Electroencephalographic Measures of Depressivity:

Alpha Asymmetry and Fractal Dimension

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Abstract

Recent research has suggested that neurofeedback, utilising alpha asymmetry or fractal dimension as an index of depression, may be an effective treatment for depressed individuals. In this thesis the relationships between frontal alpha asymmetry (FAA), parietal alpha asymmetry (PAA) and Higuchi's fractal dimension (HFD) with PID-5 depressivity were investigated to assess their potential as signals for neurofeedback. Resting EEG previously recorded from a general sample of 66 individuals was analysed. The data of male and female participants was analysed separately. Optimised eye condition and bandwidth were determined with one way, repeated measure ANOVAs. Optimal specific measures of FAA, PAA and HFD were then identified by the proportion of PID-5 depressivity accounted for. The optimal FAA measure was obtained from the frontopolar electrode pair (Fp2 – Fp1) in the 10-12Hz sub-band. It was the only measure that was reliable in both male and female participants. PAA between the lateral electrode pair (P8 – P7) in the 8-10hz sub-band reliably correlated with depressivity in female, but not male, participants. HFD was reliable at every electrode in female, but not male, participants and displayed intercorrelation between all electrodes in both genders. A combined model using all three optimal measures showed that the proportional variance of FAA, PAA and HFD was mainly additive, with little variance shared between measures. The results suggest that FAA at the frontopolar electrode pair (Fp2 – Fp1) in the 10 – 12Hz band may be the optimal AA measure for neurofeedback protocols targeting depression. Correlations between AA and depressivity were often site- and band-specific; reliable correlations observed in one location did not necessarily generalise to other locations. Correlations between HFD and depressivity were not site-specific with most variance shared between sites. There was little overlap between the variance accounted for by FAA, PAA and HFD; indicating that the information conveyed by each is due to distinct neural processes, which may be associated with distinct aspects of depressivity and, potentially, other trait measures. Future work should assess replicability and the extent to which the results are specific to depressivity.

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List of Abbreviations

AA	Alpha Asymmetry
ANOVA	Analysis of Variance
CBT	Cognitive Behavioural Therapy
CVD	Cardiovascular Disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DALY	Disability Adjusted Life Year
EC	Eyes Closed
EEG	Electroencephalogram
EO	Eyes Open
FAA	Frontal Alpha Asymmetry
FC	Full Channel
HFD	Higuchi's Fractal Dimension
IAF	Individual Alpha Frequency
KFD	Kat's Fractal Dimension
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MetS	Metabolic Syndrome
MRA	Multiresolution Analysis
PAA	Parietal Alpha Asymmetry
PID-5	The Personality Inventory for DSM-5
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressants

CHAPTER 1: INTRODUCTION

Overview of Depression

Depressive illnesses are one of the most common mental health disorders. Depression is now the leading cause of disability in the world (WHO, 2017). It has a 12-month prevalence in New Zealand of over 5% (Oakley-Browne, Wells, & Scott, 2006). It is characterized by negative mood, loss of pleasure, decreased quality of life, suicide risk, and poor prognosis. Millions are affected annually around the world with consequences that extend past the individual to families, communities, and the economy. The mainstream treatments that are available often fail to adequately treat depressive symptoms and produce undesirable side-effects. It is critical that we identify depression-specific biomarkers that can be used as a benchmark to identify response to treatments, improve diagnosis and assist in the development of new or improved treatments. Current attempts at identifying promising electrophysiological biomarkers of depression have met with mixed results (Allen & Reznik, 2015; Debener et al., 2000) but suggest that the alpha wave band has some relationship to depression. Neurofeedback protocols train individuals to alter alpha power in the brain; and recent research suggests this may be a promising self-administered treatment for depression (Peeters, Ronner, Bodar, van Os, & Lousberg, 2014; Wang et al., 2016). The primary aim of this thesis is to identify the best frontal alpha asymmetry measure for use in neurofeedback protocols.

Defining depression

Major depressive disorder (MDD) is a mood disorder characterised by negative mood, loss of pleasure, decreased quality of life, suicide risk, poor prognosis and can also include weight changes, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of worthlessness and guilt, diminished cognitive abilities and recurrent thoughts of death/suicide (American Psychiatric Association, 2013). MDD is thought to afflict over 4% of the global population at any given point in time, which suggests that at this moment 300 million people are suffering from MDD (Ferrari et al., 2013). The percentage of mild MDD cases (10.4%) is drastically overshadowed by moderate (38.6%),

severe (38.0%) and very severe (12.9%) cases (Kessler et al., 2003). These findings show a top-heavy distribution of symptom severity with over 50% of MDD sufferers experiencing severe symptoms. MDD brings with it significant costs at both the economic and individual level.

Depressive mental illnesses are diverse in both symptomatology and expression. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5; American Psychiatric Association, 2013) provides diagnostic information for a multitude of different depressive disorders and subtypes. The benefit of having such a wide variety of diagnoses is that people suffering from uncommon forms of depressive symptoms are more likely to be diagnosed and treated. From a clinical perspective, this grouping of symptom clusters that are treated similarly is useful because it allows for simplified diagnosis and treatment. From a research perspective, there is a question to be asked: How broad a definition is too broad?

The utility of the broad diagnoses seen in depression, particularly in Major Depressive Disorder (MDD), has been questioned in recent years. There are at least 170 different ways patients meet the criteria for a diagnosis of MDD (Zimmerman, Ellison, Young, Chelminski, & Dalrymple, 2015) with this number theoretically being as high as 1497 (Ostergaard, Jensen, & Bech, 2011). While these combinations have depressed mood in common, for many patients this will be where the similarity ends; with distinct symptom profiles being the norm (Fried & Nesse, 2015). The heterogeneity of MDD and the failure of treatment to help a significant proportion of patients (Ostergaard et al., 2011) suggest that progress in this domain requires a careful reappraisal of the dominant view of depression as a natural kind (Fried, 2015).

Somatic effects of depression

There is considerable evidence of depression acting as a risk factor for cardiovascular-related diseases (CVD; Goldston & Baillie, 2008; Holt et al., 2013; Kuper et al., 2009; Lett, 2004; Rudisch & Nemeroff, 2003; Rugulies, 2002). Support for this is strong, with powerful effects observable in a cohort of over 1.9 million individuals (Daskalopoulou et al., 2016). Depression increases the

likelihood of adverse outcomes and mortality in CVD (Barth, Schumacher, & Herrmann-Lingen, 2004; Freedland & Carney, 2013; Rudisch & Nemeroff, 2003). MDD is estimated to be responsible for 3% of ischemic heart disease's disability adjusted life years (DALY) burden (Charlson et al., 2013).

The increased risk of cardiovascular diseases may be partially attributable to a connection between depression and metabolic syndrome (MetS). MetS refers to a cluster of metabolic factors which directly increase the risk of CVD, type 2 diabetes and all-cause mortality (Kaur, 2014). These factors include obesity, hyperglycaemia, elevated blood pressure, increased triglycerides and decreased HDL cholesterol (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). There is a wealth of research that has found an increase of MetS prevalence in depressed populations (Kahl et al., 2012; Seppala et al., 2012; Vancampfort et al., 2014). The relationship appears to be bi-directional (Pan et al., 2012) and the combination of both MetS and depressive symptoms appears to confer an additive risk for type 2 diabetes (Schmitz et al., 2016) and CVD (Vaccarino et al., 2008). Recent evidence also suggests that antidepressant use may increase likelihood of occurrence and worsen pre-existing MetS (Corruble et al., 2015; Crichton, Elias, & Robbins, 2016; Hiles, Revesz, Lamers, Giltay, & Penninx, 2016).

As with cardiovascular disease, a history of depression also confers an added risk for future dementia. In the case of Alzheimer's disease, a history of depression increases the odds of development, even when the onset of depression is decades prior to the Alzheimer's disease (Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008; Green et al., 2003). Early onset depression may also be a risk factor for dementias in general (Simoes do Couto et al., 2016). The relationship between depression and dementia isn't entirely clear with evidence that depression may be a prodrome and a risk factor depending on time of onset (Late vs. early onset; da Silva, Goncalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013). Depression is known to involve reductions in brain volume, particularly in the hippocampus and amygdala (Schmaal et al., 2016) with longer periods of depression corresponding to greater decreases in hippocampal volume (Buddeke et al., 2017).This pattern of decreased hippocampal volume is also a distinguishing feature of Alzheimer's disease (den Heijer et al., 2006).

Suicide

Depressive disorders of any kind have very serious and deadly effects on the physical health of those affected. Suicide, the taking of one's own life, is a common behaviour in depression. The suicide rate for affective disorders is thought to be 6% (Inskip, Harris, & Barraclough, 1998). Longitudinal data shows that severity correlates with differences in suicide rates. 3.1% of moderate and 13.7% of severe MDD patients attempt suicide (Bradvik, Mattisson, Bogren, & Nettelbladt, 2008). This dose-dependent relationship between suicide and depression severity is of great concern as over 50% of MDD sufferers are in the severe range of MDD (Kessler et al., 2003).

Global Cost of MDD

The economic cost of depressive illnesses is massive. The 2010 Global burden of disease study (Ferrari et al., 2013) ranked MDD as the second largest contributor to years of healthy life lost due to disability (YLD) and 11th highest contributor to DALYs globally. This burden is higher in New Zealand with MDD ranking as 4th in Australasia for DALY's (Ferrari et al., 2013). It should come as no surprise that this scale of disability comes with a large economic burden. A 2011 report from the World Economic Forum placed the estimated economic cost of mental illness at $2.5 trillion U.S dollars in 2010 (Bloom et al., 2011) and is expected to rise to $6 trillion by 2030. Reduced efficiency and absenteeism due to MDD have been reported to cost U.S. businesses up to $36 billion annually (Kessler et al., 2006). A study investigating the cost of chronic conditions to DOW Chemicals Company found that individuals with a primary health condition of depression or anxiety cost the company $15,000 per year in decreased productivity (Collins et al., 2005). An Australian study found that compared to healthy controls depressed employees cost between $1,620 and $3,900 extra in lost productivity; with an estimated $8 billion total loss in Australia as a result (McTernan, Dollard, & LaMontagne, 2013). The economic costs of depressive illnesses are enormous and presents a prime target for cost-effective intervention and prevention.

