectively monitor patient's response in real time, and determine the optimal level of exposure for the treatment to occur (Brouwer, Neerincx, Kallen, van der Leer, and ten Brinke, 2011). Treatment effects have been observed during ET sessions in patients with specific phobias, as measured by self-reports (see Zlomke and Davis, 2008 for a review). However, there has been little research on the neural basis of within-session inhibitory learning during ET. So far, two brain imaging studies have investigated the effects of ET sessions on the brain by measuring within-session changes in neural activity in phobic participants during repeated exposure to fearful stimuli. The study conducted by Veltman et al., (2004) compared brain activity from arachnophobic participants to healthy controls employing a symptom provocation paradigm which involved a

continuous presentation of series of pictures of either spiders or butterflies. They found habituation effects in the bilateral anterior medial temporal lobe, including the amygdala, reflected in the decline of Regional Cerebral Blood Flow (rCBF) in phobic participants during repeated exposure to pictures of spiders. In particular, right amygdala activity showed habituation effects after 5–15 minutes of exposure. More recently, the study conducted on patients with social anxiety disorder found a within-session reduction in amygdala rCBF, as well as decreased anxiety ratings and heart rate during the stressful speech in front of an audience– from one speech to another (after 2.5 minutes) (Åhs et al., 2017). However, both of those studies employed Positron Emission Tomography (PET) to measure brain response. PET has a low temporal resolution, therefore, limits the accuracy of data acquisition in the temporal domain (Varvatsoulias, 2013). Alternative brain imaging methods give better temporal resolution, theoretically making them more relevant for monitoring within-session changes. Such technologies include Functional Near-Infrared Spectroscopy (fNIRS) or Electroencephalography (EEG). Although fNIRS has a lower spatial resolution, it offers a better temporal resolution that would allow better insight into what is happening in the brain during the treatment session (Ohtani, Matsuo, Kasai, Kato, and Kato, 2009). Two studies have employed fNIRS to measure temporal changes in the brain during Eye Movement Desensitisation and Reprocessing (EMDR) treatment for PTSD, showing a potential of using fNIRS as a tool for within-session brain monitoring during a treatment (Amano et al., 2016; Ohtani et al., 2009). Although the aforementioned studies have provided some insight into the neural activity during ET session, so far there are no studies which investigated within-session brain activity during VRET.

Measuring within-session brain activity during VRET would help to understand what changes occur, and when they occur in the brain during a single session. Previous studies demonstrated that VRET has a potential to trigger inhibitory response and emotional regulation after the treatment (described in details in Chapter 3 – Systematic Review), however they did not demonstrate on which stage of VRET these changes occur, what is the minimal amount and duration of VRET to achieve a therapeutic effects as measured from the neural activity.

10. Conclusion

Emerging technological advances in neuroimaging and Virtual Reality (VR) offer unprecedented opportunities for the researchers and clinicians to design new tools and applications in research and therapy. Combining VR with neuroimaging could bridge the gap between the naturalness of response and controllability of research and therapy. Previous studies combined fMRI or EEG with VR, however, those technologies significantly influence the naturalness of the response by restraining the freedom of movement, potentially could provoke anxiety in vulnerable populations, and moreover, hides the body, as well as others, from the view of the user. Recent developments in wireless brain imaging technology (fNIRS) offers a compromise between the spatial resolutions of fMRI and temporal resolution of EEG. The compact, portable and wireless design of the system allows for the combination of fNIRS with IPT, in which participants can freely move around the environment with others. This has potential applications in mental health, which has recently focused attention on VRET. VRET has already demonstrated efficacy in the treatment of many anxiety disorders. However, neural mechanisms underlying VRET are still not understood. Previous researchers emphasised the role of inhibition, inhibitory learning, and emotional reappraisal during exposure therapy. The PFC plays a crucial role in fear inhibition and emotional regulation. Although previous studies demonstrated increased activity in the DLPFC and MPFC in healthy participants when they encountered threatening stimuli in VR, as well as after the successful VRET treatment, the neural substrates of fear inhibition and inhibitory learning in ecologically valid VR remain unknown. Moreover, there are no studies investigating what is happening during VRET sessions. Therefore, this project will measure PFC activity changes in response to virtual stimuli, while avoiding equipment that might unduly impact naturalness of response. The approach of this project is to combine a VR display system in which participants can move, while the neural signature of fear inhibition, and the physiological signature of fear, can be measured. Specifically, the current project utilises immersive projection technology combined with wireless fNIRS to measure the prefrontal response, and physiological monitoring to measure physiological indicators of arousal in VRET with improved ecological validity.

Chapter 3 Systematic Review – The neural basis of VRET

1. Introduction

The aim of the previous chapter was to provide a general background, theoretical framework, and core concepts of neuroscience of VRET for this PhD. The aim of this chapter is to provide a systematic review, critical evaluation and address the gaps in knowledge of the current evidence on the neural basis of Virtual Reality Exposure Therapy (VRET).

VRET has been demonstrated to be a promising treatment for a range of anxiety disorders in four meta-analyses (Morina, Ijntema, Meyerbröker, & Emmelkamp, 2015; Opriş et al., 2012; Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008), however neuropsychological mechanisms underlying its efficacy are still not well understood. Some researchers used psychophysiological monitoring during VRET arguing that it will provide more objective methods to assess emotional state of the patients and improve the progress of a treatment (Diemer et al., 2016; Norrholm et al., 2016). However, the evidence for the impact of VRET on physiological reaction is mixed. Combining VRET with neuroimaging would help to understand its neural mechanisms, aid tailoring more efficient VRET interventions to evaluate treatment effects and confirm their ecological validity and potential benefits or directions in research and clinical application. Moreover, it could give neurofeedback to the therapist or client about neural activity in a patient's brain during the treatment session. This chapter reviews the current literature on the neural basis of VRET. Brain imaging was previously combined with VRET to investigate the inhibitory function and emotional regulation in substance use disorders, specific phobias and PTSD. VRET neuroimaging studies emphasised an essential role of the prefrontal cortex (PFC) in the regulation of emotion and inhibition to reduce the fear responses and thus reduction of anxiety, phobias and PTSD symptoms.

Employing brain imaging methods to VRET may help a therapist to deliver more effective treatment, but it can also help to evaluate the technology used, treatment protocol effects and confirm their ecological validity and potential benefits or directions in research and clinical application. Moreover, neuroimaging could be

implemented within VRET as a real-time neurofeedback (Pfurtscheller & Leeb, 2011). This approach holds a big potential particularly in the treatment of neurological and psychiatric disorders. Applying neurofeedback in psychotherapy allows a therapist to monitor how a patient responds to the treatment and adjust the progress of the treatment to the patient's state of the mind (Schoenberg & David, 2014).

A meta-analysis conducted by Etkin and Wagner (2007) assessing neuroimaging studies of anxiety, phobia, PTSD and emotional processing identified a "fear network" consisting of the PFC and limbic system. Healthy controls showed greater activity in the medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) when exposed to aversive stimuli. Activity in these areas has an inverse relationship with the activity in the amygdala. Conversely, patients showed decreased activity in the DLPFC and MPFC inversely correlated with increased activity in the amygdala when exposed to anxiogenic stimuli in those who suffered phobia, anxiety or PTSD (Etkin & Wager, 2007). Previous studies demonstrated that traditional Exposure Therapy (ET) restore a balance within a fear circuit (Hauner, Mineka, Voss, & Paller, 2012), however, the neural basis of VRET is still poorly understood.

2. Methods

2.1. Aim

The aim of this systematic review was to critically evaluate and synthesise the current evidence relevant to the impact of virtual exposure treatment on brain function. The objective was to identify brain areas and patterns of neural activity triggered by evocative VR simulations.

2.2. Search strategy

A systematic online database search was performed on PubMed, MEDLINE, ISI Web of Science, and Google Scholar by entering various combinations of search items related to four categories:

- Brain imaging method - fMRI, PET, EEG, fNIRS, NIRS, brain activity
- VR - VRET, virtual reality exposure, virtual therapy, virtual treatment
- Disorder – anxiety, phobia, PTSD, addictions, fear, mood disorder, fear

- Cognitive function – inhibition, inhibitory learning, cognitive reappraisal, emotional regulation, fear conditioning, extinction

Moreover, references from articles were scanned for additional relevant studies. Although systematic reviews usually focus on assessing the results of controlled trials, neuroscience of VRET is an emerging research area, therefore there are no carefully designed controlled trials or studies available at the moment. For that reason, the scope of this literature review was broadened by including all the studies, which employed any combination of brain imaging and virtual reality exposure which involved fear inhibition and emotional regulation task. Additionally, this review included two studies which employed a fear conditioning paradigm within VR. Classical conditioning and extinction learning are considered as possible mechanisms underlying traditional ET (Bouton, 2002; McNally, 2007; Tryon, 2005). However, because those studies do not directly employ any form of VRET, they are reviewed in subsection 3.2.

Studies relevant to the topic were included if they used (1) any combination of VRET and neuroimaging, (2) were performed on either healthy participants or patients with mental disorders such as anxiety, phobia, PTSD or addiction, (3) activity in the neural fear circuit must be reported.

Studies were excluded if they (1) were not published in peer-review journals, (2) were case studies, (3) did not directly investigate the neural basis of emotional inhibitory response or cognitive reappraisal in VR

All studies that met the inclusion criteria were critically reviewed in terms of study aims and objectives, methodology, population, sample size and technology used.

3. Results

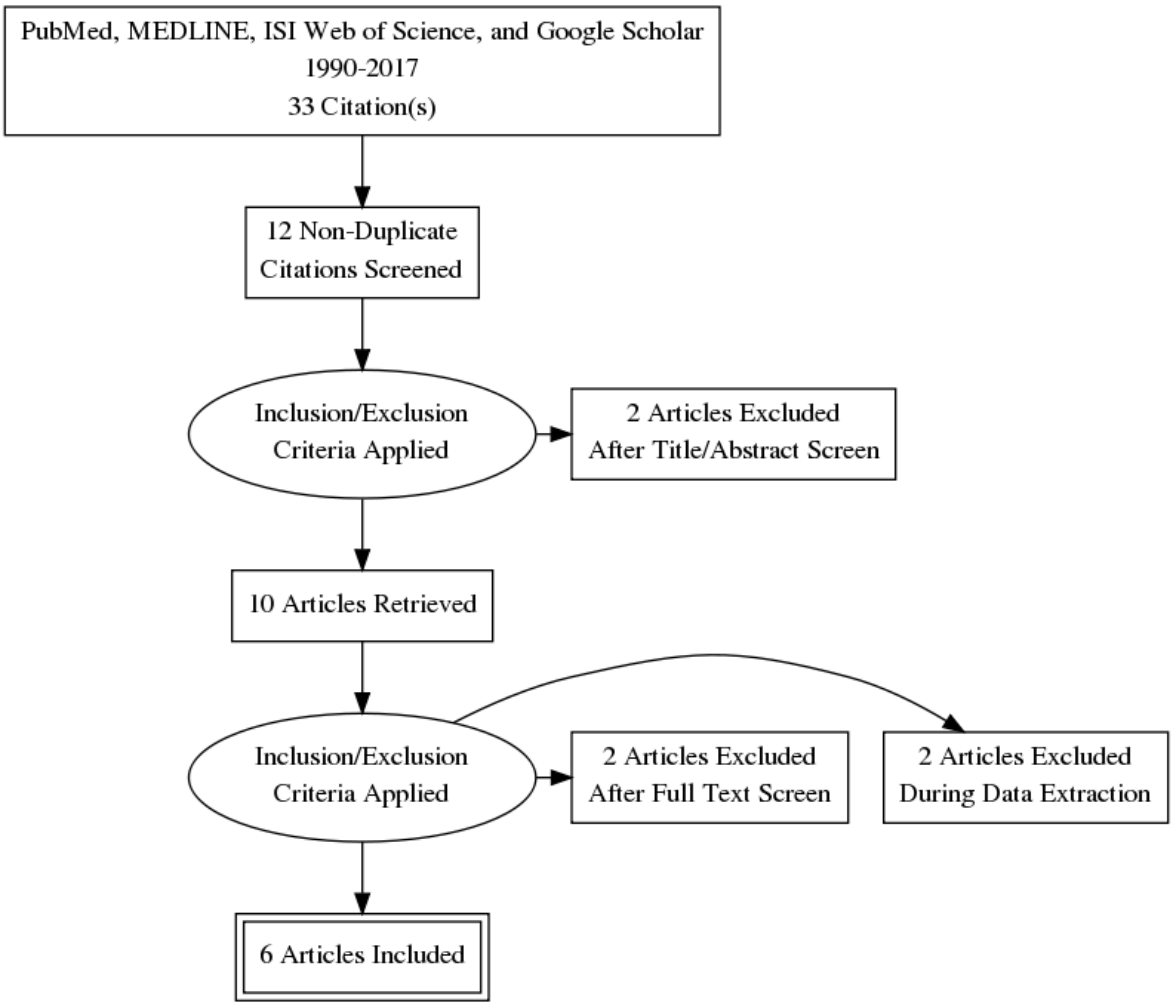

Figure 2 PRISMA Flow Diagram for search strategy results

The search yielded thirty - three studies, and of these twenty-one were duplicates, which were removed. From twelve non-duplicates, two studies were excluded after the abstract screen because they were study protocols. From the ten retrieved studies, two were excluded after the full text screen because they investigated the neural basis of motor inhibitory learning rather than emotional inhibitory learning. Another two studies were excluded because they did not report brain activity. From remaining studies six met inclusion criteria. We identified four studies employing fMRI and two using EEG. In five of those studies, VRET was delivered through HMD and one study used desktop VR and navigation pad. All six studies are described below.

3.1. Studies

VRET for addictions

Three studies investigated the neuronal mechanisms of VRET for addiction treatment. Inhibitory control plays a crucial role in substance dependence treatment, allowing patients to resist cravings (Smith, Mattick, Jamadar, & Iredale, 2014). The regulation of craving for substance abuse cue-exposure therapy (CET) is associated with inhibitory control indicated by increased activity in the PFC (Seo et al., 2013).

Lee and colleagues (2005) used fMRI to compare the efficacy of using 2D images and 3D virtual environments as a tool for delivering VRET for smoking cessation. The main aim of this study was to investigate if utilising VR is a superior method to evoke smoking cravings in comparison to traditional 2D photos. Eight participants were recruited from the smoking cessation program. During the experiment, they were exposed to neutral and smoking-related cues delivered through 2D pictures in one condition, and VR in the second condition using fMRI-compatible goggles. Participants showed increased brain activity when viewing the smoking-related cues in the right superior frontal gyrus, right middle frontal gyrus, and left orbital gyrus, left anterior cingulate gyrus, left supplementary motor area, right inferior temporal gyrus, right lingual gyrus, and right precuneus when exposed to 2D images. When participants were exposed to smoke-related cues in VR, additionally they showed increased activity in the left superior temporal gyrus, right superior frontal gyrus, and left inferior occipital gyrus, which indicates more attention, visual balance and spatial orientation. The result of the study indicated that 3D VR may be superior to 2D images regarding ecological validity and naturalness of the response by activating brain areas involved in 3D perception and navigation, as well as the prefrontal attentional network (Lee, Lim, Wiederhold, & Graham, 2005). The study, however, suffers several limitations. First of all, the sample size (N = 8) was very small, which might be insufficient to detect the effects of VR on brain activity (Desmond & Glover, 2002). Secondly, participants were recruited from the smoking cessation program, but authors do not specify what type and how much treatment participants had already received. Although authors interpreted increased activity in the PFC during exposure to smoke-related cues as increased attentional demand, the result might also indicate that participant who underwent successful treatment, showed increased activity in the PFC as a result of response inhibition. The lack of involvement of active-smokers and control groups in the study makes results difficult to interpret.

Another study performed by Moon and Lee (2009) employed a similar paradigm, but instead of a single session, participants received six sessions of VRET. The study recruited eight volunteers for a smoking cessation program. Participants were exposed to cues in a virtual bar, which could trigger cigarette cravings, such as alcoholic drinks, a pack of cigarettes, a lighter, ashtrays, posters advertising alcohol and cigarettes or an avatar smoking a cigarette. The fMRI scan was performed before and after the treatment. The results revealed increased activity in the left inferior frontal gyrus and left superior frontal gyrus in response to smoking-related cues associated with a reduction of nicotine cravings and better self-control (Moon & Lee, 2009). However, similarly to the study conducted by Lee et al., (2005), this study had a small sample size (N = 8), lack of active smokers and non-smoking control group. However, both of those studies demonstrated a potential of combining VR therapy with fMRI as a method to measure brain activity related to nicotine cravings and addictions. Another study on VRET for addictions by Lee et al., (2009) used EEG to measure the effect of exposure on brain response. Although EEG has lower spatial resolution than fMRI, it has a better temporal resolution (Crosson et al., 2010), but is also relatively less expensive and could be portable (Xu & Zhong, 2018), which could potentially make it easier and more cost-effective to combine with VR. Lee and colleagues (2009) compared the effect of 10 sessions of VRET for twenty alcohol dependence (ADP) patients with eighteen healthy controls. The simulation consisted of simulations of alcohol-related cues (such as drinks: beer, whiskey, wine, and drinking-related environments: pub, restaurant, whiskey garden) delivered through VR goggles. EEG was measured before and after the treatment. The results revealed increased alpha wave in PFC and a decrease in alcohol cravings in ADP who received VR exposure treatment after 10 sessions (Lee et al., 2009).

VRET for anxiety disorders – phobia, mood regulation and PTSD

Three of the studies investigated the neural basis of VRET for anxiety disorders.

Clemente et al., (2014) used fMRI in order to assess brain activity during VRET for assessment of specific phobia. They recruited 11 participants with a mild phobia of animals. They designed a simulation with three rooms – “clean”, “dirty” and “phobic”. In the clean room, participants could navigate without a risk of encountering feared animals. The dirty room was the same however darker and dirtier and could trigger the anxiety in participants that feared animals may appear at any time. In the phobic room,

however, they could encounter feared animals at any moment. Participants were given a simple visual search task – to find red keys. Each of the conditions lasted 20 seconds. The SPM (Statistical Parametric Mapping) contrast clean versus phobic revealed increased activity in the right DLPFC (superior frontal gyrus). They also found activity in the occipital lobe related to increased visual attention. Although authors concluded that activity in the superior frontal gyrus (SFG) (BA 9/32) is related to self-awareness (Clemente et al., 2014), however SFG plays also a role in a reappraisal of negative stimuli (Falquez et al., 2014) and inhibitory function (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010).

One study conducted by Rodríguez et al., (2015) employed a wireless commercial EEG Emotiv Epoc system combined with desktop VR for mood induction and regulation procedures. Twenty-four healthy participants navigated through a virtual park designed to induce sadness. The mood in VR was induced using sad music or sad pictures (for example combat zones or funerals). Participants were divided into three groups, each of which was asked to use different mood regulation procedure – cognitive reappraisal, expressive suppression (described in details in chapter 2, section 6.2) or no-strategy control group. The result, however, failed to detect significant results as measured by EEG for cognitive regulation groups, but there was an increase in alpha waves in a control group during VR mood induction. To date, this is the only study, which combined wireless brain imaging and VR to investigate emotional regulation. The lack of significant results in this study could be related to the small sample size. On the other hand, the study employed a low-cost commercial EEG system, which performs significantly worse than professional medical EEG devices and therefore does not provide reliable results for clinical applications (Duvinage et al., 2013). Therefore, there is a need for a design of a specific low-cost wireless brain imaging system for clinical applications and research.

The study conducted by Roy et al., (2010) is the only randomised controlled trial (RTC) study that employed brain imaging techniques to investigate VRET for PTSD. The study involved 29 patients (15 with PTSD and TBI, 9 with PTSD, 1with TBI, and 4 controls). From the group of 15 patients with PTSD were randomised – 7 to the VRET condition and 8 to the ET condition. From 15 PTSD patients, 8 completed the treatment and 6 dropped out. The treatment phase involved 12 or more 90-min sessions of VRET or ET over 6 weeks. The VRET condition immersed participants into simulations of virtual Iraq and Afghanistan using an HMD. Functional Magnetic

Resonance (fMRI) was used before and after the treatment to assess improvement in brain function after VRET. The result of the study from 8 participants revealed decreased activity in the amygdala, anterior cingulate cortex and increased activity in the lateral prefrontal cortex when compared to scans acquired prior to the treatment (Roy et al., 2010). Unfortunately, the authors did not report the difference between VRET and ET condition or correlations between other measures.

Neural basis of fear conditioning and extinction learning in virtual reality

The literature search yielded two publications on fear conditioning in VR. Although those studies did not directly investigate the neural basis of VRET, traditional ET is often explained by principles of fear conditioning and extinction learning (Hofmann, 2008), therefore they were included in this systematic review as they are conceptually relevant to this PhD project. Both of those studies employed VR environments displayed on the screen inside fMRI. In the first study by Alvarez and colleagues (2008), thirteen healthy participants were exposed to a virtual house and airport, of which one was used as conditioned context and paired with an electric shock delivered to the foot, which served as unconditioned stimuli, and no shock was delivered in the second context. The shock context conditioning significantly activated the right hippocampus, amygdala, orbitofrontal cortex, thalamus, inferior prefrontal cortex, insula and parietal cortex. The second study performed by the same research group (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011), used three VR environments (a restaurant, casino and bank), one in which an electric shock was predictably signalled by an auditory cue, a second in which the shock was delivered unpredictably and was not paired with a cue, and a third which served as no-shock condition . The result of the study found that both predictable and unpredictable virtual threat evoked increased activity in the dorsal amygdala, but unpredictable threat evoked additionally increased activity in the bed nucleus of the stria terminalis complex (BNST). Moreover, the unpredictable threat also led to increased activity in the insula, inferior frontal cortex, middle frontal cortex, superior frontal cortex, parietal cortex, amygdala-hippocampal area and anterior cingulate cortex and deactivation in orbital cortex. These brain regions are known to be involved in fear conditioning and extinction as well as emotional regulation, especially fear inhibition and cognitive reappraisal of fear (Hartley & Phelps, 2010).

Both studies demonstrated a role of the PFC in contextual fear conditioning in VR. These results were consistent with previous non-VR neuroimaging studies on fear conditioning (Gilboa et al., 2004; Milad, Rauch, Pitman, & Quirk, 2006; Quirk, Martinez, & Nazario Rodriguez, 2007). However, both of those studies have several limitations, therefore their implication to VR research is unclear. First of all, in both studies scenarios were pre-recorded, therefore participants passively viewed the simulations and were not able to control and navigate within VR. Studies showed that passive viewing of VR environment impacts cognitive function and task performance differently than dynamic interaction (Jang, Vitale, Jyung, & Black, 2017; Roussou & Slater, 2017). Therefore, more studies are needed on fear conditioning in VR which would allow participants to freely move around and interact with the VR environment.

4. Discussion

The aim of this systematic review was to critically evaluate and synthesise the current evidence relevant to the impact of virtual exposure treatment on brain function. The objective was to identify brain areas and patterns of neural activity triggered by evocative VR simulations. The search yielded six studies related to the topic. The number and design of those studies were however insufficient to perform a meta-analysis. In line with previous non-VR neuroimaging studies on ET, this review indicated a potential role of the PFC in VRET, in particular, the DLPFC and MPFC. The role is that of regulation of emotion and fear inhibition to reduce fear responses. In turn, this reduces anxiety, phobia and PTSD symptoms, as well as cravings for addictions through inhibitory function. Successful VRET treatment, therefore, should restore balance within the prefrontal - amygdalar fear circuit. Unfortunately, due to the small number of studies, there is limited evidence of how VRET affects brain function. The majority of studies that were found investigated the effect of a single VRET session on brain function. The only RTC study investigated the effect of multiple VRET sessions on brain function employing fMRI (Roy et al., 2010), however, the sample size was small, therefore the study identified trends, but no significant results. Moreover, to date, there are no studies investigating what is happening during a VRET session. This is perhaps because the field of neuroscience of VRET is a relatively new research area.

Furthermore, the lack of studies could be linked to the limitations of current technology. The majority of low-cost HMDs are not magnet friendly, therefore cannot be used within fMRI machines (Adamovich, August, Merians, & Tunik, 2009). On the other hand, EEG is susceptible to signal interference from peripheral devices (Usakli, 2010). The literature search found two studies which combined EEG with VR (Lee et al., 2009; Rodriguez, Rey, Alcaniz, Rodrigues, & Alcañiz, 2013), which indicated increased alpha waves in the PFC during VRET, however because of limited spatial resolution of EEG it is difficult to detect brain activity from a specific region within the PFC. Only one of those studies by Rodriguez et al., (2013) employed a wireless EEG device, which possibly facilitates ecological validity because of the improved naturalness of response and freedom of movement, however, the reliability of this device was not confirmed for research and clinical applications (Duvinage et al., 2013). fNIRS offers a potential compromise between spatial the resolution of fMRI and the temporal resolution of EEG (Irani et al., 2007). Moreover, because of its portable and lightweight design, fNIRS can also come as a wireless brain imaging system (Nieuwhof et al., 2012; Piper et al., 2014). Employing wireless brain imaging devices could significantly improve the ecological validity of VRET research because it enables more natural movement, especially when combined with VR systems which also allow freedom of movement, such as CAVE VR systems. All existing studies evaluated the effect of VRET delivered through an HMD, except one study which used the screen to deliver VR for mood induction (Rodriguez et al., 2013), and two studies which used VR for fear conditioning (Alvarez et al., 2008, 2011). However, the last two used pre-recordings and did not allow interaction with the simulation and freedom of movement. Coehlo et al., (2008) emphasised the role of movement in the treatment of acrophobia. The study showed that anxiety levels, which are important for successful treatment, were higher in patients who were physically moving during exposure to heights, and that locomotion also improves a sense of presence (Slater, Steed, McCarthy, & Maringelli, 1998). However so far there are no studies which combined fNIRS with VRET to measure within- and between-session brain response to VRET with improved ecological validity and this PhD project seeks to address this gap.

5. Conclusion

The previous studies demonstrated that the PFC mediates a process of emotional regulation in VRET-based experiments. There is a need for better designed randomised controlled trials, with larger samples, employing different VR systems, to verify the efficacy of VRET and its impact on brain function. So far, there are no studies of the effect of VRET in CAVE-like VR on brain activity.

Table 1 Summary and description of studies included in the systematic review

Author, Year	Participants	VRET (type, #of sessions)	Results	Limitations
Lee et al., 2005	N = 8, from smoking cessation program	1 session of VRET for smoking cessation, single session, fMRI + HMD	↑ DLPFC R, MPFC L, VLPFC L, SMA L, occipital cortex, temporal cortex during VRET	No control group, no active smokers, small sample size
Moon et al., 2009	N=8, from smoking cessation program	6 sessions of VRET for nicotine craving, fMRI + HMD	↑ DLPFC L, VLPFC L after VRET	No control group, small sample size
Lee at al., 2009	N=20 ADP (VRET), N=18 ADP (CBT), N=15 healthy (VRET)	10 sessions of VRET for alcohol dependence, EEG + HMD	↑ frontal alpha activity after VRET	Small sample size
Clemente et al., 2014	N= 11with mild phobia	Single session VRET for small animals' phobia, fMRI + HMD	↑ DLPC R and occipital cortex L during VRET	Small sample size, single session, no control group
Rodrigues et al., 2014	N=24 healthy (N=8 CR, N=8 ES, N=8 CG)	Single session VRET for mood regulation, EEG + screen	No significant results in ER group; ↑ frontal alpha activity in CG	Small sample size, cheap EEG system
Roy et al., 2010	N=7 (VRET for PTSD), N=8 (PE, control),	12 sessions of VRET for PTSD, fMRI + HMSs	↑ DLPFC, and MPFC; ↓ amygdala after VRET	Small sample size
Alvarez et al., 2008	N= 13 healthy participants	Fear conditioning; fMRI + screen	↑ hippocampus, amygdala, OFC, thalamus, PFC, insula, parietal lobe during aversive VR condition	Small sample size, pre-recordings; passive VR
Alvarez et al.,2011	N= 14 healthy participants	Fear conditioning; fMRI + screen	↑ amygdala, BNST, insula, PFC, hippocampus, ACC ↓OFC during unpredictable VR threat	Small sample size, pre-recordings; passive VR

Chapter 4 Methods

1. Introduction

This chapter describes the methods used in this thesis to achieve the goals of this research project. Specifically, this part outlines the research process, experimental design, research methods, instruments used in this project, selection of the sample, methods of data collection and analysis. Mainly, this chapter focuses on describing a rationale for choosing research methods used in this project. Finally, in the end are described the ethical considerations related to this PhD project.

2. Research process

The research process is defined as the sequence of steps that the researcher goes through to answer the research question (Barker, Pistrang, & Elliott, 2002). At its core, this PhD thesis is about measuring activity in the PFC indicative of fear inhibition, reappraisal and inhibitory learning in VRET with improved ecological validity using technology which better suits clinical applications. This research process can be further broken down into several research steps highlighted below.

2.1. Formulating Research Problem

According to The National Health Service Survey (Mcmanus, Bebbington, Jenkins, & Brugha, 2016*)*, 1 in 6 people in the UK experience a common mental health problem, of which the most common are:

- Generalised anxiety disorder 5.9 in 100 people
- Depression 3.3 in 100 people
- Phobias 2.4 in 100 people
- Obsessive-compulsive disorder OCD 1.3 in 100 people
- Panic disorder 0.6 in 100 people
- Post-traumatic stress disorder (PTSD) 4.4 in 100 people
- Mixed anxiety and depression 7.8 in 100 people

ET is one of the most effective treatments for anxiety-related disorders (Abramowitz, 2013). However traditional ET has many disadvantages such as an

inadequate engagement of a patient, lack of controllability or high drop-out rate (Imel, Laska, Jakupcak, & Simpson, 2013; Zandberg, Rosenfield, Alpert, McLean, & Foa, 2016). VR offers a promising new approach to improve ET (discussed in details in Chapter 2, Section 7). Although VRET has demonstrated its efficacy in the treatment of anxiety disorders (Opriş et al., 2012; Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008), still very little is known how it impacts on the PFC activity. To date, a few studies compared pre- and post-treatment functional changes in neuronal activity after VRET (more details in Chapter 3), however, so far there are no studies which investigated what is happening within VRET session (discussed in details in chapter 2, section 9). Moreover, this thesis argues, that previous studies employed technologies which are not the most optimal for clinical applications and might obscure the naturalness of response.

The initial aim of this PhD project was to investigate the PFC response to VRET for PTSD. The research project proposal was developed in collaboration with Albert Skip Rizzo - Director for Medical Virtual Reality Institute for Creative Technologies at USC, who has an Honorary Chair at the University of Salford. The project proposed to employ Bravemind, which is a clinical, interactive, VRET tool developed at USC for assessment and treatment of PTSD. Bravemind involves simulations of virtual Afghanistan and Iraq, and the treatment session is supported by a clinician controller, which allows for control of the type of stimuli and dose of exposure delivered to the client (Rizzo et al., 2010). It is currently used in the USA at over 60 sites, including VA hospitals, military bases and university centres. The project anticipated to test Bravemind in the UK using military veterans with the involvement of Alan Barrett - Consultant Clinical Psychologist at Pennine Care NHS Foundation Trust and Clinical Lead for the Military Veterans' Service. Unfortunately, after several ethical issues which arose throughout the first year of this PhD, during the stage of software testing and implementation, the Research Ethics Committee suggested changing a focus of this project to less complex mental disorders, such as specific phobias. The argument was that the technology has not been tested in the UK for its safety, therefore might cause a potential risk to vulnerable populations. As a result, this PhD was ameliorated in the second year changing its focus from PTSD to acrophobia.

2.2. Literature review

The literature reviews were undertaken in parallel to the process developing research questions and design, in order to assess the existing body of knowledge and identify gaps. This step helped to formulate research questions and hypothesises in the light of theoretical and conceptual framework, to improve a research methodology and to contextualize findings of this project (Boote & Beile, 2005).

The searches were performed using several sources such as MedLine, PsycINFO, Web of Science, Scopus, Research Gate or Google Scholar. Additionally, main researchers, teams and publications were identified, and further publications were obtained through forward and backwards referencing.

This PhD brings up several disciplines, therefore it consists of two separate literature reviews:

- Background literature review, which focuses on the description of the theoretical framework, core concepts, historical developments and breakthroughs from the fields of virtual reality, neuroimaging and virtual reality exposure therapy.
- Systematic literature review, which provides a detailed literature survey and critical evaluation of the neuroscience of VRET

The initial focus of the literature review was to gain an understanding of how VRET impacts on brain activity and which technology was previously employed to address this research question. Building upon past research the project formulated research questions, established aims objectives and developed the experimental design. The research questions, aims, objectives and hypothesises for each of the studies are presented in the relevant chapters: for the pilot study - in chapter 5, for the participant study on healthy volunteers - in chapter 6, and for the participant study involving acrophobic volunteers - in chapter 7.

3. Research design

This PhD project employs quantitative research methods because it is easier to replicate by other researchers, it is less prone to researcher bias due to rigid adherence to rigorous design, better precision in the measurement process and because of well-established statistical data analysis methods.

The within-subject design (participants perform a task under the same conditions) was employed for all three experiments in order to reduce the number of errors in the variance associated with individual differences (for example in hemodynamic response), as well as to increase statistical power.

For stimuli presentation, this project employed an event-related design in the pilot study, during which conditions were presented randomly. However, this approach usually requires an event to be separated by inter-stimulus intervals (Huettel et al., 2004), was not optimal to implement in Octave because it would require either several system reboots, or participants leaving the simulation area every 20 seconds. To maintain a more naturalistic approach, the experimental design was improved after the pilot study. For the second and third study, a blocked design was adopted. The blocked design is a commonly used paradigm in fMRI studies. It consists of epochs of "on" and "off" periods alternated through the scanning session. During the "on" period, a stimulus of the same condition is presented sequentially, and the "off" period serves as a baseline or rest period. In contrast, event-related design presents stimuli in arbitrary order separated by an inter-stimulus period (Huettel et al., 2004). Although a block design has many disadvantages (Amaro & Barker, 2006), for this project it was the optimal strategy for a stimulus presentation. The block design was employed in order to facilitate naturalness of the response and mimic the real-life situation in which usually there are no inter-stimulus periods or breaks. However, the rest period between each of the blocks was used in order to allow hemodynamic response function (HRF) to return to the baseline before the onset of the other condition. The block design is more efficient in terms of detection of statistical power when the number of participants and trials is lesser (Friston, Holmes, Price, Büchel, & Worsley, 1999), and it is more robust to uncertainty in the temporal domain. In the second and third experiment, each run consisted of three blocks – early, middle and late. This approach was adopted in order to measure the temporal within-session brain activity. This was the optimal approach because of the current limitations of the NIRStar software, which does not allow more than four temporal markers when used in a wireless mode (NIRx Help Center, 2015).

4. Measures /variables

4.1. Brain response - Oxygenated Haemoglobin (HbO)

This project assesses the potential of using Functional Near-Infrared Spectroscopy (fNIRS) in virtual reality. fNIRS measures changes in a hemodynamic response associated with the neural activity from the sub-surface of the brain using near-infrared light. fNIRS has been validated for application in human brain imaging research (Ferrari & Quaresima, 2012). Many neuroimaging studies also cross-validated the use of fNIRS comparing with other brain imaging methods such as fMRI (Steinbrink et al., 2006; Turner et al., 2013; Yuan & Ye, 2013), EEG (Blokland, Spyrou, & Thijssen, 2013; Hirshfield & Chauncey, 2009), TDCS (Choe et al., 2016; McKendrick et al., 2015), or TMS (Kozel et al., 2009; Parks, 2013).

Brain response to stimuli is associated with increased local oxygen consumption leading to increased cerebral blood flow (CBF) and volume (CBV). This results in an increase in oxygenated haemoglobin (HbO) and total haemoglobin (HbT), and a decrease in deoxygenated haemoglobin (HbR) (Strangman et al., 2002). fNIRS can measure changes in HbO and HbR concentration due to their distinct characteristic optical back-scattering properties in the near-infrared spectral range. fNIRS utilizes low-intensity near-infrared light in the range between 650 nm and 950 nm through the intact skull (Villringer & Dirnagl, 1995). The light is transmitted 1.5 -2 cm into the brain by placing LED optodes (sources) on the surface of the skull (Strangman et al., 2002). Because of the back-scattering properties of the head tissue, some fraction of the near-infrared light will reach the surface of the skull at the particular detector location, which can be recorded by NIRS as an indicator of neuronal activity.

Selection of fNIRS the chromophore

This project mainly focuses on the results based on the HbO chromophore, and HbR results are reported in the appendix because the majority of data did not satisfy the threshold significance at level $p < 0.05$. The choice of the haemoglobin chromophore to represent NIRS brain activity is still under debate in neuroscientific communities (Bendall, Eachus, & Thompson, 2016). For this project several factors determined the selection of HbO as representative of brain activity:

Firstly, HbO changes are considered by some researchers as the most sensitive parameter of task-related hemodynamic responses with the close correlation to BOLD signal as measured by fMRI (Doi, Nishitani, & Shinohara, 2013; Hoshi, Kobayashi, & Tamura, 2001; Strangman et al., 2002). Previous studies employed mainly fMRI to investigate the neural basis of VRET, therefore the intention was to compare the outcome of this project to existing evidence in order to confirm the validity of the method of combining fNIRS with VR.