The Current State of Treatment and Barriers to Access

The primary methods of treating MDD are pharmacological and psychological. Pharmacological treatment is the prescription of antidepressant medications, this kind of treatment takes place through either a licenced psychiatrist or general practitioner. Psychological treatment is administrated through a clinical psychologist. Behavioural and cognitive techniques are used to assist the patient in recovering and managing their depressive symptoms. Often these methods are applied in conjunction with each other. Each has distinct benefits, consequences and barriers to access.

Pharmacological management

There are many types of antidepressant medication. The oldest classes of antidepressants are monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The inhibition of monoamine oxidase by MAOIs results in increased levels of monoamines including serotonin, norepinephrine and dopamine. MAOIs are particularly dangerous as their inhibition of monoamine breakdown means that the consumption of anything that boosts monoamine levels can result in toxicity (Riederer, Lachenmayer, & Laux, 2004). TCAs inhibit the reuptake of serotonin and norepinephrine from the synaptic cleft and so increase levels but through a different mechanism than MAOIs and, importantly, with much less dangerous side effects. Newer classes of antidepressants include serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs). SNRI's inhibit the reuptake of both serotonin and norepinephrine, while SSRIs inhibit the reuptake of serotonin. These newer classes have similar efficacy to MAOIs and TCAs, but are much better tolerated. In all classes of antidepressants, the focus is set on increasing the bioavailability of monoamines, primarily serotonin and norepinephrine (Ruhe, Mason, & Schene, 2007).

Prescribing practices

The pharmacological management of depression in New Zealand appears to be based on the work of Thase and Rush (1997) in which the authors proposed a staging model for determining

treatment-resistance and a method of prescription for depression. Thase and Rush (1997) proposed beginning with SSRI monotherapy then progressively moving on to other classes (SNRI, TCA and MAOI) if each subsequent treatment is ineffective after 4-6 weeks with the final option being electro-convulsive therapy (ECT). This progression follows the tolerability of the different drugs, starting with the most tolerable (SSRIs) as the first step. At each stage, the possibility of increasing dosage, switching within class and augmentation are also presented. The Best Practice Advocacy Centre New Zealand (BPACNZ, 2009) suggests a second SSRI be used if a first fails. New Zealand clinical guidelines for management after this point are detailed by Ellis and Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (2004), which follows a similar trajectory as Thase and Rush (1997) though is much more detailed.

Efficacy of pharmacological management

The efficacy of antidepressant drugs is a topic that has received a lot of attention. The largest antidepressant medication trial conducted thus far is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Gaynes et al., 2008).The study investigated the efficacy of antidepressant medications in a sample of 4041 outpatients. The study used 4 sequential levels of treatment. Patients who responded to treatment at any level could remain on the effective medication, while the others were given the option of moving onto the next level of the trial. Reported results were promising with cumulative remission rates of 33% at level 1, 50% after 2 level, 60% after 3 levels and 70% after the 4th level of the trial (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007).

A detailed analysis of the research methods applied in the STAR*D trial reveals some points of concern. The cumulative remission rates were calculated from one of the study's secondary measures and not the primary outcome measure (Hamilton Rating Scale for Depression; HRSD) discussed in the studies design (Rush et al., 2004). This appears to have resulted in inflated remission rates (Pigott, Leventhal, Alter, & Boren, 2010). There is evidence of a series of rounding errors which resulted in a steady increase in reported efficacy (Pigott, 2011). The reported cumulative remission rates assume that if those who dropped out had remained in the study they would have responded at the same rate as those who stayed (Rush et al., 2006). However, it had been previously stated that

patients with missing HRSD scores on exit would be considered as non-remitters, a priori (Trivedi et al., 2006). Application of that criterion would have resulted in a cumulative response rate of 37.6% (1,518 out of 4,041 patients; Pigott et al., 2010), instead of the claimed 70%.

There are other barriers to determining the efficacy of antidepressants. The difference between placebo and active treatment is a topic of significant debate. The work of Kirsch et al. (2008) found antidepressants were only significantly better than placebo for very severe MDD patients. Later reanalysis of the same data set suggests that the difference between placebo and antidepressants is 5% for mild, 12% for moderate and 16% for severe MDD (Vohringer & Ghaemi, 2011). Another issue is the rate of spontaneous recovery. The proportion of untreated depression cases that remit within 12 months is predicted to be as high as 53% (Whiteford et al., 2013). The rates of spontaneous remission appear to be much lower in treatment-resistant populations with 3.6% remitting with a 12 month period (Dunner et al., 2006).

Overall, the current research is in favour of antidepressants having a significant benefit in cases of moderate and severe MDD, although the placebo effect does account for a sizable proportion of the total effect. The benefit of antidepressant treatment is dependent upon the severity of depression with more severe cases having a higher rate of response to the treatment.

Psychotherapeutic approaches

Psychotherapy aims to treat mental illness using psychological rather than medical means. Research on the efficacy of psychotherapies is extensive, Cognitive Behavioural Therapy (CBT) is the most widely evidenced form of psychotherapy. In the interest of simplicity this discussion will focus on CBT exclusively; due in part to the prevalence of research assessing its efficacy but also because differences between types of psychotherapy are often minor (Cuijpers, van Straten, Andersson, & van Oppen, 2008; Tolin, 2010), even when compared to newer types like metacognitive therapy (Jordan et al., 2014). CBT is focused on imparting cognitive and behavioural skills that patients can use to manage their symptoms. Parts of this therapy often include the patient being taught about the cognitive model of depression, learning to identify and challenge their own thought processes and altering

behaviour patterns (Enright, 1997). CBT is often used in the treatment of mood disorders, especially depression and anxiety (Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016).

Efficacy of CBT and CBT plus drugs

The differences between different kinds of psychotherapy may be small (Barth et al., 2004) but favours CBT as the most effective psychotherapy for depression and anxiety (Tolin, 2010). The efficacy of CBT in treating MDD is small to moderate (Barth et al., 2013; Butler, Chapman, Forman, & Beck, 2006; Dubicka et al., 2010; Furukawa et al., 2017). This is comparable to that of pharmacological treatment with antidepressants (Karyotaki et al., 2016; Roshanaei-Moghaddam et al., 2011; Wiles et al., 2013).

Pharmacotherapy and CBT are often used in combination to treat MDD. The use of this combined therapy improves the overall efficacy of treatment (Barth et al., 2013; Karyotaki et al., 2016; Thase, 2007; Wiles et al., 2013) although this may not hold equally across severities (de Maat, Dekker, Schoevers, & de Jonghe, 2007). Patients who undergo CBT seem to have a reduced rate of relapse compared to pharmacotherapy (Beshai, Dobson, Bockting, & Quigley, 2011; Vittengl, Clark, Dunn, & Jarrett, 2007). MDD has a relapse rate of 33.5% to 50% (Warden et al., 2007), which makes any reduction in relapse rate highly desirable.

The effectiveness of CBT, both alone and in combination with pharmacotherapy, make it a valuable tool for treating MDD. CBT has the added benefit of avoiding the side effect profiles that come with pharmacotherapy while maintaining a similar level of efficacy. Overall combined therapy is the optimal method for treating depression effectively.

Barriers and problems associated with pharmacotherapy and CBT

The efficacy of pharmacotherapy and psychotherapy are not the only important factors in the treatment of MDD. The ability and willingness of patients to engage with treatment is of critical importance. There are a wide range of barriers to engaging effectively with mental health care. The

most obstructive of these appear to be attitudinal barriers such as patients desire to handle the problem on their own, perceived ineffectiveness of treatment, and stigma. There are also structural barriers such as financial cost (Andrade et al., 2014).

Depression is, by nature, at odds with treatment-seeking behaviour. Seeking treatment requires that the patient be motivated to actively seek out and engage with mental health professionals, to keep scheduled appointments, and interact socially and be open with unfamiliar people. These things are in stark contrast to the withdrawn and internalising behaviours that characterise depression. It follows naturally that there will be significant barriers to treatment associated with this conflict. The desire to handle the problem themselves (Andrade et al., 2014) and the reduced perceived need for treatment (Mohr et al., 2010) are likely to be symptoms of this issue. These problems are compounded by perceptions of social and economic stigma that come with diagnostic labelling.

Health care of any kind is rarely cheap, mental health care is no exception to this. The financial cost of treatment functions as a structural barrier to accessing mental health care with household income having a significant correlation to seeking treatment (Carragher, Adamson, Bunting, & McCann, 2010; Simon, Fleck, Lucas, Bushnell, & Group, 2004). Self-reported barriers to treatment also show financial cost as being a major issue (Andrade et al., 2014). The cost effectiveness of CBT and pharmacotherapy is acceptable at a governmental level (Hollinghurst et al., 2014; Vos, Corry, Haby, Carter, & Andrews, 2005). Improved investment into mental health care is likely to bring with it significant long term returns (Chisholm et al., 2016). Unfortunately, even in countries with well-funded mental health systems access to mental health care is still limited by income (Steele, Glazier, & Lin, 2006).

Overcoming these barriers is difficult as many of the issues are fundamental in nature. The financial cost of treatment to the individual can be lowered through government funding, though this is redistribution of costs and not a true reduction. Engaging with mental health professionals will always require motivation on behalf of the individual and some element of social interaction. An alternative possibility is to work with these barriers instead of against them. The development of tools such a neurofeedback offers this possibility.