To date, the most complex quantitative comparison between fNIRS and fMRI signals revealed a higher correlation between HbO and BOLD and suggested this result is because of a higher signal-to-noise ratio (SNR) of the HbO than HbR parameter (Strangman, Culver, Thompson, & Boas, 2002). HbR tends to have lower SNR, which possibly could be related to smaller tissue penetration of the short-wavelength light related to deoxygenated signal (Fishburn & Norr, 2014). For that reason, the amplitude of HbR is often smaller than that of HbO (Abdelnour & Huppert, 2009; Cui, Bray, & Reiss, 2010; Wolf et al., 2002). It has been also suggested that HbO and HbR have different temporal and spatial characteristics. The study which performed simultaneous fMRI and fNIRS signals comparison using the same statistical fixed-effect group analyses approach to both fNIRS and fMRI data, revealed that while the time courses of HbO and HbR are similarly correlated, the spatial behaviour of HbO is more consistent with the BOLD signal than HbR (Toronov, Zhang, & Webb, 2007). This result was in the line with the previous study by Wolf et al. (2002) who found that the temporal responses of HbO and HbR measured from the motor cortex were asymmetric, and HbO attained its peak value a few seconds faster than HbR. On the other hand, the same effect was not observed in the visual cortex (Toronov et al., 2007; Wolf et al., 2002). Because this PhD project investigated when the brain response to VRET changes, the choice of HbO was more relevant to the research question of this thesis. Another factor for choosing HbO was the approach to data analysis. Cui et al., (2011) found a correlation between the BOLD signal and both HbO and HbR in the PFC across multiple cognitive tasks using SPM (Statistical Parametric Mapping), but the effect was stronger for HbO. Okamoto et al., (2004) found a stronger correlation between HbO and BOLD during a naturalistic apple peeling task, using statistical parametric mapping (SPM) analysis. On the other hand, there are some studies which found a stronger correlation between HbR and BOLD.

However, these studies used HOMER (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006) or subject-specific (Toronov et al., 2003) approach for data analysis, which is different than the one used in this project. SPM approach was used for data analysis because it is the standard approach for fMRI data analysis (the analysis is described in details in section 8.3) as well as PET, EEG and EMG (Friston, 2007).

This project focuses on the emotional processing of fear, therefore another reason for choosing HbO as an indicator of brain response was influenced by previous literature. Previous studies which employed fNIRS to measure brain response during emotional stimuli processing found a significant increase of HbO in the PFC during exposure to negative stimuli (Glotzbach et al., 2011; Herrmann, Ehlis, & Fallgatter, 2003; Yoko Hoshi et al., 2011; Ozawa, Matsuda, & Hiraki, 2014). Other studies which used fNIRS to compare brain response in healthy controls and patients with anxiety disorders found that patients showed smaller HbO increase in the PFC than healthy participants during emotional processing (Liu et al., 2014; Yokoyama et al., 2015), that suggests that they might have difficulties in activating regions of PFC related to emotional regulation (Bendall et al., 2016). This project will attempt to measure brain response to VRET in both healthy and phobic populations.

4.2. Heart rate (HR)

Increase in physiological arousal such as heart rate can be associated with abnormalities in fear inhibition function, which has been linked with the hypoactivity in the amygdala. Some studies demonstrated that the amygdala has an influence on heart rate acting through the sympathetic nervous system (Costanzo et al., 2014; Davis, 1992). Heart rate (HR) is known to increase with exposure to threatening stimuli (Abelson & Curtis, 1989). Increased HR allows blood to deliver faster and more oxygen and nutrition to the muscle in order to prepare for “fight-or-flight“(Taelman et al., 2009). The past literature showed that everyone’s HR increases when exposed to heights, but decrease over multiple exposures as a result of habituation (Holden & Barlow, 1986). In acrophobic participants, the average HR increase during exposure to heights is about 13 BMP (Emmelkamp & Felten, 1985). Because this project involved both acrophobic participants and healthy controls, the HR increase was expected to be lower for healthy controls in comparison to acrophobic participants.

Meehan (2002) in his experiment reported the significant difference in HR in healthy participants between the training room and the pit room, measured as-

∆Heart Rate = Mean Heart Rate Pit Room - Mean Heart Rate Training Room

This project uses the same HR measure in order to assess psychophysiological reaction to VR and compare the results to the outcome of Meehan's experiment. HR monitoring was employed during the second and third experiment.

4.3. Electrodermal activity (EDA)

EDA is defined as autonomic changes in the electrical properties of the skin. It arises from the amount of sweat secretion from sweat glands (Boucsein, 2012). EDA response is controlled by the sympathetic nervous system, which drives human behaviour and emotions at an unconscious level, therefore an increase of EDA amplitude is often interpreted as an increase in sympathetic nervous system activity (Lidberg & Wallin, 1981). In psychophysiological research autonomic skin response serve as an indication of emotional arousal and is used as an objective index of emotional states (Critchley, 2002) and it can be easily evoked by threatening stimuli or during fear conditioning and extinction (Faghih et al., 2015). Recently, in clinical research EDA has been used for assessment of anxiety and mood disorders (Rosebrock, Hoxha, Norris, Cacioppo, & Gollan, 2017; Vahey & Becerra, 2015), as well as to measure progress and efficacy of the treatment in ET (Wangelin & Tuerk, 2015) and VRET (Norrholm et al., 2016). Meehan (2002) in his experiment reported the significant increase in EDA (similarly to HR), in healthy participants when they entered the pit room. EDA was measured as-

∆Skin Conductance = Mean Skin Conductance Pit Room - Mean Skin Conductance Training Room

This project uses the same EDA measure in order to assess psychophysiological reaction to VR, investigate the correlation of brain activity and physiological response, and compare the results of this study to the outcome of Meehan's experiment. EDA monitoring was employed during the third experiment in this project. This is mainly because of the several technical problems with the HR monitor, which arose during the second experiment.

4.4. Fear of Heights (Acrophobia)

Acrophobia is a type of phobic anxiety disorder under the category of specific phobia according to the ICD – 10 (ICD-10, F40.241, World Health Organization). It is defined as an irrational and pathological fear of heights, which results in an excessive response and avoidance of situations involving heights, such as taking a lift, walking upstairs, climbing ladders, moving close to windows, crossing bridges, etc. All participants in this project were assessed for acrophobia using the Height Anxiety Questionnaire (HAQ) developed by Cohen (Cohen, 1977) - a self- report measure which assesses the severity of anxiety related to heights. The HAQ is a 20-item questionnaire describing situations that involve heights. Participants rated their anxiety on the 7-point scale ranging from 0 (not anxious at all) to 7 (extremely anxious). The HAQ was sent to participants 24h prior to the experiments in order to assess the severity of fear of heights (See Appendix 2).

4.5. Subjective Unit of Discomfort Scale (SUDS)

SUDS is a self-report which measures the subjective level of distress or anxiety experienced by a participant on a scale 0 (not anxious at all) to 100 (extremely anxious) (Wolpe, 1973).

4.6. Presence

The presence is a subjective feeling of "being there" often defined as "the propensity of people to respond to virtually generated sensory data as if they were real" (Sanchez-Vives & Slater, 2005). Lombard and Ditton defined presence as "the perceptual illusion of non-mediation, that occurs when a person fails to perceive or acknowledge the existence of a human-made medium in his/her communication environment and responds as he/she would if the medium were not there" (Lombard, Ditton, Grabe, & Reich, 1997).

Therefore, presence could be understood as a cognitive state in VR that results from an interplay between cognition, emotion and perception (Diemer, Alpers, Peperkorn, Shiban, & Mohlberger, 2015). To achieve presence in VR firstly the user must perceive a stimulation via their perceptual system, which relies on multimodal cues such as visuals, sounds, smells or haptics. Presence, therefore, depends on the quality of the sensory input and its cognitive processing. This is correlated with the concept of immersion (Sanchez-Vives & Slater, 2005; Slater, 2003; Slater & Lotto, 2009; Usoh, Catena, Arman, & Slater, 2000). While presence is a subjective psychological response to VR, immersion refers to the objective level of fidelity that a particular VR provides, and it relies on the technology such as display resolution, size, frame rate, refresh rate, field of view, stereoscopy (Slater, 2003). The possibility to move naturally and interact freely with VR simulation also facilitates presence (Coelho, Tichon, Hine, Wallis, & Riva, 2006). The level of immersion depends on how close the VR system resembles the real world, and therefore it impacts on the level of presence, so the higher the immersion, the higher the presence (Slater, 2003). Highly immersive VR systems, therefore, provide a better illusion of "non-mediation" enhancing engagement in VR (Price & Anderson, 2007). In order to achieve a level of presence and engagement the user needs to direct their attention to the VR environment and concentrate on the stimuli and events within a simulation (Witmer & Singer, 1998) which requires suspension of virtual disbelief – a feeling of being present in a VR, despite having the knowledge of being present in a different place in the real world (Cruz-Neira, Sandin, DeFanti, Kenyon, & Hart, 1992). The level of immersion and presence leads to an emotional response of the user to VR environment (Baños et al., 2008). For example, a high level of presence in evocative simulations (for example Pit Room, described in detail in section 7) will evoke a fear response (reflected in increased arousal) (Meehan et al., 2002). The ability to trigger an emotional response is particularly important in VRET. According to the emotional processing theory (described in chapter 2, section 6.2), the pathological fear structures can be activated by input that matches elements the fear network. The activation of the fear structure, as measured by an increased arousal, is necessary for emotional processing to occur and therefore a reduction in anxiety. (Foa et al., 1986). Therefore, facilitating emotional response to VR by increasing presence potentially leads to better treatment outcome (Parsons & Rizzo, 2008).

Presence can be measured in several ways such as questionnaires, behavioural response (for example postural sway during exposure to virtual heights), physiological measures (for example skin conductance or HR) or brain activity (Kober et al., 2012), although neuroscience of VR and presence is still in its infancy, and there is no clear evidence regarding neural networks underpinning presence in VR.

In order to measure the presence, in the second experimental study, the Slater-Usoh-Steed Questionnaire (SUS*)* presence questionnaire was used (See Appendix 3), which contains 7 items that measure presence rated on scale 1 to 7 (Usoh et al., 1999; 2000). Although there are many newer and improved presence questionnaires, the SUS was employed because it was used in original and Meehan's experiment, to compare the results and assess the quality of our simulation. However, many participants reported that they found some SUS questions confusing, therefore in the third study, the IPGroup Presence Questionnaire was used.

Igroup Presence Questionnaire (IPQ) is the 14-item scale used for measuring the subjective sense of presence in VR. Participants are asked to rate their presence on a 7-point Likert scale. The three subscales which assess different components of presence: spatial presence (consisting of five items), involvement (consisting of four items) and realism (consisting of four items). Moreover, there is one additional item to assess general presence (see Appendix 4). Unlike SUS, IPQ demonstrated its efficacy and validity in factor analysis (Schubert, Friedmann, & Regenbrecht, 2001).

4.7. Cybersickness

Simulator Sickness Questionnaire (SSQ) - is the 16- item tool that assesses possible side effects of VR exposure on a 4-point Likert scale Simulator measuring side effects of the VR simulation in the scale from 0 to 3, where 0 is coded as "none", 1 – "slight", 2 – "moderate" and 3 – "severe". A total score on the questionnaire is 48 which indicates severe symptoms and 0 indicates no symptoms (Kennedy & Lane, 1993). Cybersickness occurs as one of the unintended side effects of using VR technology. The symptoms of cybersickness are similar to motion sickness and can include: a headache, eye strain, pallor, stomach awareness, nausea, vomiting, sweating, disorientation, fatigue or drowsiness (Kennedy & Fowlkes, 1992) (see Appendix 5).

5. Sample

In this project, the primary measure was brain response. However, in neuroimaging studies, sample size and power calculation are more complicated due to the fact that the data consists tens of thousands of correlated voxels (channels), therefore applying the single-outcome power analysis may not be appropriate for estimating the sample size (Hayasaka, Peiffer, Hugenschmidt, & Laurienti, 2007). Although analyses of power and sample size methods have been established for PET (Andreasen et al., 1996; Kapur, Hussey, Wilson, & Houle, 1995; Wahl & Nahmias, 1998) and fMRI (Desmond & Glover, 2002; Friston, Holmes, & Worsley, 1999; Hayasaka et al., 2007), so far there are no tools to estimate a power and sample size for fNIRS studies. Desmond and Glover (2002) determined that a minimum twenty-four participants that were necessary to give an accurate brain activation map with a sufficient level of power (80% true positive rate) in fMRI studies. Because this project compares the results to previous VR-fMRI studies, the compromise was to refer to previous similar both fNIRS and fMRI studies in order to determine a sample size.

The first study which involved combining fNIRS and VR for neurorehabilitation obtained significant results at $p < 0.001$, employed a between-subject design with two groups – $N = 15$ and $N = 8$. Another two studies which employed within-subject design revealed statistically significant results using eight (Seraglia et al., 2011) and twenty-one healthy participants (Moro et al., 2014). Unfortunately, none of the aforementioned studies described a method for determining a sample size. Some VRET–fMRI studies involved a small sample size $N = 8$ (Moon & Lee, 2009), while another RTC study recruited more participants $N = 29$, however only eight completed post-treatment brain scan (Roy & Francis, 2010). In this project, the sample size was determined by referring to those studies.

6. Instruments and equipment

The selection of the instruments and equipment which were utilised in this project was determined by an approach to maximise the ecological validity of the design. The concept of ecological validity endeavours for the creation of experimental settings, which closely resemble real-life situations in terms of appearance and functionality. Consequently, this project implemented a combination of technologies which facilitate

the naturalness of response in terms of locomotion (whole body movement), sense of embodiment (seeing own body), freedom of interaction with a simulation, co-presence of others, without constraining participants by wires or bulky and heavy equipment.

6.1.Wearable Functional Near-Infrared Spectroscopy system - NIRSport

In order to improve the ecological validity of VRET, the choice of brain imaging method was limited to compact wireless devices, which promote freedom of movement without restraining a user by wires and cables, and consequently, facilitate naturalness of response. These might include EEG (Török et al., 2014) or fNIRS (Piper et al., 2014). Although EEG provides good temporal resolution, it has many drawbacks such as susceptibility to motion artifacts, electronic signal interference (Islam, Rastegarnia, & Yang, 2016), and low spatial resolution (Fazli et al., 2012). Despite having a lower temporal resolution than EEG, fNIRS offers a better spatial resolution allowing the localization of brain activity to specific cortical regions (Naseer & Hong, 2015). Moreover, it is potentially a more appropriate neuroimaging method for ecologically valid VR applications because of its improved tolerance for participant's movement and electronic noise from other peripheral VR devices (Irani et al., 2007; Kamran, Jeong, & Mannan, 2015). fNIRS has been implemented as a tool for monitoring brain activity underlying motor control in freely moving subjects, while maintaining data quality with minimal motion artifact (Herold et al., 2017). Moreover, the recent decade in cognitive neuroscience has demonstrated that fNIRS provides the ability to measure brain activity within the PFC (Masataka, Perlovsky, & Hiraki, 2016). This PhD employed NIRX NIRSport device (NIRSport 8-8, NIRX Medizintechnik GmbH, Berlin, Germany) (Figure 3). This is a portable, wearable, battery-operated multichannel fNIRS system consisting of 8 LED illumination sources and 8 active detection sensors, which can be arranged in 64 channels (http://nirx.net/). Each illumination diode contains two light sources of 760 nanometers (nm) and 850 nm. Each detection sensor contains a Silicon photodiode (SiPD, BPW34, Siemens, Germany). The optodes can be freely arranged in 64 channels according to the International 10-20 EEG system. NIRSport can measure brain activity in both stationary and wireless mode. Although the latter is limited regarding software flexibility, it allows free movement without tethering the participant to big recording machines.

NIRSport was used in all three experiments. The system was significantly improved after the pilot study demonstrated the impact of motion artifact on data quality. To reduce this issue, the spring-loaded grommets were purchased, which were used for the setup and montage of optodes (see appendix 1). Using NIRX spring-loaded grommets significantly reduced the subject preparation time by the setup which does not require manual parting of hair and therefore allowed the gel-free faster application. Additionally, purchased stiffing elements were used to minimise optodes displacement, distancing ring to improve participant's comfort and a mesh backpack to prevent software crashes due to the overheating of the recording device.

Figure 3 NIRSport

6.2. Immersive Projection Technology Display - Octave

In VR a method of immersion in VR might impact on the naturalness of response (Diemer, Alpers, Peperkorn, Shiban, & Mohlberger, 2015). HMDs are currently commonly used VR mediums in research and therapy (Simone, Schultheis, Rebimbas, & Millis, 2006). However, in clinical application, HMDs pose a risk of hiding the therapist from the view of the user, and therefore obscure the client-therapist relationship, which provides safety grounding in therapy (Roberts et al., 2016). Moreover, many HMDs such as Oculus Rift of Samsung Gear VR do not allow natural locomotion or have a very limited tracking range (Juan & Pérez, 2009). HTC has recently released the wireless version of Vive HMD, however, the design of the

headset, which covers eye and forehead area, would not allow for the placement of NIRS optodes on the PFC to measure brain activity within-session during VRET. On the other hand, surrounding projection technology, such as CAVE-like systems (Cruz-Neira et al., 1993) have the potential to address many of those issues, immersing a user into a surrounding room-sized VR simulation that supports both natural locomotion and interaction with others (Muhanna et al., 2015). CAVE-like systems could be particularly useful as a tool for delivering VRET with improved ecological validity as they allow natural movement within the simulation. Coehlo et al., (2008) emphasised the role of movement in acrophobia treatment. The study showed that anxiety levels were higher in patients who were physically moving during exposure to heights and that locomotion also improves the sense of presence (Slater, Steed, McCarthy, & Maringelli, 1998). Such Cave – like systems provide an opportunity for combining with portable brain imaging devices without obscuring data quality.

Octave (Figure 4) is an octagonal cave-like Immersive Projection Technology (IPT) space approximately 5 meters across which allows natural locomotion and which is big enough to allow a small group of people to mingle. Immersive Projection is delivered via the surrounding walls and floor display. The floor display allowed simulation of virtual heights, on which participants could freely walk. There are 8 surrounding wall screens 2600mm x 1969mm with resolution 1400x1050 pixels, and 96Hz refresh rate. There are 14 Christie S+3K mirage projection units of which 6 cover the floor and eight rear wall projectors. The Octave image is generated by the workstation with 2x Xeon E5-2650 giving 32 threads, 64GB memory, SSD and 4xNvidia K5000 with the k-sync card running a single desktop through 4 mosaic instances. Parallax is provided by the optical motion tracking system Vicon MX-F40 controlled by a Dell workstation running Windows 7 and Vicon Tracker 2.0 and custom designed optical markers on the glasses. The users in Octave wear XPAND 3D Shutter Glasses Lite RF (X105-RF-X1) with the shuttering frequency 96 Hz which are synchronized with the screen displays. This tracks the position and orientation of the user's head so that the system refreshes the displays according to head orientation and position, allowing for the creation of head-movement parallax. The simulation is updated to the single user wearing the glasses, although other people can present within Octave space passively participating in the simulation. This can potentially increase the risk of cybersickness in some users due to the sensory mismatch. On the other

hand, the design of glasses worn in Octave allows for measuring the PFC response during VRET. The glasses have a lightweight design, therefore NIRSCap could be worn without a risk of optode displacement. This could not be achieved with current HMDs which are designed in a way that would not allow for measuring brain activity from the PFC. The immersive acoustic system is controlled by Mac Pro with 2 x Intel ® Xeon® CPU X5570 @ 2.93 GHz and 3.06 GHz, 32 Gb RAM running Windows 7 (64-bit). Octave was used in all three experiments. While the hardware was not changed between each of experiment, the software was updated in order to improve the simulation.

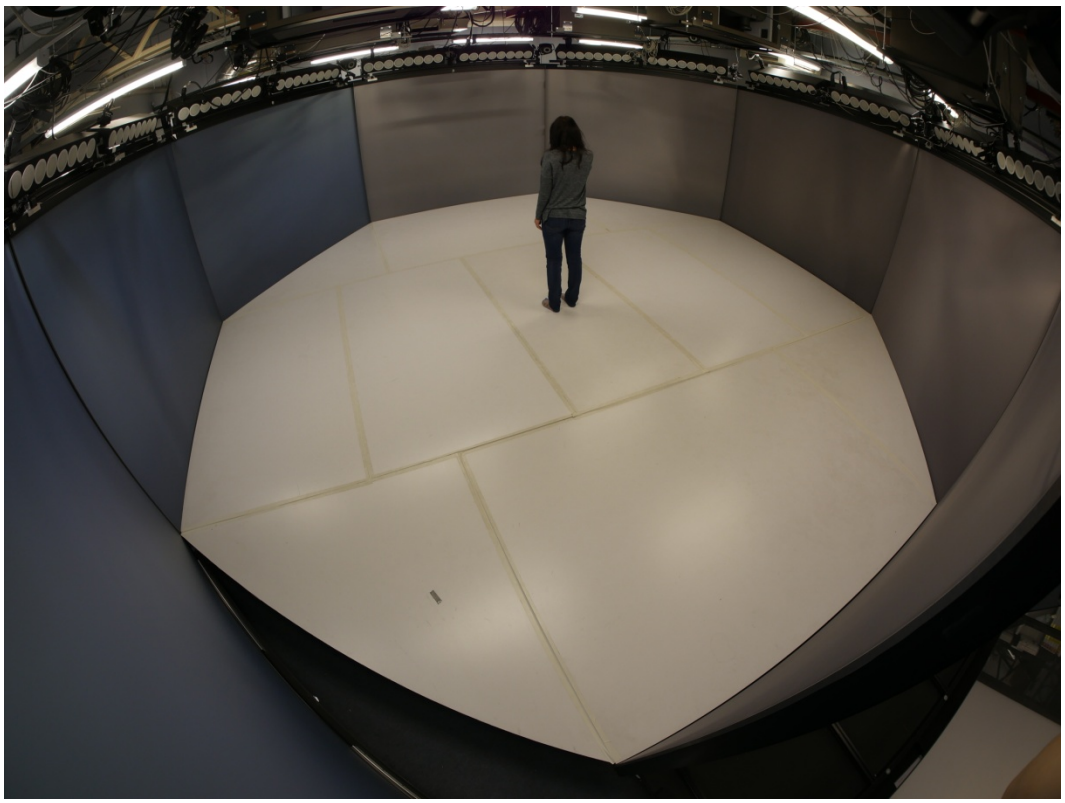

Figure 4 IPT Octave Laboratory octagonal configuration.

6.3. Physiological monitoring module – Zephyr Bioharness

Wireless physiological monitoring systems provide information about physiological arousal which can be indicative of emotional states. The signals can be recorded or monitored in real-time during movement and performance. Bioharness (Zephyr Technology, Annapolis, US) is compact and wireless physiological

monitoring device that consists of an adjustable fabric chest strap worn around the chest and attached lightweight transmitter unit that captures and transfers physiological data on the wearer via mobile and fixed data networks (Figure 5). Bioharness was used in all three experiments to record the participant's heart rate during exposure to virtual heights.

Figure 5 Zephyr Bioharness Heart Rate Monitor

6.4.NeuLog EduLogger Galvanic Skin Response (GSR/SCR) Sensor

Similar to Bioharness, EduLogger is a wireless, portable physiological monitoring device that measures the conductivity of the skin, in particular of fingers in moving subjects. The device includes the USB module which can be attached to PC, tablet or mobile phone, WiFi Module which allows data transmission across the network, battery module which allows wireless data acquisition and GSR module with 10 nS resolution and sampling rate 20 S/sec., with two GSR probes attached by means of durable rubber-coated wires and two white Velcro finger connectors. Electrodes are attached to the index and ring fingers of the non-dominant hand to improve the comfort of participants (Figure 6).

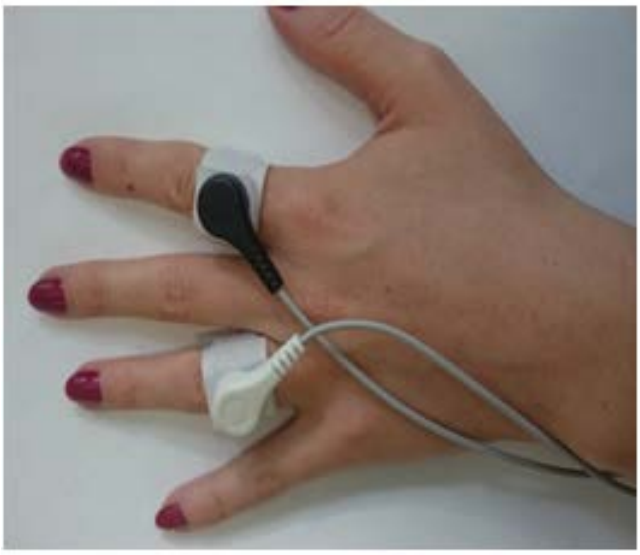

Figure 6 EduLogger GSR Sensor electrodes placement

7. The Pit Room Simulation

The Pit Room is the classic presence experiment developed by Mel Slater and colleagues in 1995 (Slater et al., 1995; Usoh et al., 1999). The experiment was replicated by other researchers in many presence studies. The pit room experiment consists of two rooms – the training room and the pit room. The training room looks like a normal room with furniture (tables, chairs, lamps etc.) walls, and normal floor. The pit room has no floor, but a wooden plank placed above the furnished room 6 meters below (Figure 7).

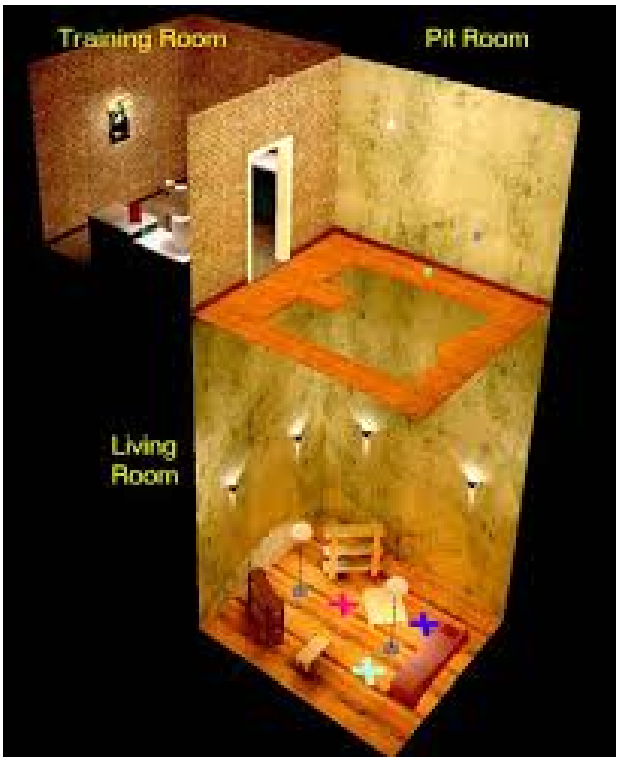

Figure 7 The original version of Pit Room simulation

In the pit room, a participant can walk on the wooden plank looking down to the pit room. Meehan et al. used the pit room experiment in order to measure physiological response in healthy participants in three presence studies. Heart rate, skin conductance and skin temperature were measured when participants were performing a task in the training room and in the pit room. The experiment was conducted under three conditions – frame rate (investigated if the higher frame rate increases the feeling of presence), passive haptics (investigated if adding passive haptics – physical wooden ledge, increases the feeling of presence), and multiple exposures (investigated if the feeling of presence decreases with multiple exposures). In all experiments, participants could walk around in both rooms. The results demonstrated that in the higher frame rate impacts on presence and anxiety. Participants displayed a higher level of arousal when they were in the pit room, in comparison to the training room. Also adding passive haptic to the experiment significantly increased measures of heart rate, skin conductance and skin temperature in the pit room. Unfortunately, the heart rate was not measured in the multiple exposures experiment; however, the study showed that the presence, anxiety and physiological measures (skin conductance and skin temperature) decreased from the first to the second exposure (Meehan et al., 2002). In

2005 Meehan et al., used the pit room in the study which investigated the impact of latency on presence, anxiety and arousal. There were two experimental conditions – low latency and high latency. Although the study did not find an effect of latency, there was a significant difference in the heart rate and skin conductance between the training room and the pit room (Meehan, Razzaque, Insko, Whitton, & Brooks, 2005).

Zimmons and Panter have used the pit room experiment in 2003 in the study, which investigated the influence of rendering quality on the presence and task performance in VR. The experiment involved five conditions – low texture resolution, high texture resolution, low-fidelity lighting quality, high-fidelity lighting quality, and the control condition rendered with the black-white texture. Participants were asked to drop objects to the pit room while their physiological reactions were measured. The result found no difference between all of five conditions, however, there was a significant increase in heart rate and skin conductance when participants performed a task in the pit room in comparison to the training room (Zimmons & Panter, 2003).

The pit room experiment and its modifications were later used by many other groups in studies investigating presence (Khanna, Yu, Mortensen, & Slater, 2006; Phillips et al., 2012; Slater et al., 2009), self-embodiment (Ries, Interrante, Kaeding, & Anderson, 2008) and balance (Cleworth et al., 2012) and presence in augmented reality (Juan & Prez, 2010).

This project uses the Pit Room experiment for three different reasons:

- It is the classic VR experiment previously used by many researchers, therefore its efficacy well documented
- Previous studies demonstrated that the pit room experiment triggers an emotional response (measured as an increase in physiological reaction) even in healthy participants
- The scenario and task encourage movement, which improves the ecological validity and the naturalness of response, therefore it allows for testing the integration of the brain imaging module physiological monitoring module and virtual reality space in which people can freely move

This project extends the classic Meehan's Pit Room experiment which measured physiological response, by adding another variable by measuring the brain response.

8. Data analysis

8.1. Statistical Parametric Mapping (SPM)

This PhD project uses the Statistical Parametric Mapping approach in order to analyse the fNIRS data. SPM is the standard statistical technique used in analysing functional brain images. SPM was introduced by Karl Friston from UCL and it is currently considered as a gold standard for fMRI data analysis (Friston et al., 1995; Friston, 2007; Worsley & Friston, 1995).

SPM analysis refers to the construction and assessment of spatially extended statistical processes to test a hypothesis about regionally specific effects in the functional brain images (Friston et al., 1995). SPM uses general linear model (GLM) which explains brain signal as a linear combination of task-related explanatory variables (regressors) and the non-task-related error term. This approach allows a better method to avoid false positives/negatives in the study because in GLM physiological signals are additional regressors (Tachtsidis & Scholkmann, 2016). Moreover, some research groups demonstrated that GLM approach is superior regarding its statistical power when compared to a standard approach, which uses block averages by calculating mean values for each experimental condition (Plichta, Heinzel, Ehlis, Pauli, & Fallgatter, 2007; Schecklmann, Ehlis, Plichta, & Fallgatter, 2008).

The algorithm implemented in SPM estimates brain activity voxel by voxel using the univariate statistical parametric test to assess brain response under different experimental conditions. The SPM analysis is carried out in a few steps. Firstly, the data is preprocessed in order to remove noise, motion artifacts, align and normalise images. The next step is the model estimation, which estimates how good the model or hypothesis fit the actual brain data using multiple regression. Each experimental condition is modelled in the design matrix, which is then assessed by SPM by convolving the design matrix with the hemodynamic response function (Figure 8). The model estimation results in beta weight values for each condition at each voxel.

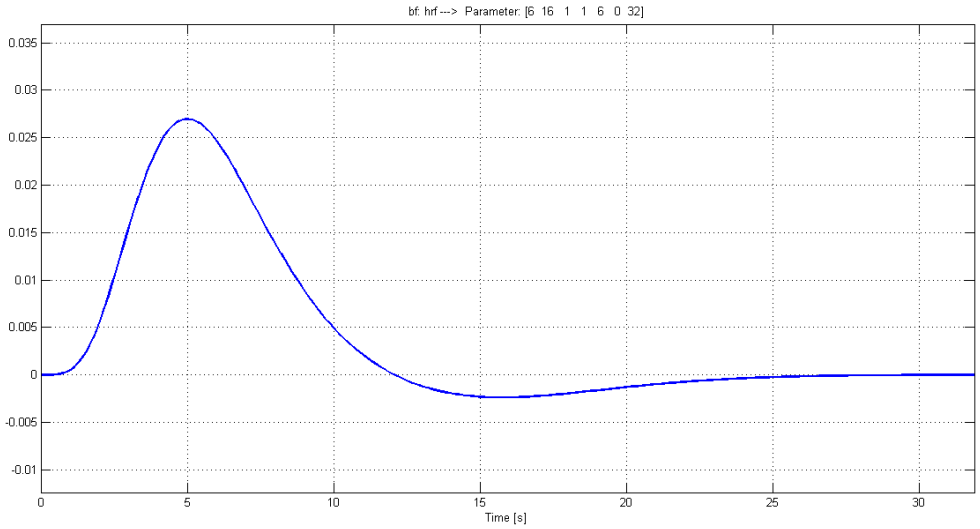

Figure 8 Canonical Hemodynamic Response Function (HRF). The hemodynamic response starts to rise after 2 seconds, picks 4-6 sec after the onset of neural activity and decreases to the baseline within 30 seconds. Taken from NIRSLab v2014.

The next step is the contrast analysis. At this step, SPM uses parameter estimates and calculates the sum of beta weights and identifies which voxel has a greater contribution to the particular brain activity under a particular experimental condition. SPM contrast vector is the core concept of SPM analysis. SPM contrast compares between activation levels evoked by experimental/independent variables conditions calculating appropriate statistics and assigns every voxel a t- or f-score. This computation results in statistical parameter maps (t– or f- maps) which are simply the distribution of parameters from each voxel assembled onto a 3d images which are expressed in t- or f- scores. The t-score is defined as the weighting coefficient to the HRF and its standard error (Friston et al., 1995; Friston, 2007). Therefore, a high t-score could be interpreted as a high correlation between brain signal and modelled HRF. In SPM thresholded t-maps display only those voxels which were active at the certain probability p-threshold therefore significantly influenced by the experimental condition. The GLM SPM analysis is carried out on two levels. On the first level analysis, SPM computations are performed for each individual subject. On the second level analysis, SPM uses statistics from the first level ("within-subject") analysis in order to perform a group ("between-subjects") analysis (Friston, 2007). Some researchers also perform the third – level analysis – Region Of Interest (ROI) analysis. ROI analysis is performed after channel/voxel-wise analysis to look further into

specific regions of interest in the brain in order to explore the data. ROI analysis can be used in cases when the voxel-wise analysis revealed no significant results, in order to investigate why there was no activation (Poldrack, 2007). Each brain scan contains thousands of data points per each subject. Therefore ROI analysis allows to overcome the problem of multiple comparisons in fMRI data analysis and thus control for type I errors (Nieto-Castanon, Ghosh, Tourville, & Guenther, 2003). ROIs can be defined a-priori or a-posteriori, depending on experimental hypothesis or experimental design. The signal within ROI is calculated by averaging the signal across the voxels predefined for the specific ROI and then instigated using an appropriate statistical test (Poldrack, 2007).

8.2. Statistical Parametric Mapping for Functional Near-Infrared Spectroscopy analysis

Regarding fNIRS, the most common approach for data analysis is t-test or ANOVA which calculates average values for a specific task. However, this approach does not assume fixed time course of the hemodynamic response (Jong Chul Ye, Tak, Jang, Jung, & Jang, 2009). SPM for fNIRS was for the first time introduced in 2009 by Ye et al (Jong Chul Ye et al., 2009), and currently, there is an increasing number of the research groups using NIRS-SPM (Tak & Ye, 2014).

This project uses NIRS-SPM for a few reasons. Firstly, because in functional neuroimaging research, SPM has demonstrated a greater statistical power than other approaches. Secondly, because it provides better tools for noise and motion correction by using GLM approach. Thirdly, because it takes into account the shape of the hemodynamic response function. Finally, because SPM was used in the majority of fMRI studies which investigated the neural basis of fear inhibition and learning. This project aims to compare and reaffirm the results obtained from previous brain imaging studies. However, this project uses equipment and methods, which potentially are more ecologically valid and therefore facilitate the naturalness of the response and movement.

9. Ethical considerations

This project was a subject of many ethical issues. As mentioned earlier, initially the research problem was focusing on VRET for PTSD, however, on the second year

of this PhD, the focus was shifted to VRET for simple phobias. The main ethical consideration was related to the complexity of PTSD, which involves four clusters of symptoms: intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity (American Psychiatric Association, 2013), therefore PTSD sufferers might have many potential triggers that can bring up symptoms, such as certain sights, sounds, smells, thoughts feelings or situations (Rauch et al., 2012). This could pose a potential risk to patients when considering that the novel combination of technologies employed in this project has not been tested yet. Therefore to test the technology, after receiving several feedbacks and suggestions from the Ethics Committee, the project shifted the focus to specific phobia, which involves usually fear of specific objects or situations (American Psychiatric Association, 2013), in order to decrease a risk of potential negative effects of VR on participants. At first, the project recruited healthy volunteers in order to evaluate the feasibility of the design and test adequacy and compatibility of the instruments used in this project in terms of signal interference, signal noise and equipment compatibility, comfort, utility and safety. The pit room simulation used in this project might potentially trigger an emotional response (Meehan et al., 2002), therefore the project involved a clinical psychologist to assess a potential risk of distress which could be caused by both simulation and equipment. The risk assessment was carried out on 22/01/2016 by Dr Linda Dubrow-Marshall, who is a Counselling and Clinical Psychologist, HCPC Registered, who stated that the study represents a very low risk of causing psychological distress (see Appendix 9). Moreover, a participant with a moderate fear of heights was invited to provide a feedback and suggestions on the experiment prior to data collection. The consultant scored 70 on the HA Questionnaire which is towards the end of the moderate level on the scale. She assessed the experiment and provided the feedback. The consultant stated that she considered the technology and simulation to be safe and effective for triggering low-level arousal. She did not experience any discomfort associated with brain measuring module or display technology (scoring 0 – no symptoms at all on the Simulator Sickness Questionnaire). The consultant stated during the interview that the technology would be useful for the treatment of fear of heights, and that could help her to overcome fear of heights if she stayed longer in the simulation or asked to return for multiple sessions. She stated that although she experienced the impression of height, she enjoyed the experience and found it interesting.