Neurofeedback as a Possible Treatment Method

Neurofeedback is a method that may be useful in treating depression and navigating some of the barriers to traditional treatments. Neurofeedback protocols use the electroencephalogram (EEG) to monitor specific aspects of cortical activity and relays that information back to the participant. The subject attempts to regulate their cortical activity using the feedback information as a guide. The plausibility of neurofeedback as a clinical tool has been investigated as far back as 1994 (Baehr, Rosenfeld, & Baehr, 2001) and research continues to this day (Peeters, Oehlen, Ronner, van Os, & Lousberg, 2014; Peeters, Ronner, et al., 2014; Quaedflieg et al., 2016). Although more research is needed, research indicates that the efficacy of neurofeedback may be similar to that of traditional methods (Cheon, Koo, & Choi, 2016; Peeters, Oehlen, et al., 2014). Neurofeedback is attractive because it could help overcome some of the attitudinal barriers to treatment, could be more convenient and cost-effective than traditional methods, and targets biological, evidence-based signals.

Attitudinal barriers

The desire to deal with depression on one's own and the perception of not needing help are two of the most significant attitudinal barriers to treatment (Andrade et al., 2014; Mohr et al., 2010). Neurofeedback could overcome these barriers due to the potential for self-administration. Unlike seeking help from mental health professionals, neurofeedback protocols only require an EEG headset for recording and a computer or laptop for providing feedback. Those who wish to deal with depression themselves could prefer neurofeedback to traditional treatment as it is a tool they can use to help themselves rather than a concession that they require external help. Those who experience low perceived need of treatment might be less averse to neurofeedback because it doesn't require engaging with mental health facilities to utilise. In both cases neurofeedback is less likely to be negatively affected by these barriers than other treatment methods are. With cheap headsets now available neurofeedback could be undertaken unsupervised at home.

Cost and convenience

The structural issues of cost and convenience are also significant barriers to treatment. The cost of CBT is quite high with private appointments often costing over $100 per hour (Vos et al., 2005). Other costs, such as transportation, time taken off work and prescriptions, further increase the financial strain. A self-administered neurofeedback protocol would require a one-off investment instead of an hourly rate. This could potentially save the individual significant costs, especially as many of the additional costs associated with traditional treatment would be avoided entirely. The equipment could also be loaned or hired if not needed on a regular basis.

Targeting of Biological Signals

Alpha asymmetry

Neurofeedback protocols for depression aim to alter the balance of alpha wave power in the frontal cortex (Peeters, Oehlen, et al., 2014; Peeters, Ronner, et al., 2014; Quaedflieg et al., 2016). Resting alpha waves have a property which distinguishes them from other frequencies. Alpha waves increase in amplitude when participants close their eyes and are attenuated when participants opened their eyes (Kirschfeld, 2005). This supports the idea that brain activity is responsive to external stimuli and that resting alpha activity is inversely related to brain activity. fMRI imaging of frontal regions shows that an increase in resting alpha wave activity correlates with a decrease in cortical activity (Laufs et al., 2003). Due to these findings, the alpha bandwidth has been the focus of a great deal of research.

The study of mood and emotion is important to the understanding of many mental health disorders including depression. Early studies investigated the possibility of hemispheric asymmetry in the alpha band being a measure of trait-like affective response (Tomarken, Davidson, & Henriques, 1990; Tomarken, Davidson, Wheeler, & Doss, 1992) with greater relative left activity predicting positive response and greater relative right activity predicting negative response. The measurement of asymmetric alpha power distribution is now referred to as alpha asymmetry. It is calculated by taking

the logarithmic power scores of an electrode pair and subtracting the left electrode from its homologous right electrode. The result is an index of the relative power difference between the pair with negative scores indicating higher left power and positive scores indicating higher right power.

A more focused branch of research has assessed the relationship between alpha asymmetry and depression. Although state based variation occurs, there appears to be a large trait-like component to alpha asymmetry that relates to depression. About 40 – 50% of anterior alpha asymmetry appears to stem from a latent trait, while the rest is due to state based differences (Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005; Hagemann, Naumann, Thayer, & Bartussek, 2002). Alpha asymmetry shows test-retest reliability in healthy and depressed groups across time spans of weeks (Allen, Urry, Hitt, & Coan, 2004; Tomarken et al., 1992) and years (Vuga et al., 2006). It is predictive of depression in longitudinal studies of adolescents (Mitchell & Possel, 2012; Possel, Lo, Fritz, & Seemann, 2008). Lifetime MDD status correlates with alpha asymmetry regardless of current symptom severity (Stewart, Bismark, Towers, Coan, & Allen, 2010). Similarly, individuals with childhood onset depression show altered alpha asymmetry compared to controls even when symptoms are low (Miller et al., 2002). Children descending from families with a history of depression also exhibit increased alpha asymmetry (Bruder et al., 2012). All this evidence points towards the correlation between alpha asymmetry and depression being dependent upon stable trait features of both.

The study of alpha asymmetry has also extended to anxiety. The rate of comorbidity between depression and anxiety disorder is extremely high (Approximately 60%; Kessler et al., 2003). With such a common relationship in place anything that correlates with one is almost certain to correlate with the other. Unsurprisingly, anxiety and alpha asymmetry appear to be correlated (Avram, Baltes, Miclea, & Miu, 2010; Bruder et al., 1997; Demerdzieva & Pop-Jordanova, 2011; Manna et al., 2010). As in depression, alpha asymmetry may also predict future anxiety scores (Blackhart, Minnix, & Kline, 2006). Thus, we have a picture in which two highly comorbid mood disorders are correlated with alpha asymmetry that demonstrates trait-like features.

Unfortunately, inconsistent results are commonplace in alpha asymmetry literature. This issue has been commented on in several reviews (Allen & Reznik, 2015; Olbrich, van Dinteren, & Arns, 2015; Thibodeau, Jorgensen, & Kim, 2006). Some studies find positive results (Arns et al., 2016;

Bruder et al., 1997; Diego, Field, & Hernandez-Reif, 2001) while others find small, or no significant results (Blackhart et al., 2006; Gold, Fachner, & Erkkila, 2013; Segrave et al., 2011). This inconsistency of findings makes the interpretation of results difficult. The main problem is the variety of methodologies applied. While the alpha band used is typically between 7 – 14Hz, there is considerably variability between studies. For example, bands used include: 7.5 – 11.5hz(Lopez-Duran, Nusslock, George, & Kovacs, 2012), 7.5 – 12.5Hz(Miller et al., 2002), 8 – 12Hz(Gold et al., 2013) and 8 – 13Hz (Debener et al., 2000). There are also methods to calculate individualised alpha bands such as individual alpha frequency (IAF; Doppelmayr, Klimesch, Pachinger, & Ripper, 1998) and peak alpha frequency (PAF; Angelakis, Lubar, Stathopoulou, & Kounios, 2004). With such variability in methodology, corresponding variability in results is to be expected.

Of interest to this thesis are the differences between fixed and individualised alpha bands. The use of the same fixed alpha bandwidth for each participant has been argued against. There are significant inter-individual differences in expressed alpha frequencies (Bazanova, 2012; Doppelmayr et al., 1998; Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014; Smit, Wright, Hansell, Geffen, & Martin, 2006). The presence of these differences at the individual level suggests that the use of fixed bands may not capture the desired signals in some participants and may include unwanted information in others. Klimesch (1999) described a method for calculating individualised alpha frequency (IAF) bands based on the alpha peaks centre of mass. This has seldom been applied in studies analysing AA and depression and with mixed results. One study finding no significance (Segrave et al., 2011) and another finding significance specifically in females (Tement, Pahor, & Jausovec, 2016).

The choice of electrode sites used for calculating AA is another major focus of this thesis. The electrode sites investigated vary between studies. Meta-analysis of depression- and anxiety-specific research found that F4/F3 was the only electrode pair to reach significance in depression (Thibodeau et al., 2006). However, this finding may reflect the absence of studies looking at many of the sites individually as many studies average power across left and right hemispheres. For example: Fp2/1 had nonsignificant results, but this conclusion was drawn from a single study. Subsequent studies that have used multiple electrode sites have found differing results with some null results for depression and anxiety (Segrave et al., 2011) and others showing positive (Demerdzieva & Pop-Jordanova, 2015).

The parietal regions are often neglected in favour of frontal sites despite there being significant findings in parietal sites (Stewart, Towers, Coan, & Allen, 2011). Detailed investigation of the roles played by other electrode pairs in both frontal and parietal regions is needed to improve our understanding of the relationships between AA and depression.

Fractal dimension

AA is not the only measure that can be used for neurofeedback. The focus on AA began in the early 1990's (Allen, Iacono, Depue, & Arbisi, 1993). Since then technological developments have resulted in vast improvements in computing power. This allows for timely usage of increasingly complex signal analysis techniques. During the 2000's the use of nonlinear dynamical methods began to be used widely in EEG analysis (Stam, 2005). Recently, research has shown that these nonlinear measures may be useful in differentiating depressed from non-depressed individuals (Ahmadlou, Adeli, & Adeli, 2012; Akar, Kara, Agambayev, & Bilgic, 2015; Bachmann, Lass, Suhhova, & Hinrikus, 2013; Hosseinifard, Moradi, & Rostami, 2013).