Before recruiting participants with acrophobia, the project demonstrated that the technology was safe in two studies conducted on healthy participants. Moreover, to minimise potential risks, this project recruited a non-clinical population with moderate acrophobia. All participants were provided with the Participant Information Sheet (PIS) a minimum of 24 hours prior to consenting to participate in the study, describing the nature of the experiment, potential risk and sufficient information to decide whether they want to take a part in the study; they also were informed that they can withdraw at any time during the experiment. All participants were informed that in case they would experience any discomfort or distress, the experiment would be terminated immediately and the participant would be given a debrief by the researcher. If the distress or discomfort continued, the researcher would contact security who are now the central point of contact for both physical and psychological first aid, and/or will contact student life for further support. These were provided on the Participant Information Sheet.

With the exception of photographs and videos – data from which a participant could have been potentially recognised, all data was completely anonymous. Participants were photographed or video-recorded only if they have given their consent. The Participant Information Sheet explained that the video data might be used for data analysis or to promote and explain our research on seminars or conferences. Level of consent was determined and selected by the participant through text boxes on the consent form.

Another ethical issue that arose during this project was related to potential health risks. Because VR can trigger a seizure, the project excluded participant with epilepsy, history of seizures or blackouts (Nichols & Patel, 2002). Furthermore, wearing fNIRS device can potentially cause slight discomfort and headaches in some participants, therefore the project excluded participants who suffer migraines. Additionally, the time of wearing NIRSport Cap was limited to maximum 30 minutes (including set-up and data acquisition).

Chapter 5 Experiment I: Pilot study: Testing a potential of combining Functional Near-Infrared Spectroscopy (fNIRS) with Immersive Projection Technology (IPT)

1. Introduction

This chapter describes the research protocol for the pilot study. At first, the aim and objectives of this pilot study are described, next the chapter describes the research design and materials used in the pilot study, the approach taken in data analysis and the results.

This pilot study recruited eleven volunteers (N = 11) to walk on the virtual plank approximately 6 meters above the floor. During the task, a brain oxygenation changes were recorded from the prefrontal cortex as a neural index of fear inhibition and emotional reappraisal, and heart rate as a physiological index of the fear response.

2. Methods

2.1. Aims and objectives

The aim of the pilot study was to measure the PFC brain response to virtual threatening stimuli in healthy controls, indicative with fear inhibition and emotional reappraisal while avoiding equipment that might excessively impact on the naturalness of the response. The objective of this study was to test the feasibility of the protocol in terms of the design, integration of technology, utility, signal-to-noise ratio and comfort. This pilot study was performed in order to debug the simulation, assess the equipment, and experimental procedures for the following main studies.

This project employed the virtual reality display system in which participants can move, while the neural index of the fear inhibition and physiological index of fear can be measured. However, the greater movement implies the risk that equipment might dislodge, especially the displacement of the measuring sensors may introduce motion artifacts making the data difficult to analyse and interpret. Moreover, infrared signals from the equipment might interfere, introducing instrumental noise to the data.

Combining various technologies could be also uncomfortable for participants, therefore this pilot study was also designed in order to determine the implementation of the devices while maintaining the participant's comfort.

In order to achieve these aims and objectives, this pilot study introduces integration of the brain imaging module (NIRSport), physiological monitoring module (Bioharness) and virtual reality space (Octave), in which people can freely move with others. The novelty of this project is that the equipment promotes natural movement around the VR space.

2.2. Research question

The pilot study aimed to answer the question whether the PFC brain activity indicative of fear inhibition and emotional reappraisal can be measured in VR with improved ecological validity through a combination of wireless fNIRS and IPT without impacting on the naturalness of response? If so, what are the neural correlates of fear inhibition in ecologically valid VR healthy in participants? Can an emotional response be triggered in ecologically valid VR?

2.3. Hypothesis

This pilot study tested three experimental hypothesises: (1) participants exposed to the threatening virtual stimuli (pit room) would show an increased oxygenation in the MPFC and DLPFC in contrast to the safety virtual stimuli (training room), (2) participants exposed to the threatening virtual stimuli (pit room) would show an increased heart rate in contrast to the safety virtual stimuli (training room), (3) activity in the MPFC and DLPF would be negatively correlated with the HR.

Moreover, the purpose of this pilot study was to assess the integration of technology used in this PhD project to determine the acceptable level of movement without introducing motion artifacts and noise to the data.

In this pilot study two response variables/DV were measured:

- HbO - mean brain oxygenation changes = mean HbO (pit) – mean HbO (training) – measured by SPM contrast vector

- Δ HR – mean HR= mean HR (pit) – Mean HR (training)

The explanatory variable/IV was:

Conditions – training room and pit room.

2.4. Instruments and equipment

Octave

Immersive Projection Technology (IPT) Octave – Octave (Figure 9) is an octagonal cave-like Immersive Projection Technology (IPT) space approximately 5 meters across, which is big enough to allow a small group of people to mingle. Immersive Projection is delivered via the surrounding walls and floor display. There are 8 surrounding wall screens 2600mm x 1969mm with resolution 1400x1050 pixels, and 96Hz refresh rate. There are 14 Christie S+3K mirage projection units of which 6 cover the floor and eight rear wall projectors. Octave image is generated by the workstation with 2x Xeon E5-2650 giving 32 threads, 64GB memory, SSD and 4xNvidia K5000 with k-sync card running a single desktop through 4 mosaic instances. Parallax is provided by the optical motion tracking system Vicon MX-F40 controlled by Dell workstation running Windows 7 and Vicon Tracker 2.0 and custom designed optical markers on the glasses. The users in Octave wear XPAND 3D Shutter Glasses Lite RF (X105-RF-X1) with the shuttering frequency 96 Hz which are synchronized with the screen displays. This tracks the position and orientation of the user's head so that the system refreshes the displays according to head orientation and position, allowing for the creation of head-movement parallax. The immersive acoustic system is controlled by Mac Pro with 2 x Intel ® Xeon® CPU X5570 @ 2.93 GHz and 3.06 GHz, 32 Gb RAM running Windows 7 (64-bit)

Figure 9 Participant present in Octave with the researcher (Pilot study)

Functional Near-Infrared Spectroscopy (fNIRS) NIRSport

Functional Near-Infrared Spectroscopy (fNIRS) – In order to measure changes in cerebellar oxygenation changes NIRSport (NIRsPORT 8-8, NIRX Medizintechnik GmbH, Berlin, Germany) was used. is a portable, wearable, battery-operated multichannel fNIRS dual-wavelength system consisting of 8 LED illumination sources and 8 active detection sensors, which can be arranged in 64 channels (http://nirx.net/) (see Figure 9). Each illumination diode contains two light sources of 760 nm and 850 nm. Each detection sensor contains a Silicon photodiode (SiPD, BPW34, Siemens, Germany). The optodes can be freely arranged in 64 channels according to the International 10-20 EEG system. The system is operated by main data battery – operated acquisition instrument. The data is acquired and transferred to a lightweight laptop. The main instrument and controlling notebook can be worn in a backpack allowing freedom of movement during data acquisition.

Emitters were placed on positions F3, AF7, AF3, Fz, Fpz, AF4, F4, AF8, while detectors were placed on positions F5, F1, Fp1, AFz, F2, Fp2, and F6. Twenty channels were set up covering prefrontal cortex (Figure 10). The source-detector distance was 3 cm. Optodes were placed on the participant's head using EasyCap (http://easycap.brainproducts.com/) relative to the international 10/20 system (Jasper, 1958)

The data was acquired with the NIRStar acquisition Software (version 2014, NIRx Medical Technologies LLC) running on Windows 7 (64-bit) laptop with Intel® Core™ i5-4200 CPU @ 1.60 GHz 2.30 GHz with 4.00 GB RAM. The blood oxygenation was measured at two near infra-red light wavelengths of 760nm and 850nm, with the sampling rate 7.81 Hz.

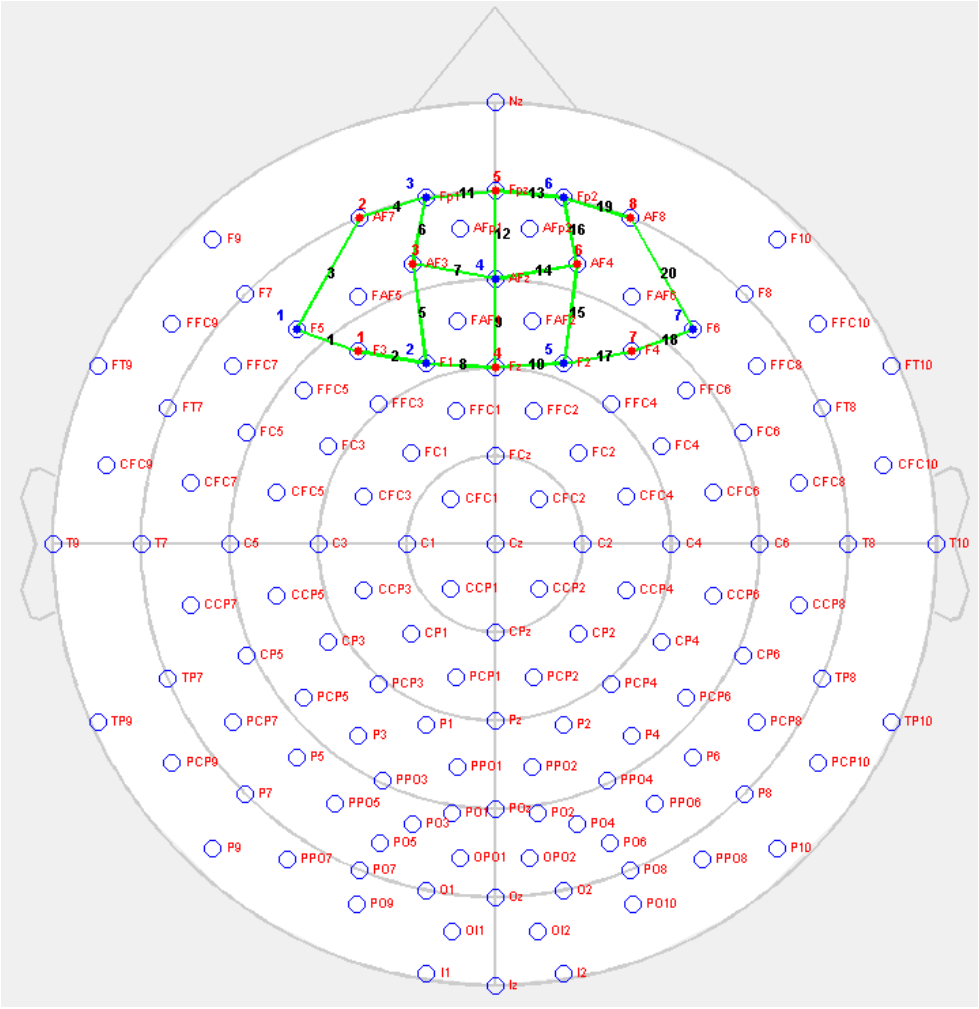

Figure 10 fNIRS optode placement on prefrontal cortex (red=source, blue=detector, green=channel)

Bioharness

Bioharness (Zephyr Technology, Annapolis, US) is a compact and wireless physiological monitoring device that consists of an adjustable fabric chest strap and attached transmitter unit that captures and transfers physiological data on the wearer via mobile and fixed data networks. As an indicator of the fear response, heart rate data was recorded with the sampling rate 250 Hz.

Network

Network – 10GigE Fibre, 1GiGE and wireless g networking was used to transmit the data (event markers) between machines controlling simulation and data acquisition devices. The researcher placed event markers manually over the network at the onset of each experimental condition. Event markers are necessary for event-related data analysis. The data was transferred over the network using HotKeyNet (http://www.hotkeynet.com/). HotKeyNet is a multiboxing software that allows controlling several programs on different machines/client simultaneously over the network from one master/server machine. The Octave PC was set up as the server, whilst machines controlling fNIRS and HR data acquisition were set up as the clients using custom code.

2.5. Materials and methods

Participants

Eleven healthy participants recruited from the University of Salford staff and fellow PhD students participated in this experiment (4 females and 7 males, mean age 33.18, SD = 4.72). Unfortunately, due to the technical difficulties, software crashes and motion artifact, the data from six participants were excluded from the analysis.

Scenario

The scenario was created using Unity 4.3.3 game engine (academic version Unity 64-bit) (https://unity3d.com/). The simulation in Octave is supported by MiddleVR (version 1.4.2) for unity (http://www.middlevr.com/middlevr-for-unity/). MiddleVR is a middleware solution that allows for a connection of VR peripheral devices such as tracking, projectors and controllers.

The VR environment consisted of two rooms: the training room, which looked like a normal room with a floor and furniture, where participants familiarised themselves with

the virtual environment and trained the task; and the pit room which had no floor but a wooden ledge on which participants stood, walked and looked down onto the pit room (which looks like an ordinary room with floor and furniture) approximately 6m below the plank (Figure 11).

The video showing the simulation can be found here –

https://youtu.be/xoithELXtX8

https://youtu.be/nxQjhUH5-N0

Figure 11 Pilot study - Pit Room simulation – view into the pit room (left), view in the training room (right)

Task

Prior to the experiment participants were allowed to familiarise themselves with the virtual environment and practice the task for about 5 minutes. This strategy also served in order to minimise the "novelty effect" – the risk that participants would show increased physiological response because they saw something new. This is the standard approach to minimise the impact of confounding variables. Following practice and familiarisation participants returned to the preparation area, and they were fitted with the Bioharness. Then the Easycap made of elastic fabric was put on a participant's head and then 16 optodes (8 sources and 8 detectors) were placed on the participant's scalp. In order to ensure an optimal connection and signal measurement, the water-based conductive gel was used in order to part the hair using a wooden stick. The whole procedure could take about 30 minutes, depending on the thickness of the participant's hair. The fNIRS system was then calibrated for the optimal amplitude and signal-to-noise ratio. The quality of the

optical densities was then assessed visually by the researcher. If the level of the noise in a data was too high, the researcher readjusted the noisy optode ensuring optimal contact with the scalp.

After the data acquisition was assessed and met satisfactory quality criteria, the researcher set up the software for the data acquisition. The retaining cap which shields the ambient light and reduces the risk of optode displacement was placed over the Easycap. The data was recorded using a battery-operated fNIRS system which is powered by the laptop and the data is saved and stored on the hard drive. The fNIRS battery and the laptop were placed in the backpack, which must be worn by a participant during the whole experimental session.

After the preparation, participants were lead to Octave and asked to perform a simple walking task. In the training room participant walked on the floor, and in the pit room participant walked on the virtual plank. Although the original pit room experiment involved carrying an object from one room to another (Meehan et al., 2002), this experiment employed only a simple walking task (Figure 12). This approach was taken in order to control for the confounding variables.

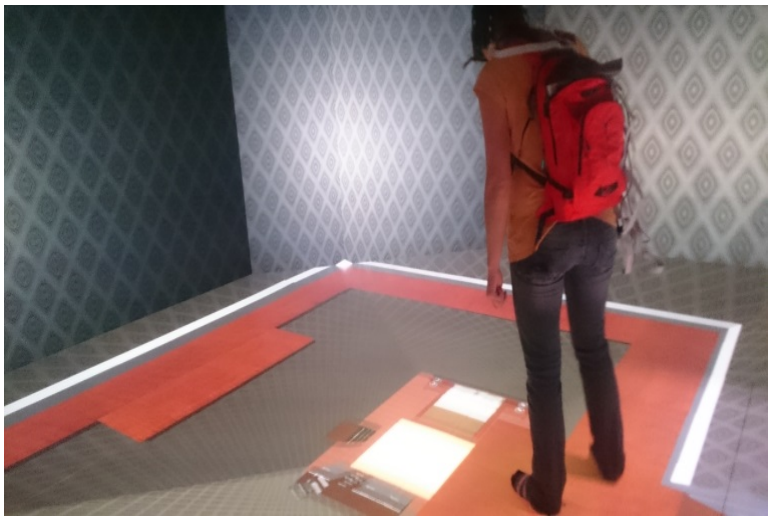

Figure 12 Participant looking down into the pit room

2.6. Design

The pilot study employed a within-participants design. Each participant performed the task under the same two experimental conditions – training room and pit room. There were 10 trials, each lasting 30 seconds (10 = 5 x training room+5 x pit room). 30 seconds baseline was recorded prior to the first stimuli onset when participants were instructed to

step on the actual floor in the training room, stay still, close their eyes, clear their mind and relax. After the baseline participants heard pre-recorded audio instructions generated in a random order, to move either to the training room or move to the pit room. The whole experiment lasted 330 seconds. The study employed an event-related design where participants spent 30 seconds in the training room and 30 seconds in the pit room in random order. There were no breaks between conditions.

The researcher was present in the VR area during the whole experiment placing the event markers on the data manually every 30 seconds to indicate order and onsets of trials. This approach was taken in order to minimise the number of confounding variables such as pressing a mouse button or using the controller which could potentially involve additional attentional resources or activity related to the motor performance. The data sent over the network using HotKeyNet – the multiboxing software that allows sending the data between multiple machines by placing markers on the fNIRS raw time series.

3. Data analysis

3.1. fNIRS data analysis

Signal-To-Noise (SNR) estimation

Data was first visually inspected in order to identify noisy channels and trials during a calibration process. Due to the motion artifacts throughout the whole time series, four participants were excluded from the data analysis. Another two were removed due to a software crash. The remaining data from 5 participants was assessed for a period of time containing motion artifacts prior to the experimental session which was manually removed. The signal quality was calculated in Octave in order to assess the signal interference between NIRSport and Vicon tracking system. The procedure was performed with both tracking system ON and OFF for each participant. The Quality Scale tool in NIRStar was used to analyse signal quality after the calibration procedure for each participant. The quality scale provides information about a variety of parameters that affect the signal quality such as gains, signal level, noise level and hemodynamic index. These parameters are calculated based using standard deviations of the extrapolated HbO signal due to a higher amplitude. The quality scale presents the quality of the signal using a colour bar (Figure 13). The example signal quality test is shown in Figure 14.

Signal Quality	NScout Gain [10^x]	NSport Gain [10^x]	Level [V]	Noise [%]
Excellent	1 - 6	0 - 2	0.09 - 1.40	< 2.5
Acceptable	7	3	0.03 - 0.09 1.40 - 2.50	2.5 - 7.5
Critical	0 8	-	0.01 - 0.03 > 2.50	> 7.5
Lost	-	-	< 0.01	-

Figure 13 The signal quality scale indicator (taken from NIRStar Manual)

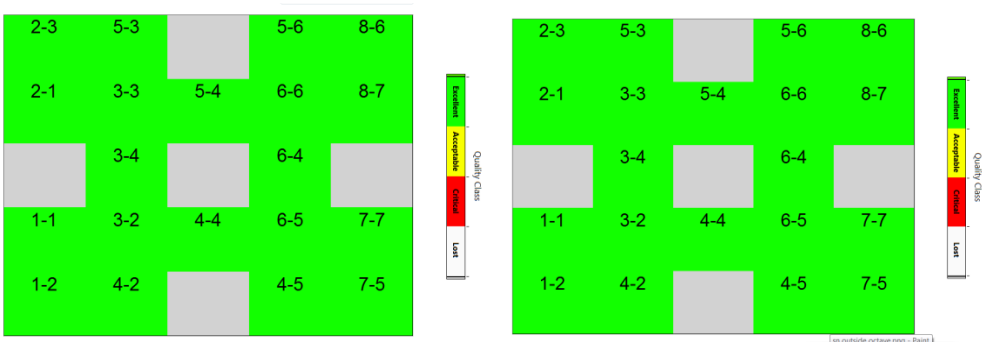

Figure 14 Example fNIRS signal quality test in Octave with Vicon tracking on (left) and off (right).

The next step involved calculating the coefficient of variation (CV) offline in order to quantify the signal-to-noise for the raw time series for each participant and each channel for both NIRS wavelengths (Schmitz et al., 2005). CV is mathematically defined as 100 times the standard deviation divided by the mean value, where the standard deviation and mean are computed from all the raw-data values in the measurement time series. NIRSLab software provides a Raw Data Checking feature (Figure 15) which allows identifying the noisy channels. fNIRS channels were removed when respective channels exceeded a variation coefficient of 15% (Piper et al., 2014).

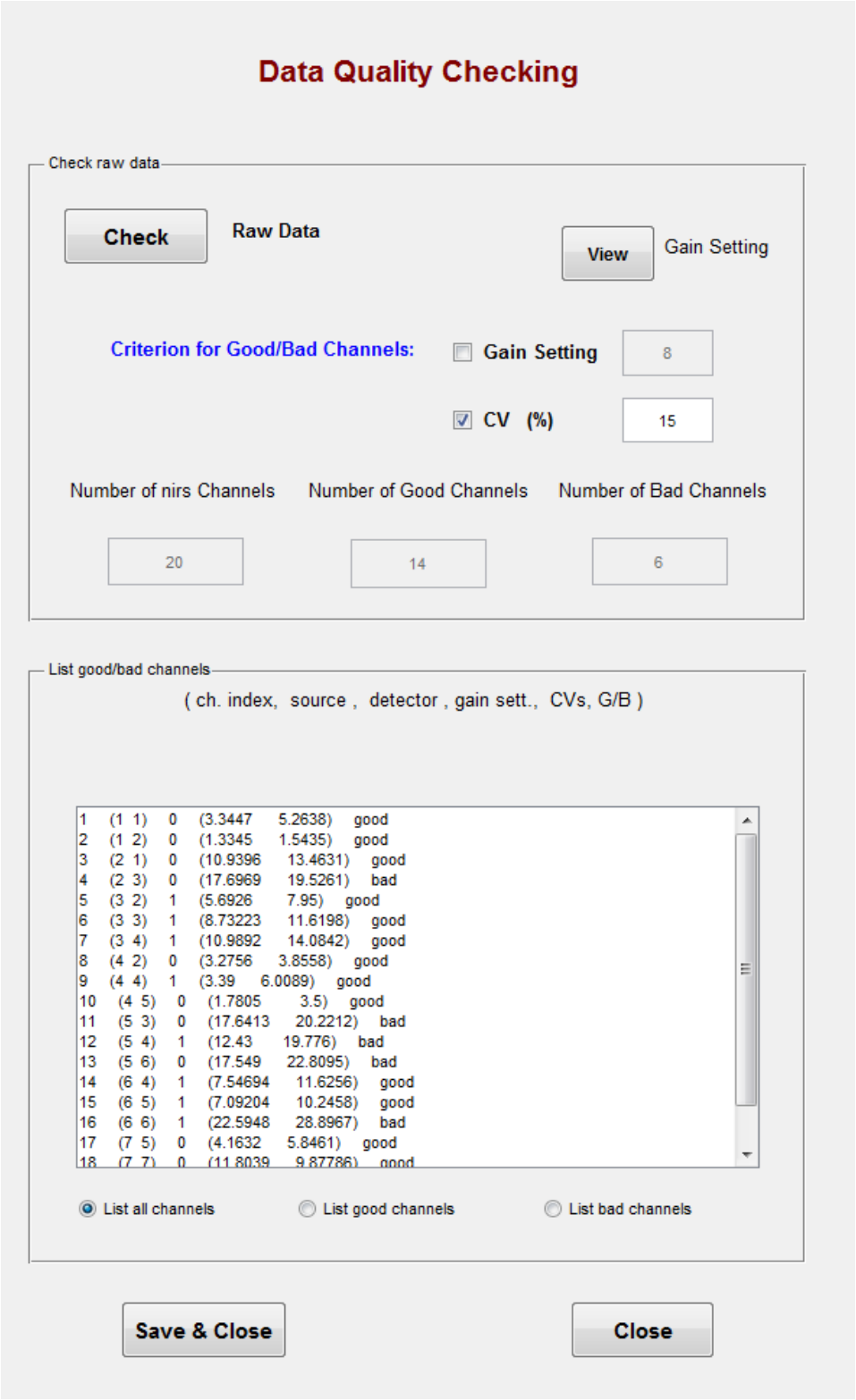

Figure 15 Raw Data Quality Checking Tool for calculating STN in NIRS data. Example SNR test

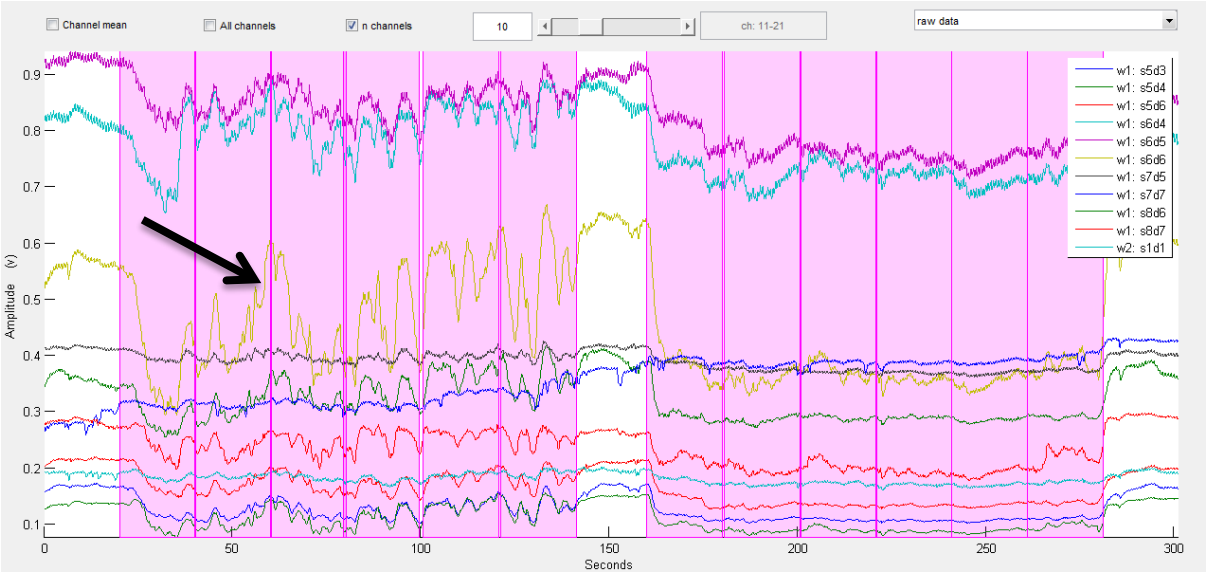

Figure 16 Example of removed noisy channels (sudden spikes in time series) contaminated by motion artifacts

Preprocessing

The remaining fNIRS data were preprocessed and analysed using NIRSLab (NIRSLab version 2014 NIRX Medical Technologies). Optical densities were converted to the average haemoglobin concentration changes using the modified Beer-Lambert law (Cope & Delpy, 1988) for each channel and each subject. Oxy- (HbO) and deoxy – (HbR) and total (HbT) haemoglobin time series were band-pass filtered with low cutoff frequency 0.01 Hz and high cutoff frequency 0.2 Hz to remove drifts, respiratory and cardiac signals from a raw NIRS data. A differential pathlength factor of 7.25 for 760nm and 6.38 for 850nm was applied (Essenpreis et al., 1993). Molar extinction coefficients ε for HbO at 760 nm = 1486.5865 cm−1/M and 850 nm = 2526.391 cm−1/M, were applied from W. B.Gratzer, Med.Res. Council Labs, Holly Hill, London and N. Kollias, Wellman Laboratories, Harvard Medical School, Boston. Raw data was converted to the average haemoglobin concentration changes using the modified Beer-Lambert law for each channel, each trial, each block and each subject

GLM

Statistical data analysis was performed using NIRS-SPM (SPM 8) analysis tool implemented in NIRSLab in order to identify regions of the brain activated during the virtual height exposure. Data were modelled with GLM.

1st level analysis

The first level design matrix containing two regressors modelling two conditions (training and pit) was generated by convolving with the canonical hemodynamic response function provided by SPM8 (Friston et al., 1996). Discrete cosine transform basis function was used for temporal filtering and precoloring HRF was used for the serial correlations. t-contrasts were then created for HbO concentration changes to generate statistical parametric maps of activation for two regressors: training and pit, for each channel, each condition and each subject. SPM t-maps were generated by using two contrasts: training versus pit and pit versus training and thresholded at $p < 0.05$ (corrected). To control the family-wise error rate, NIRS-SPM implements an algorithm for Sun's tube formula and Lipschitz-Killing curvature based expected Euler characteristics for p-value correction (Tak, 2009; Ye, Tak, Jang, Jung, & Jang, 2009).

2nd level analysis

At the group analysis SPM group HbO t–statistics were calculated to identify the channel significantly activated by exposure to virtual heights with the significance level threshold set at $p < 0.5$ (corrected) according to the false discovery rate method FDR used in fMRI studies (Singh & Dan, 2006). The estimated anatomical location of each channel was determined using anatomical locations of international 10-10 system cortical projections of EEG sensors (Koessler et al., 2009; Okamoto & Dan, 2005).

ROI analysis

At the 3rd level analysis, a Region Of Interest analysis (ROI) was performed, which is a common practice in neuroimaging studies after channel/voxel-wise analysis to look further into specific regions of interest in the brain (Poldrack, 2007). Because there was no significant difference in total HbO between blocks, ROIs were averaged across all the blocks to investigate which brain area was mostly activated during the task and whether the activity was correlated with other explanatory variables. Using the probabilistic assessment of cortical projection sensors underlying 10-20 system anatomical surface locations (Koessler et al., 2009; Okamoto et al., 2004). Four ROIs - left DLPFC, right DLPFC, left MPFC and right MPFC were defined on the basis of BA atlas (Brodmann, 1909) to be represented by channels: 1, 3, 5 and 7 (L DLPFC); 14, 15, 18 and 20 (R DLPFC); 6 and 11 (L MPFC); 13, and 16 (R MPFC) respectively. The HbO beta-

estimates from those channels were extracted for each subject and each condition and then averaged within each of the ROIs across the selected channels and blocks (Poldrack, 2007). Next, a student t-test was performed on each ROI separately. This approach was taken because putting ROIs as a factor in ANOVA analysis could cause a bias in the statistical analysis due to the different optical properties in different ROIs (Kroczek et al., 2015; Yanagisawa et al., 2010).

3.2. HR data analysis

Unfortunately, due to several software and hardware crashes, as well as motion artifacts and Bioharness sensor displacement, all the HR data was moved from the analysis.

4. Results

The aim of this pilot study was to measure fear inhibition response to virtual threatening stimuli while avoiding equipment that might unduly impact naturalness of the response. This study hypothesised that participants exposed to virtual heights will show increased oxygenated haemoglobin changes (HbO) in MPFC and DLPFC.

4.1. fNIRS data analysis results

GLM

Figure 17 shows the results for NIRS SPM group analysis (pit room versus training room). SPM contrast for group analysis (pit room versus training room) at the significance threshold level $p < 0.05$ revealed no significant results. The further analysis showed a trend below the significance threshold towards increased HbO in the MPFC (channel 12, $t(4) = 1.99$, $p = 0.1175$, two-tailed) and the DLPF (channel 15, $t(4) = 1.81$, $p = 0.1445$, two-tailed) when participants were exposed to the virtual heights in the pit room in comparison to the training room. Increase in oxygenated haemoglobin levels in the MPFC and DLPFC potentially indicated fear response inhibition when participants were exposed to the virtual threat.

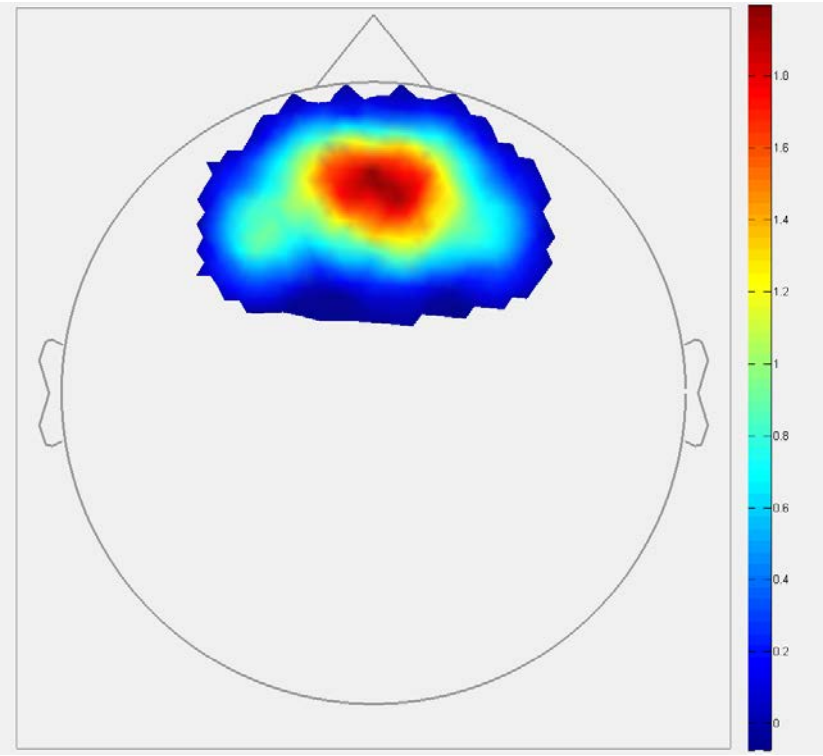

Figure 17 SPM Activation t-map of HbO changes in the pit room contrasted with training room. A colour scale represents the t-value for each channel (unthresholded)

ROI analysis

The channel-wise analysis did not reveal any significant results, therefore the further analysis was performed on each of the ROIs separately to investigate if there was any significant signal change during exposure to virtual heights.

A paired-samples t-test was conducted to determine if there was a statistically significant difference between training and pit. The result revealed that there was no significant difference in HbO beta estimates between training and pit condition in the left DLPFC t (4) = -.978, p < .384, two-tailed (Figure 18). In addition, there was no significant difference in HbO beta estimates between training and pit condition in the right DLPFC t (4) = -.844, p < .446, two-tailed (Figure 19). Similarly, that there was no significant difference in HbO beta estimates between training and pit condition in the left MPFC t (4) = -.876, p < .430, two-tailed (Figure 20), and no significant difference in HbO beta estimates between training and pit condition in the right MPFC t (4) = -.939, p < .401, two-tailed (Figure 21).

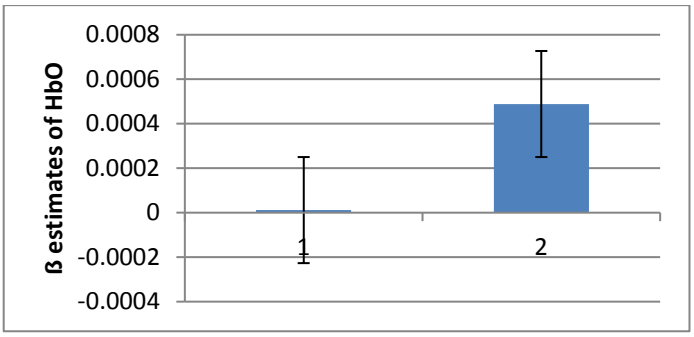

Figure 18 Left DLPFC ROI (1- training, 2 –pit)

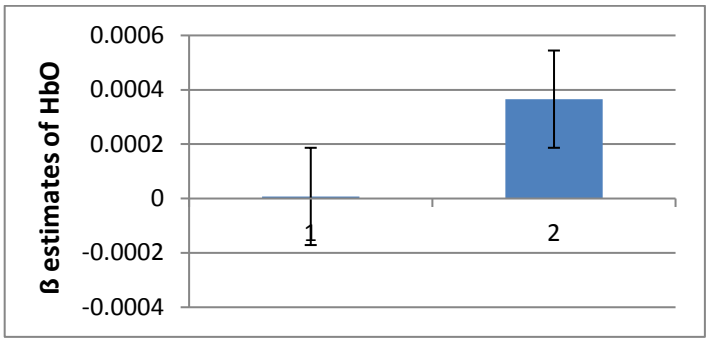

Figure 19 Right DLPFC ROI (1- training, 2 –pit)

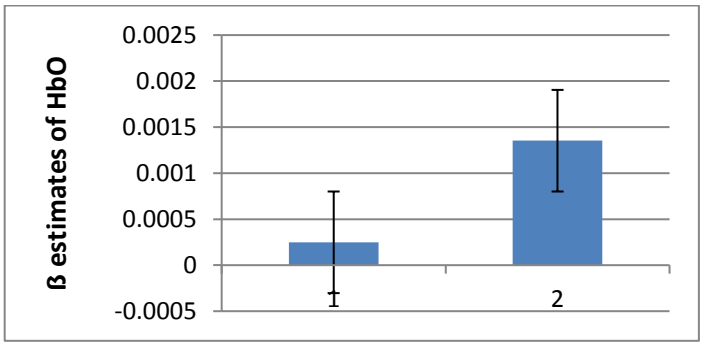

Figure 20 Left MPFC ROI (1- training, 2 –pit)

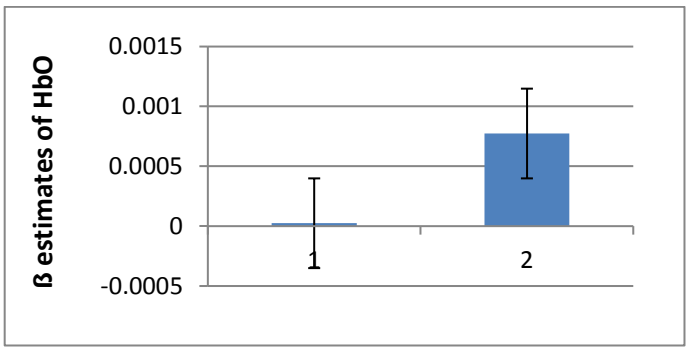

Figure 21 Right MPFC ROI (1-training, 2-pit)

4.2. HR data analysis results

There were no results from the HR data analysis.