Fractal dimension is a nonlinear measure, which has been applied to neurofeedback (Wang, Sourina, & Nguyen, 2010) and also to depression (Ahmadlou et al., 2012). The purpose of fractal dimensions is best understood when the limitations of topological dimensions are made obvious. Normally when the dimension of something is considered we refer to its topological dimension; a 1-dimensional object is defined only by its length (a straight line) and a 2-dimensional object is defined by both length and width (a plane). A straight line can be plotted on a plane, stretching and twisting this straight line will result in it taking up more space on the plane than it did before. It is still a line though it has only length and not width so it still has a topological dimension of 1. You can stretch and twist the line until it takes up every point of space on the plane, thus the 1-dimensional line becomes a 2-dimensional plane. Logically, at some point in this process of twisting and stretching, the line stopped being truly 1-dimensional, but wasn't yet 2-dimensional either. However, topological dimension is always an integer (1, 2, 3 etc) so it cannot describe this change adequately.

Fractal dimension is one way of addressing this issue and has been described as a measure of the complexity or space-filling capacity of a pattern. A straight line will still have a fractal and topological dimension of 1, but as it is stretched and twisted to take up more space the fractal dimension will increase fractionally (i.e 1.1, 1.2, 1.3) until the line fills the plane. At which point, the fractal and topological dimensions will both be 2. EEG time series can be plotted as a line on a 2-dimensional graph. As EEG complexity increases, the space filled by the line will also increase. These changes will be reflected by the fractal dimension of the time series. In this manner, fractal dimension can be used as an index of EEG complexity, the closer to 2 the fractal dimension of the EEG signal becomes, the more complex the signal is.

Two commonly used methods for calculating the fractal dimension are Higuchi's Fractal Dimension (HFD; Higuchi, 1988) and Katz's Fractal Dimension (KFD; Katz, 1988). The HFD provides a highly accurate measure of the fractal dimension but greater sensitivity to noise, the KFD is less accurate but faster and more resilient to noise (Esteller, Vachtsevanos, Echauz, & Litt, 2001). Comparison of the methods showed that, in the analysis of EEG the KFD values are often not correct and are unduly influenced by both amplitude and frequency of the signal (Raghavendra & Narayana Dutt, 2009). So, Higuchi's method of calculating the fractal dimension should generally be used when analysing EEG signals and KFD is not assessed in this thesis.

The Present Research

As reviewed above, depression a common mental health disorder affecting a large proportion of the global population. In addition to its negative psychological symptoms, depression confers increased rates of cardiovascular disease, neurodegenerative disease and metabolic syndrome. Treatments of depression are various, covering both psychological and pharmaceutical domains. Current treatment options are often not enough to ensure remission. Investigating methods of treatment that can compensate or mitigate barriers to current treatments is needed. Neurofeedback is a potential method for treating depression that may circumvent several attitudinal and structural barriers to traditional treatment options. Current neurofeedback protocols focusing on depression use AA as a

target for manipulation despite the literature providing inconsistent results on the links between AA and depression. This inconsistency may be the result of varying methodologies.

The aim of this thesis is to identify the optimal AA measure to use for neurofeedback and compare this with HFD as a possible distinct alternative. Several methodological variables will be assessed to determine the optimal way to calculate AA. These include: participant gender, eye condition, frequency bandwidth, and appropriate choice of electrode pair. Frontal AA (FAA) posterior AA (PAA), and HFD will be optimised separately as they are likely to involve distinct neural sources. The optimised measures will be placed into a stepwise linear regression model together. The results of the stepwise regression will give insight into the significance of the measures and whether they are additive. Part correlations will give further insight into the relationships between measures and the unique contributions of each. In all cases the criterion will be the proportion of The Personality Inventory for the DMS-5 (PID-5) depressivity scale that the measures account for. The assumption is that at least some of the brain activity specific to depression is causal and that its inhibition by neurofeedback would be therapeutic.

PID-5 depressivity

Prior studies investigating the relationship between depressive symptoms and alpha asymmetry have tended to compare clinical samples with healthy controls. As discussed previously, previous research points towards a stable trait-like relationship between asymmetry and depression. Instead of using a clinical depression scale we will use the PID-5 depressivity subscale. The PID-5 is designed to identify traits distributed within the whole population. This contrasts with clinical scales, which diagnose psychopathology in a specific group with all scores representing some degree of dysfunction. PID-5 depressivity is trait focused, designed to measure a single underlying source of population variation, and also correlates well with depressive and dysthymic symptoms (Klein, Bufferd, Ro, & Clark, 2014). Importantly, its high scores enter and traverse the clinical range. This generality, purity and range make it ideal for the present experiment since it allows recruitment that

does not explicitly involve a patient population, a single factor source of variation against which to correlate measures, and a capacity to extend to the clinical domain.

Gender

There are clear gender differences in EEG signals (Armitage & Hoffmann, 2001). These differences have been observed in the alpha band and within depression populations (Miller et al., 2002). Gender specific differences have also been investigated specifically regarding alpha asymmetry and depression (Arns et al., 2016; Jaworska, Blier, Fusee, & Knott, 2012). With wider EEG literature and specific alpha asymmetry literature showing major differences between genders it seems reasonable to keep the data analysis of participants separated by gender a priori. Therefore, in this thesis participants were split based on gender for all levels of analysis to ensure the most accurate results were obtained.

Eye condition

Typically, AA experiments use alternating blocks of open and closed eye conditions. AA scores are then calculated across both eye conditions. The alpha rhythm is strongest when the eyes are closed, and attenuated when the eyes open. Logically there could be significant differences between open and closed conditions and so open, closed, or combined could be optimal. All three options will be tested.

Frequency bandwidth

The accuracy of the fixed alpha band (8 – 13Hz) has been questioned. Doppelmayr et al. (1998) argued that a variety of factors can alter the distribution of EEG sub-bands between individuals and that the calculation of individual specific bandwidths might be more accurate. The authors compared a variety of different measures and concluded that individually determined alpha bands (IAF) were more accurate than fixed bands for identifying event related activity. The IAF is determined by identifying the central alpha peak between 6 and 14Hz. The points at which the peak

begins to rise and cease to fall are then marked $f1$ and $f2$ respectively. The gravity frequency between these two points is then calculated as (Σ (power * frequency))/(Σ (power)). The resulting frequency is the central alpha frequency from which sub-bands can be defined. This approach has been tested in depressed populations only once, with results showing a correlation between antidepressant use and greater right alpha power but no correlation between depression and alpha asymmetry. A comparison of fixed band alpha and IAF will be conducted to determine any differences between the two. The optimal bandwidth will then be used in analysing frontal and parietal alpha asymmetry.

Frontal alpha asymmetry electrode pairs

Most research has focused solely on the midfrontal area (F4 – F3) with any other electrode pairs being averaged for hemispheric comparisons rather than used individually. Despite this focus, findings continue to be unreliable. Following the same specific routines that provide inconsistent results is unlikely to be of much benefit. Instead, a wider view will be applied in this thesis. The popularity of the midfrontal area has resulted in a lack of research exploring other electrode pairs. This thesis will investigate the merits of a wider variety of electrode pairs. In the frontal region Fp2 – Fp1, F4 – F3, F8 – F7 and a synthesised AF4 – AF3 channel will be analysed individually. The optimal FAA measure identified will be considered the best location for use during neurofeedback. Note that the use of the synthesised AF4-AF3 pair was suggested to us by Prof. Dr. Gerhard Stemmler (personal communication) as likely to provide the most accurate AA values.

Hypothesis 1: Alpha asymmetry at F4 – F3 will account for the greatest proportion of PID-5 depressivity variance in the frontal region. Most research has targeted this area suggesting that it is the most applicable site.

Parietal alpha asymmetry electrode pairs.

PAA has been linked to depression and there are claims it has been neglected (Stewart et al., 2011). PAA will be calculated for P8 – P7 and P4 – P3. The eye condition and bandwidth will be the

same as identified in the prior FAA analyses. If the optimal PAA measure improves the FAA:depressivity model when included it will suggest that PAA and FAA are tapping into different processes; alternatively if PAA does not contribute unique variance to the model it will suggest that both frontal and parietal AA assess the same mechanism.

Hypothesis 2: The optimal PAA measure will contribute significant unique variance when included in the FAA model. The effect will still be seen when HFD is included in the same model.

Higuchi's fractal dimension

HFD has previously been used in neurofeedback protocols (Wang et al., 2010) and has been correlated with depression (Akar et al., 2015; Bachmann et al., 2013). HFD also analyses the spatial content of the signal, which AA cannot. This opens the possibility for both AA and HFD to be synergistic if used together. In this thesis HFD will be calculated for each frontal and parietal channel using the eye condition identified for the AA measures. Bandwidth will necessarily differ from AA as the Fourier transform used to acquire a specific bandwidth would discard the spatial content that HFD analyses. Instead two different bandwidths will be assessed: the full channel spectrum and a wavelet decomposed signal which approximates the alpha band. There is not enough prior research to warrant an electrode-specific hypothesis, the hypothesis for HFD is a question of whether any variance identified is unique to HFD or if it is shared with AA.

Hypothesis 3: HFD will contribute significant unique variance when paired with FAA, PAA and when FAA, PAA and HFD are all included in a single model.

CHAPTER 2: METHODS

The details provided in the experimental portion of this methods section are based on previous descriptions provided by Shabah Shadli and Julia McIntosh (See McIntosh, 2015), who carried out the testing of the participants, with the result that portions of this text overlap their reports. All data segmentation and analysis was carried out by me.

Participants

Participants for the study were recruited from the general population using Student Job Search and consisted primarily of students from the University of Otago. A total of 68 participants completed the experiment, 2 were excluded from analysis due to excessive artefacts in their EEG data. This left 66 participants (41 females and 25 males) for data analysis. The ages of participants were between 18 and 37 years and averaged 21.44 ($SD = 3.544$) years. Ethical approval for the experiment and recruitment was obtained from the University of Otago Ethics Committee (Approval number: H15/005). Participants were reimbursed at a rate of $15 per hour for their time and inconvenience spent participating in the experiment. Participants who had undergone medical and/or psychological treatment for any type of emotional disorder were excluded from the study. Although handedness was not an exclusion criterion all participants were right handed. Informed consent was obtained from all participants prior to participation in the experiment (See Appendix A for information and consent form).

Apparatus/Materials

Presentation of stimuli

PC computer monitors (Screen size: 360mm x 375mm) were used to present task stimuli and the questionnaire program. Participants were seated on an office chair in front of the computer desk with the monitor at eye level.

Questionnaires & demographics

Participants were presented with computer-delivered questionnaires. These questionnaires were identical to those used by McIntosh (2015). They were delivered in two parts: the first was presented prior to the EEG task; the second was delivered after completion of the EEG task. The first set of questionnaires contained the Spielberger State – Trait Anxiety Inventory Y-form (STAI; Spielberger, Gorusch, Lushene, Vagg, & Jacobs, 1983) Trait Anxiety items, the Eysenck Personality Questionnaire-Revised (EPQ-R; Eysenck & Eysenck, 1993) Extraversion and Neuroticism items and the Behavioural Activation System/Behavioural Inhibition Systems (BIS/BAS; Carver & White, 1994) BIS scale items. The second set contained the Anhedonia, Anxiousness, Depressivity, Emotional Lability, Intimacy Avoidance, Perseveration, Risk Taking, Restricted Affectivity, Separation Insecurity and Withdrawal scale items from the Personality Inventory of the DSM-5 (PID5; American Psychiatric Association, 2013). Questions about sleep and history of depression were also included. In addition to the various scales participants also provided demographic information about themselves. This included age, gender ethnicity and handedness. For the purposes of this study only the PID-5 Depressivity scale was used to measure trait depressivity. The PID-5 has good reliability and validity (Krueger & Markon, 2014) and scores can encompass both clinical and community samples (Markon, Quilty, Bagby, & Krueger, 2013).

EEG recording

EEG data were recorded (by either Julia McIntosh or Shabah Shadli) using a 32-channel Waveguard EEG cap (ANTneuro, Netherlands). Three different sizes of cap were available to ensure that participants were fitted with adequately sized caps. These sizes were large (57-64cm), medium (53-57cm) and small (47-53cm). The electrodes on the cap were arranged in accordance with to the 10 -20 electrode placement system. EEG was recorded from 18 channels: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, and P8. The EEG used a linked ears reference recorded at A1 and A2. To improve scalp conductance and improve EEG recording clarity Electro-gel (Electro Cap International, USA) was injected into all electrodes using a 3ml syringe and a Precision Glide 16-gauge blunt needle (Becton, Dickenson & Co, New Jersey, USA). Impedance between scalp and electrodes was measured using an ASA Neurotechnology EEG machine. Resting EEG data was recorded in 1 minute blocks of eyes open (EO) or eyes closed (EC). As power frequencies are known to differ between these conditions (Barry, Clarke, Johnstone, Magee, & Rushby, 2007) markers were placed in the data to differentiate conditions. Recording of data was conducted at a sampling rate of 256Hz and raw EEG was filtered using a 1 – 36Hz bandpass filter. A total of 8 minutes of resting data was recorded with the eyes open (EO) and eyes closed (EC) blocks arranged as follow: EO, EC, EO, EC, EC, EO, EC, EO. All experiments took place in a certified body protected area for electrical recording in the Department of Psychology at the University of Otago.

Procedure

Upon their arrival participants were all given information sheets describing the experiment in detail (see Appendix A). Participants were given the opportunity to ask about anything that they wished regarding their participation. Signed informed consent was obtained from those participants who desired to continue in to the experimental session (Appendix A).

Prior to commencing any tasks, participants were fitted for an EEG cap. The experimenter first measured the circumference of the participants head to ensure the correct sized cap was used. A blue marker was then used to mark the locations of FP1 and FP2 according to the international 10:20

system. Participants were then seated at a computer where they completed the first part of the questionnaire program after being instructed to work continuously and not to dwell too long on any single question. This part of the experiment would typically take 10 – 15 minutes to complete.

In the next stage of the experiment participants were moved into a certified body protected area for electrical recording. The participant was seated in front of another computer screen and the appropriate size EEG cap was fitted to them by the experimenter. Once fitted the cap was connected to the ASA Neurotechnology EEG machine which allowed the experimenter to view the impedance of each electrode. Electrode gel was injected into each electrode using a blunt needle. Gentle abrasion by the needle was used to move dead skin and hair, increasing the conductance between scalp and electrode. In this manner impedance was reduced to below 20KΩ for every electrode to ensure clear EEG recording. This process often took 20 – 40 minutes to complete.

Two tests were then conducted by the experimenter to ensure that the EEG was recording properly. First participants were instructed to close their eyes and relax for a brief period of time to accentuate alpha rhythm. After this the experimenter asked participants to blink their eyes continuously for a few seconds. Through observation of the recording EEG during these tasks the experimenter determined whether the recording system was functioning correctly. In cases where it appeared that the recording was not functioning correctly the experimenter would return to adjusting the impedances. Once the experimenter was satisfied that the recording was functioning smoothly and accurately recording of resting EEG would begin. A visual display on the monitor told the participants when to close their eyes. The experimenter verbally informed the participant when they needed to open their eyes.

Following the resting EEG task participants undertook a Stop-Signal Task. Data from the SST are not analysed or discussed in the current thesis. After the SST task the EEG cap was disconnected from the ASA Neurotechnology device and the cap was removed from the participants' head by the experimenter. Markings made during the fitting process were wiped off using cleansing wipes and paper towels were provided for the participants to remove any electrode gel. Participants then returned to the computer to complete the second part of the questionnaire program (which included the

depressivity questions). Upon completion, the participants were given monetary reimbursement for their time and inconvenience of $15 per hour.

Data Processing & Analysis

Note that, unlike the data collection, all data processing and analysis were carried out by me; as was development of the EEGLAB procedures and MATLAB code required for the analyses.

Primary pre-processing

EEG data and associated event markers were exported from ASA and imported to the EEGLAB toolbox for MATLAB. As the location and name of each channel did not carry over from ASA to EEGLAB, a separate EEGLAB-compatible file was created. This file listed names and polar coordinates matching the original EEG recording. As this procedure had not been carried out in the laboratory before, I tested it using differing sine waves and by comparing ASA data with EEGLAB data to ensure it was accurate. As the EEG recording included both Stop Signal Task and resting EEG the event markers were used to select only data collected during the resting task. These data were then split into eyes open and eyes closed datasets for each participant. Each dataset was split into 1 second (256 sample) epochs with no overlap in preparation for artefact rejection, as EEGLAB requires data to be epoched for some artefact rejection methods. All this initial processing was automated using MATLAB scripts developed by me as part of this project.

Artefact rejection

The epoched data sets were visually inspected for gross artefacts. Identified epochs with artefact were removed from the dataset and boundary markers were inserted to mark their previous location. Independent component analysis (ICA) was applied to the remaining epoched data. ADJUST 1.1 (Mognon, Jovicich, Bruzzone, & Buiatti, 2011) was used to analyse the ICA results and remove

artefact components to leave 'clean' EEG. The artefact-free datasets were then converted from epoched to continuous data and two synthesized channels were created. AF3 was approximated by averaging F3 and Fp1; AF4 was approximated by averaging F4 and Fp2. Note that these averages are of the raw waveforms and prior to Fourier transform.

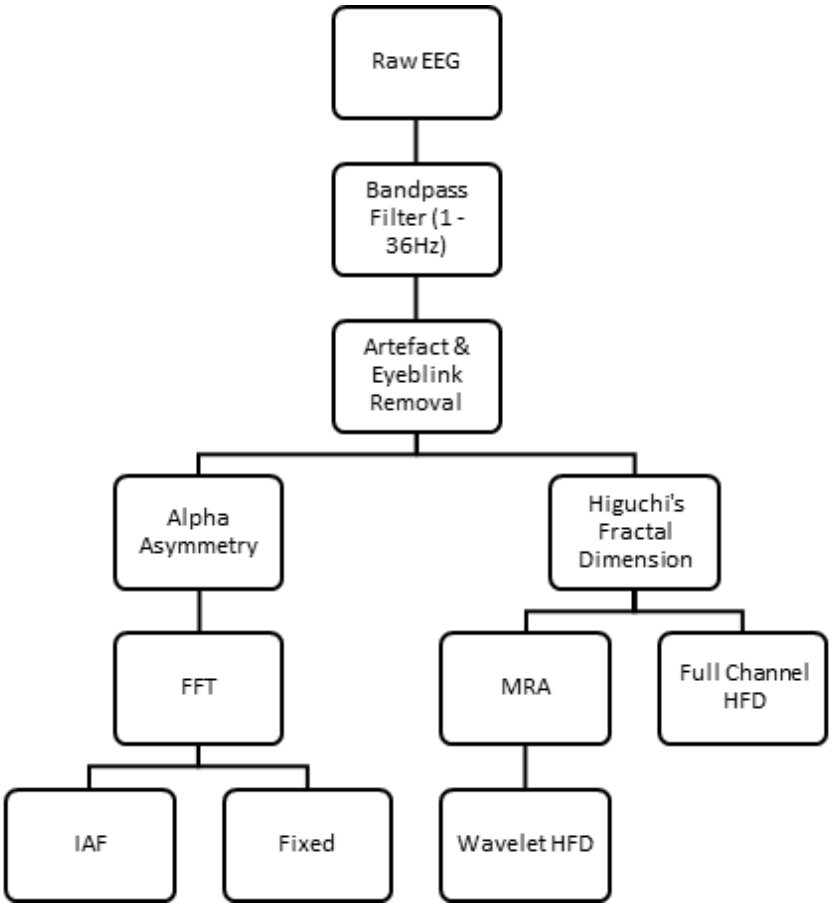

Figure 2.1. EEG processing pathway. As AA and HFD measures analyse details of data that are mutually exclusive the processing pathway splits after artefact and eye blink removal. IAF = Individual Alpha Frequency; Fixed = Fixed alpha bandwidth; HFD = Higuchi's Fractal Dimension; MRA = Multiresolution Analysis.