4.3. Signal quality

The tests did not show signal interference between near-infrared light from NIRSport and Octave tracking system. However, the level of movement impacted on the signal quality. Over 50% of data was removed from the analysis due to the motion artifacts. From the remaining channels, 7 were removed (out of 100). Because this was the first study, which combined fNIRS with CAVE-like VR system, it was not possible to compare the results to other studies in terms of signal quality and motion artifact.

5. Discussion

The main concern in this pilot study was possible interference of the near infrared light from fNIRS and the motion tracking system. By measuring signal-to-noise ratio, this was proved ungrounded.

The result of the pilot study demonstrated that fNIRS in CAVE-VR during free locomotion is sensitive to a sudden excessive movement. As the objective of this study was to promote freedom of movement, the level of motion impact was investigated using NIRStar features. The result found some motion artefacts in the data. This was potentially a problem given that this application encouraged this. However, such a level of bend did not arise from a fear response or experimental protocol, but rather participants wanting to experiment with the experience. Moreover, this study aimed to investigate how much movement is too much to keep artefact-free data, therefore participants were allowed to move without any restrictions.

Initially, our measurement system was highly unstable. This came from the desire to maximise freedom of movement and approach. Physiological data can be communicated wirelessly from the sensors to the computer. Several technological issues such as laptop overheating and software crashes were related to the high system

requirements for brain data acquisition which requires a high-end laptop. The solution was to put a high-end laptop in a mesh backpack.

Many devices that sample infrared through the skin are susceptible to skin pigmentation. Furthermore, some researchers have reported problems with fNIRS and certain hair and skin colours (Wassenaar & Van den Brand, 2005). The participants had a range of skin and hair colour. The only correlated issue that participant's hair thickness affects fNIRS signal quality, therefore participants with a particularly thick or curly hair should be excluded from the experiment.

The HR data was excluded from the further analysis due to the several software crashes, motion artifacts and sensor displacement. This was later resolved by installing additional software.

6. Conclusion

Virtual Reality offers the potential to bridge the gap between ecological validity and controllability (Rey & Alcañiz, 2010). Both ecological validity and controllability are important in exposure therapy, as a balance must be drawn between engagement and retraumatisation. While VRET is beginning to demonstrate its efficacy, the study of the neurological process is in infancy. This study has argued that a problem shared between VRET and neuroscience of VR is the use of equipment that as a side effect might increase anxiety or reduce a naturalness of response. This project has proposed a solution that integrates wireless brain imaging and large VR in which users can move freely.

The aim of this pilot study was to measure fear inhibition response to virtual threatening stimuli while avoiding equipment that might unduly impact the naturalness of the response. The objective of this study is to test the feasibility of the protocol in terms of the design, integration of technology and signal-to-noise ratio. The results of our pilot study suggested non-significant trends that indicate the potential for this integration of technology to evoke fear inhibition in virtual reality. This study has demonstrated the feasibility of the protocol and identified some technical issues, which were then resolved.

Although the study did not reveal any statistically significant results, promising trends indicated that VR can potentially activate the PFC areas indicative of emotional regulation and fear inhibition which can be measured by wireless brain imaging device. Results of this study demonstrated increased haemoglobin oxygenation (HbO) in the right MPFC and right DLPFC when participants were exposed to the virtual heights, what might indicate fear inhibition in VR. These results are consistent with previous neuroimaging studies (Quirk & Beer, 2006). However, our study did not constrain the natural movement of the participant. The potential impact of this work is to open the door to a more ecologically valid study of neuroscience within virtual reality and perhaps in the future, adaptive immersive neurofeedback techniques.

Chapter 6 Experiment II: The neural basis of fear inhibition in virtual reality in healthy controls

1. Introduction

This chapter describes the pit room experiment which builds upon the outcome of the pilot experiment. At first aims and objectives of this project are described, and then research questions, hypothesis and variables. The next section introduces the experimental protocol. Then the chapter describes how the data was analysed and the result of the study. At the end of the chapter discussion and conclusion are presented.

The pilot experiment demonstrated that the technology used was safe and able to measure inhibitory response while promoting naturalness of movement. Although the result of the study was not statistically significant, the study demonstrated the trend that HbO concentration increases in the MPFC and DLPFC when people are exposed to the virtual threat. This trend was consistent with previous fMRI studies which identified the activity in these brain areas as an index of fear inhibition in healthy participants (Jovanovic et al., 2013; Quirk, Garcia, & González-Lima, 2006). Moreover, the pilot study demonstrated that integration of IPT and wireless fNIRS system allows freedom of movement to a certain degree without introducing motion artifacts to the data. The study assessed the feasibility of the protocol, debugged the experimental design, software and the system.

Several ameliorations were implemented in this study. This study utilised brain imaging technology (fNIRS) and psychophysiological measuring device (Bioharness) in order to measure a fear response and its inhibition to virtual heights. Likewise, in the pilot study, this project employed the Pit Room VR scenario, however, the simulation was designed and improved using an upgraded software (Unity 5 and MiddleVR 1.6.1.). Many issues which were encountered in the pilot study were resolved - software was debugged, the issues with parallax were fixed, the floor collider was removed and the system was optimised in order to minimise the latency in order to improve the naturalness of the simulation, enhance a feeling of presence and minimise a risk of cybersickness.

The simulation was ameliorated by placing a wooden plank on the floor in the training room. This approach was implemented in order to ensure that the task is the same in both training room and pit room. Otherwise, it could be difficult to deduce whether the brain activity measured during the task performance in the pit room was associated with fear inhibition or balance control.

Additionally, small 2D markers with numbers were placed on both planks in order to prevent participants from walking into screens and also indicate the borders of the tracking area in VR space. Three participants that took part in the pilot study reported confusion over the distinguishing virtual walls from the Octave screens. This, on the one hand, demonstrates that they were immersed into the simulation, but on the other hand, could cause a potential harm to the participants, or damage to the Octave screens.

The experimental design was improved. This study employed a blocked design for fNIRS data acquisition. The blocked design is a commonly used paradigm in fMRI studies. It consists of epochs of "on" and "off" periods alternated through the scanning session. During the "on" period a stimulus of the same condition are presented sequentially, and the "off" period serves as a baseline or rest period. In contrast, event-related design presents stimuli in arbitrary order separated by an inter-stimulus period (Huettel et al., 2004). Although a blocked design has many disadvantages (Amaro & Barker, 2006), for this project it was the optimal strategy for stimulus presentation. The blocked design was employed in order to facilitate naturalness of the response and mimic the real-life situation in which usually there are no inter-stimulus periods or breaks. However, the rest period between each of the blocks was used in order to allow hemodynamic response function (HRF) to return to the baseline before the onset of the other condition. The blocked design is more efficient in terms of detection of statistical power when the number of participants and trials is lesser, and it is also more robust to uncertainty in the temporal domain. This experiment consisted of three blocks – early, middle and late. This approach was adopted in order to measure the within-session effect of cognitive appraisal and inhibitory learning (within-session habituation). Specifically, the session was divided into three blocks to investigate the temporal dynamic of inhibitory learning – when the change occurs during a VRET session; which brain areas are activated during the course of VRET session; how the pattern of neural activity unfolds and changes at the beginning, during and at the end of VRET session.

Additionally, this experiment included two questionnaires (presence questionnaire and cybersickness questionnaire) and a post-experimental interview in order to assess the quality and comfort of the simulation, equipment and VR system.

2. Methods

2.1. Aims and objectives

The aim of this study was to measure an inhibitory response, inhibitory learning, cognitive reappraisal and the fear response to VR with improved ecological validity while avoiding equipment that might excessively impact on the naturalness of the response. The objective of this study was to measure the PFC response to threatening virtual stimuli using an integration of technology which facilitates naturalness of movement and response – wireless brain imaging device, wireless heart monitor and cave-like virtual reality system. The PFC oxygenation was measured as an index of fear inhibition and learning and cognitive reappraisal. Heart rate was measured as an indicator of the fear response to the VR simulation. The within-subject blocked design was employed in order to measure inhibitory learning (within-session habituation) during the exposure to the threatening virtual stimuli. Moreover, the objective of this study was to investigate whether fear inhibition and learning in VR are correlated with the levels of reported presence and anxiety.

2.2. Research question

This experiment was designed in order to answer the questions - what is the neural mechanism underlying fear inhibition in ecologically valid virtual reality in healthy participants? What is the mechanism underlying cognitive reappraisal in VR with improved ecological validity? What are the temporal characteristics of those mechanisms? Does the learning effect occur during a single session? Is the magnitude of inhibitory response correlated with the magnitude of the physiological arousal? Is the magnitude of fear inhibition correlated with the level of subjective presence and initial fear of height?

2.3. Hypothesis

This study tested the hypothesises that (1) participants exposed to the threatening virtual stimuli (pit room) would show an increased oxygenation in the MPFC and DLPFC

in contrast to the safety virtual stimuli (training room), (2) the magnitude of the activity in the MPFC and DLPFC would increase over time (from block to block) (3) participants exposed to the threatening virtual stimuli (pit room) would show an increased HR in contrast to the safety virtual stimuli (training room), (4) HR would decrease over the time (from block to block) (5) activity in the MPFC and DLPF would be negatively correlated with the HR, (6) activity in the MPFC and DLPFC would be positively correlated with HAQ scores, (7) activity in the MPFC and DLPFC would be positively correlated with SUS scores, (8) HR would be positively correlated with HAQ scores , (9) HR would be positively correlated with SUS scores

2.4. Response and explanatory variables

In this study the following response variables/ depended variables were measured:

- HbO (changes in oxygenated haemoglobin levels) between the pit room and the training room
- ΔHR (changes in HR in BPM) between the pit room and the training room
- subjective feeling of presence (SUS)
- fear of heights/anxiety (HAQ)

Two explanatory variables/independent variables were:

- Conditions – training room and pit room
- Blocks, which serve as a learning phase – early, mid and late

2.5. Instruments and equipment

Octave

Immersive Projection Technology (IPT) Octave (Figure 22) is described in chapter 4, section 6.2. and chapter 5, section 2.4. In this experiment, the same setup was used as in the pilot study. No changes were made in the hardware.

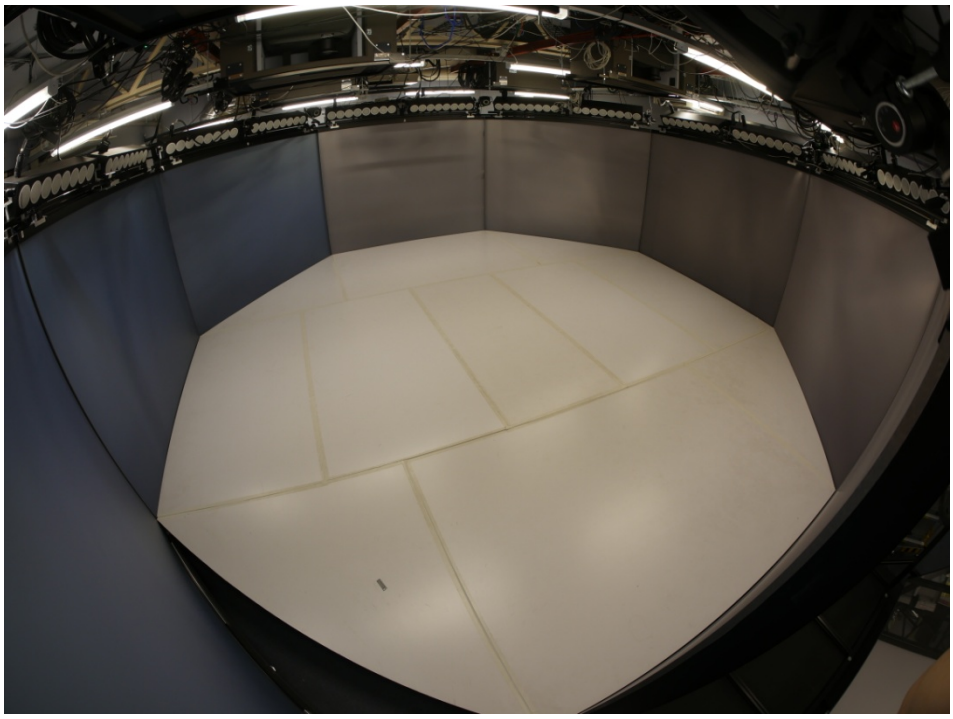

Figure 22 Octave octagonal configuration. Besides 8 wall projectors there are also 6 celling projectors which cover the floor display

fNIRS NIRSport

Functional Near-Infrared Spectroscopy (fNIRS) – In order to measure changes in cerebellar oxygenation changes we used NIRSport (NIRsPORT 8-8, NIRX Medizintechnik GmbH, Berlin, Germany). The system is described in chapter 4, section 6.3. and chapter 5, section 2.4. The system was significantly improved after the pilot study by purchasing the spring-loaded grommets which were used for the set up (see appendix 1). Using NIRX spring-loaded grommets significantly reduced subject preparation time by the set-up which does not require manual parting of a hair and therefore allowed the gel-free faster application. Additionally, to improve participant's comfort, distancing rings were purchased, that minimise pressure during data acquisition. To minimise motion artefacts, stiffing elements and a new improved retaining cap were purchased.

As in the pilot study, emitters were placed on positions F3, AF7, AF3, Fz, Fpz, AF4, F4, AF8, while detectors were placed on positions F5, F1, Fp1, AFz, F2, Fp2, and F6. Twenty channels were set up covering the prefrontal cortex. The source-detector distance was 3cm. Optodes were placed on the participant's head using EasyCap

(http://easycap. brainproducts.com/) relative to the international 10/20 system (Jasper, 1958).

The data was acquired with the NIRStar acquisition Software (version 2014, NIRX Medical Technologies LLC) running on the high-end Windows 7 *MSI GS30 Shadow* laptop, which has Intel Core i7-4870HQ processor, 16GB RAM and Iris Pro Graphics 5200. The blood oxygenation was measured at two near infra-red light wavelengths of 760nm and 850nm, with the sampling rate 7.81 Hz.

The system was operated by the main data battery – operated acquisition instrument. The data is acquired and transferred to a lightweight laptop. The main instrument and controlling notebook can be worn in a backpack allowing freedom of movement during data acquisition. In order to prevent equipment overheating, a new mesh backpack was purchased, which allows the air circulation during the data acquisition.

Bioharness

Zephyr Bioharness (Zephyr Technology, Annapolis, US) is described in chapter 4, section 6.3. and chapter 5, section 2.4.

Network

The network setup is described in chapter 5, section 2.4. No changes were made in the configuration.

Questionnaires

Height Anxiety Questionnaire (HAQ)

This study recruited only healthy participants who did not suffer from acrophobia. Therefore, in order to screen participants for excessive fear of heights, the study employed the Height Anxiety Questionnaire (HAQ) developed by Cohen (Cohen, 1977). The HAQ consists of 20 items describing 20 everyday life situations which can trigger fear of heights. The questionnaire was sent to the volunteer via email a minimum of 24 hours before the experiment. Participants were asked to rate these situations from 0 to 6 (0 indicates no anxiety, 6 indicates maximum anxiety). A total score on the questionnaire is

120 which indicates maximum fear of heights, 0 indicates no anxiety. Only participants who scored below the two-third of the questionnaire scores (mean score below 40) were invited to participate (Steinman & Teachman, 2011).

Presence questionnaire- Slater-Usoh-Steed (SUS) questionnaire

Presence is a subjective feeling of "being there" often defined as "the propensity of people to respond to virtually generated sensory data as if they were real" (Sanchez-Vives & Slater, 2005). The Presence Questionnaire was used, which contains 7 items that measure presence rated on scale 1 to 7, where 1 indicates the low presence, and 7 indicates the high presence (Usoh et al., 1999; 2000). The SUS was used in Meehan's Pit Room experiment (Meehan et al., 2002), therefore in order to compare the results, the same questionnaire was used.

Simulator Sickness Questionnaire (SSQ)

Cybersickness occurs as one of the unintended side effects of using VR technology. The symptoms of cybersickness are similar to motion sickness and can include: a headache, eye strain, pallor, stomach awareness, nausea, vomiting, sweating, disorientation, fatigue or drowsiness (Kennedy & Fowlkes, 1992). Simulator Sickness Questionnaire (SSQ) was developed by Kennedy and colleagues (Kennedy et al., 1993). It consists of 16 items measuring side effects of the VR simulation in the scale from 0 to 3, where 0 is coded as "none", 1 – "slight", 2 – "moderate" and 3 – "severe". Please see the appendix. A total score on the questionnaire is 48 which indicate severe symptoms and 0 indicates no symptoms.

3. Materials and methods

3.1. Participants

Twenty-seven healthy participants (N = 27, 16 males and 11 females, average age = 33.11, SD = 7.27) were recruited by advertisement on the University of Salford campus through posters, emails and SONA system (Desmond & Glover, 2002). All participants were paid the equivalent of £5 for their participation in the study. Each participant was pre-screened for fear of heights using the Height Anxiety Questionnaire developed by Cohen (Cohen 1977) which was sent to the volunteer via email minimum 24 hours before

the experiment. Only participants who scored below the two-thirds of the questionnaire scores (mean score below 41 = 30%) were invited to participate (Steinman & Teachman, 2011). Participants were also excluded from this study if they had suffered an epileptic episode, have felt unwell during a virtual reality or IMAX theatre experience, often suffer from a migraine, or have skin that is excessively sensitive and thus might get damaged by sensors. Moreover, participants who had particularly thick, curly or "bushy" hair were excluded due to the fNIRS limitations.

3.2. Ethics

All Participants were presented with the Participant Information Sheet that advised them of the potential risks associated with the experiment such as cybersickness and discomfort related to the brain monitoring module. They were informed about data anonymization and confidentiality, and they were advised that they could withdraw from the experiment at any time without giving any reasons. Written informed consent was obtained from all participants prior to the experiment. Ethical approval HSCR 15/88 was granted by the University of Salford Postgraduate Ethics Committee (see appendix).

3.3. Scenario

The scenario was created using Unity 5 game engine (academic version 5.1.0f3 64-bit) (https://unity3d.com/). To run the simulation in Octave MiddleVR for Unity (version 1.6.1f6) was used http://www.middlevr.com/middlevr-for-unity/. MiddleVR is a middleware solution that allows for a connection of VR peripheral devices such as tracking, projectors and controllers. The environment consisted of two rooms: the training room and the pit room. Both rooms had a virtual wooden plank placed on the floor, which size was 40 cm wide. The training room looked like a normal room with floor and furniture. The wooden plank was placed directly on the floor. In the training, room participants familiarised themselves with the virtual environment and trained the task. The pit room had no floor but the wooden ledge on which participants could stand, walk and look down onto the pit room (which looked like an ordinary room with floor and furniture) approximately 6m below the plank (Figure 23), and the video is available via following the link - https://youtu.be/tlrC2hf5I1Y

Figure 23 Pit Room simulation (top view into the pit room, bottom – view in the training room)

3.4. Task

Participants attended the experimental session at prearranged time slots. Each participant was provided with the Participant Information Sheet and Height Anxiety Questionnaire at least 24 hours prior to the experiment. On arrival, they were instructed about safety in Octave and given a consent form to sign if they agreed to do the experiment. Then they were introduced into the Octave and the simulation. The researcher explained the task and instructed participants about the level of the movement they were allowed to perform in order to minimise the motion artifacts in the data. All participants were informed that the number markers on the plank were not associated with the task, but rather served as an indicator of the tracking area. They were told to ignore the numbers during the experimental session. Then participants were allowed to familiarise themselves with the virtual environment and practice the task up to 5 minutes. Following practice and familiarisation participants were fitted with the monitoring equipment. At first,

participants were led to the private area, and the researcher helped them to fit the Bioharness. After this, the researcher put the NIRSport on the participant scalp. The fNIRS system was then calibrated for the optimal amplitude and signal-to-noise ratio. The quality of the optical densities was assessed visually by the researcher. If the level of the noise in a data was too high, the researcher readjusted the noisy optode ensuring optimal contact with the scalp. After the data acquisition was assessed and met satisfactory quality criteria, the researcher set up the software for the data acquisition. The retaining cap which reduces the ambient light and reduces the risk of optode displacement was placed over the Easycap. The data was recorded using a battery-operated fNIRS system which is powered by the laptop and the data is saved and stored on the hard drive. The fNIRS battery and the laptop were placed in the backpack which must be worn by a participant during the whole experimental session. After the preparation participants were led to Octave and asked to perform a simple walking task on the wooden plank in both training and pit room.

3.5. Design

This experiment employed a within-subject design in order to reduce the number of errors in the variance due to natural human variances in the data. All participants were tested under the same conditions.

For the task, a blocked design was adopted. The whole experimental session consisted of 3 blocks: (1) Early block, (2) Middle block, (3) Late block. Each block lasted 240 seconds and was proceeded with the pre-task 20-seconds baseline.

There were 2 experimental conditions within each block divided into 12 trials, each lasting 20 seconds:

- Training room (6 trials)
- Pit room (6 trials)

Each condition was proceeded with 20 seconds rest for the hemodynamic response to return to the baseline. Block sequences between participants were randomised – participants were instructed to move to either training room or pit room in random order. Figure 24.

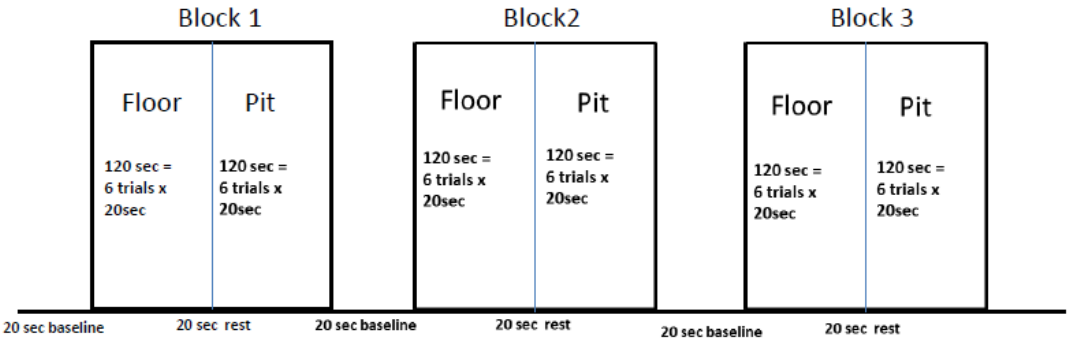

Figure 24 Pit Room experiment experimental procedure

During the session, participants heard pre-recorded audio instructions: “Please take a rest”, “Move to the training room” or “Move to the pit room”. The experiment started with 20-second baseline prior to the first stimuli onset, when participants were instructed to step on the actual floor in the training room or step outside the simulation. They were instructed to stay still, close their eyes, clear their mind and relax. After the baseline participants heard audio instruction to move either to the training room or move to the pit room in random order. The task in both rooms was the same – participants were walking on the wooden plank in the training room for 120 seconds and walking on the wooden plank in the pit room for 120 seconds. There were 20 seconds breaks between each condition and each of the blocks in order for the hemodynamic response to return to the baseline. The experimenter was present in the experimental area during the whole experiment placing the markers on the data manually every 20 seconds. After the experiment, NIRSport and Bioharness were removed. Then participants were asked to fill two questionnaires in – Presence Questionnaire (SUS) and Cybersickness Questionnaire. After the experiment, there was a short interview with the researcher in order to gather feedback about the experiment and ensure that participants did not experience any side effects and could safely leave the lab.

3.6.Data analysis

fNIRS data analysis

Preprocessing

Data was first visually inspected in order to identify noisy channels and trials. Due to the motion artifacts throughout the whole time series, four participants were excluded from the data analysis. The remaining data was assessed for a period of time containing motion artifacts prior to the experimental session which was manually removed. Then the coefficient of variation (CV) was used in order to quantify the signal-to-noise for the raw time series for each participant and each channel (Schmitz et al., 2005). Channels which showed CV with the value exceeding 15% were rejected from the analysis (Piper et al., 2014). A total number of channels removed from the analysis: block 1 – 25 (out of 460) channels removed, block 2 – 14 (out of 460) channels removed, block 3 - 12 (out of 460) channels removed.

fNIRS data was preprocessed and analysed using NIRSLab (NIRSLab v2014 NIRX Medical Technologies). HbO, HbT and (HbR) time series were baseline – corrected and band-pass filtered with low cutoff frequency 0.01 Hz and high cutoff frequency 0.2 Hz to remove drifts and noise from the data. A differential path length factor of 7.25 for 760nm and 6.38 for 850nm was applied (Essenpreis et al., 1993). Molar extinction coefficients ε for HbO at 760 nm = 1486.5865 cm−1/M and 850 nm = 2526.391 cm−1/M, were applied from W. B.Gratzer, Med.Res. Council Labs, Holly Hill, London and N. Kollias, Wellman Laboratories, Harvard Medical School, Boston. Raw data was converted to the average haemoglobin concentration changes using the modified Beer-Lambert (Delpy et al., 1988) law for each channel, each trial, each block and each subject

GLM

Statistical data analysis was performed using NIRS-SPM (SPM 8) analysis tool implemented in NIRSLab (version 2014) in order to identify regions of the brain activated during the virtual height exposure. Data was modelled with GLM. The regressors were modelled via convolution by the hemodynamic response function provided by SPM8 (Friston et al., 1996). Discrete cosine transform basis function was used for temporal filtering and precoloring HRF was used for the serial correlations.

1st level analysis

In the first level analysis for each individual participant and block, t-contrasts were then created for average HbO concentration changes to generate statistical parametric maps of activation for two regressors: training and pit, for each channel and each subject and each block. The data for both conditions (training and pit) was baseline corrected. SPM t-maps were generated by using two contrasts: training-pit and pit-training, and thresholded at $p < 0.05$ (corrected).

– contrasts vectors:

(training – pit) – to investigate brain areas significantly more activated for the training condition versus pit

(pit – training) - to investigate brain areas significantly more activated for the pit condition versus training

2nd level analysis

At the group analysis, SPM group HbO t–statistics were calculated to identify the channel significantly activated by exposure to virtual heights with the significance level threshold set at $p < 0.05$ (corrected) according to the false discovery rate method FDR used in fMRI studies (Singh & Dan, 2006).

The estimated anatomical location of each channel was determined using anatomical locations of international 10-10 system cortical projections of EEG sensors (Koessler et al., 2009; Okamoto & Dan, 2005).

Within-session inhibitory learning

In order to measure the learning effect – the difference between blocks, a 3x2 repeated measures ANOVA was performed due to the limitations of the NIRSLab software which is still in development and does not allow for a comparison between separate scanning sessions, in order to investigate whether there was a significant difference between blocks in mean HbO concentration changes. The separate analysis was performed in SPSS (IBM SPSS version 20). All the beta coefficients were extracted

from the first level analysis for each participant, channel, condition and block (Plichta et al., 2006). Betas were then averaged for each condition and each block resulting in 6 experimental variables: block 1 – training and pit, block 2 – training and pit, block 3 – training and pit. A 3x2 repeated measures ANOVA was performed with two within-subject factors: block (early, mid and late) and condition (training and pit).

ROI

At the 3rd level analysis a Region Of Interest analysis (ROI) was performed. ROIs were defined a priori across all the channels using the probabilistic assessment of cortical projection sensors underlying 10-20 system anatomical surface locations (Koessler et al., 2009; Okamoto et al., 2004). Four ROIs (left DLPFC, right DLPFC, left MPFC and right MPFC were defined on the basis of BA (Brodmann, 1909) to be represented by channels: 1, 3, 5 and 7 (L DLPFC); 14, 15, 18 and 20 (R DLPFC); 6 and 11 (L MPFC); 13 and 16 (R MPFC) respectively. The HbO beta-estimates from those channels were extracted for each subject from the first level analysis and then averaged within each of the ROIs across the selected channels (Poldrack, 2007). Average beta estimates were next analysed with a t-test on each ROI separately. This approach was taken because putting ROIs as a factor in ANOVA analysis could cause a bias in the statistical analysis due to the different optical properties in different ROIs (Kroczek et al., 2015; Yanagisawa et al., 2010).

3.7. HR data analysis

The data was initially inspected for motion artifacts in Bioharness Acqknowledge (version 14.1). Unfortunately, only data from twelve participants was used for the analysis. The data from four participants was excluded due to software crash, and the data from seven participants (six females and one male) were excluded due to noise and a sensor displacement.

Mean HR BMP for each participant, block and condition were calculated in Acquknowledge. Then the data was extracted and group analysis was performed in SPSS (IBM SPSS version 20). The data was checked for normality using SPSS function "Explore" and Shapiro-Wilk test. In order to investigate the change in mean HR between conditions in each of three blocks, mean HR in the training room were extracted from the mean HR in the pit room according to Meehan's approach (Michael Meehan et al., 2002)

Furthermore, the project investigated if changes in brain activity (indicative of fear inhibition and cognitive reappraisal) are correlated with changes in HR (indicative of emotional arousal) during exposure to virtual heights. For correlation analysis, the average difference in HR between the training room and pit room was used (Meehan et al., 2002). The data was then analysed using SPSS.

Pearson`s correlation tests were conducted to assess the relationship between mean ΔHR and HbO in the pit room. Also, the correlation between HR and reported presence and height anxiety was calculated.

3.8. Questionnaire data analysis

Preparation and analysis of the questionnaire data was conducted in SPSS (IBM SPSS version 20). All the data was checked for normality using SPSS function "Explore" and Shapiro-Wilk test. For all the questionnaires descriptive statistics (means and standard deviations) were calculated. Additionally, COUNT function was used for the SUS questionnaire. Originally Usoh et al. used the SUS questionnaire in order to determine the height and the low threshold of presence. The high presence threshold was determined by using 6 and 7 as high responses (Usoh et al., 2000). Meehan in his Pit Room study proposed that using 5 as a high threshold better correlates with conditions (Meehan et al., 2002), therefore in this experiment also 5 was considered as a high presence threshold. The overall score was then calculated as a number of high responses (Usoh et al., 2000). For correlation analysis between HbO and self-reported measures, both channel-wise and ROI-wise analysis were performed in SPSS (Kroczek, Haeussinger, Fallgatter, Batra, & Ehlis, 2015).

4. Results

4.1. fNIRS data analysis results

Voxel-wise GLM

Voxel-wise brain imaging data analysis results are presented from each of three blocks – early, middle and late. ROI data analysis was averaged across all three blocks.

Block 1

HbO SPM t - contrast analysis for the group analysis (Pit Room versus Training Room) at the significance threshold level $p < 0.05$ (corrected) revealed a significant increase of task-related HbO concentration changes in the bilateral DLPFC (Figure 4). The contrast Training Room versus Pit Room did not reveal any channel being more activated when participants performed a task in the Training Room. The results are summarised in Table 2 and Figure 25.

Block 2

HbO SPM t - contrast analysis for group analysis (Pit Room versus Training Room) at the significance threshold level $p < 0.05$ (corrected) revealed a significant increase of HbO concentration changes in the bilateral DLPFC and bilateral MPFC (Figure 4). The contrast Training Room versus Pit Room did not reveal any channel being more activated when participants performed a task in the Training Room. The results are summarised in Table 2 and Figure 25.

Block 3

HbO SPM t - contrast analysis for group analysis (Pit Room versus Training Room) at the significance threshold level $p < 0.05$ (corrected) revealed a significant increase of HbO concentration changes in the bilateral DLPFC and bilateral MPFC (Figure 4). The contrast training room versus pit room did not reveal any channel being more activated when participants performed a task in the training room. The results are summarised in Table 2 and Figure 25.

Table 2 Summary of results for all three blocks (channel number, t-value, anatomical label and Brodmann areas)

Block	Channel	T - value	Label	Brodmann Area
1	Channel 7	2.32	DLPFC L	BA 9
	Channel 9	2.60	DLPFC R	BA 9
	Channel 14	2.94	DLPFC R	BA 9
	Channel 15	2.21	DLPFC R /Frontal Eye Fields	BA 8/9
	Channel 19	2.07	DLPFC R	BA 46
2	Channel 1	3.39	DLPFC L	BA 46
	Channel 2	2.75	Frontal Eye Fields	BA 8
	Channel 5	3.30	DLPFC L /Frontal Eye Fields	BA 8/9
	Channel 6	3.31	MPFC L	BA 10
	Channel 7	3.31	DLPFC R	BA 9
	Channel 8	3.37	Frontal Eye Fields L	BA 8
	Channel 9	3.30	DLPFC B	BA 9
	Channel 12	2.63	DLPFC B	BA 9
	Channel 13	2.02	MPFC R	BA 10
	Channel 14	3.42	DLPFC R	BA 9
	Channel 15	2.72	DLPFC R /Frontal Eye Fields	BA 8/9
	Channel 19	2.52	DLPFC R	BA 46
3	Channel 1	4.55	DLPFC L	BA 46
	Channel 2	2.92	Frontal Eye Fields	BA 8
	Channel 3	3.31	DLPFC L	BA 46
	Channel 4	3.37	MPFC L	BA 10
	Channel 5	2.46	DLPFC L /Frontal Eye Fields	BA 8/9
	Channel 6	4.39	MPFC L	BA 10
	Channel 7	3.17	DLPFC L	BA 9
	Channel 8	2.29	Frontal Eye Fields L	BA 10
	Channel 9	3.58	DLPFC R	BA 9
	Channel 10	3.37	Frontal Eye Fields R	BA 8
	Channel 12	3.73	MPFC R	BA 10
	Channel 13	2.45	MPFC R	BA 10
	Channel 14	3.17	DLPFC R	BA 9
	Channel 15	4.10	Frontal Eye Fields L	BA 8/9
	Channel 16	4.75	MPFC R	BA 10
	Channel 17	2.46	Frontal Eye Fields R	BA 8
	Channel 18	2.25	DLPFC R	BA 46
	Channel 19	2.52	DLPFC R	BA 46
	Channel 20	3.05	DLPFC R	BA 46

All p values < 0.05 (corrected)

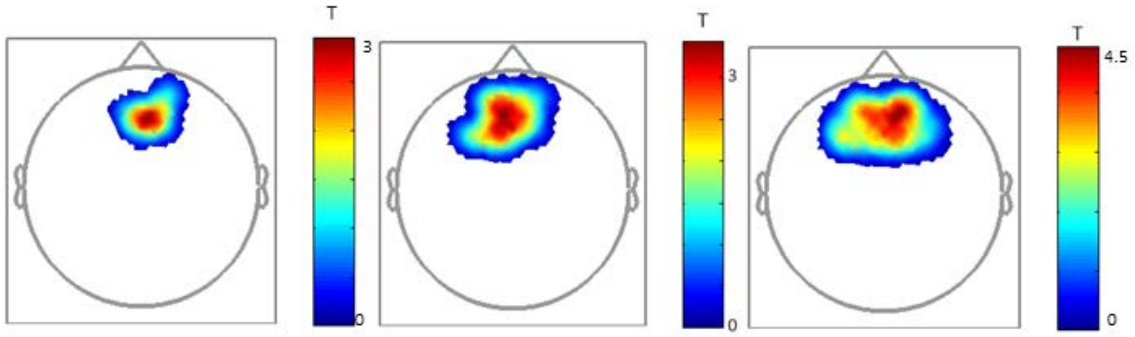

Figure 25 Second level group (n=23) SPM activation t-maps of HbO Pit Room versus Training Room for each of 3 blocks 1- early, 2- mid and 3-late, respectively. The colour bar represents t-value

Within-session inhibitory learning

A 3x2 repeated measures ANOVA with two within-subject factors – block (early, mid and late) and condition (training and pit) revealed no significant effect of the block $F(2, 44) = .908$, $MSE = 6.909$, $p = .411$, $\eta p^2 = .040$, however there was a significant effect of the condition $F(1, 22) = 78.198$, $MSE = 706.607$, $p < .001$, $\eta p^2 = .780$. HbO was significantly higher for the pit room condition than training room in each of the three blocks (mean difference of the t-value 2.066). Figure 26 shows trends towards increased HbO across from the early to the late block. The interaction between block and condition was not significant $F(2, 44) = .553$, $MSE = 387.896$, $p = .573$, $\eta p^{2 =} \cdot 024$.

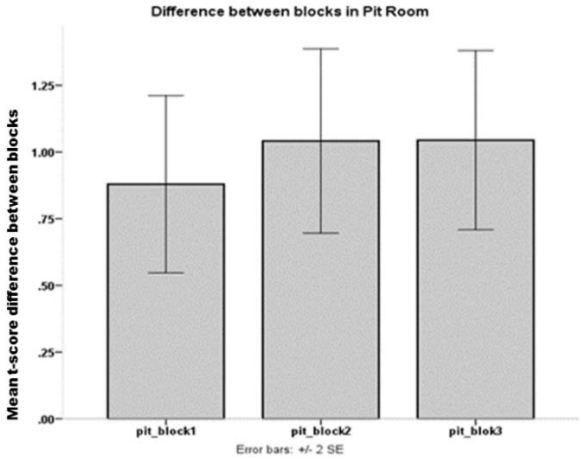

Figure 26 Difference between all blocks - early, mid and late, respectively. HbO t-scores were extracted from 2nd level SPM analysis (n=23) from unthresholded t-maps (pit room versus training room). The vertical line represents average t – scores from the 2nd level analysis. Error bars represent the standard error of the mean across all participants.