After artefact removal, the processing pathway splits. In this thesis, we are investigating both AA, which is a power measure localised in the frequency domain, and HFD, which is calculated from the signal localised in its time domain. Unfortunately, a signal cannot be localised in both time and frequency. This is because time and frequency domains are the inverse of each other; increased frequency resolution comes at the cost of reduced temporal resolution and vice versa. It is a fundamental limit imposed by the signal itself (Gabor, 1946).

To gain accurate AA measurements we used the FFT to localise the EEG signal in the frequency domain. In the process, we lose the time domain information of the signal. We learn the

amplitude of the signal at specific frequencies, but have no idea when those frequencies occurred. For HFD we need to retain time domain information but we also want to investigate the fractal dimension of the alpha band. To achieve this, we used multiresolution analysis (MRA; Mallat, 1989) which allows us to strike a balance between temporal and frequency resolution which is explained in greater depth later in this chapter. HFD could then be calculated for both the MRA decomposed signal and the full bandwidth signal (referred to as full channel (FC) dataset).

Power-frequency processing

Alpha asymmetry analysis requires signal power to be localised by frequency. The FFT is used to localise the signal by frequency and the signal power is then calculated from the FFT output as amplitude squared. The relationship between FFT output and frequency resolution is:

$$N = Fs/dF \tag{1}$$

$$\therefore dF = Fs/N \tag{2}$$

Where *N* is the number of samples, *Fs* is the sampling rate and *dF* is the frequency increment (resolution). Our sampling rate was 256Hz, to obtain a frequency resolution of 0.5Hz our epochs needed to have 512 samples each. FFTs assume that the input waveform is one period in a periodic signal, which is problematic in the case of EEG signals as epochs are likely to contain truncated data. This results in spectral leakage and may skew the results of the FFT. To avoid this, we applied a Hanning window to the data which was defined as:

$$w(n) = \left(0.5\left(1 - \cos\left(2\pi\frac{n}{N}\right)\right)\right),\ 0 \leq n\ \leq N \tag{3}$$

Where N is the total number of samples and $n = 0, 1, 2, \ldots, N$. The window applies a weighting function to the epoch reducing the amplitude of the outside edges of the data and increasing the amplitude of the central points. Epochs were overlapped 25% at each end to account for the attenuating effect that windowing has on the outside edges of the epochs.

Power extraction

The FFT of each windowed epoch was calculated using MATLAB's indigenous FFT function (GIVE NAME). As the FFT calculation involves summing across the number of data points the output is divided by the length of the input. Each bin of the normalised output represents one step of the frequency increment. The Nyquist frequency is half of the sampling rate; frequency bins above the Nyquist frequency are discarded due to aliasing.

$$Y(k) = Y\left(1, 2, \dots, \left(\frac{N}{2}\right)\right) \quad (1)$$

We then multiply the remaining data by two to account for the amplitudes discarded. When windowing the data, a weighting factor is applied across the epoch. To acquire the correct amplitudes this weighting factor must be accounted for. A scaling factor is calculated that reverses the weighting effecting and the epoch is multiplied by this factor.

$$A = \left(\frac{2}{wnt} \cdot Y\right) \quad (1)$$

$$p = A^2 \quad (2)$$

Where A is amplitude, p is power and the scaling factor (*wnt*) is calculated as:

$$wnt = mean\big(w(n) \cdot w(n)\big) \quad (1)$$

The resulting data consists of a series of frequency bins which contain absolute power values specific to that frequency, which were then converted to a natural logarithm to reduce the influence of scale differences and skewness resulting from the power transform. A third dataset for each participant was obtained by averaging together open and closed power values to create combined condition power scores. Logarithmic power scores were then averaged across all epochs of each dataset to give us an index of average absolute power. Both the FFT and power extraction processes were run using MATLAB scripts that I wrote. They were tested using time series constructed from sine waves to ensure that each step produced the correct results.

Fixed alpha frequency bands

For the fixed band alpha asymmetry measure an alpha band of 6 – 12Hz was used. This bandwidth is based on the "transition frequency" (Doppelmayr et al., 1998); the point at which alpha desynchronises from theta. This bandwidth was split into 4 sub-bands: low 2 (6-8Hz), low 1 (8-10Hz), high (10-12Hz) and total (6-12Hz).

Fixed alpha asymmetry. AA scores were calculated for each frontal (Fp2 - Fp1, Af4 - Af3, F4 – F3, F8 – F7) and parietal (P4 – P3, P8 – P7) homologous electrode pair by subtracting the logarithmic average alpha power within each sub-band of left electrodes from right electrodes (ln (Right) – ln (Left) alpha power). AA scores were calculated for every sub-band in each pair, resulting in four AA scores in each homologous pair, e.g., for the homologous pair Fp2/Fp1 the following AA scores were calculated: $Fp2 - Fp1_{low\ 2}$, $Fp2 - Fp1_{low\ 1}$, $Fp2 - Fp1_{high}$ and $Fp2 - Fp1_{total}$.

Individual alpha frequency bands

Proposed by Klimesch, Schimke, and Pfurtscheller (1993) IAF is a measure that can be used to calculate individual alpha bandwidths. To obtain IAF for each subject we first took the average power over all electrodes and plotted it over frequency. The frequency window is manually determined by visual inspection of the plotted data. $f1$ is the point at which the main alpha peak begins to ascend; $f2$ marks the end of descent. We then calculate the gravity frequency between $f1$ and $f2$ as follows:

$$Gravity\ Frequency = \frac{\sum(power\ \times frequency)}{\sum power}$$

The resulting gravity frequency is the point within the alpha spectrum that marks the transition between high and low alpha bands. Across participants the mean IAF values were 9.91Hz and 9.9Hz for eyes closed and eyes open conditions, respectively. The alpha band was split into low 2 (IAF-4Hz to IAF-2Hz), low 1 (IAF-2Hz to IAF) high (IAF to IAF+2) and total (IAF – 4Hz to IAF +2Hz).

IAF alpha asymmetry. AA scores were calculated in the same manner as for the fixed bands except with average alpha power in each sub-band calculated according to the IAF sub-bands.

Multiresolution analysis

Two measures of HFD were calculated: (1) the HFD of the time localised signal across the entire bandwidth of the channel and (2) the HFD of an approximate alpha bandwidth. The full channel HFD is calculated directly from the filtered and artefact free EEG signal. To obtain an approximate alpha bandwidth MRA is used.

MRA applies complimentary lowpass and highpass filters to the signal. The filters are symmetrical around the central frequency of the signal. In this experiment, a Daubechies 4th order wavelet is used for the filtering, in the same manner as Adeli, Ghosh-Dastidar, and Dadmehr (2007). Applying these filters splits the signal in two, with the low frequency components contained in one signal and the high frequency components in the other. Each of these new signals now contain half the frequencies of the original, the signals are also down sampled by a factor of 2 to reflect their new frequency ranges. This process is repeated until the desired bandwidth is reached.

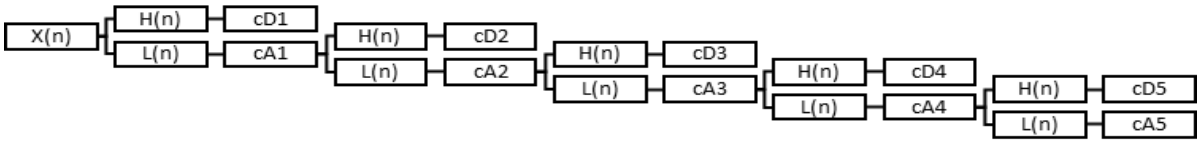

Figure 2.2. Multilevel wavelet decomposition tree

At each step of the decomposition the number of samples is halved. Therefore, it is crucial to ensure that the original signal has enough samples to allow an accurate HFD to be calculated from the output of the MRA. To obtain accurate fractal dimension scores Accardo, Affinito, Carrozzi, and Bouquet (1997) suggest that $N \geq 125$. The band approximating alpha (8-16Hz) requires 4 levels of wavelet decomposition to extract. To ensure that the extracted bandwidth contained $N \geq 125$ data points 25% overlapping epochs of 20 seconds each were used. At our sampling rate of 256Hz this gave each epoch a total of 5120 data points and leaving a total of 320 data points after 4 levels of halving.

Higuchi's fractal dimension

Higuchi's Fractal Dimension (Higuchi, 1988) is a method of calculating the Fractal Dimension (FD) of a time series. For EEG signals the HFD will return a value between 1 and 2 with higher values indicating increased complexity within the signal. A fractal is self-similar at all scales, large or small. The HFD creates multiple time series by subsampling the signal repeatedly. This creates the original signal at a variety of different scales.

The length of the curve for each new time series is then calculated and averaged across the sets. This is repeated for the different scales and plotted on a doubly logarithmic graph. The fractal dimension is the slope of this graph.