ROI

Consistent with the voxel-wise analysis, the ROI analysis did not reveal a significant difference between each of the ROI in the magnitude of activation in relation to any of the blocks, however, there was a significant difference in HbO between the training room and the pit room (Figure 27). Because there was no significant effect of the ROI, the further analysis examined HbO in each of the ROIs separately (the rationale behind this ROI analysis approach is described in chapter 4, section 8). A paired sample t-test was conducted to determine if there was a statistically significant difference between training and pit in each of the ROIs. There was a significant difference in HbO parameter estimates in the left DLPFC between training (M = .0002, SD = .00028) and pit (M = .0007, SD = .00048); t (22) = -6.115, p < .001, two-tailed. . There was a significant difference in HbO parameter estimates in the right DLPFC between training (M = .0002, SD = .00028) and pit (M = .0006, SD = .00042); t (22) = -6.628, p < .001, two-tailed. There was a significant difference in HbO parameter estimates in the left MPFC between training (M = .0003, SD = .00045) and pit (M = .0009, SD = .00063); t (22) = -7.740, p < .001, two-tailed. There was a significant difference in HbO parameter estimates in the right MPFC between training (M = .0003, SD = .00043) and pit (M = .0010, SD = .00061); t (22) = -7.531, p < .001, two-tailed.

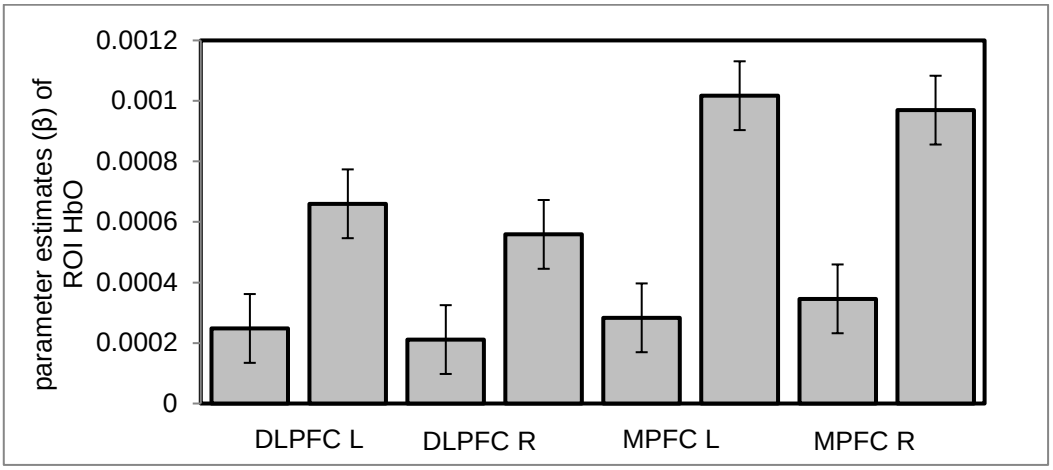

Figure 27 Activation within each of the ROIs for training condition (left) and pit room condition (right) averaged across all of the three blocks. The vertical axis represents parameter estimates Error bars represent the standard error of the mean across all participants (n=23).

4.2. HR data analysis results

A 3x2 repeated measures ANOVA with two within-subject factors – block (early, mid and late) and condition (training and pit) revealed no significant effect of the block $F(2,20) = 2.827$, $p = .101$, and no significant effect of condition $F(1, 10) = 4.917$, $p = .051$. The interaction between block and condition was also not significant $F(2, 20) = .325$, $p = .679$. Although the results were not significant, there was a trend towards mean difference of 1.124 BPM (Figure 28) when participants were exposed to the virtual height in the pit room in contrast to the training room regardless of the block.

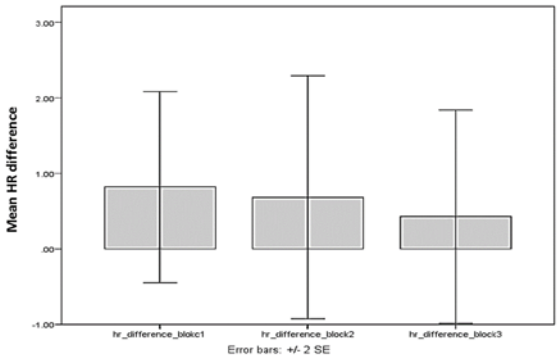

Figure 28 Δ HR showed a trend towards decrease across three blocks in the Pit Room

4.3. Questionnaire data analysis results

Height Anxiety Questionnaire

HAQ questionnaire was administered to participants at least 24 h prior to the experiment in order to determine if participants fulfilled the eligibility criteria. Only participants who scored below 40 (low height anxiety) on the HAQ questionnaire were invited to participate in the study. The mean score was 16.39, SD = 12.59.

Presence

The SUS questionnaire was used in order to assess the quality of the simulation. The overall mean SUS score was 4.43, SD 1.02. Overall 39% participants reported high presence. The correlation analysis did not show any significant correlations between SUS scores and other measurements. Table 3 shows average SUS scores for each of six questions.

Table 3 Average Presence scores (Means and Standard Deviations)

Question	SUS means score and SD
Q1	X = 4.45 SD = 1.17
Q2	X = 4.33 SD = 1.52
Q3	X = 4.66 SD = 1.37
Q4	X = 4.33 SD = 1.40
Q5	X = 5.0 SD = 1.76
Q6	X = 4.25 SD = 1.67

Cybersickness

All our participants scored very low on the questionnaire (mean score 1.8, SD = 2.63) which demonstrated that the Octave system may cause only a slight cybersickness in some participants.

4.4. Correlations

A Pearson's correlation coefficient was calculated to assess the relationship between the HbO, ROI, ΔHR, reported presence, and reported anxiety for the pit room condition.

Brain activity - HbO

There was no correlation between overall HbO and ΔHR in the Pit Room condition across all the blocks r = -.031, N = 12, p = .923 (two-tailed). Therefore, a correlation analysis was performed between ΔHR change and each of the channels, however, there were no significant results. The correlation analysis between Δ HR change and each of the ROIs also did not reveal significant results.

The correlation analysis between each of the channels and HAQ revealed a significant negative correlation between HAQ and HbO in the early block in the pit room in the B DLPFC showed by channel 9 (r = -.426, N = 23, p = .048, two-tailed), and in the late block (r =. -512, N = 23, p = .013, two-tailed). Surprisingly the correlation between HAQ and HbO in the middle block was not significant.

The correlation between HAQ and the DLPFC was confirmed in correlation analysis between ROI and HAQ. The correlation analysis between each of the ROI revealed a significant negative moderate correlation between HAQ and left DLPFC (r =. -483, N = 23, p = .020, two-tailed) and a strong negative correlation between anxiety scores and right DLPFC (r =. -655, N=23, p =.001, two-tailed) (Figure 29) .

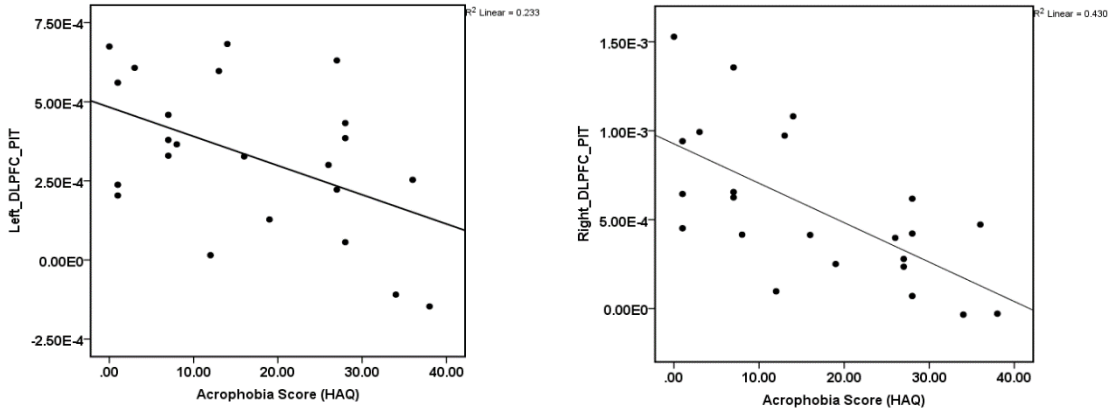

Figure 29 The correlation between HAQ and DLPFC ROI - left DLPFC (left) and right DLPFC (right)

Heart rate

There was no significant correlation between ΔHR (average difference between training and pit conditions M =1.124 BPM) and any of the other measures.

Presence

There was no significant correlation between the reported presence (average mean M = 4.43) and any of the other measures.

5. Comments and post-experimental interview

Immediately after the experimental session, there was a short interview with the researcher in order to ensure that participants did not experience any side effects of the VR experience and also to obtain the feedback about the equipment and simulation.

Most of the participants felt well during the simulation. Despite one participant reporting moderate cybersickness symptoms, she said that could probably be due to the fact that she was feeling hungry and sleepy.

Most of the participants found the Pit Room simulation engaging and realistic. They said that the Octave allows a high degree of immersion and they reported a high level of presence. Most of the participants said that although they knew there was no real pit in the simulation, they still were worried they could fall down. Only one participant stepped on the part of the floor simulation where the pit room was simulated. The rest of the participants reported that they found it "very uncomfortable" to step off the wooden plank onto the simulated pit. Most of the participants did not find wearing NIRSport particularly painful or uncomfortable. Some reported a slight pressure but they said it was a bit like wearing a "swimming cap".

The participants were asked to provide feedback on the naturalness of movement in Octave. All participants reported that the movement felt natural and they did not experience any issues regarding the walking in VR space.

Some comments and feedback are reported below:

"I was reacting as if it was real, and although I was a bit scared, I knew I was safe"

"The simulation was compelling and I enjoyed it, but the task was a bit boring towards the end"

"I was not afraid of falling. I was more fascinated. The depth makes it real"

"I lost the balance in the Pit Room even thou it was not real"

"I was impressed by the graphic. The walls looked real"

"At the beginning, I was a bit scared, but it goes away over time"

"I think the depth and 3d effect makes it look as real. It makes it feel like standing on the ledge"

"Wearing NIRSport was not too bad. You feel pressure, but it was like a swimming cap"

"I liked the VR so much that I have forgotten I was wearing NIRSport"

6. Discussion

The aim of this study was to investigate the neural basis of fear inhibition, cognitive reappraisal and inhibitory learning during virtual reality exposure. Participants were exposed to two virtual rooms, in which one had much of the floor missing, revealing a drop below. Changes in HbO concentration in the PFC were measured in three blocks using fNIRS. A key methodological objective was to maximise ecological validity by allowing freedom of movement and sight of one's own body. This was approached by combining wearable fNIRS within IPT. The stimuli was adapted from a classic VR presence experiment - Pit Room (Meehan et al., 2002), which demonstrated a psychophysiological response to virtual heights. The study hypothesised that participants exposed to the fear-evoking VR stimuli would show an increased HbO in the PFC, which would increase over the time as a neural signature of inhibitory learning within a session. While previous evidence for within-session learning has been inconclusive, this study employed a brain imaging technique with improved temporal resolution in regard to other studies. Additionally, the study hypothesized that the magnitude of the activity in the PFC would be negatively correlated with the subjective height anxiety score (HAQ scores).

Consistent with the first hypothesis, the HbO concentration changes in the MPFC and DLPFC increased significantly when participants experienced virtual heights. This was across all three blocks when the response to the pit room was compared to that of the training room. At the beginning of the exposure (early block) to the virtual height, there was a significant increase in the bilateral DLPFC. In the middle block, there was HbO increase in the bilateral DLPFC, and bilateral MPFC, Similar pattern of activation was found in the late block showing a significant increase in HbO concentration changes in the bilateral DLPFC and bilateral MPFC, however, the magnitude of activity increased as demonstrated by a number of significantly active channels and t-scores. This result was consistent with previous fMRI studies, demonstrating the role of the DLPFC and MPFC in emotional regulation (Courtin, Bienvenu, Einarsson, and Herry, 2013; Jovanovic and Norrholm, 2011; van Rooij et al., 2014). While the MPFC inhibits the amygdala activity through direct inhibitory connections, the DLPFC inhibits the amygdala indirectly through the process of cognitive reappraisal (Hartley & Phelps, 2010).

The pattern of neuronal activation showed a trend to extend from the activity in the DLPFC, then recruiting additionally the MPFC within-session across three blocks. However further analysis showed that the difference in magnitude of activation was not significant between HbO changes from the first to the last block. This could be for a few reasons. Firstly, previous studies performed on rats demonstrated that fear extinction training and new memory consolidation training might involve a gradual delayed neuroplasticity in the PFC (Takehara, Kawahara, and Kirino, 2003). The lack of within-session effects in brain activity was consistent with previous neuroimaging studies which demonstrated within-session activity reduction in the amygdala during repeated exposure to stressful stimuli, but not in hippocampus and PFC in social anxiety treatment (Åhs et al., 2017) and in spider phobia (Veltman et al., 2004). However, these studies employed PET which has limited temporal resolution. The current study employed fNIRS but did not identify significant within-session differences despite its better temporal resolution than PET. The reviews performed by Craske and colleagues (Craske and Kircanski, 2008) concluded that the current evidence is limited and provides mixed results regarding within-session learning effects in ET. Although the majority of studies do not find support for within-session habituation as a predictor of outcome in ET, still more research and evidence is needed. The lack of within-session effect may also indicate the importance of sleep in the treatment outcome. In this experiment participants only had a 20-second break between each of the blocks, which may be insufficient for learning to occur. Previous studies demonstrated that sleep following successful psychotherapy facilitates therapeutic efficacy by strengthening the consolidation of new non-fearful memory established during therapy through neuroplasticity process (Kleim et al., 2014). There is considerable evidence from neuroscience of motor control and learning that sleep enhances learning through the formation and strengthening of novel connections in the brain following skill acquisition (Albert, Robertson, and Miall, 2009). Furthermore, this study recruited healthy participants, who did not show an impaired inhibitory response, therefore limiting the scope for improvement. Perhaps those with clinically significant difficulties involving activation of the fear structure (such as in PTSD), will have a greater potential for improvement. Similarly to Amano and colleagues (Amano et al., 2016) who used fNIRS during EMDR on healthy controls, the current study detected trends rather than significant changes related to inhibitory learning in healthy participants. However, because the current study is the first one which investigates the

neural basis of fear inhibition and inhibitory learning employing fNIRS and IPT, its purpose was twofold. Firstly, the study assessed whether the combination of such technologies has the potential to trigger and measure inhibitory response in general. Secondly, this study served as a baseline for next the study, which investigated inhibitory response and inhibitory learning in VRET in phobic participants.

The strong negative correlation between HAQ and HbO in right the DLPFC suggests that participants who had lower acrophobia score, also had a greater ability to suppress fear during the exposure to the virtual height and vice versa. The magnitude of activity in right the DLPFC could potentially give therapists an additional objective measure of the severity of phobia or anxiety, and levels of fear. Recently some researchers called for further study of objective indicators of anxiety disorders. Christova and colleagues (Christova, James, Engdahl, Lewis & Georgopoulos, 2015) proposed using magnetoencephalography (MEG) as a potential tool to detect neural biomarkers for diagnosing PTSD. Employing brain imaging as a diagnostic tool could help to identify not only abnormalities in brain networks associated with these disorders but also its magnitude in order to assist in the objective tagging of clients to determine who is to be prioritised based on greatest clinical need. This could be especially useful considering recent tragic events involving terrorist attacks or disasters, where large numbers of people were affected in a single incident, resulting in pressures on existing services (Moran, Webb, Brohi, Smith, and Willett, 2017). With hundreds of individuals at risk of developing a phobic response, anxiety disorder, or PTSD following such incidents, fNIRS would appear to be a useful diagnostic tool. This brain imaging tool may offer a helpful and welcome solution due to its portability, usability, and low cost. fMRI and PET scanners are expensive to acquire and maintain (Crosson et al., 2010) therefore it would be costly for clinics to employ them as a diagnostic tool. Moreover, fMRI and PET scanners could potentially induce anxiety in susceptible participants because of their confined design and noise (Crosson et al., 2010). Due to their stationary nature, unlike fNIRS they cannot be relocated to different clinics or even to patient's home. Furthermore, fNIRS could constitute not only a good diagnostic tool, but also provide information about the progress of the treatment for monitoring not only within-session brain activity during the treatment but also changes in the brain function after the treatment to verify patient's improvement and efficacy of the therapy (Amano et al., 2016). Regarding

physiological response, there was no significant difference in HR between the pit room and the training room. Although Meehan et al., reported that the HR increased an average 6.3 (BPM) in the pit room compared to the training room (Meehan et al., 2002), this study failed to replicate this result. The analysis showed a trend which might indicate that when the participants performed a task in the Pit Room, the average HR increased by 1.24 BPM. The lack of the significant result may be due to two reasons. Firstly, this study involved only healthy participants who did not suffer acrophobia. Even though exposure to height would trigger a fear response in most of the individuals, still the magnitude of this response would be significantly lower than in those who suffer acrophobia. Wiederhold et al. (1998) demonstrated that there is a difference in physiological response between healthy participants and patients when they are immersed in evocative VR. Phobic participants show a stronger response when exposed to virtual threat than non-phobic participants (Wiederhold et al., 1998). Roy et al., (2013) compared HR responses from recently deployed military service members during fear conditioning and the task performed in combat-related virtual reality – "Virtual Iraq". There were two conditions in VR task – danger and safety. The sample was divided into two groups – those who scored high on the PTSD checklist (PCL-M), and those who scored low. During fear conditioning, there were three blocks – early, middle and late. The results of the experiment showed that the high symptom group had significantly greater ΔHR changes than those who scored low on the PTSD checklist. Although in the low symptom group ΔHR increased slightly between safety and danger condition across the blocks, the effect was not as strong as in those who scored high on the PTSD checklist (Roy & Costanzo, 2013). Schafer et al also failed to detect a significant increase in HR during exposure to virtual height in healthy participants (Schafer, Koller, Diemer, & Meixner, 2015).

The second and most possible reason why this study failed to obtain a significant result in HR measurement was the sample size. Due to the motion artifacts, only data from twelve participants was analysed, which may not be enough to obtain a statistical power. Moreover, the data that was removed was mainly from female participants. One of the most notable disadvantages of Bioharness learned from this experiment was that the device is less usable in female participants. Due to the design of the Bioharness, it was very challenging to fit some female participants with the device due to the anatomy. The validity and reliability of the device were demonstrated in a few

previous studies, however, one of the limitations of those studies was that the sample included only male participants (Hailstone & Kilding, 2011; Johnstone et al., 2012a, 2012b). Therefore, a reasonable resolution must be found in order to make the Bioharness more usable for female participants.

The analysis showed no difference in ΔHR between blocks. This outcome again is probably related to the small sample size for the HR data. An alternative reason could be that the study involved only healthy participants. Previous studies did not support the assumption that HR decreases significantly over the time in evocative VR in healthy participants. Jang et al., (2002) in his study which involved non-phobic participants exposed to the two VR scenarios of which one was flying and the other was driving while measuring HR, HRV, SC and presence. They found that SC increases when the participant is placed in stressful VR, however, decreases after 7 minutes. On the contrary, the same result was not found for HR and HRV as the result of the study did not show a significant decrease in HR during a single exposure. Another study recruited 44 participants with a fear of height in order to investigate the relationship between within-session habituation and a treatment outcome. Participants received in vivo exposure therapy for acrophobia while Subjective Units of Distress (SUDS), Behavioural Avoidance Test (BAT) and HR were measured. Neither changes in SUDS scores or heart rate were associated with the treatment outcome. The results of the study did not support the relationship between within-session habituation (decrease in HR) and a successful treatment outcome. On the contrary, they confirmed the relationship between-session habituation and the treatment outcome, and moreover, there was no relationship between within- and between-session habituation as measured by HR and subjective reports (Baker et al., 2010). The review performed by Craske (2008) demonstrated mixed results regarding the relationship between HR and WSH. On the one hand, some researchers reported a correlation between HR and WSH (Pitman et al., 1996). On the other hand, others failed to demonstrate that HR decreases over the single session (Wilhelm et al., 2005)

Although other neuroimaging studies using fNIRS or fMRI demonstrated a strong correlation between activity in the PFC and elevated HR during stressful tasks in the real word (Sakatani, 2012; Shi et al., 2014; Wang et al., 2005), this study did not find such a correlation in VR when participants were exposed to the threatening

stimuli. The lack of the significant result could be again due to the small sample size for the HR data, which was insufficient to detect a statistical power. Moreover, there are no studies which would investigate the correlation between the PFC activity and HR in VR, therefore it is difficult to make any claims, however, the hypothesis had to be rejected.

In addition, VR technology offers a potential in diagnosis and treatment of anxiety, phobias and PTSD. Firstly, because it allows creating scenarios that would be difficult or unsafe to create clinics or during in-vivo exposure. This could include scenarios of terrorist attacks or disasters. Moreover, such scenarios are highly controllable and can be personalised for each patient. Secondly, VR immerses the participant into simulations which resemble life-like scenarios, therefore promoting ecological validity. Some VR systems, such as HMDs are portable and can be moved between clinics or even to the patient's home. CAVE-like systems are more expensive and non-portable, however, they allow for more naturalistic movement and interaction. In Meehan's Pit Room experiment, which employed HMD, over 25% of participants scored above the high threshold in SUS questionnaire (Meehan et al., 2002). In this experiment, over 39% of participants reported a high presence. This result might indicate that CAVE-like systems such as the Octave, could potentially be better than HMDs regarding the capability of triggering presence and anxiety (Juan and Pérez, 2009). It was demonstrated in a few studies that the presence during VRET is an essential factor for the therapy to trigger emotions and thus enhance a therapeutic effect (Alsina-Jurnet, Gutiérrez-Maldonado, and Rangel-Gómez, 2011).

In Meehan's experiment over 25% of participants scored above the high threshold in SUS questionnaire (Meehan et al., 2002). In this experiment, over 39 % of participants reported a high presence. This result indicates that cave-like systems such as Octave might be superior to HMDs regarding the capability of triggering presence, and therefore a capability to facilitate the naturalness of response. It was demonstrated in a few studies that the presence during VRET is an essential factor for the therapy to trigger emotions and thus therapeutic effect (Alsina-Jurnet, 2011). However, this experiment did not find the correlation between HbO in the DLPFC or MPFC and SUS scores. Some previous studies suggested that significant correlations between subjective presence and fear ratings are more often found in clinical samples

than healthy controls in VR studies (Alsina-Jurnet, Gutierrez-Maldonado, & Rangel-Gomez, 2011; Bouchard, St-Jacques, Robillard, & Renaud, 2008; Diemer et al., 2015; Peperkorn & Mühlberger, 2013; Price, Mehta, Tone, & Anderson, 2011). The lack of correlation may be related to the fact that this experiment involved only healthy participants. On the other hand, some researchers argued the reliability of the SUS questionnaire. For that reason, the upcoming experiment will use an alternative presence questionnaire - Igroup Presence Questionnaire (IGP). The IGP distinguishes between three different levels of presence (spatial, involvement and realness) and it was verified as a valid and reliable tool for measuring subjective feeling of presence (Schubert, Friedmann, & Regenbrecht, 2001).

7. Conclusion

The aim of this study was to investigate the neural basis of inhibitory response, inhibitory learning and cognitive reappraisal during virtual reality exposure. This is the first study which combined fNIRS and IPT for this purpose. Results revealed increased HbO concentration in the DLPFC and MPFC during exposure to the fear-evoking VR, indicative with cognitive reappraisal and fear inhibition. The result is consistent with previous neuroimaging studies that had not used VR. Within-session inhibitory learning was measured at much higher temporal resolution than in previous studies. Consistent with previous studies a trend was shown in inhibitory learning within the session. This was the first study that investigated the neural correlates of fear inhibition and inhibitory learning by combining a VR display in which people can move around and see their body, with wearable neural imaging that gave an acceptable compromise between spatial and temporal resolution. This perhaps provides more ecologically valid results, moreover, this approach allows a more natural experience and response than previous combinations of VR and neural imaging, used to evoke and measure inhibitory response and learning. This is because it allows the participant/client to move freely within a comfortable space, rather than confining, restricting or taking them away from the comfort of others, such as a therapist.

These findings have a potential impact across understanding, diagnosis, assessment and treatment of a range of mental disorders. In terms of understanding, it contributes to the evidence that little inhibitory learning takes place during virtual

reality exposure therapy and that inhibitory response during a virtual reality exposure session is consistent with that in imaginal therapy. A new and relatively low-cost method for obtaining a direct objective measurement of inhibitory response to controllable and repeatable stimuli has been demonstrated that could aid diagnosis and assessment. Such a measurement could also aid therapists to determine the appropriate dose and, across sessions, measure treatment outcome. Deficits in inhibitory function manifest in anxiety disorders, specific phobias and PTSD (Jovanovic et al., 2008). Controllably evoking and measuring inhibition is useful in understanding, diagnosis and treatment. The method used in this study is as effective as others in evoking and measuring inhibitory response, however, it is potentially more natural. This naturalness may contribute to improved ecological validly and be less distressing for some clients. Perhaps in the future, this might lead to adaptive immersive neurofeedback techniques for therapy. The approach has an application, particularly where fear could be induced by the technology itself, for example by separation from a therapist or restricting movement, which play a crucial role in therapy.

Chapter 7 Experiment III: The neural basis of fear inhibition in VRET in acrophobic participants

1. Chapter overview

This chapter describes the VRET experiment involving participants with moderate acrophobia. This experiment built upon the outcome of the pit room experiment which involved healthy controls. At first aims and objectives of this project are described, and then the research question, hypothesis and variables. The next section introduces the experimental protocol. Then the chapter describes how the data was analysed and the result of the study. At the end, the chapter presents the conclusion and discussion.

The previous chapter has shown that people reporting none or low acrophobia show increased brain activity in the DLPFC and MPFC indicative of cognitive reappraisal and fear inhibition. The current study investigated further how VRET impacts on the PFC activity in participants with a moderate fear of heights, when the change occurs and how many sessions are needed in order to restore the PFC activity to normal. Previous studies demonstrated that successful ET increases neural activity in the DLPFC and MPFC (Hauner et al., 2012; Roy, Costanzo, Blair, & Rizzo, 2014). However, there has been little study of within-session effects during ET or the impact of VRET on functional brain activity. Moreover, there are no studies that have looked at both at the same time. Although VRET has been combined with neuroimaging before (Roy et al., 2010), previous studies have used technologies that do not adequately balance the quality of measurement and naturalness of response. Specifically, they employed technologies which limit the participant's locomotion and obstruct the view of one's body. Therefore, to promote ecological validity, this study employed wireless brain imaging and a large CAVE-like Immersive Projection Technology (IPT). Combining wireless fNIRS with IPT systems allows a more natural movement without losing sight of one's own body while maintaining data quality.

This study used the same experimental protocol as the previous one, however with a different cohort and the number of sessions was increased. Moreover, additional measures were added (Electrodermal Skin Activity and Subjective Units of Distress Scale) to the experimental design in order to investigate if the PFC activity correlated

with other measures. The IPGroup Presence Questionnaire was used to measure presence (Schubert et al., 2001).

The simulation was improved by upgrading the software (Unity academic version 5.1.0f3 64-bit and MiddleVR version 1.6.1f6). NIRS data acquisition (NIRStar version 2014) and data analysis (NIRSLab version 2017.6) were also upgraded providing a better recording and analysis tools due to the several fixed bugs.

2. Methods

2.1. Aims and objectives

The primary aim was to measure brain activity within the PFC indicative of fear inhibition and cognitive reappraisal, both within and across VRET sessions, using a combination of technologies that provide a reasonable resolution while promoting ecological validity and fit to clinical use. The secondary aim of this study was to measure within- and between-session psychophysiological response to VRET as an indicative of emotional arousal and fear. Moreover, this study also measured within- and between-session subjective fear ratings. Fourteen volunteers (N = 14) with mild acrophobia assessed with Height Anxiety Questionnaire (Cohen, 1977), took a part in a three-session VRET involving two virtual rooms, in which one appeared to have much of the floor missing, revealing a (virtual) drop below. No other therapy was given. Neural activity was measured both within- and between-sessions. For within-session changes in oxygenated haemoglobin concentration (HbO) in the PFC were measured in three blocks using fNIRS. For between-session effects, this study investigated the difference in HbO in the PFC between the first block of the first day and the last block of the last day of exposure. A key methodological objective was to maximise ecological validity by allowing freedom of movement and sight of one's own body. This was approached by combining wearable fNIRS within IPT. The stimuli were adapted from a classic VR presence experiment - Pit Room (Meehan et al., 2002), which demonstrated a psychophysiological response to virtual heights.

2.2. Research question

This study aimed to answer several questions about how VRET with improved ecological validity impacts on the prefrontal activity in acrophobic participants. Do individuals with fear of heights show decreased brain activity in the DLPFC and

MPFC when exposed to virtual heights? Can VRET normalise the PFC activity to closer to the one that was demonstrated in healthy participants? If so, how many VRET sessions are necessary to detect significant changes? Do changes occur within a single session? Are those changes correlated with other psychophysiological measures? Can VRET trigger emotional arousal in acrophobic participants? Does the arousal decrease within a single or across multiple sessions? Does it correlate with other measures? Can the within-session fear response be measured using self-reports? Does it decrease within single or multiple sessions? Are self-reports correlated with other measures? Finally, does the feeling of presence in VRET impacts on PFC activity, arousal and subjective fear ratings?

2.3. Hypothesis

The study hypothesized that: (1) participants with moderate acrophobia exposed to virtual heights will show decreased activity in the PFC when exposed to virtual heights at the beginning of VRET as measured by HbO; (2) the activity (HbO) in the PFC will increase over time from block to block; (3) the activity (HbO) in the PFC will increase over time from session to session; (4) SUDS will drop over time from block to block (5) SUDS will drop over time from session to session; (6) activity in the PFC would be negatively correlated with SUD scores; (7) activity in the PFC would be negatively correlated with the subjective height anxiety scores (HAQ scores) at the beginning of the VRET; (8) activity in the PFC would be positively correlated with the subjective height anxiety scores (HAQ scores) at the beginning of the VRET at the end of the VRET; (9) participants with moderate acrophobia will show increased HR when exposed to virtual heights at the beginning of VRET (10) HR will decrease over time from block to block; (11) HR will decrease over time from session to session; (12) HR will be positively correlated with SUD scores; (12) HR would be positively correlated HAQ scores (13) HR will be positively correlated with EDA (14) participants with moderate acrophobia will show increased EDA when exposed to virtual heights at the beginning of VRET (10) EDA will decrease over time from block to block; (11) EDA will decrease over time from session to session; (12) EDA would be positively correlated with SUD scores; (12) EDA would be positively correlated HAQ scores

2.4. Participants

Fourteen (n = 14) participants (twelve females, two males, mean age M = 42.30, SD = 16.57) with a moderate fear of heights were recruited from the Anxiety UK charity (4) and staff and student communities of the Universities of Salford (1) and Manchester (9). Each participant was pre-screened for fear of heights using Height Anxiety Questionnaire (Cohen, 1977). Only participants with a medium fear of heights, who scored higher than one-third of the questionnaire scores, but lower than three-thirds (mean score above 41 = 30% and below 90) were invited to participate (Steinman & Teachman, 2011). Participants were also excluded from this study if they had suffered an epileptic episode, have felt unwell during a virtual reality or 3D cinema experience, often suffer from a migraine, or have skin that is excessively sensitive and thus might be damaged by sensors. All participants were presented with the Participant Information Sheet (PIS), which advised them of the potential risks associated with the experiment such as cybersickness and discomfort related to the brain monitoring module. The PIS also informed participants about data anonymization and confidentiality and they were advised that they could withdraw from the experiment at any time without giving reasons. Written informed consent was obtained from all participants prior to the experiment. Ethical approval HSCR 15/88 was granted by the University of Salford's Health Sciences Ethics Committee.

2.5. Measures

Brain activity measured by Functional Near-Infrared Spectroscopy (fNIRS) - measures changes in a hemodynamic response associated with the neural activity from the sub-surface of the brain using near-infrared light (Ferrari & Quaresima, 2012). Brain response to the stimuli is associated to the increased local oxygen consumption leading to the increased cerebellar blood flow (CBV) and volume (CBV) which results in an increase in an oxygenated haemoglobin (HbO) and a total haemoglobin (HbT), and a decrease in deoxygenated haemoglobin (HbR) (Strangman et al., 2002). fNIRS can measure changes in HbO and HbR concentration due to their distinct characteristic optical back-scattering properties in near-infrared spectral range (Villringer & Dirnagl, 1995). This project mainly focuses on the results based on average HbO concentration changes, as this is considered as the most sensitive parameter of task-related hemodynamic responses with the close correlation to BOLD signal as measured by

fMRI, and it has a better signal-to-noise ratio (Doi, Nishitani, & Shinohara, 2013; Y Hoshi, Kobayashi, & Tamura, 2001; Strangman et al., 2002).

- Height Anxiety Questionnaire (HAQ) - developed by Cohen (1977) - a self- report measure which assesses the severity of anxiety related to heights. The HAQ is a 20-item questionnaire describing situations that involve heights. Participants rated their anxiety on the 7-point scale ranging from 0 (not anxious at all) to 7 (extremely anxious). The HAQ was administered to participants 24 hours beforehand in order to assess the severity of the fear of heights.
- Subjective Unit of Discomfort Scale (SUDS) - is a self-report which measures the subjective level of distress or anxiety experienced by a participant on a scale 0 (not anxious at all) to 100 (extremely anxious) (Wolpe, 1973).
- Igroup Presence Questionnaire (IPQ) - is the 14-item scale used for measuring subjective sense of presence in VR. Participants are asked to rate their presence on a 7-point Likert scale. The three subscales which assess different components of presence: spatial presence (consisting of five items), involvement (consisting of four items) and realism (consisting of four items). Moreover, there is one additional item to assess general presence (Schubert et al., 2001).
- Simulator Sickness Questionnaire (SSQ) - is the 16- item tool that assesses possible side effects of VR exposure on a 4-point Likert scale (Kennedy & Lane, 1993).

Both IPQ and SSQ were administered at the end of the last session to assess and get feedback regarding general experience during the experiment.

2.6.Response and explanatory variables

In this study following response variables/ depended variables were measured:

- HbO (changes in oxygenated haemoglobin levels) between the pit room and the training room
- ΔHR (changes in HR in BPM) between the pit room and the training room
- skin conductivity (EDA)
- subjective fear ratings (SUDS)
- initial fear of heights (HAQ)
- subjective feeling of presence (IPQ)

Three explanatory variables/independent variables were:

- Conditions – training room and pit room
- Blocks - early, mid and late within VRET session
- Sessions – first, second and third day of VRET

2.7. Instruments and equipment

Immersive Projection Technology (IPT) Octave

Octave system was described in previous chapters – chapter 4, section 6.2 and chapter 5, section 2.4. No changes were made in the hardware setup.

fNIRS NIRSport

Functional Near-Infrared Spectroscopy (fNIRS) is described in previous chapters: chapter 4, section 6.1, chapter 5, section 2.4 and chapter 6, section 2.5. No further changes were made in NIRSport setup since the study, which involved healthy volunteers.

Zephyr Bioharness HR Monitor

Zephyr Bioharness (Zephyr Technology, Annapolis, US) is described in chapter 4, section 6.3 and chapter 5, section 2.4.

Edu Logger GSR Sensor

EduLogger is a compact and wireless physiological monitoring device. Electrodermal activity was recorded with 10 nS resolution and sampling rate 20 S/seconds. Electrodes were attached to the index and ring fingers of the non-dominant hand to improve the comfort of participants.

Network

The network is described in chapter 5, section 2.4. No further changes were made in the network setup.

Stimuli

This study used the same Pit Room simulation that was used in the study with healthy controls described in chapter 6, section 3 (Figure 30). No changes were made in the environment, however, the software was updated to optimise the simulation. The scenario was created using Unity 5 game engine (academic version 5.1.0f3 64-bit)

(https://unity3d.com/). To run the simulation in Octave MiddleVR for Unity (version 1.6.1f6) was used http://www.middlevr.com/middlevr-for-unity/.

Figure 30 The Pit Room - Experimental stimuli: left - view in the training room, right – view looking down into the room below.

2.8. Procedure

Each participant was provided with the Participant Information Sheet and Height Anxiety Questionnaire (HAQ) at least 24 hours prior to the experiment. On arrival they were instructed about safety in Octave and given a consent form to sign if they agreed to do the experiment. Then they were introduced into the Octave and the simulation. The researcher explained the task and instructed participants about the level of the movement they were allowed to perform in order to minimise the motion artifacts in the data. Then participants were allowed to familiarise themselves with the virtual environment for about 5 minutes. Following practice and familiarisation participants were fitted with the NIRSport. The fNIRS system was then calibrated for the optimal amplitude and signal-to-noise ratio. The quality of the optical densities was then assessed visually by the researcher. If the level of the noise in the data was too high, the researcher readjusted any noisy optode ensuring optimal contact with the scalp. The retaining cap, which reduces the ambient light and reduces the risk of optode displacement, was placed over the EasyCap. The data was recorded using a battery-operated fNIRS system which is powered by the laptop and the data is saved and stored on the hard drive. The fNIRS battery and the laptop were placed in the backpack which must be worn by a participant during the whole experimental session. Then participants were fitted with Bioharness and EduLogger. After the preparation, participants were led to Octave and asked to perform a simple walking task on the wooden plank in both training and pit room. Participants were asked to rate their

subjective units of distress (SUDS) of fear on a Likert scale ranging from 0-100, where 0 indicated “not at all anxious”, and 100 indicated “extremely anxious. The researcher recorded the SUDS scores during each break between blocks. The procedure for each of the three sessions was the same, except that the familiarisation phase was conducted only on the first day. After each session, participants were asked to return for the next session the next day or maximum after 48 hours. This approach was taken in order to minimise the risk of participants being exposed to heights in real life between sessions. As the aim of this study was to investigate only the effect of virtual heights on acrophobia, participants were instructed to avoid any situations involving heights in daily life between sessions, until the experiment is completed. After the last sessions participants were asked to fill two questionnaires: IPGroup Presence; and Cybersickness in order to evaluate user’s general experience related to the quality of the VR system and simulation (Kennedy & Fowlkes, 1992). Afterwards, there was a short informal interview with the researcher in order to gather feedback about the experiment and ensure that the participant experienced no side effects and could safely leave the lab. An example of a recorded experimental session with acrophobic participant can be found via following the link - https://youtu.be/Z_4bItw3pjU

2.9. Experimental design

This study employed the same experimental design (Figure 31) that was used in the study with healthy controls, which is described in chapter 6, section 3. The only difference was that during the between-block breaks, participants were asked to rate their discomfort on the SUDS scale. The experimenter was present in the experimental area during the whole experiment. The presence of the researcher also provided a safety cue for the participant to minimise a risk of anxiety when exposed to virtual heights. The same procedure was repeated for all of three sessions.