The HFD first generates new time series described as:

$$X_k^m;\ X(m),\ X(m+k),\ X(m\ +2k),\dots X\left(m\ +\left[\frac{N-m}{k}\right]\times k\right)\ \ (m=1,2,3,\dots,k), \qquad (1)$$

Where X is the original time series, *m* indicates the initial time and *k* is the interval time. For each of the new time series X_k^m the length of the curve is calculated by:

$$L_m(k)=\left\{\left(\sum_{i=1}^{\left[\frac{N-m}{k}\right]}|X(m+ik)-X(m+(i-1)\cdot k|\right)\frac{N-1}{\left[\frac{N-m}{k}\right]\cdot k}\right\}/k \qquad (2)$$

While the length of the curve for $k, L(k)$ is the average value over k sets of $L_m(k)$. If $L(k)$ is proportional to k^{-D} then the curve has the fractal dimension D. D is the slope of a least mean squares straight line applied to $L(k)$ and k plotted on a doubly logarithmic graph.

$$\log\big(L(k)\big)\sim\log(\tfrac{1}{k}) \qquad (3)$$

Statistical analysis

All statistical analysis was conducted using IBM SPSS Statistics package (version 24). One-way, repeated measures ANOVAs were used to compare FAA eye condition, bandwidth, and HFD bandwidth. Signed proportion of variance (R^2 value * 100, with the signed direction of correlation added) gives us the variance of PID-depressivity accounted for as a percentage, while including the

sign ensures that the direction of correlation is not ignored. Importantly, percent variance avoids the skew of raw correlation scores. These ANOVAs are comparing the mean proportional variance accounted for by each condition. The conditions that account for the greatest proportional variance will be used considered optimal, if differences are not apparent then the condition most commonly used in previous literature will be preferred. Optimal conditions for FAA were also applied to PAA. HFD used the same eye condition as FAA and PAA, but an optimised HFD bandwidth was obtained by comparing the proportional variance of FC and MRA conditions.

Frontal alpha asymmetry

With the optimal conditions for eye and bandwidth defined, the sub-bands of homologous electrode pairs were regressed against PID-5 depressivity using linear regression. The strongest sub-bands for each pair were identified from their R values. Regressions were run comparing the strongest sub-bands both within and between homologous pairs. Within pairs the previously identified sub-band was paired with each other sub-band (i.e., Fp2 – $Fp1_{high}$ paired with Fp2 – $Fp1_{total}$, then with Fp2 – $Fp1_{low\ 2}$ and so on) and a regression was run on each pair. The resulting part correlations were then analysed to determine if the strongest sub-band was representative of the total variance accounted for within the homologous pair. Between homologous pairs regressions compared the strongest sub-band from each homologous pairs (i. e., Fp2 – $Fp1_{high}$ paired with AF4 – $AF3_{high}$). The part correlations from these regressions can be used to determine whether the variance accounted for by one homologous pair is representative of other homologous pairs. Note that the goal of these analyses is to demonstrate minimal differences between measures and so a significance test is not appropriate. If the variance accounted for by these paired measures is shared between them, then the strongest of the two can be said to be representative of the other. However, if there is a low proportion of variance accounted for by each and part correlations remain high, then one measure is not representative of the other as their contributions are unique.

Parietal alpha asymmetry

The same analyses used for FAA were used for parietal alpha asymmetry (PAA).

Higuchi's fractal dimension

There are no sub-bands for HFD and it is calculated at every electrode. To keep the HFD analysis like the AA analysis, the strongest HFD scores from homologous pairs were selected based on their R value. The part correlations were compared both within pairs and between pairs as was done in the AA analysis. The optimal measure (or combination thereof) was determined in the same manner as FAA and PAA.

Combined measures

The additivity of PID-5 depressivity variance accounted for by FAA, PAA and HFD was analysed using stepwise linear regression. Stepwise regression identifies the strongest correlate, then checks for other variables that add additional significant variance to the model step by step. If the different measures all provide the same variance, then only the strongest will be included as the others won't contribute extra variance to the model. However, if the variables all contribute significant unique variance the model will include them all. It is expected that all three variables will be included in the stepwise model. The extent of additivity (or lack thereof) will be further analysed through the part correlations of the variables pairwise and as a group.

CHAPTER 3: RESULTS

This chapter provides the results of the data analysis, split into four separate sections. The first section deals with optimisation of frontal alpha asymmetry (FAA), which is the primary focus of this study. The second and third sections deal with optimisation of parietal alpha asymmetry (PAA) and Higuchi's fractal dimension, respectively. In each case the issue is to choose the optimal representative measure and test how far it captures the available variance. The fourth section then assesses how far these distinct types of representative measure make unique contributions to prediction of depressivity.

As discussed at the end of chapter 1, the separation of gender was justified a priori and so separate analyses at every stage were conducted for male and female participants. Comparison of different eye and bandwidth conditions was conducted using the signed proportion of variance (%). This was obtained from R^2 values, multiplied by 100 to give percentage of variance accounted for by the variable in question. Including the original sign of the correlation (+/-) ensures that the direction of correlation is not lost. Furthermore, signed proportion is inherently normalised – the values can only range between -100% and +100%. These comparisons were completed using one-way, repeated-measures ANOVA.

Comparisons of eye (open/closed/combined) and bandwidth conditions calculated for FAA were also used in PAA. This ensures consistency between the various AA measures. HFD used the same eye condition as FAA but cannot use the same bandwidth as the AA measures because it is not a power spectrum measure. Instead, the HFD of full channel bandwidth and an approximated alpha band were compared. This ensured that eye condition and bandwidth remained consistent across all measures, reducing the number of conditions to the minimum necessary.

The strongest predictor variables can be readily identified using their zero order correlations. That approach ignores the deeper structure of the data, potentially losing vital information. To ensure important relationships were not missed, the part correlations of all variables were investigated. This allowed us to identify what the unique contributions of each variable are and provide greater confidence that we are not missing anything when selecting a single representative measure.

Unless stated otherwise, all correlations discussed are between predictor variables (FAA, PAA and HFD) and PID-5 depressivity.

Alpha Asymmetry – Eye Condition

Introduction

The difference in PID-5 correlation between open, closed and combined eye conditions were compared using a one-way, repeated-measures ANOVA. The three conditions, in the order closed, combined, open were treated as successive levels for the purpose of linear and quadratic trend analysis. The means and standard deviations for each gender are displayed below in Table 3.1. Females displayed positive mean correlations in the combined and open eye conditions while males displayed negative correlations in those conditions. In both genders, the mean variance accounted for is higher in combined and open conditions than in the closed condition.

Table 3.1

Mean and standard deviation of signed proportion of variance by eye condition and gender.

Gender	Mean (SD)			N
	Closed	Combined	Open	
Female	-0.61(.51)	2.88(4.88)	3.08(3.82)	32
Male	-3.07(.83)	-7.16(1.36)	-7.06(1.55)	32

Results

Female. Sphericity was not violated ($\chi^2 = 4.754$, $p = .093$). There was an effect of eye condition on depressivity correlations ($F(2, 62) = 18.940$, $p < .001$, $\eta^2 = .379$). The closed eye condition provided lower values than the open eye condition([linear] $F(1,31) = 24.454$, $p < .001$, $\eta^2 = .441$). Combined eye condition differed from the average of open and closed conditions ([quadratic]$F(1,31) = 10.294$, $p = .003$, $\eta^2 = .249$). Pairwise comparison showed that open and combined conditions were not reliably different from each other ($p = .724$), showing that the quadratic effect was fuelled by the difference between combined and closed eye conditions.

Male. Mauchly's Test of Sphericity indicated that sphericity had been violated ($\chi^2 = 13.869$, $p = .001$) and therefore degrees of freedom were taken as Greenhouse-Geisser estimates.

There was an effect of eye condition on depressivity correlations ($F(1.460, 45.250) = 4.373$, $p = .029$, $\eta^2 = .124$). The open eye condition appears to be stronger than the closed eye condition however, this trend was on the margin of significance ([linear]$F(1,31) = 4.064$, $p = .053$). The combined eye condition provided stronger correlations than the average of open and closed conditions ([quadratic] $F(1, 31) = 5.512$, $p < .025$, $\eta^2 = .151$). Pairwise comparisons showed that this effect was largely driven by the difference between combined and closed ($p = .001$) as no difference with the open eye condition existed ($p = .947$).

Discussion

In male and female participants, the combined eye condition provided stronger correlations than the average of open and closed conditions. This effect was largely driven by the closed condition which was consistently weaker than the combined condition. The open condition was not substantially different to the combined eye condition in either of the groups.

These results indicate that either combined or open eye conditions could be preferred. The benefit of the combined eye condition is that it has been used extensively in the literature. The open eyes condition has not been targeted in the resting AA literature. Therefore, the combined eye condition was selected for the following analyses due to its prevalence in the literature and the lack of significant differences between combined and open eye conditions.

Alpha Asymmetry - Frequency Band Type (Fixed versus IAF)

Introduction

To determine whether fixed or IAF frequency bands are best, a one-way repeated measures ANOVA was used. Given the results in the previous subsection, only combined eye variables were included, so the number of variables in each condition is halved from the previous analysis, which had fixed and IAF scores for each variable. Mean and standard deviation for each gender are displayed in Table 3.2. In both bands, females display positive mean values while males display negative values.

Table 3.2
Mean and standard deviation of signed proportion of variance by frequency band type and gender.

Gender	Mean (SD)		N
	Fixed	IAF	
Female	3.071(1.269)	2.705(1.207)	16
Male	-7.916(2.322)	-6.404(1.468)	16

Results

Female. As can be seen in Table 3.2, female participants exhibited somewhat stronger average signed proportion of variance in the fixed band. This difference was not reliable ($F(1,15) = .609$, $p = .447$).

Male. The Fixed band in male participants showed somewhat stronger (negative) signed proportion of variance than IAF although the difference is not reliable ($F(1,15) = .650$, $p = .433$).