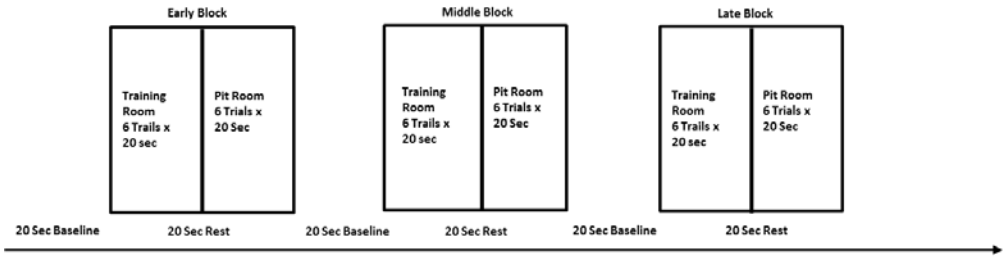

Figure 31 The experimental design – One session consisted of three blocks – early, middle and late, separated with 20-sec baseline. Each block consisted of two conditions – training room and pit room separated with twenty seconds rest. The same procedure was repeated over three VRET sessions.

2.10. Data Acquisition

The data was acquired with the NIRStar acquisition Software (version 2014, NIRX Medical Technologies LLC) running on Windows 7 (64-bit) laptop with Intel® Core™ i5-4200 CPU @ 1.60 GHz 2.30 GHz with 4.00 GB RAM. The blood oxygenation was measured at two near infra-red light wavelengths of 760nm and 850nm, with the sampling rate 7.81 Hz.

2.11. Data Analysis

Preprocessing and statistical data analysis was performed according to the same procedure as for the study on healthy controls using Statistical Parametric Mapping NIRS-SPM (SPM 8) (Friston, 2007; Tak, 2009; Ye et al., 2009) analysis tool implemented in NIRSLab, which was updated to the newest version (version 2017.6) to identify brain regions activated during the virtual height exposure.

Data was modelled with GLM. The regressors were modelled via convolution by the hemodynamic response function provided by SPM8. Discrete cosine transform basis function was used for temporal filtering and precoloring HRF was used for the serial correlations. In the first level channel-wise analysis for individual participant and block t-contrasts were then created for average HbO and HbR concentration changes, to generate statistical parametric maps of activation for two regressors: training and pit, for each channel and each subject. The data for both conditions (training and pit) was baseline corrected using a baseline recorded prior to each of the blocks separately. SPM t-maps were generated by using two contrasts: training-pit and pit-training, and thresholded at $p < 0.05$ (corrected). At the group analysis SPM HbO t– statistics were calculated to identify the channel significantly activated by exposure to virtual heights with the significance level set at $p < 0.05$ (corrected). The estimated anatomical location of each channel was determined using anatomical locations of international 10-10 system cortical projections of EEG sensors (Koessler et al., 2009).

Neuronal changes associated with between-session effects were determined by calculating the differences between the last block of the last session and the first block of the first session. Firstly, the beta coefficients were retrieved from the first level analysis for each subject, channel, block and session. Then results from the first session were extracted from results from the last session using MATLAB (R2017b), resulting in sets of paired betas for each subject and channel. The paired-beta images were

further analysed using group-wise contrast analysis in NIRSLab SPM. The significance level was set up at $p < 0.05$ (corrected).

In order to investigate the effect of within-session changes in brain activity, HbO beta values were extracted from the first level analysis for each participant, session, block and channel. These were averaged across session and block and further analysed in SPSS, due to the limitations of NIRS software.

The Region of Interest (ROI) analysis was performed according to the same procedure as for the study involving healthy controls. The correlation analysis was performed to investigate the correlation between within- and between-session brain activity in each of the ROIs and physiological data (HR and EDA) and SUDS.

Psychophysiological (HR and EDA) data was analysed using SPSS (IBM SPSS, Version 24). All the data were checked for normality using SPSS function "Explore" and Shapiro-Wilk test. The SUDS data which deviated from normal distribution was analysed using non-parametric Friedman and Spearman's correlation tests. Descriptive statistics (means, medians and standard deviations) were calculated for all the questionnaires.

Preparation and analysis of the questionnaire data were conducted in SPSS (IBM SPSS, Version 24). All the data were checked for normality using SPSS function "Explore" and Shapiro-Wilk test. The SUDS data which deviated from normal distribution was analysed using non-parametric Friedman and Spearman's correlation tests. Descriptive statistics (means, medians and standard deviations) were calculated for all the questionnaires.

3. Results

3.1. Within-session learning

fNIRS data

SPM contrast analysis for the group effects (pit room > training room), at the significance threshold level $p < 0.05$ (corrected), revealed no significant difference between training and pit conditions during both first and second sessions of the experiment. Moreover, for both the first and second sessions, there was no significant effect of the blocks. However, the group demonstrated significant results during the

third session. All the results from the third session are summarised in table 4 (t-values, Broadman areas and anatomical labels) and figure 32 (SPM t-maps).

Session 3

Block 1 - SPM contrast analysis (pit room > training room) at the significance threshold level $p < 0.05$ (corrected), revealed a significant increase of HbO concentration changes in the bilateral DLPFC.

Block 2 - SPM contrast analysis (pit room > training room) at the significance threshold level $p < 0.05$ (corrected), revealed a significant increase of HbO concentration changes in the bilateral DLPFC and bilateral MPFC.

Block 3 - SPM contrast analysis (pit room > training room) at the significance threshold level $p < 0.05$ (corrected) revealed a significant increase of HbO concentration changes in the bilateral DLPFC and bilateral MPFC.

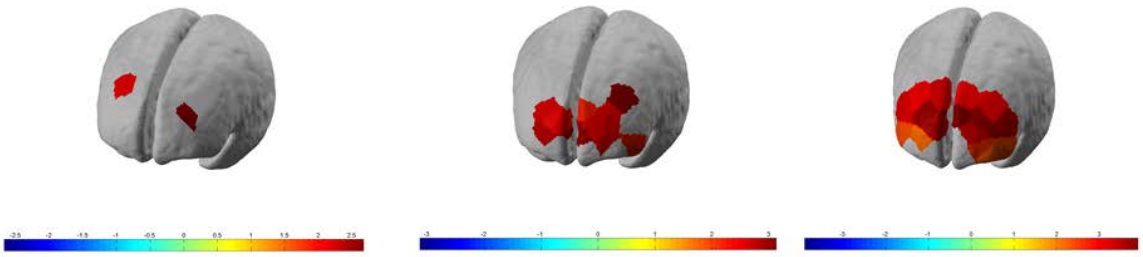

Figure 32 Session 3 - group (n=13) SPM activation t-maps of HbO pit room > training room threshold level p < 0.05 for each of 3 blocks 1- early, 2- mid and 3-late, respectively. The colour bar represents t-value

Table 4 Summary of results for all three blocks (channel number, t-value, anatomical label and Brodmann areas). All p values < 0.05 corrected

Block	Channel	T - value	Label	Brodmann Area
1	Channel 5	2.68	DLPFC L/ Frontal Eye Fields	BA 8/9
	Channel 17	2.13	DLPFC R/ Frontal Eye Fields	BA 8/9
2	Channel 2	3.13	Frontal Eye Fields	BA 8
	Channel 3	2.20	DLPFC L	BA 46
	Channel 5	2.54	DLPFC L/ Frontal Eye Fields	BA 8/9
	Channel 6	2.58	MPFC L	BA 46
	Channel 7	2.51	DLPFC L	BA 9
	Channel 9	2.24	DLPFC B	BA 9
	Channel 12	2.97	DLPFC B	BA 9
	Channel 14	2.51	DLPFC R	BA 9
	Channel 15	2.64	DLPFC R/ Frontal Eye Fields	BA 8/9
	Channel 16	2.79	MPFC R	BA 46
3	Channel 1	3.42	DLPFC L	BA 46
	Channel 2	2.96	Frontal Eye Fields	BA 8
	Channel 3	3.38	DLPFC L	BA 46
	Channel 4	2.23	MPFC L	BA 10
	Channel 5	3.55	DLPFC L /Frontal Eye Fields	BA 8/9
	Channel 6	2.68	MPFC L	BA 10
	Channel 7	3.21	DLPFC L	BA 9
	Channel 8	2.29	Frontal Eye Fields L	BA 8
	Channel 9	3.91	DLPFC R	BA 9
	Channel 10	3.19	Frontal Eye Fields R	BA 8
	Channel 14	3.66	DLPFC R	BA 9
	Channel 15	3.67	DLPFC R /Frontal Eye Fields	BA 8/9
	Channel 16	2.11	MPFC R	BA 10
	Channel 17	2.97	Frontal Eye Fields R	BA 8
	Channel 18	3.25	DLPFC R	BA 46
	Channel 20	2.42	DLPFC R	BA 46

The analysis did not reveal any significant results for the first two sessions of the experiment in relation to within-session effects. However, there were significant results for the third session. Mauchly's Test of Sphericity indicated that the assumption of sphericity had not been violated χ^2 (2) = .467, p = .792. A 3x2 repeated measures ANOVA with two within-subject factors – block (early, mid and late) and condition (training and pit), revealed a significant effect of the block F (2,24) = 5.352, MSE = 1.8204E-7, p = .012, ηp^2 = .308, and a significant effect of the condition F (1,12) = 21.163, MSE = 1.3122E-7, p =. 001, ηp^2 = .638. The interaction between block and condition was not significant F (2, 24) = 2.802, MSE = 3.4057E-8, p = .081, ηp^2 = .189. Post hoc comparison using Bonferroni correction indicated that HbO concentration changes were significantly higher in the pit room than in the training room (mean difference in beta values = 0.000377, p = .001). There was no significant effect of the block (p = .081). Additionally, there was a non-significant trend (below the threshold) towards an increase in the average brain activity between the first and the third block during the third session (mean difference in beta values = 0.000377, p = .039).

SUDS

Means, medians and SDs for SUDS during VRET are presented in table 5. The Friedman test demonstrated that there was a significant reduction in SUDS depending on the block and across all three sessions of VRET χ^2 (8) = 62.387, p = 0.001. Post hoc analysis was conducted using a series of Wilcoxon signed rank tests.

Session 1 - The results showed that SUD scores dropped significantly between first and second block (Z = -1.994, p = .046) and second and third block (Z = -2.588, p =.010).

Session 2 - The results showed that there was a significant difference in SUD scores which dropped significantly between first and second block (Z = -2.739, p= .006) and second and third block (Z = -2.428, p = .015).

Session 3 - The results showed that there was a significant difference in SUD scores which dropped significantly between first and second block (Z = -2.598, p= .009) and second and third block (Z = -2.622, p = .009).

Table 5 Subjective Units of Distress for each session and each block – means, standard deviations and medians

SUDS	*M*	SD	Median
Day1_Block1	53.0769	18.87883	50.0000
Day1_Block2	50.0000	19.03943	50.0000
Day1_Block3	43.8462	15.56624	45.0000
Day2_Block1	43.4615	14.19868	40.0000
Day2_Block2	38.0769	14.22124	40.0000
Day2_Block3	34.2308	13.66964	30.0000
Day3_Block1	32.3077	15.76063	30.0000
Day3_Block2	25.7692	14.83888	20.0000
Day3_Block3	20.3846	12.98421	20.0000

Psychophysiological data

The analysis showed no significant effects of the session, block and condition for both HR and EDA. Moreover, there was no correlation between HR and EDA with any other measures. For that reason, the psychophysiological data was removed from further analysis.

3.2. Between-session learning

fNIRS data analysis results

SPM contrast analysis [(last session > first Session) (pit room> training room)] at the significance threshold level $p < 0.05$ (corrected), revealed a significant increase of HbO concentration in the left DLPFC (Figure 33).

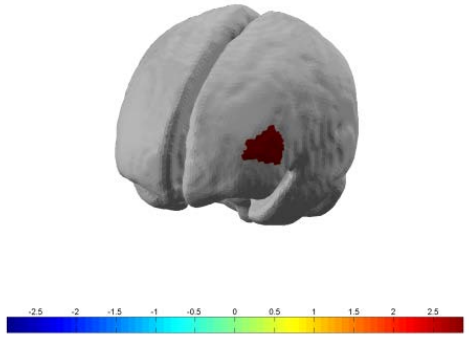

Figure 33 Between-session (last session – first session) t-contrast, revealed significant increased HbO in left DLPFC during exposure to virtual heights.

SUDS data analysis results

There was no significant drop in SUDS from the first to the second session (Z = -.240, p=.810), however, there was a significant reduction in SUDS between second and third session (Z = -2.684, p =. 007).

3.3. Correlations

The correlation analysis between HAQ and each of the ROIs revealed a significant negative correlation between HAQ and HbO during exposure to virtual heights in the late block of the last session in the DLPFC R (r = -.582, N=13, p=.037, two-tailed), and in the MPFC R (r = .-679, N = 11, p = .022, two-tailed) (Figure 34). There was no significant correlation between SUDS and any of the ROIs.

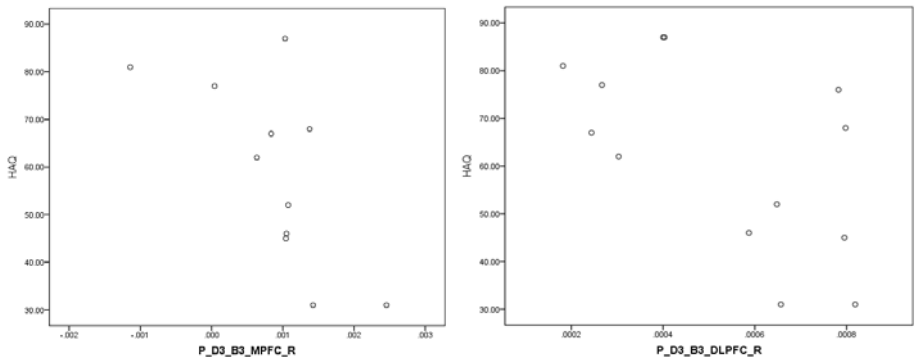

Figure 34 The correlation between the right MPFC (left) and right DLPFC activity at the end of VRET and initial severity of acrophobia

3.4. Questionnaires analysis results

The IPGroup Presence questionnaire was used in order to assess the quality of the simulation. The overall mean presence score was 4.43, SD 1.02. Results are presented in table 6.

Table 6 Presence scores measured by the IPG – means and standard deviations

Presence	*M*ean	Standard Deviations
Spatial Presence	5.29	0.93
Involvement	3.96	1.27
Realness	3.96	1.28
General Presence	5.38	0.96
Total average presence	4.65	0.95

The correlation analysis between each of the ROIs and presence revealed a significant positive correlation between HbO in the DLPFC R during exposure to virtual heights and in the late block of the last session and presence (realness) (r = .563, N = 13, p = .045, two-tailed) (Figure 35).

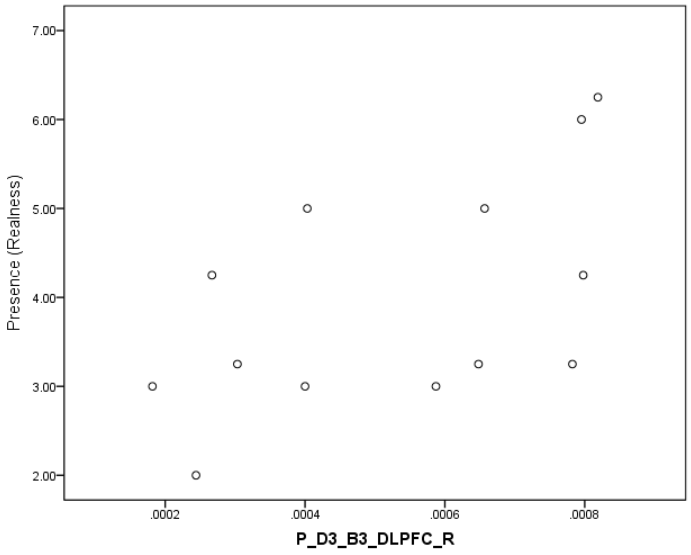

Figure 35 The correlation between the right DLPFC activity at the end of VRER subjective feeling of presence (realness subscale)

The Cybersickness questionnaire was used in order to assess the user's experience and safety related to the VR system. Most of the participants scored reasonably low on the questionnaire (mean score 3.23, SD = 3.00), only two of them experience slight symptoms of Cybersickness. The result demonstrated that the Octave system combined with fNIRS may cause only a slight cybersickness in some participants, but generally is safe for phobic participants.

4. Discussion

The aim of this study was to measure brain activity within the prefrontal cortex (PFC), both within and across VRET sessions in participants with moderate acrophobia. Additionally, this study investigated the correlation between brain activity and subjective fear ratings - (SUDS and HAQ) and emotional arousal (HR and EDA) within and between VRET sessions. A key methodological objective was to maximise ecological validity by allowing freedom of movement and sight of one's own body. This was approached by combining wearable Functional Near-Infrared Spectroscopy (fNIRS) within large Immersive Projection Technology (IPT). The stimuli were adapted from a classic VR presence experiment - Pit Room (Meehan et al., 2002), which demonstrated a psychophysiological response to virtual heights in healthy participants.

The contrast analysis showed no difference in brain activity between the training room (control condition) and the pit room (virtual height condition) at the beginning of VRET, that indicates participants with acrophobia fail to activate the dorsolateral prefrontal cortex (DLPFC) and the medial prefrontal cortex (MPFC) when exposed to fear-evoking virtual stimuli. The result is consistent with previous neuroimaging studies which suggested that participants with anxiety disorders, phobias and PTSD exhibit functional deficits in activity in the DLPFC (Etkin, Büchel, & Gross, 2015; Etkin & Wager, 2007; Hauner et al., 2012; Lipka, Hoffmann, Miltner, & Straube, 2014; Straube, Mentzel, & Miltner, 2007; Voss & Paller, 2012) and MPFC (Liberzon & Sripada, 2007; Quirk, Likhtik, Pelletier, & Pare, 2003; Shin & Liberzon, 2009; Williams et al., 2006). The current study found a trend of within-session inhibitory learning reflected in an increased brain activity at the end of VRET in the DLPFC and MPFC. Specifically, at the beginning of the third session (first block), the activity in bilateral DLPFC was found, which then extended to bilateral MPFC during

second block (after 4.2 minutes) and increased in magnitude during a third block (after 8.4 minutes). Åhs et al. (2017) found changes in brain activity after 2.5 minutes of exposure to the fear-evoking pictures, and Veltman et al., (2004) suggested that within-session habituation effect could be detected within 5-15 minutes. Both of those studies found changes in brain activity in the amygdala, but not the PFC, within a single session. It is possible that changes in the PFC occur more gradually and require more time than neuroplasticity (structural and functional changes in the brain following extinction learning) in the amygdala (Takehara et al., 2003). The current study utilised fNIRS which has limited penetration depth (Ferrari & Quaresima, 2012) and therefore cannot measure the signal from the amygdala, however, this study demonstrated that within-session neuronal changes in the PFC can be detected in VRET.

This pattern of within-session activation might indicate that VRET initially triggers cognitive reappraisal of virtual stimuli, which next leads to inhibition of irrelevant emotional responses. This could be related to the fact that DLPFC plays a role in the conscious reappraisal of emotional stimuli and the regulation of emotion (Hartley & Phelps, 2010; Rauch, Shin, & Phelps, 2006), and MPFC plays a role in emotional inhibition (Phelps, Delgado, Nearing, & LeDoux, 2004) during VRET. Although the DLPFC does not have direct neural connections to the amygdala, it may take advantage of the mechanism of inhibition and extinction learning to reduce fear response via MPFC which projects to the amygdala (Delgado, Nearing, LeDoux, & Phelps, 2008; Hartley & Phelps, 2010). The MPFC has shown to inhibit the amygdala activity in fear inhibition and extinction (Giustino & Maren, 2015; Ongür & Price, 2000). Extinction has a critical role in exposure-based treatments and it is explained by the inhibitory learning model (Craske, Treanor, & Conway, 2014). The current study demonstrated that inhibitory learning and cognitive reappraisal in VRET occur during the third session. This suggests that the VRET-induced brain function normalisation does not occur instantly, but rather requires multiple sessions to trigger changes in the brain related psychotherapeutic effect. Although some studies on traditional psychotherapy showed that even a single treatment session can impact brain activity (Hauner et al., 2012), others detected neuronal changes after the second session (Schienle, Schäfer, Hermann, Rohrmann, & Vaitl, 2007), or more sessions (Roffman, Marci, Glick, Dougherty, & Rauch, 2005). On the other hand neuroimaging studies of VRET detected brain changes after six sessions in the treatment of nicotine

cravings (Moon & Lee, 2009), or twelve or more sessions for treatment of PTSD (Roy & Francis, 2010). The current study detected changes in brain activity during the third session due to a few potential factors. Firstly, this study recruited participants with a moderate phobia, therefore fewer sessions might be required to detect changes in brain activity following VRET. Secondly, unlike previous studies, this project utilised IPT VR system combined with wireless fNIRS, which promotes naturalness of movement and response. Using these technologies may facilitate the therapeutic effect due to improved ecological validity. Especially movement can be important in the treatment of acrophobia due to its ability to trigger a higher level of anxiety which reflects activation of the fear network, which is necessary for habituation to occur (Coelho et al., 2008). Thirdly, contrary results regarding a number of sessions in VRET could be related to different experimental designs and different durations of the sessions (Van Minnen & Foa, 2006). In this experiment, one VRET session lasted only 15 minutes, which might not be sufficient for the learning to occur and that could be the reason this study failed to detect within-session effects in brain activity during first two sessions. However, studies on perceptual learning suggested that the learning of a new skill requires a period of consolidation (Hauptmann, Reinhart, Brandt, & Karni, 2005) therefore inhibitory learning might not occur during early sessions of VRET. Further studies should investigate what is the optimal duration of the efficient VRET treatment during a single exposure. Another potential factor influencing a lack of within-session effects at the beginning of VRET could be related to the motion artifacts in fNIRS data. Especially during the first session noisy channels and trials were removed from data analysis. Most of the volunteers who participated in this study did not have prior VR experience in IPT, therefore increased motion artifact during the first session could be related to an orienting response and novelty of the experience (Gogan, 1970). Further studies should consider the necessary time required for familiarisation with VR.

Between-session changes in brain activity were measured as a difference between the first block of the first session and the last block of the last session. The result revealed significant HbO increase in the left DLPFC after VRET, indicating that acrophobic participants were able to reappraise the fear-evoking stimuli after the treatment. The left lateralisation of between-session activation could be related to the previous finding which suggested that negative stimuli are processed in the right

hemisphere, and positive affect with the left hemisphere (Davidson & Irwin, 1999). Specifically, the left DLPFC supports retrieval of the memory related to positive emotional information (Balconi & Ferrari, 2013). Thus, this pattern of activation might reflect down-regulation of fear responses mediating positive reappraisals of threatening virtual stimuli after VRET.

Unfortunately, due to several technical difficulties, the psychophysiological data was not included into the analysis despite several attempts to ensure sensors placement and a further process of data clearing. Therefore, it appears that Zephyr Bioharness and NEULog EduLogger GSR sensor are not suitable for this kind of research, which will be discussed in the next chapter.

Regarding subjective fear ratings, the results demonstrated a significant drop in SUDS between second and third session, but not first and second, consistent with previous evidence from studies on CBT (Hayes, Hope, & Heimberg, 2008; Norton, Hayes-Skelton, & Klenck, 2011). Moreover, within-session reduction in subjective fear rating occurred across all three sessions. This indicates that VRET triggers within – session anxiety reduction from the first session, however between – session effects occur from the second session. This might indicate that fear inhibition learning in VRET as measured by subjective anxiety ratings does not occur instantly but requires some time for consolidation. The decrease in SUDS within- and between-session demonstrated that VRET has a potential as an effective tool in the reduction of acrophobia symptoms. Previous studies on Prolonged Exposure Therapy demonstrated that between-session reduction of the level of anxiety as measured by SUDS is an essential contributor to symptom reduction and treatment efficacy (Sripada & Rauch, 2015). In particular, studies involving patients with PTSD showed that greater reductions in SUDS between the first and last exposure session were correlated with greater PTSD symptom decrease at the end of the session and also at the follow-up assessment (Van Minnen & Foa, 2006). On the other hand, the evidence on the correlation between the within-session drop in SUDS and efficacy of the treatment is mixed (Bluett, Zoellner, & Feeny, 2014; Craske & Liao, 2012). This study demonstrated that VRET facilitates a reduction in subjective anxiety both within- and between sessions.

The current study did not find a significant correlation between brain activity and subjective anxiety. Changes in brain activity as measured by fNIRS did not exhibit the same patterns as SUDS. Other studies which investigated the neural basis of VRET did not report a correlation between brain activity and subjective reports, therefore it is difficult to compare the results of this study to previous ones (Clemente et al., 2014; Roy & Francis, 2010). Previous studies on traditional ET found a correlation between SUDS and activity in the amygdala, but not PFC (Åhs et al., 2017; Veltman et al., 2004), therefore more studies are necessary to establish if the process of neuroplasticity triggered by VRET affects brain regions differently regarding time-scale. On the other hand, this result could be related to the small sample size not being sufficient to detect the correlation. Some studies claimed that subjective or psychophysiological measures often do not correlate with brain activity (Liberzon et al., 1999; Robinson, Staud, & Price, 2013). However, studies which investigated brain function during traditional ET found a positive correlation between subjective reports and neural activity in the amygdala and insula (Schienle et al., 2007; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006), but no PFC. Limited spatial resolution of fNIRS does not allow us to measure the signal from amygdala or insula (Liu, Cui, Bryant, Glover, & Reiss, 2015), therefore it is difficult to determine if such a correlation occurs during VRET. Perhaps more fMRI studies are needed to determine the correlation between brain activity and subjective anxiety ratings in VRET. The current study, however, found a correlation between the initial level of fear of heights measured by HAQ and changes in brain activity. In particular, a negative correlation between HAQ and activity in the right DLPFC and MPFC was found at the end of the treatment which indicates that participants with an initial lower fear of heights have a better ability to reappraise and suppress the fear, and they improve more at the end of the treatment in VRET. Perhaps, participants with a higher level of acrophobia would need more sessions to improve.

Furthermore, correlational analysis of self – reported presence questionnaire data demonstrated that increase in HbO in the right DLPFC at the end of VRET was related to IPQ realness subscale in line with previous evidence (Diemer et al., 2016). The “realness” of the environment is a principal quality of presence in VR, which triggers the same emotions in users that would be experienced in the real environment. Therefore, the realness of VRET is an important factor for fear structure activation,

which allows for an extinction to occur (Price, Mehta, Tone, & Anderson, 2011). The evidence of a role of presence in VRET is mixed. While some studies reported a positive correlation between presence and level of anxiety in VRET (Price & Anderson, 2007), other studies failed to demonstrate such a relationship (Merel Krijn et al., 2004). The meta-analysis performed by Ling et al., (2014) found a medium effect size and correlation between self-reported presence and anxiety during VRET. The current study demonstrated that feeling of presence and realness of simulation also affects brain activity and leads to a better therapeutic outcome at the end of VRET. The fact that this project did not find a correlation between other presence subscales and brain activity could be related to small sample size. Another factor influencing this result might be related to the lack of prior VR experience of participants, who perhaps require a longer time to familiarise themselves with the experience in order to develop a better sense of presence.

All participants in this study reported relatively low cybersickness, and this appears to demonstrate that combining wireless fNIRS and IPT does not cause negative symptoms and indicates this combination of technology to be safe and comfortable for phobic participants.

Employing brain imaging in VRET could aim not only to understand its neural mechanisms but also could help to identify neural biomarkers as a treatment predictor to determine the intensity and length of VRET, as well as identify potential responders. Employing prediction approaches based on neural biomarkers have a capacity to ameliorate the accuracy in predetermining a therapeutic response (Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2014). Previous studies used pre-treatment brain activity as a predictor of successful Cognitive Behaviour Therapy (CBT) response. In Generalised Anxiety Disorder pre-treatment neural activity in the amygdala, anterior cingulated cingulate cortex (ACC), insula, MPFC and DLPFC during exposure to fearful stimuli was correlated with better treatment response to CBT for generalised social anxiety disorder (Klumpp, Fitzgerald, Angstadt, Post, & Phan, 2014), and social anxiety disorder (Doehrmann et al., 2013, Klumpp et al., 2015; Klumpp, Fitzgerald, & Phan, 2013). Reinecke et al. (2014) found that increased pre-treatment activation in the bilateral insula and left DLPFC during emotional regulation task predict a better response to exposure - CBT for panic disorder. In PTSD abnormal

activity in amygdala and ACC were used as a predictor of the CBT outcome (Bryant et al., 2008). Another study used Go/No-Go task to examine neural correlates of inhibitory function to predict treatment response for CBT in PTSD patients. Greater activity in the left dorsal striatal and frontal regions were correlated with better treatment response. The result showed that neural circuits underlying inhibitory control play a role in a therapy outcome (Falconer, Allen, Felmingham, Williams, & Bryant, 2013). The recently published control study by Fonzo et al., (2017) employed fMRI and TMS to investigate the neural activity underpinning emotional reactivity and regulation as a predictor of successful ET for PTSD. The authors demonstrated that activity in PFC regions during spontaneous processing of threatening stimuli may serve as a predictor of treatment response to ET in PTSD Fonzo et al., (2017). Improving mental health diagnosis process became an urgent matter recently as there is a growing number of individuals suffering PTSD and anxiety disorders as a result of terrorist attacks, refugee crisis and disasters (Moran et al., 2017). Employing VR combined with brain imaging as a diagnostic tool might further improve identification of traits to govern treatment due to flexibility and controllability of the technology.

5. Potential Efficacy of VRET – feedback from participants

After the experiment, four participants provided an update and feedback on how this study helped them to overcome their fear of heights:

Alex,

You may remember that a few weeks ago I participated in your trial to reduce phobias and fear of heights.

I'm glad to say that the effects of the trial have lasted. One of my favourite areas in Crete is the Aradena Gorge. Two years ago I stood on the bridge in the linked photograph and feel distinctly anxious look down through the wooden slats which make up the road. This year I returned to stand on the bridge and didn't feel anything like as anxious as I had on the previous visit.

http://www.cretanbeaches.com/en/gorges-and-canyons-in-crete/west-crete-gorges-chania/aradena-gorge

Many thanks for helping me overcome my fear.

Some info to add to your data. I went on a mini cruise on 3 Dec. The central staircase had stairs you could see through, I've no risers, which I hate. The drop was about 90

feet from the top stair and clearly visible. I was able to use the stairs without a qualm which I wouldn't have been able to do I assure you before the experiment so I am really pleased.

Hi Alex,

I did it today! I did both bridges top and bottom! Whoop whoop! I was still anxious but I did them! Never been on them before. Talked myself over them. After those sessions I was determined to get over those bridges. I have been visiting this place for 15 years and this was the first time I have been over them. My family were so surprised. Thank you.

Hi Alex. I tried a small step ladder and I was ok. Thank u mate x

6. Limitations of the study

There are several limitations to this study. First, the sample was small involving only 13 participants in data analysis, therefore the results require replication. Secondly, the project recruited only participants with a moderate acrophobia, therefore future studies should be conducted on a clinical sample to investigate if VRET combined with brain imaging has the same effect on participants with a severe phobia, as well as other disorders. Thirdly, all participants received only three sessions of VRET, which might be insufficient to detect lasting changes in the brain. Additionally, the duration of each session was only 15 minutes. Therefore, further studies should perhaps involve a bigger sample size, more sessions, and longer sessions. Although this study did not have a control group, it serves as a preparation for a future randomised controlled trial.

7. Conclusion

In conclusion, this study demonstrated a significant increase in the prefrontal cortex activity, indicative of inhibiting and cognitive reappraisal of fear, during the third session of virtual reality exposure therapy, in phobic participants. To date, this is the first study to examine within-session neural response to Virtual Reality Exposure Therapy. Furthermore, previous studies have demonstrated significant improvements as measured by a drop in anxiety symptoms after 8 to 12 sessions. As the neural basis for exposure therapy for phobia is thought to be similar to other disorders, such as PTSD, anxiety and addictions, these findings are likely to be transferable. A further

novelty of this experiment was the use of a combination of neural imaging and virtual reality technology that might promote ecological validity and reduces additional stress for the client. This approach thus lends itself to reproduction, with lower cost display equipment, in clinical and other settings. Such could be incorporated into understanding, diagnosis, resilience training and treatment.

Chapter 8 General Discussion

1. Introduction

The main aim of this PhD was to investigate the within- and between-session PFC response to VRET with improved ecological validity. Consistent with previous evidence from neuroimaging studies, the activity within the PFC is indicative of fear inhibition and cognitive reappraisal of emotions during exposure to evocative stimuli. A further aim was to investigate psychophysiological (HR and EDA) response to VRET as an indicator of emotional arousal consistent with the fear response. Moreover, the project investigated how objective measures correlate with subjective fear ratings (HAQ and SUDS) and presence.

Chapters 5, 6 and 7 presented experimental studies. This chapter summarises the main findings of those experiments and discusses the contribution of this project to the existing theoretical knowledge, research methodology in neuroscience and virtual reality, the potential impact on clinical applications, limitations and provides recommendations for future research.

2. Summary of Experiments and Findings

The point of departure of this thesis builds upon existing knowledge in the neuroscience of ET and VRET. Exposure Therapy (ET) demonstrated its efficacy in the treatment of phobias, anxiety and PTSD (Ougrin, 2011; Rothbaum & Schwartz, 2002), however, it suffers many drawbacks, such as high drop-out and non-response rate because of an inadequate level engagement of a patient in the treatment (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). VRET demonstrated similar efficacy in terms of symptom reduction (Opriş et al., 2012), but offers an alternative tool to facilitate patient's engagement. Various neuroimaging studies provided evidence that participants with phobias, anxiety and PTSD exhibit abnormal decreased brain activity in the PFC when compared to healthy controls (Etkin & Wager, 2007; Sartory et al., 2013). Successful ET hence normalises brain activity within the prefrontal-amygdalar fear circuit (Roy, Costanzo, Blair, & Rizzo, 2014). However, previous studies have employed technologies which restrict people's movement and

hide their body, surroundings and therapist from view. This project used an unprecedented combination of brain imaging and VR technology - Functional Near infra-red Spectroscopy (fNIRS) and Immersive Projection Technology (IPT), to avoid these drawbacks. Although there are a few studies which investigated the effect of VRET on brain function after treatment, this study utilised technologies which promote ecological validity to measure brain changes after VRET treatment. Furthermore, there are no studies which measured brain activity within VRET session to investigate at which point the improvement occurs, how many sessions are necessary and how long the exposure should last.

The pilot study had two main aims. Firstly, the study was conducted to investigate the PFC neuronal activity and psychophysiological response underpinning fear inhibition and emotional reappraisal in healthy participants exposed to evocative VR with improved ecological validity. This was approached by combining wireless brain imaging device – fNIRS with a large CAVE-like VR display system – Octave. The secondary aim was to test the feasibility of the protocol in terms of the design, integration of technology, utility, signal-to-noise ratio and comfort. The pilot study was conducted in order to debug the simulation, assess the equipment, and experimental procedures for the following main studies. In this study, eleven healthy participants were asked to walk on the virtual wooden plank, while their brain activity and HR were recorded. The pilot study did not yield statistically significant results, however, showed a trend towards increased brain activity in the PFC when participants were exposed to heights. Moreover, the study indicated a potential for this integration of technology to evoke a fear response and measure the neuronal activity indicative of fear inhibition and reappraisal in VR. The result demonstrated the feasibility of the study and all the technical problems were identified and resolved.

The second study hinged upon the results of the pilot study. The experimental protocol was improved to avoid unnatural response and excessive movement, the simulation was redesigned, the software was debugged and updated, the issues with parallax were fixed, the floor collider was removed and the system was optimised in order to minimise the latency. Additionally, to minimise motion artifacts, the NIRSCap was upgraded with spring-loaded grommets and stiffing elements. This significantly reduced a time of preparation as well as discomfort for participants. To

prevent software crashes, a high-end laptop and a mesh backpack were purchased to prevent overheating of NIRSport recording device. The aim of this study was to measure the PFC brain activity indicative of fear inhibition and cognitive reprisal, and a psychophysiological response indicative of emotional arousal, within a single session of VRET with improved ecological validity. This was achieved by combining wireless brain imaging device – fNIRS NIRSport with a large CAVE-like VR display system – Octave. The study involved twenty-seven healthy participants walking on the virtual wooden plank while their brain activity and HR were recorded. The result showed increased activity in the DLPFC and MPFC during exposure to virtual heights consistent with fear inhibition and appraisal measured in previous neuroimaging studies that had not used VR. Although the study did not detect significant within-session neuronal changes, the trend was revealed towards involvement the bilateral DLPFC at the beginning of session consistent with emotional reappraisal. This pattern of activation extended to the bilateral MPFC during the second block (2.4 minutes) of exposure and increased in magnitude during the third block. Unfortunately due to equipment failure, the study did not find a significant effect of VRET on HR, however, the analysis demonstrated a trend towards an increased HR when participants were exposed to virtual heights, which then decreased during the course of the experiment. The study demonstrated how a healthy brain responds to a single session of VRET.

Following the outcome of the second experiment, this project sought to explore the effect of multiple VRET sessions on acrophobic participants. The third study investigated the neural and psychophysiological response to three sessions of VRET for acrophobia using the same research methodology and protocol. Within- and between-session activity in the PFC measured by wireless fNIRS in large IPT. Emotional arousal was measured using HR and EDA monitors. Consistent with previous fMRI studies, the analysis showed decreased activity in the DLPFC and MPFC during the first and second exposure when compared to healthy participants (from the former study). The activity increased toward normal (similar to the result that was demonstrated in the second study involving healthy participants) across three sessions. Within-session effects were found during the third session indicated by increased activity in the DLPFC at the beginning of the session which extended to the MPFC towards the end of the session. Between-session effects were associated with increased activity in the left DLPFC. Moreover, the brain activity as measured by HbO

at the end of VRET was negatively correlated with the initial level of fear of heights (HAQ). The magnitude of improvement as measured by the PFC activity was correlated with a subjective feeling of presence – perceived realness of VR.

3. Contributions

3.1. Contribution from the literature review

The first contribution was an undertaking of a new literature survey and identifying gaps in existing knowledge about the neural basis of VRET. Because this project was multidisciplinary, it required the literature review to cover a broad area of topics – mechanisms of traditional ET, neuroscience of ET, combining brain imaging with VR, neuroscience of VR, neuroscience of anxiety disorders and neuroscience of VRET. To date, there are no well-designed studies about the brain response to VRET. The identification of a possible trend in existing evidence suggests that VRET restores balance within the fear circuit. Some studies provided an indication that the PFC mediates emotional regulation in VRET. Unfortunately, the lack of well-designed studies did not allow to perform a meta-analysis. Nevertheless, to the best of our knowledge, we performed the first systematic review that summarised existing studies about the neural basis of emotional regulation in VRET.

3.2. Contribution to the theoretical knowledge

Role of the prefrontal cortex in VRET

This thesis contributes to the understanding of the role of the PFC in VRET by measuring both within-session and between-session brain activity indicative of fear inhibition and cognitive reappraisal. This should help to recognise how VRET affects brain response. Monitoring brain function between sessions allows for investigating how VRET affects neuroplasticity, and thus its therapeutic efficacy. Previous studies suggested that activity in the PFC subserves fear inhibitory function and cognitive reappraisal of emotions during ET (Craske & Liao, 2012; Jovanovic & Norrholm, 2011; Quirk, Garcia, & González-Lima, 2006). In particular, the medial prefrontal cortex (MPFC) has a direct inhibitory function, and the dorsolateral prefrontal cortex (DLPFC) has an indirect inhibitory function over the amygdala (Hartley & Phelps, 2010; Phelps et al., 2004). The amygdala controls automatic responses which are

associated with fear, arousal and processing of emotions (LeDoux, 2003). Previous neuroimaging studies performed on healthy participants found an increased activity in the MPFC and DLPFC during perception of fear-evoking stimuli (Etkin et al., 2015; Quirk & Beer, 2006). On the contrary, studies comparing healthy controls to patients with phobias, anxiety and PTSD, showed a decreased activation in the DLPFC and MPFC correlated with an increased activity in the amygdala in the patient population during symptom provocation (Etkin & Wager, 2007; Ipser et al., 2013; Schuitevoerder et al., 2013). Hypoactivation in the MPFC and DLPFC could indicate deficits in fear inhibition and reappraisal, while hyperactivation in the amygdala could indicate an abnormally exaggerated fear response to threat (Duval et al., 2015). Successful ET restores a functional balance within the fear circuit consistent with increased activity in the PFC, negatively correlated with the amygdala activity even after one session of treatment (Hauner et al., 2012; Schienle et al., 2007). Similar results were obtained in functional neuroimaging studies on VRET. Previous studies investigated the impact of VR treatment on brain activity in Cue Exposure Therapy for nicotine cravings (Lee, Lim, Wiederhold, and Graham, 2005; Moon and Lee, 2009), alcohol dependence (Rodriguez, Rey, Alcaniz, Rodrigues, and Alcañiz, 2013; Rodríguez, Rey, Clemente, Wrzesien, and Alcañiz, 2015), animal phobia (Clemente et al., 2014) and PTSD (Roy & Francis, 2010). The aforementioned studies employed fMRI or EEG before and after the treatment to assess an improvement in brain function following VRET. In line with studies conducted in vivo, the results demonstrated increased activity in the PFC, inversely correlated with the activity in the amygdala. However, the number of studies was limited, demonstrating rather a trend than evidence supporting the clinical efficacy of VRET.

This project employed fNIRS to measure the within- and between-session PFC response to VRET with improved ecological validity in both healthy controls, who received one session of VRET, and participants with moderate acrophobia, who received three sessions of VRET. Results indicated that during exposure to the virtual threat, healthy participants showed increased brain activity in the PFC from the beginning of the session (first block). Specifically, the activity in the bilateral DLPFC was found (five channels, average t-score 2.42). During the second block, DLPFC activity increased in magnitude (10 channels, average t-score 3.07), and additionally, the bilateral MPFC was recruited (two channels, average t-score 2.66). This pattern of

activity increased more during the third block, demonstrating increased activity in the bilateral DLPFC (16 channels, average t-score 3.14) and bilateral MPFC (three channels, average t-score 3.86). This result might indicate that healthy participants use emotional regulation strategies when they encounter a fear-evoking stimulus in VRET. In particular, when exposed to fear-evoking VR stimuli, at first participants engage emotional reappraisal strategy, which is followed by fear inhibition at during VRET. Participants with acrophobia demonstrated a similar pattern of activation, however only during the third session of VRET. At the beginning of VRET, participants showed hypoactivation in the PFC, which might indicate deficits in emotional regulation during exposure to fear-evoking VR. These results are consistent with another non-VR fNIRS study which compared the PFC activity in healthy controls to patients with social phobia, showing that individuals with social phobia exhibit decreased HbO in the PFC in contrast to healthy controls (Yokoyama et al., 2015). The current project showed that this hypoactivation could be restored to normal – more similar to the activity seen in healthy controls, during the third session of VRET. In particular, during the first block, exposure to virtual heights triggered an increased activity in the bilateral DLPFC (2 channels, average t-score 2.40). Similarly, to healthy controls, activity in the DLPFC increased in magnitude (8 channels, average t-score 2.59), also bilateral MPFC was recruited (two channels, average t-score 2.68). Finally, during the third block, this pattern increased in magnitude in the bilateral DLPFC (14 channels, average t-score 3.15) and bilateral MPFC (two channels, average t-score 2.39). This result indicates that VRET initially triggers a cognitive reappraisal of fear-evoking virtual stimuli by altering the meaning and appraisal about the potential danger of virtual heights in the self-reflective process. That next leads to a change of emotional impact of virtual heights and therefore inhibition of irrelevant fear response later during VRET session. The result is consistent with the model of emotional regulation proposed by Gross (1998). According to this model, emotional regulation involves a different temporal characteristic of reappraisal and suppression of negative emotions. The neural process underlying this model was later investigated by Goldin et al., (2008). In particular, they demonstrated using fMRI that reappraisal resulted in the early DLPFC responses, while suppression resulted in the late MPFC responses during watching negative emotions-eliciting films. In this project, we observed similar temporal dynamics within the PFC in VRET using fNIRS in both healthy and acrophobic individuals. This occurs within a single VRET session, however, while this

can be detected during the first session in healthy participants, phobic patients might need multiple sessions of VRET. This is because healthy participants do not exhibit functional abnormalities in the PFC and thus have no deficits in emotional regulation. On the other hand, acrophobic participants who fail to recruit the PFC regions mediating cognitive appraisal of emotions (DLPFC) and fear inhibition (MPFC) during the first two sessions of VRET, might restore the inhibitory function during the third session of VRET.

Moreover, regarding the magnitude of activation, the effect is more prominent in healthy participants regarding the number of channels activated to represent the PFC activity, as well as t-values above the significance threshold. However, the effect was not strong enough to demonstrate significant within-session learning, but rather a trend. This outcome was not surprising and probably occurred because of the "ceiling effect", as healthy participants might not have much "room" to improve. On the contrary, although acrophobic participants demonstrated lower activity regarding the number of channels above the threshold, they showed a significant within-session improvement. The activity in the DLPFC and MPFC at the end of VRET, increased towards more normal, resembling activity as measured in non-phobic participants. This supports the claim regarding the ability of VRET to trigger within-session learning in the treatment of phobias. Results from both groups are summarised in table 7.

Table 7 Summary of results from healthy and acrophobic participants. Within-session PFC activity

	Block 1	Block 2	Block 3
Healthy Participants	DLPFC B (5)	DLPFC B (10) MPFC B (2)	DLPFC B (16) MPFC B (3)
Acrophobic Participants (3rd session)	DLPFC B (2)	DLPFC B (8) MPFC B (2)	DLPFC B (14) MPFC B (2)

Between-session inhibitory learning was found after three sessions of VRET in this project. Other studies demonstrated that improvement occurs after six (Moon & Lee, 2009) or twelve or more (Roy & Francis, 2010). It is possible that VRET with

improved ecological validity leads to the improvement quicker than a traditional approach providing more naturalistic settings and therefore facilitating the naturalness of response.

Between-session learning was indicated by an increased activity in the left DLPFC. The left hemisphere appears to be involved in processing positive affect, while the right hemisphere process negative emotional stimuli (Davidson & Irwin, 1999). Therefore, this result might indicate down-regulation of the fear response mediating positive reappraisals of fear-evoking virtual stimuli after the VRET treatment, but unlike healthy participants - not during.

In both healthy and phobic participants the activity in the DLPFC was negatively correlated with the initial acrophobia severity as measured by the Height Anxiety Questionnaire. In particular, in healthy participants activity in the bilateral DLPFC was negatively correlated with the initial fear of heights, but the stronger effect was found in the right DLPFC. Similarly, this project found the right lateralisation in phobic participants, however at the end of the treatment, but unlike healthy participants, not during VRET. The right hemisphere has been shown to process negative stimuli (Davidson & Irwin, 1999). Therefore participants who score lower on the acrophobia questionnaire before VRET show better ability in the negative stimuli reappraisal after VRET session. Additionally, healthy participants showed a negative correlation between HAQ and activity in the left DLPFC throughout the session which mediates the process of positive reappraisal (Davidson & Irwin, 1999). This could indicate that the healthy brain might down-regulate fear responses in VRET mediating positive reappraisals of threatening virtual stimuli during VRET. Patients with a fear of heights gained this ability at the end of VRET. Surprisingly, this project found a correlation between HAQ and MPFC in acrophobic, but not healthy participants. Schnyer et al., (2004) suggested that right MPFC might play a role in episodic memory retrieval. Emotions such as fear might serve as a contextual cue for episodic memory retrieval (Allen, Kaut, & Lord, 2008). Therefore it is possible that acrophobic participants with a lower level of phobia recall information about the specific emotional state from previous VRET sessions in order to reappraise and inhibit the irrelevant fear response. The other possible explanation could be related to the small sample size. Perhaps future studies should investigate this correlation further.

The effect of VRET on the PFC activity, and therefore its therapeutic effect, appears to depend also on the level of presence. The third study found that an increase in the right DLPFC at the end of VRET was related to IPQ realness subscale in the second study. This result was consistent with a previous study the which investigated the impact of virtual heights on subjective ratings of fear and presence (Diemer et al., 2016). The "realness" of simulation is a principal quality of VR, which triggers the same emotions in users that would be experienced in the real environment. Although the evidence regarding a role of presence in VRET is mixed, the current project demonstrated that the presence and realness of simulation impacts on the PFC activity, and therefore leads to the better therapeutic outcome in phobic participants. Conversely, this project did not find a correlation between the PFC activity and presence in the study which involved healthy controls. Most likely, the lack of such a correlation is linked to the fact that this project used a different presence questionnaire (SUS), which some participants found confusing. For that reason in the third study, IGroup Presence Questionnaire (IPQ) was used, which not only appeared to be clearer to participants but also previously demonstrated its reliability and validity (Schubert et al., 2001).

Contrary to expectations, this project did not find a significant correlation between the within-session PFC activity and subjective fear ratings measured by SUDS. Additionally, the result of this project could not be compared with other studies on the neural basis of VRET because such a correlation was not previously reported (Clemente et al., 2014; Roy & Francis, 2010). On the other hand, studies on traditional ET found a correlation between SUDS and brain activity, however, the effect was found in the amygdala, but not the PFC. The amygdala plays a role in detection and processing of fear (Davis, 1992), therefore it is possible that the subjective ratings of fear correlate better with the amygdala activity than the PFC, which mediates cognitive regulation of emotions (Quirk & Beer, 2006). Another reason could relate to the fact that the neuroplasticity in the PFC might occur slower than in the amygdala (Takehara et al., 2003), therefore it is possible that more time is required to detect the correlation between activity in the PFC and SUDS. Besides, some studies concluded that subjective measures often do not correlate with brain activity (Liberzon et al., 1999; Robinson et al., 2013). However, it is also possible that the lack of a correlation could be related to the small sample size in this study, therefore more studies with a bigger

sample size are necessary to establish whether there is a correlation between the PFC activity and SUDS in VRET.

In order to investigate if VRET triggers the fear response, which correlates with cognitive reappraisal and fear inhibition, this project employed psychophysiological monitoring to measure HR and EDA, and subjective fear ratings (SUDS) as indicators of emotional arousal indicative of the fear response. According to the emotional processing theory, an increase of physiological response and subjective fear ratings can be used as an index of activation of the maladaptive fear structure during ET. After activation, the fear structure becomes susceptible to emotional processing trough corrective learning (Foa & Kozak, 1986). Unfortunately, because of technical difficulties, this project could not measure the fear structure activation through the physiological response (discussed in the next section). However, high SUDS scores at the beginning of VRET could be interpreted as an indicator of the fear structure activation (Rothbaum et al., 2006). While this project found that SUDS decrease within-session, the between-session reduction was detected between the second and third session. This might indicate that the corrective inhibitory learning and modification of the fear structure in VRET does not occur after one session but rather requires more time for consolidation. This could be a gradual process associated with gradual inhibitory learning. Unfortunately, this project did not find a correlation between SUDS and any other measures.

Likewise, the result also did not support the hypothesis about the correlation between the PFC activity and psychophysiological response in VRET. The original Pit Room experiment (Meehan et al., 2002) demonstrated that exposure to virtual heights triggers an emotional response even in healthy participants. The study employed HR and EDA as an objective measure of user's stress levels in evocative VR. Although the experiment found a correlation between the sense of presence and the change in HR and EDA after looking down the pit room, the brain activity was not measured. Other studies which measured within-session brain activity and HR during ET did not report the correlation between those two variables (Åhs et al., 2017; Veltman et al., 2004), and studies which investigated the neural basis of VRET, did not employ psychophysiological monitoring (Roy & Francis, 2010). Therefore it is difficult to conclude if such a correlation occurs in VRET. This project found a trend that healthy

participants had an increased HR in the pit room, which then decreased throughout the session. Besides, the sample size was small in this project, therefore it is possible this project did not find the correlation between psychophysiological measures and the PFC activity because of an insufficient number of data points. Due to several technical difficulties with HR and EDA monitors, a lot of data was excluded from the analysis. This issue is discussed below in details in the section about methodological contributions.

3.3. Methodological contributions

Improving ecological validity

This PhD contributes to methodology in both neuroscience research and ET by using a combination of brain imaging and VR technology that not only promotes ecological validity but would also allow a participant or client to fully share the experience with a mental health professional. This was approached by combining mobile fNIRS with large IPT Octave. The choice of equipment was determined by priority to acquire good quality data and controllability of design without burdening participants with excessive uncomfortable equipment which might restrain natural movement and response, as well as potentially cause anxiety. The combination of these technologies immerses a user in a surrounding room-sized VR simulation that supports both natural locomotion and interaction with a simulation, in the space without losing the sight of one's own body. This project demonstrated that this combination could be a useful tool for delivering VRET. Methodological contributions will inform the neuroscientific and VR community about the potential and advantages of combining wireless neuroimaging and large VR systems to bridge the gap between ecological validity and controllability of the design. This approach allows a more natural experience and response than previous combinations of VR and brain imaging used to evoke and measure fear inhibitory response and learning.

However, it should be noted, that this project compares its results to previous studies that employed non-consumer versions of HDMs. To date, there are no published peer-reviewed studies employing commercial wireless HMDs. Although currently, HTC Vive is available in a wireless version that allows untethered locomotion in VR, the design of the Vive HMD is not suitable to be combined with fNIRS without significantly destroying the headset in order to fit the prefrontal fNIRS set-up. As a part of this project,

fNIRS was also tested with custom-adapted Oculus Rift (see appendix). Although it was possible to combine fNIRS with the HMD without losing the quality of simulation and fNIRS data, it came with the trade-off involving the comfort of wearing the technology. It is because some parts of Oculus Rift HMD were removed to fit fNIRS cap, however, those parts also support the placement of the HMD. Moreover, Oculus Rift currently is not available in the wireless version, therefore this project employed IPT technology.

Combining fNIRS with IPT

Although some previous studies employed brain imaging to investigate the impact of VRET on the brain activity, they used technologies that do not effectively balance the quality of measurement and naturalness of response. On the one hand, fMRI although it has a good spatial resolution, it restricts movement and therefore violates the naturalness of response. On the other hand, although current wireless EEG systems allow some locomotion, still they are significantly susceptible to motion artifacts and instrumental noise from VR devices, and they offer a low spatial resolution. Wireless fNIRS systems offer a compromise between fMRI and EEG. fNIRS is thought to impose a relatively less physical and psychological burden than fMRI, therefore, this technique could be advantageous for measuring neural responses during naturalistic tasks (Balardin et al., 2017), and also can be used in a vulnerable population, especially elders, infants or people with mental disorders (Cutini & Brigadoi, 2014; Irani et al., 2007). Moreover, fNIRS is more robust to motion artifacts and exogenous noise, therefore, provides a potentially better option for measurement in ecologically valid settings (Tuscan et al., 2013). However, it should be noted, that fNIRS due to the pressure imposed by optodes on the scalp might sometimes cause a risk to patients who suffer a migraine. In order to avoid the risk of potential headaches, participants wore the fNIRS device for maximum 30 minutes (including set up and data acquisition). Moreover, one participant who had a history of migraines was excluded from the study. In order to measure brain activity optodes must be secured and in proper contact with the scalp, therefore it is very difficult to minimise the pressure while maintaining a good signal. Although this project used standard NIRS optodes, the new developments in blunt-tip and flat-tip optode designs allow using more comfortable measurement, which perhaps would be more suitable to use in clinical applications.

Employing wireless fNIRS within CAVE-like IPT VR offers a methodological advantage. Octave is a multisensory high-end VR laboratory which is larger than standard CAVE, therefore, it allows a more natural locomotion allowing for brain activity to be recorded in more naturalistic settings. The pilot study used an unprecedented combination of fNIRS and Octave to inform further research. Since these technologies were not combined before, the pilot study tested whether this endeavour is even achievable. The main concern was a possible signal interference between near-infrared light from Vicon tracking system and NIRSport. The pilot study assessed the signal-to-noise ratio to determine NIRS signal quality and demonstrated that peripheral devices in Octave did not significantly impact on the signal quality. However, this project found out that the level of movement might contaminate data with motion artifacts when combining fNIRS with IPT. This project proposed several resolutions to minimise motion artefacts and ensure signal quality such as reducing the level of motion. Especially leaning forward too excessively resulted in sudden spikes in the signal. While in the pilot study participants were allowed to move without any restrictions, during the two other studies they were advised about the level of motion. Additionally, improving the cap set-up, preparation and application reduced motion artifacts. For that reason the cap was upgraded with spring-loaded gromets, stiffing elements and a new retaining cap to allow better signal quality. This informs other researchers when combining fNIRS with VR for ecologically valid applications.

Combining psychophysiological monitoring with IPT

Several lessons regarding the usability of the equipment in VRET were learned during this project. Since the project was conceptualised, numerous test and efforts were made to set up and adapt psychophysiological monitoring devices. Especially several technical difficulties were encountered with HR and EDA monitors. Despite many adjustments and set-up modifications that were made after each study, unfortunately, this project demonstrated that the equipment was unsuitable for this kind of experiment. This outcome was particularly disappointing as psychophysiological data would be useful for hypothesis testing and validating the ability of VRET to trigger an emotional arousal within more ecologically valid settings.

One of the most notable disadvantages of HR monitor – Zephyr Bioharness learned from this experiment was that the device is less usable in female participants. Due to the design of the Bioharness, it was very challenging to fit some female participants with the device due to the anatomy. Because most of the participants who took a part in the third study were females, most of the data was unusable, and therefore excluded from analysis. The validity and reliability of Bioharness were demonstrated in a few previous studies, however, one of the limitations of those studies was that the sample included only male participants (Hailstone & Kilding, 2011; Johnstone et al., 2012a, 2012b). Therefore a reasonable resolution must be found in order to make the Bioharness more usable for female participants. Moreover, because Bioharness is woven onto strap worn around the chest, it resulted in several sensor dislocations during data acquisition caused by the backpack worn for NIRS data recording device. Perhaps other types of multiple electrode-based wearable HR monitors would be more suited for this type of VRET research.

Although Edu-Logger Galvanic Skin Response (GSR/SCR) Sensor worked without issues during stationary tests, in the wireless mode there were several drops in Wi-Fi connection that resulted in a several failed transmissions and data loss. Unfortunately, despite several attempts to troubleshoot the issue, underlying problems could not be fixed. Moreover, no studies on reliability and accuracy of Edu-Logger GSR sensor were found. Although the sensor is a cost-effective solution for measuring EDA, the future studies should invest in a more reliable solution.

3.4. Clinical contributions

Treatment tool

The results of this project hold many clinical implications. It demonstrated that VRET has potential as a tool for the treatment of mental disorders. Although this project focused on specific phobias, the efficacy might expand to other mental disorders such as anxiety or PTSD. Combining fNIRS with IPT offers also promising utility for treatment of other clinical issues within populations where the ability to inhibit irrelevant responses would be desirable, such as patients struggling with anger, aggression, irritability or addictions. The project demonstrated the potential efficacy of a method for therapeutic applications that could be replicated within clinics and

research institutes, using equipment more appropriate to ET. As VR technology becomes more affordable and available for members of the public, patients could easily access downloadable VR content to support interventions at their own homes. This could potentially reduce not only costs of treatments but also waiting lists and the associated workload on health providers while facilitating the well-being of patients. Moreover employing fNIRS constitutes a good tool for measuring progress of the treatment due its portable design that makes it easy to relocate to clinics and even to patient's home for monitoring not only within-session brain activity during the treatment, but also changes in the brain function after the treatment to verify patient's improvement and efficacy of the therapy (Amano et al., 2016).

Diagnostic tool

Combining VR with wireless brain imaging improves ecological validity, therefore it offers the potential to trigger a more natural and authentic response which might allow better diagnosis relevant to real-life situations. Traditionally diagnostics in mental health relies on interviews and questionnaires (Clark, Cuthbert, Lewis-Fernández, Narrow, & Reed, 2017), however, self-report methods can be often biased due to their subjective nature. This could potentially lead to a misdiagnosis of symptoms and thus an inappropriate treatment. VR technology might be used to provoke symptoms associated with many mental disorders (Gorrindo & Groves, 2009). This study demonstrated that on the one hand, VR has a potential to trigger a fear response associated with phobias, anxiety disorders and PTSD. On the other hand, fNIRS has the potential to measure brain activity associated with symptom provocation such as fear. For example, abnormal activity in the PFC during exposure to specific objects or situations might indicate symptoms of phobia. Therefore, combining VR with brain imaging offers a tool to improve reliability and objectivity in the diagnosis of mental disorders. Improving diagnosis strategy in mental health became an especially important matter to address recently, as more individuals are suffering mental issues such as PTSD and anxiety disorders as a result of terrorist attacks, refugee crisis and disasters. Therefore, new technological advances might aid the assessment and identification of individuals who are in urgent need of treatment.

Predictor of therapy outcome

The results of therapies might vary. Both traditional ET and VRET suffer approximately 17- 40 % drop-out and non-response rate (Goncalves et al., 2012; Schottenbauer et al., 2008). Employing brain imaging in VRET could not only help to measure the progress of the therapy, but also could help to identify neural markers of brain function that predict treatment response and determine the intensity and length of therapy, as well as identify potential responders and non-responders to VRET. The study by Ruocco et al., (2016) demonstrated that activity in the PFC as measured by fNIRS can be used as a tool to predict a treatment outcome for Self-Harming Patients with Borderline Personality Disorder (BDP). Prior to beginning therapy, patients showed less activation in the bilateral middle and inferior frontal gyrus during response inhibition, which showed an increase after the treatment. The decrease in self-harm was correlated to the right DLPFC activity, and patients showing better treatment results also showed lower activation in this region prior to beginning treatment. Reduced activation in the DLPFC during response inhibition with BPD prior to beginning treatment could reflect a diminished recruitment of inhibitory control processes subserved by the PFC. This project revealed similar results. At the beginning of VRET acrophobic participants showed decreased activity in the DLPFC and MPFC, which after the treatment was more similar to the activity that was observed in healthy controls. Moreover, this project found a correlation between initial severity of acrophobia and an increase in HbO in the right DLPFC at the end of the treatment. This result might indicate that measuring activity in the right DLPFC might potentially serve as a predictor of VRET response. However, more studies are needed to establish neural biomarkers of VRET response because this project did not find a significant correlation between brain activity during the first and the last session of VRET.

Neurofeedback

In this project, during all three experiments, the researcher was present with the participant in the simulation area and could monitor brain response in real-time during VRET. NIRStar offers features for both real-time 2D and 3D topographical rendering of cortical activation viewing on a virtual head or brain model, and real-time block average viewing of HbO, HbR and HbT. Unfortunately, NIRStar software has very limited real-time filtering methods, and it requires additional software - NIRSteam for

neurofeedback in clinical applications. However, this project demonstrated that fNIRS has a potential to facilitate neurofeedback in psychotherapy, allowing a therapist to monitor how a patient responds to the VRET and adjust the pacing of the treatment accordingly in real-time.

Client-therapist relationship

The combination of IPT and fNIRS could improve the client-therapist relationship within VRET. Octave laboratory is big enough to support multi-user experience without losing a sight of one's body or presence of others. Additionally, unlike fMRI, fNIRS does not isolate a patient within a large cylinder-shaped tube. Therefore, this project proposes using a combination of technologies that allow a client and therapist to mingle. The researcher or therapist and participant can be both immersed into surrounding VRET stimuli, which allows better controllability of the patient's engagement and therefore therapy, as well as supports non-verbal communication (Roberts, Fairchild, Campion, Wolff, & Garcia, 2016). During VRET a patient can thus be supported and reassured by the presence of the therapist, what might provide a safety grounding, and therefore improve VRET efficacy.

4. Limitations of This Research

This project has several limitations. Firstly, the generalisability of the findings is limited by the homogeneity of the sample, especially in the first and second study. Most of the participants were students at the University of Salford, therefore the sample was limited. Secondly, the third study involved participants with a moderate phobia, who were not subjects of NHS treatment, therefore it is difficult to conclude if a similar result would be found in clinical populations. Thirdly, this project focused only on specific phobia – fear of heights, so it is unclear if VRET has the same effect on other mental disorders. Moreover, the sample was small involving only 13 participants in data analysis, therefore the results require replication. Thirdly, all participants received only three 15-minute sessions of VRET, which might be insufficient to detect lasting changes in the brain. This project also did not involve a control group and there was no randomisation of participants.

Another limitation of our project is that fNIRS has restricted penetration depth (Ferrari & Quaresima, 2012), which does not allow for measuring the signal from the amygdala which plays a crucial part of the fear circuit in the brain. Insight into the amygdala activity would allow investigating if it correlates with the PFC activity during VRET, which was previously demonstrated in studies on ET (Hauner et al., 2012).

5. Recommendations for Future Research

The findings of this thesis could contribute to further understanding of the neural basis of VRET. This project demonstrated that the DLPFC and MPFC mediate cognitive reappraisal and inhibitory response within and between VRET sessions. Future studies should employ other brain imaging methods such as fMRI, EEG or PET to investigate the role of other areas of the brain in VRET. Additionally, functional MRI could allow establishing if the functional activity correlates with structural changes associated with neuroplasticity in the PFC after VRET treatment. This could be perhaps explored on a single-subject and group level. There are individual differences in brain function and structure (Dubois & Adolphs, 2016). The standard approach in cognitive neuroscience involves averaging and normalising data from multiple participants into common MNI space on the second level group analysis. Considering the individual differences in hemodynamic response function, it is possible that there are also individual differences in functional brain abnormalities. The individual approach to the analysis of brain function would allow better diagnosis of mental disorders controlling for between-subject variance in the data. However, this task could be difficult, given that each individual scan consists of thousands of data points. A machine learning approach has been proposed as a potential resolution which offers algorithms for diagnosis and detection of medical conditions (de Bruijne, 2016), which also can have a potential application in neuroscience VRET.

This project investigated how VRET impacts on the PFC activity in participants with a moderate phobia. Further studies with a clinical population are required in order to understand how VRET impacts on patient's brain function, and perhaps should involve a bigger sample size, and more, and longer sessions. Although this study did

not have a control group, it serves as a preparation for a future randomised controlled trial, which would confirm the efficacy of VRET.

Furthermore, because this project was unable to measure psychophysiological response to VRET due to several technical issues, future studies should utilise better-suited equipment for VRET research to investigate the effect of VRET on psychophysiological response and possible correlations between other variables.

6. Further work related to this research

This PhD project has led to establishing a partnership with Pennine Care NHS Foundation Trust and Manchester (Military Veterans' Service and Manchester Resilience Hub) and Greater Manchester Fire and Rescue Service. Both collaborations focus on diagnosis and treatment of PTSD. As a part of a partnership with Pennine Care NHS Foundation Trust, we were involved in developing VRET protocols for delivering assessment and treatment of combat-related PTSD for military veterans, as well as treatment of civilian victims of the Manchester Arena attack. With the support of Dr Alan Barrett, who is Consultant Clinical Psychologist at Pennine Care NHS Foundation Trust and Clinical Lead for the Military Veterans' Service, the further work related to this project led to a Patient and Public Involvement (PPI) in the research project. A war veteran, who has previously completed a treatment for PTSD at Pennine Care NHS Foundation Trust, visited our lab as a consultant to provide feedback and advice about the technology used in this project for future research. The consultant assessed different technologies mediating VRET – 360 videos in Samsung Gear VR, HMD HTC Vive and Octave and suggested that VRET should be graded according to the level of immersion and controllability. Specifically, he said that the low-end mobile VR would be useful at the beginning of VRET due to its low immersion, and the high-end resolution - IPT VR should be used as a last stage of the treatment because of its full immersion quality. This approach would allow an optimal and safe management of patient's adequate emotional engagement, therefore minimising the risk of drop-out rate. The interview with the consultant can be found via following private links, which will be deleted after the viva:

https://youtu.be/roDyQIm5r-Q
https://youtu.be/ZuFK058lCiI

https://youtu.be/EameKiteCrA
https://youtu.be/GWy5671lyAc
https://youtu.be/4lbjQurIO_A

7. Conclusion

In conclusion, previous neuroimaging studies have demonstrated that both exposure therapy and virtual reality exposure therapy normalise brain activity within a prefrontal-amygdalar fear circuit after the treatment. Moreover, there has been little study of within-session brain activity during exposure therapy, and there are no studies on within-session brain activity during virtual reality exposure therapy. This project argued that previous studies employed brain imaging and virtual reality technologies that do not adequately balance the quality of measurement and naturalness of response. This PhD project employed an unprecedented combination of brain imaging and virtual reality technology - Functional Near-Infrared Spectroscopy and Immersive Projection Technology to improve ecological validity.

The project demonstrated that Functional Near-Infrared Spectroscopy can be combined with Immersive Projection Technology to measure the PFC response while maintaining a data quality. The results demonstrated that healthy controls at the beginning of VRET session showed an increased activity in the DLPFC consistent with fear reappraisal during exposure to virtual heights. Then additionally they recruited the MPFC during the second block of the session as indicative of fear inhibition. The activity increased in both regions during the third block. On the contrary, consistent with previous non-VR MRI studies, participants with acrophobia showed decreased activity in the DLPFC and MPFC during initial exposure. This increased toward normal during the third session. Within-session effects were found during the third session indicated by increased activity in the DLPFC at the beginning of the session which extended to the MPFC towards the end of the session. Between-session effects were associated with increased activity in the left DLPFC. This project found that the DLPFC activity throughout VRET negatively correlated with the initial fear of height in healthy controls, but in acrophobic participants only at the end of VRET. Furthermore, the magnitude of the improvement was correlated with a feeling of presence in VRET. The study demonstrates a potential efficacy of a method for

immersive neuroimaging with improved ecological validity, across understanding, diagnosis, assessment, and treatment of, a range of mental disorders such as phobia, anxiety, and post-traumatic stress disorder or addictions in clinical and academic applications.

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Appendices

1. Appendix 1: NIRX NIRSport spring-loaded grommets

The pilot study demonstrated that the motion artefact might significantly impact the data quality. In order to improve the data quality as well as the comfort of participants, we purchased NIRX spring-loaded grommets with stiffing elements to allow faster set up without the need of manual parting a participant's hair and use of the gel and prevent optodes displacement during locomotion in Octave. Moreover, we purchased a better retaining cap and mesh backpack.

2. Appendix 2: Height Anxiety Questionnaire

ID:

Below we have compiled a list of situations involving height. We are interested to know how anxious (tense, uncomfortable) you would feel in each situation nowadays. Please indicate how you would feel by choosing one of the following numbers (0, 1, 2, 3, 4, 5, 6) in the space to the left of each item:

0 Not at all anxious; calm and relaxed
1
2 Slightly anxious
3
4 Moderately anxious
5
6 Extremely anxious

1. Diving off the low board at a swimming pool.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
2. Stepping over rocks crossing a stream.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
3. Looking down a circular stairway from several flights up.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
4. Standing on a ladder leaning against a house, second story.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
5. Sitting in the front of an upper balcony of a theater.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
6. Riding a ferris wheel.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
7. Walking up a steep incline in country hiking.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
8. Airplane trip (to San Francisco).
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
9. Standing next to an open window on the third floor.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
10. Walking on a footbridge over a highway.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
11. Driving over a large bridge (Golden Gate, George Washington).
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
12. Being away from window in an office on the 15th floor of a building.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
13. Seeing window washers 10 flights up on a scaffold.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
14. Walking over a sidewalk grating.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
15. Standing on the edge of a subway platform.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
16. Climbing a fire escape to the 3rd floor landing.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
17. On the roof of a 10 story apartment building.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
18. Riding the elevator to the 50th floor.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
19. Standing on a chair to get something off a shelf.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)
20. Walking up the gangplank of an ocean liner.
(Not at all anxious) 0 1 2 3 4 5 6 (Extremely Anxious)

3. Appendix 3: Slater-Usoh-Steed Questionnaire (SUS)

1. Please rate your sense of being in the virtual environment, on a scale of 1 to 7, where 7 represents your normal experience of being in a place.

2. To what extent were there times during the experience when the virtual environment was the reality for you?

3. When you think back to the experience, do you think of the virtual environment more as images that you saw or more as somewhere that you visited?

4. During the time of the experience, which was the strongest on the whole, your sense of being in the virtual environment or of being elsewhere?

5. Consider your memory of being in the virtual environment. How similar in terms of the structure of the memory is this to the structure of the memory of other places you have been today? By ‘structure of the memory’ consider things like the extent to which you have a visual memory of the virtual environment, whether that memory is in colour, the extent to which the memory seems vivid or realistic, its size, location in your imagination, the extent to which it is panoramic in your imagination, and other such structural elements.

6. During the time of your experience, did you often think to yourself that you were actually in the virtual environment?

4. Appendix 4: Igroup Presence Questionnaire (IPQ)

Please answer all questions only with reference to the Pit Room experiment.

---

1. **How aware were you of the real world surrounding while navigating in the virtual world? (i.e. sounds, room temperature, other people, etc.)?**

extremely aware	○	○	○	○	○	○	○	not aware at all
	-3	-2	-1	0	+1	+2	+3	

2. **How real did the Pit Room seem to you?**

completely real	○	○	○	○	○	○	○	not real at all
	-3	-2	-1	0	+1	+2	+3	

3. **I had a sense of acting in the virtual space, rather than operating something from outside.**

fully disagree	○	○	○	○	○	○	○	fully agree
	-3	-2	-1	0	+1	+2	+3	

4. **How much did your experience in the virtual environment seem consistent with your real world experience ?**

not consistent	○	○	○	○	○	○	○	very consistent
	-3	-2	-1	0	+1	+2	+3	

5. **How real did the Pit Room seem to you?**

about as real as an imagined world	○	○	○	○	○	○	○	indistinguishable from the real world
	-3	-2	-1	0	+1	+2	+3	

6. **I did not feel present in the virtual space.**

did not feel	○	○	○	○	○	○	○	felt present
	-3	-2	-1	0	+1	+2	+3	

7. **I was not aware of my real environment.**

fully disagree	○	○	○	○	○	○	○	fully agree
	-3	-2	-1	0	+1	+2	+3	

8. **In the computer generated world I had a sense of "being there"**

not at all ○ ○ ○ ○ ○ ○ ○ very much

-3 -2 -1 0 +1 +2 +3

9. Somehow I felt that the virtual world surrounded me.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

-3 -2 -1 0 +1 +2 +3

10. I felt present in the virtual space.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

-3 -2 -1 0 +1 +2 +3

11. I still paid attention to the real environment.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

-3 -2 -1 0 +1 +2 +3

12. The virtual world seemed more realistic than the real world.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

13. I felt like I was just perceiving pictures.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

-3 -2 -1 0 +1 +2 +3

14. I was completely captivated by the virtual world.

fully disagree ○ ○ ○ ○ ○ ○ ○ fully agree

-3 -2 -1 0 +1 +2 +3

Your age: ☐

Your gender: ○ female, ○ male

5. Appendix 5: Simulator Sickness Questionnaire

No_____ Date_____

SIMULATOR SICKNESS QUESTIONNAIRE

Kennedy, Lane, Berbaum, & Lilienthal (1993)***

Instructions : Circle how much each symptom below is affecting you right now.

1. General discomfort	None	Slight	Moderate	Severe
2. Fatigue	None	Slight	Moderate	Severe
3. Headache	None	Slight	Moderate	Severe
4. Eye strain	None	Slight	Moderate	Severe
5. Difficulty focusing	None	Slight	Moderate	Severe
6. Salivation increasing	None	Slight	Moderate	Severe
7. Sweating	None	Slight	Moderate	Severe
8. Nausea	None	Slight	Moderate	Severe
9. Difficulty concentrating	None	Slight	Moderate	Severe
10. « Fullness of the Head »	None	Slight	Moderate	Severe
11. Blurred vision	None	Slight	Moderate	Severe
12. Dizziness with eyes open	None	Slight	Moderate	Severe
13. Dizziness with eyes closed	None	Slight	Moderate	Severe
14. *Vertigo	None	Slight	Moderate	Severe
15. **Stomach awareness	None	Slight	Moderate	Severe
16. Burping	None	Slight	Moderate	Severe

* Vertigo is experienced as loss of orientation with respect to vertical upright.

** Stomach awareness is usually used to indicate a feeling of discomfort which is just short of nausea.

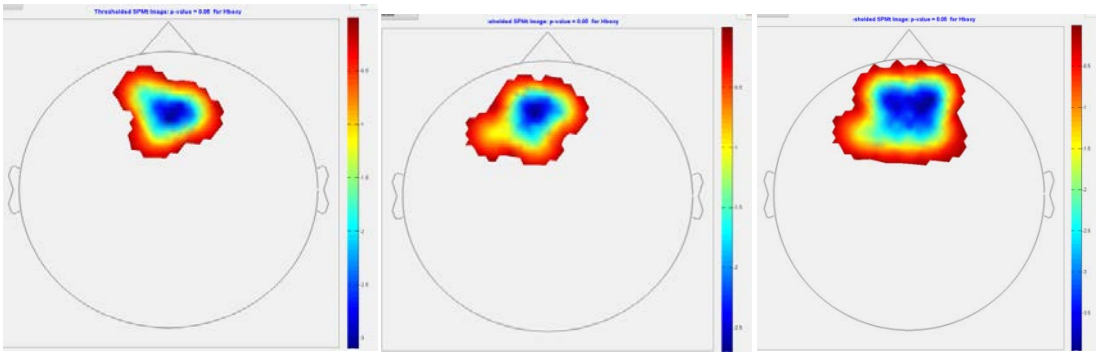
Last version : March 2013

***Original version : Kennedy, R.S., Lane, N.E., Berbaum, K.S., & Lilienthal, M.G. (1993). Simulator Sickness Questionnaire: An enhanced method for quantifying simulator sickness. *International Journal of Aviation Psychology, 3*(3), 203-220.

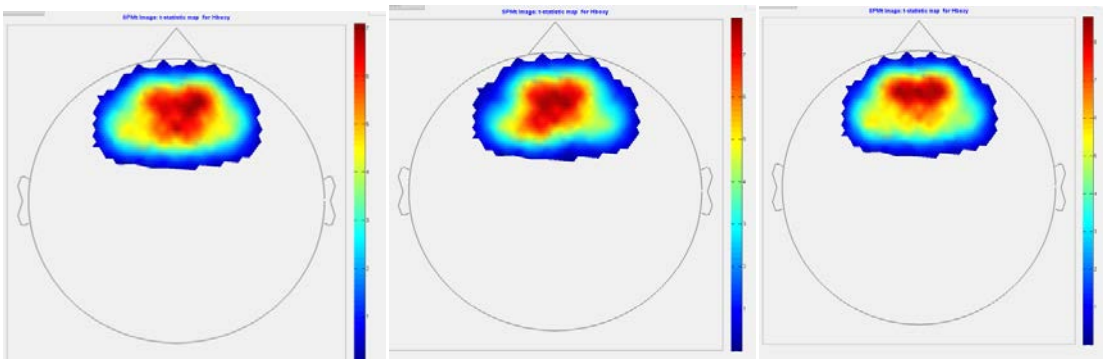
6. Appendix 6: Experiment 2 – SPM results supplementary results Training Room

6.1.Training > Pit

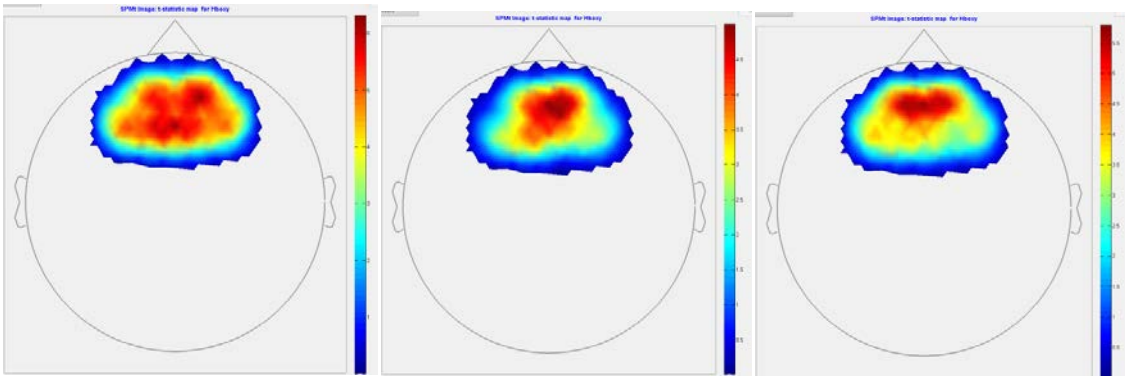
The SPM contrast analysis training versus pit revealed that there was no brain area significantly more activated in the training room in comparison to the pit room.



6.2.Pit > Baseline

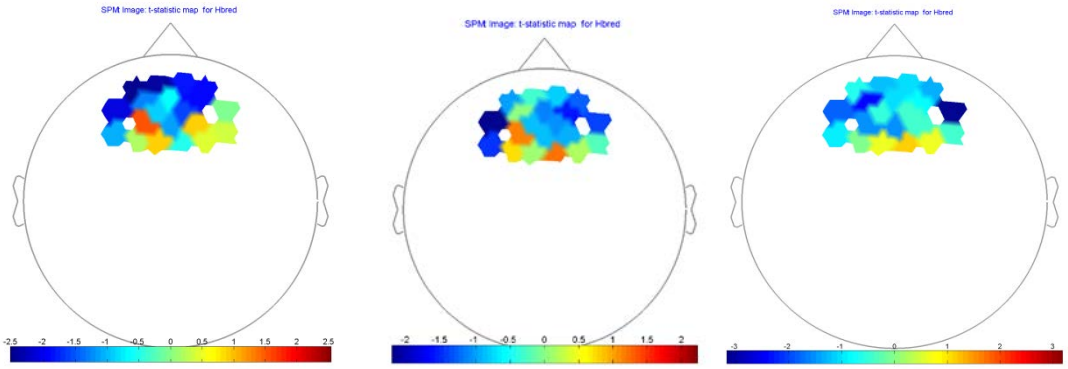


6.3.Training > Baseline



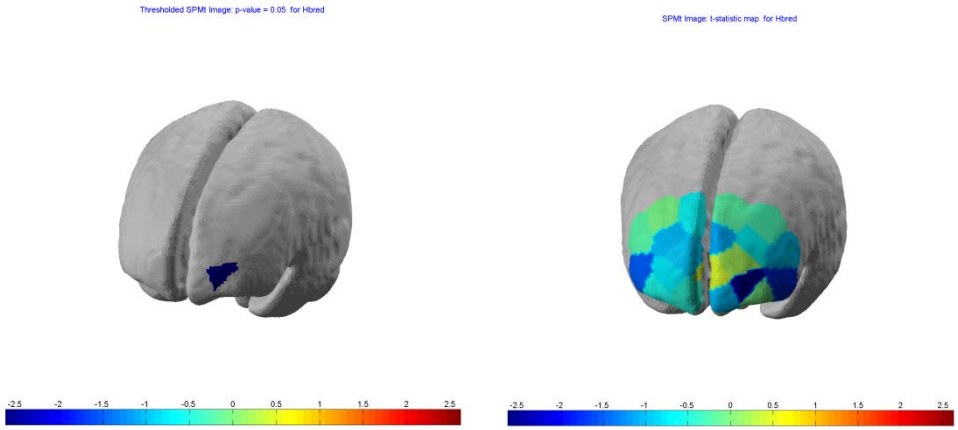
7. Appendix 7: Experiment 3 – SPM results supplementary results HbR concentration changes during exposure to virtual heights

7.1. Within-session PFC HbR activity



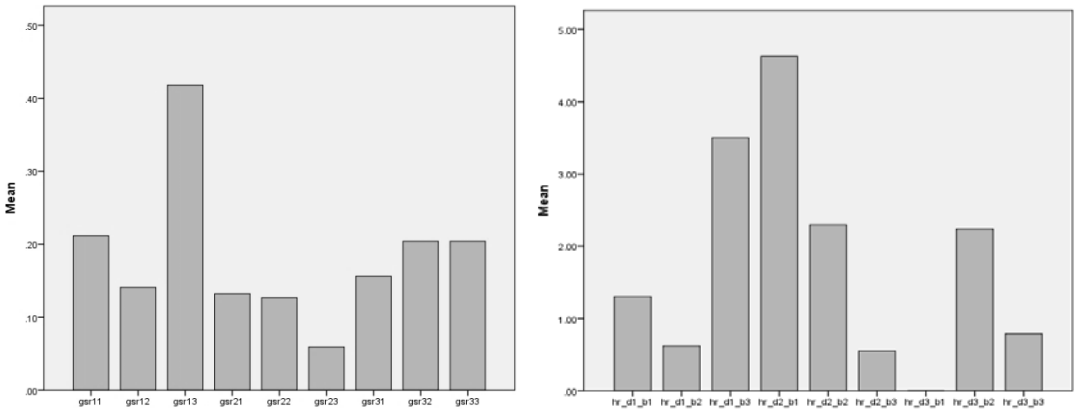
The figure shows activation map (unthresholded) of HbR (deoxygenated hemoglobin) found by group SPM analysis (contrast pit > training) of pit room experiment with acrophobic participants. Within-session effects were found in the DLPFC and MPFC. The results were less significant than HbO

7.2. Between session HbR activity



The figure shows activation maps – thresholded (left) and unthresholded (right) of HbR (deoxygenated hemoglobin) found by group SPM analysis (contrast pit > training) of pit room experiment with acrophobic participants. Between-session effect was in decrease of HbR in the left DLPFC. The results were less significant than HbO.

8. Appendix 8: Psychophysiological data results (EDA and HR)



The figure shows average changes in psychophysiological measures during exposure to virtual heights in the pit room (pit room – training room) (ΔEDA left, N = 5, ΔHR right N = 3). The analysys did not reveal any significant results or trends.

9. Appendix 9: The Pit Room Simulation Risk Assessment

Dear Alex,

I observed your pilot research study on 22nd January and followed you throughout the process of working with a participant from beginning to end.

It is my opinion that your study represents a very low risk of causing psychological distress because of the following:

1. Participants will know from the Participant Information Sheet that they will be exposed virtually to heights, so participants at high risk of distress can be expected to self-select themselves out of participation as those with fear of heights at the degree of phobia would usually avoid situations involving heights.
2. Before any measurements are taken during the study, participants are given the opportunity to put on the virtual reality headset and have an initial experience of looking at virtual heights. Anyone who would unexpectedly find that this was more stressful than they had anticipated can choose to withdraw from the study then and there.
3. Participants who are experiencing virtual reality are given rest periods during the exposure at which time they can compose themselves.
4. Participants who are experiencing virtual reality are alternated between a lower and higher height and therefore are not constantly at a high state of arousal.
5. Participants are given three opportunities in each situation and this could be expected to lead to desensitisation and a lower degree of responsiveness; actually this could even be therapeutic for some participants.
6. The researcher explained each aspect of participation in a calm and clear manner and allowed time for any questions.
7. There was a debriefing session where the researcher had the opportunity to talk to any participants who might have become distressed and could offer further resources for support.

Considering all these factors, I believe that the experimental protocol could be expected to be acceptable for any participants who chose to participate.

Kind regards,

Linda

Dr Linda Dubrow-Marshall, Ph.D., MBACP (Accred), FHEA
Counselling and Clinical Psychologist. HCPC Registered

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(I will respond to your emails within three working days)

10. Appendix 10: Ethical Approval

Research, Innovation and Academic
Engagement Ethical Approval Panel
Research Centres Support Team
G0.3 Joule House University of Salford M5 4WT T +44(0)161 295 2280

27 September 2016

Dear Aleksandra,

RE: ETHICS APPLICATION HSCR15-88 – Measuring neural and psychophysiological response to virtual stimuli. A longitudal study.

Based on the information you provided, I am pleased to inform you that your request to amend application HSCR15-88 has been approved.

If there are any changes to the project and/ or its methodology, please inform the Panel as soon as possible by contacting Health-ResearchEthics@salford.ac.uk

Yours sincerely,

[redacted]

Sue McAndrew

Chair of the Research Ethics Panel

11. Appendix 11: Questions asked in oral interview

The experimenter used the questions below as a guide during their post-session debriefing of subjects.
VR Research study: Debriefing sheet

Questions Comments

How do you feel?
(cybersickenss, technology discomfort)

What did you think about your experience?
(realism, engagement, enjoyment)

How much did you feel you were in the environment?
? >50% or <50% of the time?

Any comments on moving around?
(difficulty, natural)

Any comments on the pit room?
(fear of falling, realism)

Any comments on environment?
(what made it real, what brought you out)

How did you feel wearing fNIRS?
(pressure, discomfort)

Subject ID: .

12. Appendix 12: Testing the potential of combining Functional Near-Infrared Spectroscopy with different virtual reality displays – Oculus Rift and oCtAVE

Testing the potential of combining Functional Near-Infrared Spectroscopy with different virtual reality displays – Oculus Rift and oCtAVE

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Abstract
Combining Virtual Reality (VR) with brain imaging may improve controllability and ecological validity in neuroscienceentific research and clinical applications. The aim of this pilot study was to assess the pros and cons of combining mobile neuroimaging with two different styles of highly immersive displays, one that is warn on the head and the other that is entered. Specifically the combination of wearable Functional Near Infrared Spectroscopy (fNIRS) with either an Oculus Rift and surround immersive projection technology. . A comparison is drawn in terms of hemodynamic response from the prefrontal cortex, signal to noise ratio, comfort, freedom of movement and motion artefacts. Findings suggest that choice of display should depend on research question. The potential of this work is to improve ecological validity in research and therapy.

Keywords: virtual reality; fNIRS; brain imaging; prefrontal cortex; emotional regulation.

Introduction
Recent rapid technological advances in Virtual Reality (VR) and brain imaging offer opportunities for researchers in the field of neuroscience to investigate brain response in highly controllable and repeatable settings. VR allows to create more naturalistic environments which facilitate ecological validity (Bohil et al., 2011). Traditionally neuroscience used standard desktop displays in order to present stimuli and investigate underlying brain response. This approach however is artificial and does not resemble real life situations. Previous neuroscientific studies demonstrated that the human brain responds differently to static emotional 2D images than to interactive emotional 3D environments (Dores et al., 2014). Therefore, there is a need to develop potentially more ecologically valid combinations of VR displays and brain imaging methods. This would allow improved neuroscientific research unobscured by the limits of screens. The most commonly used VR systems are Head-mounted Displays (HMDs) and Cave Automatic Virtual Environment (CAVE) (Cruz-Neira, Sandin, DeFanti, Kenyon, & Hart, 1992). One of the disadvantages of HMDs is that it hides others from the user. Moreover, it generally restricts natural locomotion by restraining participants with cables and limited tracking. Further, the lack of naturalistic embodiment – seeing your own body in VR, may potentially impact on presence, as well as cause a cybersickness (Malik, Blake, & Suggs., 2014) in HMDs. Cave-like systems offer a solution by immersing a user into a room-sized VR simulation which supports natural locomotion and interaction in the space, without losing the sight of one's own body or others. On the other hand, Cave-like systems can be costly and expensive to maintain in clinical settings.

This chapter presents and describes testing the combination of a wearable Functional Near - Infrared Spectroscopy (fNIRS) device with two different VR displays CAVE-like Immersive Projection Technology (IPT) system – Octave, and a Oculus Rift DK2. The latter was adapted to improve comfort of fit of fNIRS. In particular, this chapter focuses on combining VR and brain imaging to investigate neural activity in the prefrontal cortex related to emotional regulation in VR, as well as SNR, motion artifact (noise in a data caused by body movement), peripheral signal interference and comfort of use. The classic VR experiment – The Pit Room (Michael Meehan et al., 2002) was employed in order to trigger an emotional response to

VR. Meehan's PIT Room experiment demonstrated that exposure to stressful VR induces emotional response, even in healthy participants. This was measured by heart rate, electrodermal response and self-report (Michael Meehan et al., 2002). When combining VR with neuroimaging, maintaining quality of the signal while allowing the naturalness of the movement and response, challenging.

Literature review

Many recent studies combined neuroimaging techniques with VR in research on human cognition and performance, such as human navigation and driving behaviour (Carvalho et al., 2006), social interaction (John A King et al., 2006), spatial memory (N. Burgess et al., 2001), violent behaviour (Mathiak & Weber, 2006), or emotion (Baumgartner & Valko, 2006). Most of these studies employed Functional Magnetic Resonance Imaging (fMRI) or Electroencephalography (EEG). The first one offers high spatial resolution, while the second offers better temporal resolution (Ferrari & Quaresima, 2012). However, lying within a huge and noisy fMRI scanner restricts freedom of movement and could possibly evoke anxiety in some participants (Irani et al., 2007). Recently, improvements have been made making EEG systems more compact, wireless and portable. This allows EEGs to be combined with VR systems in which people can more freely move (Török et al., 2014). The most challenging disadvantages of EGG are its susceptibility for motion artifacts, and electronic signal interference. fNIRS provides a tool for acquiring brain scans that are between spatial resolution of fMRI and temporal resolution of EEG within VR (Irani et al., 2007).
fNIRS was combined with VR display for the first time by Holper and colleagues (2010) as a tool for monitoring virtual motor rehabilitative training (Holper et al., 2010). Other recent studies showed fNIRS can be used in combination with VR in balance control (S Basso Moro et al., 2014), or navigation learning (Ayaz & Shewokis, 2011). However, those studies did not use fully immersive systems and did involve freedom of the movement within VR. This pilot study tested the potential of utilising technologies which would facilitate naturalness of response while measuring neural activity from prefrontal cortex.

Previous neuroimaging studies demonstrated that prefrontal cortex plays a crucial role in emotional reappraisal and cognitive regulation of emotion (Grimm et al., 2006). In particular, neuroimaging studies performed on healthy participants found increased activity in the medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) during perception of fearful pictures (Lange et al., 2003), fearful faces (Nomura et al., 2004), emotional reappraisal (Ochsner & Gross, 2005), or suppressing negative mood during decision making (Beer et al., 2006). Comparatively, studies performed on patients with depression and anxiety disorders demonstrated hypoactivation in the MPFC and DLPFC could indicate deficits in emotional regulation (Duval et al., 2015).

Method

This pilot study tested the potential of combining the wearable fNIRS device – NIRSport, with two VR display systems: a cave - like (IPT) system – Octave, and a custom fNIRS - adapted Oculus Rift DK2.The aim of this study was to measure brain response to the evocative VR. The objective of this study was to test the feasibility of the protocol in terms of the design, integration of technology and signal to noise ratio. The approach was to combine VR display systems in which participants can move freely while neural index of emotional regulation can be measured.

Devices

Immersive Projection Technology (IPT) Octave

Octave is an octagonal IPT space approximately 32.6 m^2, which is big enough to allow a small group of people to mingle. Immersive Projection is delivered via the surrounding walls and floor display. There are 8 surrounding wall screens 2600mm x 1969mm with resolution 1400x1050 pixels, and 96Hz refresh rate. There are 14 Christie S+3K mirage projection units of which 6 project to the floor with 8 rear projection systems utilised for the walls. Octave images are generated by a workstation with 2x Xeon E5-2650, giving 32 threads, 64GB memory, SSD and 4xNvidia K5000 with a k-sync card running a single desktop through 4 mosaic instances. Parallax is provided by the optical motion tracking system Vicon MX-F40, controlled by a Dell workstation running Windows 7 and Vicon Tracker 2.0, with custom designed optical markers on the glasses. The users in Octave wear XPAND 3D Shutter Glasses Lite RF (X105-RF-X1) with a shuttering frequency 96 Hz. There are no modifications required in order to measure haemodynamic responses to IPT based virtual stimuli utilising the NIRSport system, however the infrared tracking system and electronic light emitting peripheral devices may potentially introduce noise to the fNIRS data.

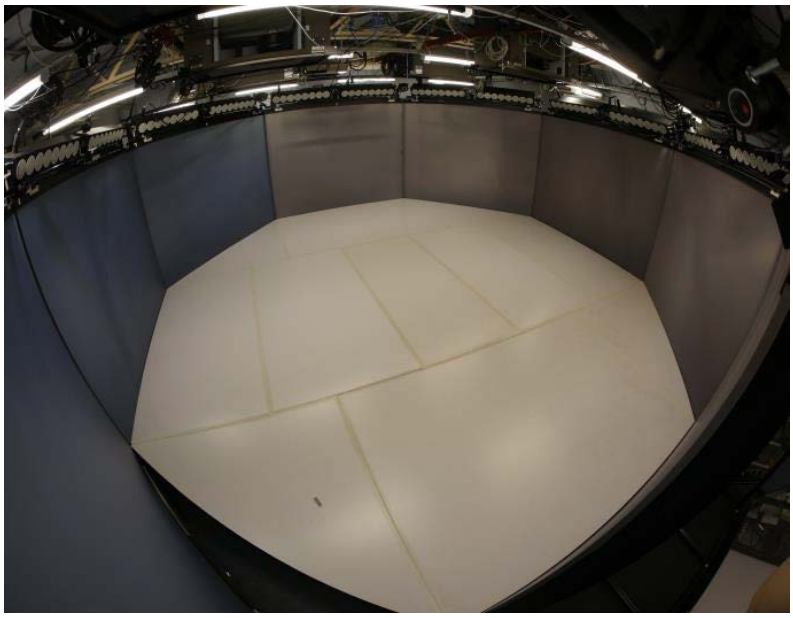

Fig.1. Octave

Custom Oculus Rift

The Oculus Rift DK2 needed adaption to allow space for the fNIRS optodes. Securing straps were changed – it was necessary to remove the 'over-the-head' strap of the oculus in order to ensure it was not in contact with probes of the NIRSport system. The remaining straps were removed and replaced with a buckled elastic strap. This helped to avoid issues caused by disturbance of probes when the HMD was put on. Due to the reduction of weight support across the top of the head, the HMDs weight was not being distributed comfortably when worn, with a moderate level of pressure on the end of the nose. In order to increase comfort, the frames of a pair of glasses were incorporated to improve support. Part of the top section of the HMD was cut away and edges were sanded to eliminate sharpness. The section removed was slightly larger than the length of a NIRSport standard probe in order to minimise chances of contact between HMD and probe during use. The lack of support across the forehead caused by removing a section of the HMD led to it leaning back toward the user at an inappropriate angle for use. Angled foam inserts combated this.

Fig.2. Custom Oculus Rift DK2 adapted for fNIRS

Functional Near Infrared Spectroscopy (fNIRS)

In order to measure changes in cerebellar oxygenation this study utilised the NIRSport system. (NIRsPORT 8-8, NIRx Medizintechnik GmbH, Berlin, Germany) which is a portable, wearable, multichannel fNIRS system consisting of 8 LED illumination sources and 8 active detection sensors. Emitters were placed on positions F3, AF7, AF3, Fz, Fpz, AF4, F4, AF8, while detectors were placed on positions F5, F1, Fp1, AFz, F2, Fp2, F6. Twenty channels were set up covering the prefrontal cortex (Fig 1.). The source - detector distance was 3cm. Optodes were placed on the participant's head using an EasyCap relative to the international 10/20 system (Jasper, 1958). The data was acquired with the NIRStar acquisition Software (v2014 NIRx Medical Technologies LLC) at two near infra-red light wavelengths of 760nm and 850nm, with a sampling rate of 7.81 Hz.

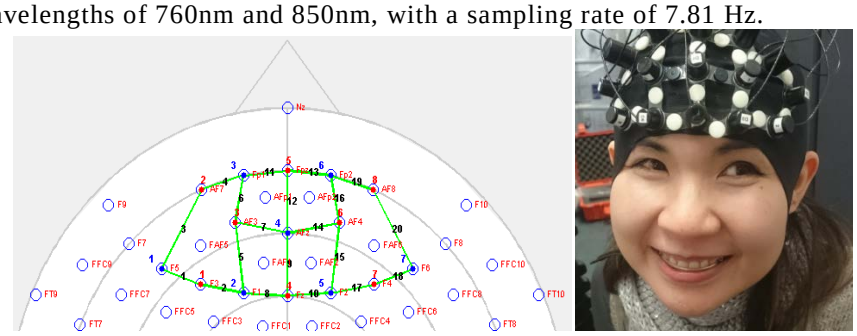

Fig.4. fNIRS optode placement (left); participant wearing fNIRS device (right)

Procedure

During the first stage of the experiment, both VR displays were combined with the NIRSport and were tested in terms of raw data quality through measuring Signal - To - Noise – Ratio (SNR). Visual inspection of the raw optical densities was carried out using NIRStar Software (version 2014, NIRx Medical Technologies LLC).

After the initial tests, eleven volunteers (N=11, 4 females and 7 males, mean age 33.18, SD=4.72) were recruited to walk on the virtual plank 6 meters above the floor in Octave. During the task, we recorded brain oxygenation changes from the prefrontal cortex as a neural index of emotional regulation.

Simulation

The scenario was created using Unity 4.3.3 game (https://unity3d.com/). The simulation in Octave was supported by MiddleVR 1.4.2 for unity (http://www.middlevr.com/middlevr-for-unity/).

The environment consisted of two rooms: the training room, which looked like a normal room with a floor and furniture, where participants familiarised themselves with the virtual environment and trained to carry out the task; and the pit room which had no floor but the wooden ledge on which participants stood and looked down into the pit room (which looks like an ordinary room with a floor and furniture) approximately

6m below the plank.

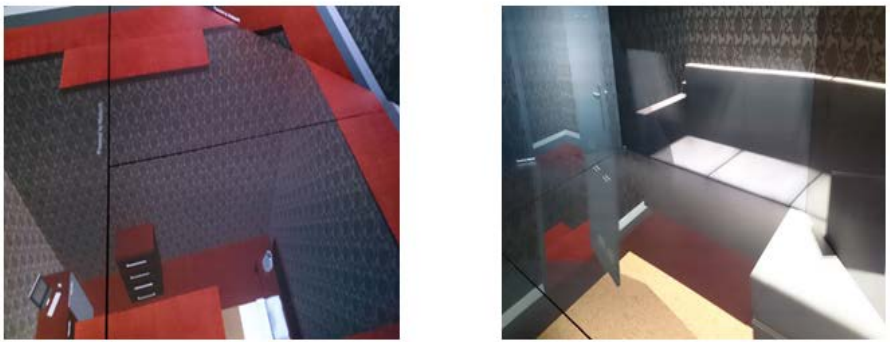

Fig.5. Pit Room experiment – view into the pit room (left), view in the training room (right)

Task

Prior to the experiment participants were allowed to familiarise themselves with the virtual environment and practice carrying out the task for about 5 minutes. During the experiment they were asked to perform a simple walking task. In the training room the participant walked on the floor, and in the pit room the participant walked on the virtual plank.

Design

The experiment employed a within-subject design. Each participant performed a task under two experimental conditions – training room and pit room. There were 10 trials split equally between the training room and pit room, with each trial lasting 30 seconds. A 30 second baseline was recorded prior to the first stimuli onset. During this participants were instructed to step on the actual floor outside of the simulation area in the training room, stay still, close their eyes, clear their mind and relax. After the baseline, participants heard pre-recorded audio instructions generated in random order, to move either to the training room or move to the pit room. The whole experiment lasted 330 seconds. We employed an event-related design where participants spent 30 seconds in the training room and 30 seconds in the pit room. There were no breaks between conditions.

Data analysis

Raw time series were assessed in NIRStar Software (version 2014, NIRx Medical Technologies LLC) by calculating a SNR and performing visual inspection of the raw optical densities using the function 'check raw data' within the software. To calculate SNR, the relative coefficient of variation (CV) was calculated for each channel. Data with CV over 15% was removed from the analysis. Raw data was converted to average haemoglobin concentration changes using the modified Beer–Lambert law for each channel, each subject, and each condition. fNIRS data was preprocessed and analysed using NIRSLab (NIRx Medical Technologies version 2014). Oxy- (HbO) and deoxy – (HbR) haemoglobin time series were band-pass filtered with low cut-off frequency 0.01 Hz and high cut-off frequency 0.2 Hz to remove drifts and noise from the data. Many previous studies have shown that HbO correlates with BOLD signals better than the HbR (Hoshi et al., 2001), therefore this study focused on HbO for further analysis.

Statistical data analysis was performed using NIRSLab - SPM (SPM8). Data was modelled with GLM. Two regressors were generated by convolving the weighted task time series with the canonical hemodynamic response function provided by SPM8 (Friston et al., 1996). Discrete cosine transform basis functions were used for temporal filtering, and precoloring HRF was used for the serial correlations. On the next level analysis T-contrasts were created for HbO changes to generate statistical parametric maps of activation for two regressors: training room, and pit room, for each channel and each subject. SPM T-maps were generated by using two contrasts: training room-pit toom and pit room-training room, and thresholded at $p < 0.05$ (corrected).

At the group analysis, SPM group ΔHbO T – statistics were calculated to identify the channels significantly activated with a significance level threshold set at $p < 0.5$ (corrected) according to the false discovery rate method FDR used in fMRI studies (Singh & Dan, 2006). The estimated anatomical locations of each channel were determined using anatomical locations of international 10-10 system cortical projections of EEG sensors (Koessler et al., 2009; Okamoto & Dan, 2005).

Findings

SNR and motion artifact analysis results

Figure 6. shows example raw time series data from a single subject acquired from both the Oculus – fNIRS test, and Octave – fNIRS test. SNR tests demonstrated that there was no significant signal interference from both VR displays – Oculus Rift and Octave.

Due to motion artifacts, 5% of the data was removed from the Oculus - fNIRS test, and 50% from Octave - fNIRS test.

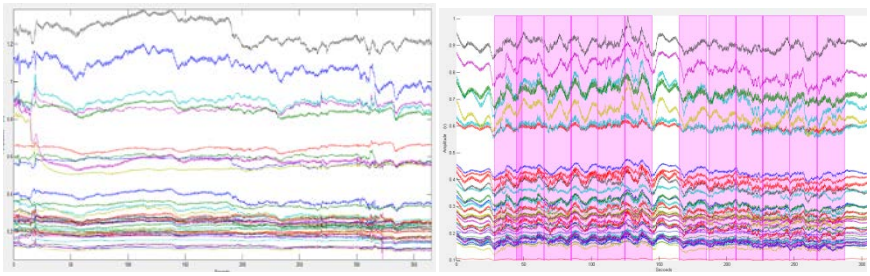

Figure 6 example time series acquired from combining fNIRS with custom Oculus Rift DK2 (left) and Octave (right). Noise appears as rapid changes (such as spikes and steps)

SPM results

Figure 7. shows the results for SPM group analysis (Pit room versus Training room). SPM contrast for group analysis (Pit room versus Training room) at the significance threshold level $p < 0.05$ (corrected) revealed no significant results. However, results showed a trend toward increased HbO in MPFC (channel 12, $t(4) = 1.99$, $p = 0.1175$, two-tailed) and DLPF (channel 15, $t(4) = 1.81$, $p = 0.1445$, two-tailed) when participants exposed to the virtual heights in the Pit Room in comparison to the Training Room.

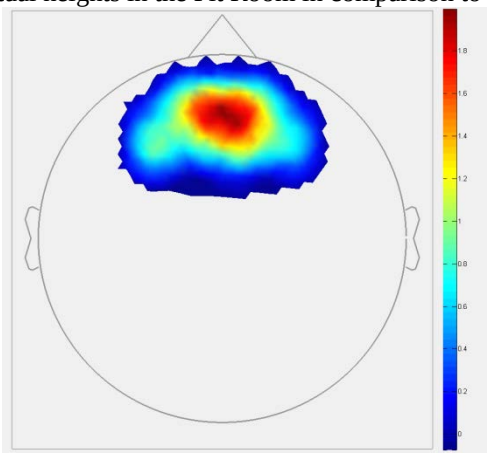

Fig.7.SPM T-map of ΔHbO in the Pit Room versus Training Room. The t-value (unthresholded) is indicated by a colour scale.

Discussion and lesson learned

The main concern in this pilot study was a possible interference of the near infrared lights from motion tracking systems on fNIRS system. By measuring SNR, this was proved an ungrounded assumption for both VR displays.

Although fNIRS is less susceptible to motion artifacts than EEG and fMRI, still it is sensitive to sudden excessive movement. As an objective of this study was promoting freedom of movement in VR, the level of motion impact was investigated. On the one hand Oculus Rift caused less motion artifacts, but it restricted freedom of movement to that head. Therefore motion artifacts were likely to have been caused primarily by optode displacement during putting the device on. On the other hand combining fNIRS and Octave caused more motion artifacts due to both the nature of the display system, as well as the experimental task itself. The data analysis revealed motion artifacts in the signal when people leant forward excessively. This was potentially a problem given the task encouraged this. However, such a level of bend did not arise from the experimental protocol, but rather participants wanting to experiment with the experience. Moreover, this study investigated how much movement is too much to keep data motion artifact free. While it was possible to remove such data, it is better practice to exclude all the data from the session.

Initially the measurement system was highly unstable. This came from the desire to maximise freedom of

movement and approach. Physiological data can be communicated wirelessly from the sensors to the computer; however several technological issues, such as the data collection laptop overheating, and software crashes, were related to the high system requirements for brain data acquisition which requires a high-end laptop. The solution was to put the brain data acquisition laptop in a mesh backpack.
The adaptations made to the Oculus Rift DK2 are would be harder with the newer commercial versions of the Oculus. This contains wiring through the headband. It is important to note that adaptation was a prototype. Further work needs to be carried out to fully integrate HMD based VR with neuroimaging methodologies. A potential solution is to utilise 3D printing techniques to incorporate an EEG/fNIR cap into a specially designed HMD.

In conclusion, combining fNIRS with both VR displays offers new opportunities for the researchers. Both VR systems have their own pros and cons (summarised in table 1). Therefore the selection of appropriate display should be determined by the experimental design and the research question.

Table 1. Advantages and disadvantages in combining fNIRS with HMDs and IPT

Oculus	Octave
Movement restricted to that of the head Single user Hides the presence of others Doesn't allow natural embodiment No risk of infrared light interference HMD can cause minimal motion artifact due to the sensor displacement	Allows Movement around the space Allows a group of people to mingle Doesn't hide presence of others The user can see their own body Higher risk of infrared light interference IPT can cause motion artifact due to the freedom of movement within VR space

Conclusions
Virtual Reality offers a solution for bridging the gap between ecological validity and controllability (Rey & Alcañiz, 2010). Both ecological validity and controllability are important in both VR and neuroscience research, and applications This study proposed and tested a solution that integrates wireless brain imaging and two VR displays – a large IPT VR solution in which users can move more freely – Octave, and a custom fNIRS-adapted Oculus Rift. The results of our pilot study suggested trends that indicate the potential for this integration of technology to evoke emotional response within VR. We have demonstrated the feasibility of the study and resolved all technical problems.
Although this pilot study did no obtain statistically significant results due to the sample size, it identified promising trends showing that VR can trigger emotional regulation response which can be measured by a wireless brain imaging device. Results of our study demonstrated trends in increased haemoglobin oxygenation (HbO) in right MPFC and right DLPFC indicating emotional regulation processes in the brain when participants were exposed to evocative virtual stimulus. These results are consistent with previous neuroimaging studies (Gregory J Quirk & Beer, 2006). However, this study did not constrain the natural movement of the participant in one of its conditions.
This pilot study lead to a further developed investigation. Since the reported investigation was conducted, the data collection for the full experiment with a larger sample was completed, and analyse is underway.
Potential impacts of this work include opening the door to more ecologically valid study of neuroscience and measurement of response in virtual reality, and potentially, adaptive immersive neurofeedback techniques in mental health and neurorehabilitation.

Biblography
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Oculus