Discussion

The fixed bandwidth tends to have higher signed proportion of variance than the IAF band. This is visible in both male and female participants, although the differences between Fixed and IAF are not reliable. The fixed band is easy to calculate, applies equally to all participants and has featured widely in research for many years. IAF may be a more accurate measurement of the alpha band but it must be calculated manually for each participant and, in our data, does not appear to provide an advantage in relation to depressivity. With higher values and simplified application, the fixed bandwidth was chosen as the better measure to be used in the other analyses of this thesis.

Frontal Alpha Asymmetry – Electrodes and Sub-bands

Introduction

The analysis of alpha asymmetry used the combined eye condition and fixed frequency band as discussed in the previous sections. For each electrode pair (Fp1 – Fp2, Af4 – Af3, F4 – F3, F8 – F7) there were 4 sub-bands. These sub-bands were low 2 (6-8Hz), low 1 (8-10Hz), high (10 – 12Hz) and

total (6 – 12Hz). There were thus 16 possible measures with which to predict depressivity from alpha asymmetry.

Results

Correlation matrices for each gender were calculated. Female correlations are displayed in Table 3.7, male correlations are displayed in Table 3.8. The frontopolar and anterior frontal electrode pairs displayed the strongest correlations. The best correlates for each electrode pair and gender are displayed in Table 3.3. Within-pair (i.e. between band) part correlations are displayed in Table 3.4 for females and Table 3.5 for males. Between-pair part correlations for males are displayed in Table 3.6, no between-pair comparisons were needed in female participants as only one pair was reliable.

Table 3.3

Best FAA measures of PID-5 depressivity in each homologous pair by gender.

	Females			Males		
Channel Pair	Sub-band	%	p	Sub-band	%	p
Fp2 - Fp1	High	16.1	.009	High	-21.8	.018
Af4 - Af3	Total	4.8	.171	High	-29.7	.005
F4 - F3	High	-1.1	.507	High	-4.0	.336
F8 - F7	Total	2.5	.326	Total	-21.3	.020

Note: All values are correlations represented as signed percentage of variance.

Female. The high and total sub-bands provided the accounted for the most proportional variance in every electrode pair. The overall best correlate was found at $Fp2 - Fp1_{high}$ ($F(1,39) = 7.487$, $p = .009$, $R = .401$). No other pair contained any reliable correlations.

As can be seen in Table 3.4, $Fp2 - Fp1_{high}$ displays a higher part correlation than any other sub-band in females. The low 2 and low 1 sub-bands account for a negligible proportion of variance (1.1% and 1.3% respectively). There may have been a suppression effect between low 2 and high sub-bands, identifiable by the sum of part correlations being greater than the proportional variance of the model (18.3% vs. 17.3%) but the effect is very small. The total band shared most of its variance with the high sub-band (11.5%). This effect is likely due to the total band encompassing the high sub-band

frequencies in its bandwidth, ensuring that they share some variance. The unique contribution of the total band is still low, only increasing the model's value by 3.3% which is not enough to justify including it with the high sub-band measure.

Male. The high sub-band accounted for the most proportional variance and was reliable at FP, AF and the lateral frontal electrode pairs (see Table 3.5). As can be seen in Table 5, the best correlates in each electrode pair were negative in direction. However, Fp2 – $Fp1_{high}$ is the only variable that is reliable in both genders, albeit with an inverted sign.

Part correlations within homologous pairs can be seen in Table 3.5. Fp2 – $Fp1_{high}$ and Af4 – $Af3_{high}$ displayed far higher part correlations than any other sub-band. Suppression effects were seen between high and low 1 sub-bands at Fp2 – $Fp1_{high}$, again visible as a higher combined unique variance than the model itself accounts for. F8 – $F7_{total}$ showed much higher values of shared variance than the other electrode pairs, this is likely due to the other being specifically high sub-band measures while the total band includes all 3 sub-bands.

Part correlations between the reliable homologous pairs can be seen in Table 3.6. A large component of variance is shared between the predictors (24.7%). When paired with Af4 – $Af3_{high}$, no other predictor accounts for a meaningful proportion of variance (all < 2.6%).

Table 3.4

PID-5 depressivity variance accounted for by the best frontal alpha asymmetry measures and each other sub-band within their electrode pair for female participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
Fp2 - Fp1					
High	16.1	4.6			
Total	14.8	3.3	7.8	11.5	19.4
High	16.1	17.1			
Low 2	0.1	1.1	18.3	-1.0	17.3
High	16.1	14.8			
Low 1	3.6	2.3	17.0	1.3	18.4

Note. All values are correlations represented as signed percentage of variance.

[a] Calculated as the sum of part correlations.

[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.

[c] The R^2 of the model, converted to proportion of variance.

Table 3.5

PID-5 depressivity variance accounted for by the best alpha asymmetry measures and each other sub-band within their electrode pair for male participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
Fp2 - Fp1					
High	-21.8	-19.4			
Total	-4.7	2.3	21.7	2.4	-24.1
High	-21.8	-21.3			
Low 2	-1.4	0.8	22.1	0.6	-22.7
High	-21.8	-24.5			
Low 1	-0.7	3.4	27.9	-2.7	-25.2
Af4 - Af3					
High	-29.7	-22.3			
Total	-8.0	0.6	22.8	7.5	-30.3
High	-29.7	-29.6			
Low 2	-0.9	0.8	30.4	0.1	-30.5
High	-29.7	-28.7			
Low 1	-1.1	0.1	28.9	1.0	-29.8
F8 - F7					
Total	-21.3	-7.2			
High	-14.6	-0.5	7.8	14.1	-21.9
Total	-21.3	-13.0			
Low2	-8.4	0.1	13.1	8.3	-21.4
Total	-21.3	-12.1			
Low 1	-9.4	0.2	12.3	9.2	-21.5

Note. All values are correlations represented as signed percentage of variance.

[a] Calculated as the sum of part correlations.

[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.

[c] The R^2 of the model, converted to proportion of variance.

Table 3.6

PID-5 depressivity variance accounted for by the best alpha asymmetry measures when paired and combined in male participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
Paired					
Af4 - $Af3_{high}$	-29.7	-8.9			
Fp2 - $Fp1_{high}$	-21.8	-1.0	-9.9	-20.8	-30.8
Af4 - $Af3_{high}$	-29.7	-10.9			
F8 - $F7_{total}$	-21.3	-2.5	-13.4	-18.8	-32.2
Fp2 - $Fp1_{high}$	-21.8	-5.4			
F8 - $F7_{total}$	-21.3	-4.9	-10.3	-16.4	-26.8
Combined					
Af4 - $Af3_{high}$	-29.7	-5.8			
Fp2 - $Fp1_{high}$	-21.8	-0.3			
F8 - $F7_{total}$	-21.3	-1.8	-7.9	-24.7	-32.5

Note. All values are correlations represented as signed percentage of variance.

[a] Calculated as the sum of part correlations.

[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.

[c] The R^2 of the model, converted to proportion of variance.

Discussion

The overall results show that the electrode pairs that best correlate with PID-5 depressivity differ between genders. Fp2 – $Fp1_{high}$ was the best correlate for females, Af4 – $Af3_{high}$ was the best correlate in males. Fp2 – $Fp1_{high}$ was also significant in males, making it the only common correlate between genders. Part correlations also show that Af4 – $Af3_{high}$ is a stronger predictor than Fp2 – $Fp1_{high}$ as it accounts for almost all the latter's variance and contributes extra on top.

The aim of this experiment is to identify the optimal electrode pair for neurofeedback protocols. Even though Af4 – $Af3_{high}$ in males is the strongest, it is also a synthetic channel and we cannot be sure that an effect of similar strength would be obtained from real channels. Though not quite as strong, Fp2 – $Fp1_{high}$ comes from recorded data which allows us more certainty. The correlation at Fp2 – $Fp1_{high}$ is also the only finding to occur in both genders, albeit with opposite signs. These factors taken together indicate that the finding at Fp2 – Fp1 is robust. For these reasons Fp2 – $Fp1_{high}$ is selected as the best frontal AA electrode pair.

Table 3.7

Zero order correlations between frontal alpha asymmetry fixed sub-bands and PID-5 depressivity in females.

	Variable	Depressivity	Af4 - Af3				F4 - F3
			High	Low 1	Low 2	Total	High
1	Depressivity	-					
2	Af4 - Af3: High	.15	-				
3	Af4 - Af3: Low1	.13	.39**	-			
4	Af4 - Af3: Low2	.11	-.24	-.07	-		
5	Af4 - Af3: Total	.22	.67***	.76***	.34*	-	
6	F4 - F3: High	-.11	.75***	.20	-.14	.48***	-
7	F4 - F3: Low1	-.06	.34*	.82***	-.07	.63***	.35*
8	F4 - F3: Low2	.05	-.13	.04	.87***	.40**	-.10
9	F4 - F3: Total	-.06	.52***	.54***	.32*	.77***	.67***
10	F8 - F7: High	.14	.17	-.06	-.12	.00	.23
11	F8 - F7: Low1	.13	.03	.50***	.09	.35	.02
12	F8 - F7: Low2	.05	-.26	-.22	.56***	.02	-.14
13	F8 - F7: Total	.16	-.02	.11	.25	.18	.06
14	Fp2 - Fp1: High	.40**	.29*	.05	-.04	.18	-.03
15	Fp2 - Fp1: Low1	.19	.18	.72***	.11	.57***	.00
16	Fp2 - Fp1: Low2	.04	-.04	-.20	.68***	.21	.05
17	Fp2 - Fp1: Total	.38**	.27*	.37**	.38**	.56***	.01

	Variable	Depressivity	F4 - F3			F8 - F7	
			Low 1	Low 2	Total	High	Low 1
1	Depressivity	-					
7	F4 - F3: Low1	-.06	-				
8	F4 - F3: Low2	.05	.14	-			
9	F4 - F3: Total	-.06	.77***	.51***	-		
10	F8 - F7: High	.14	-.02	-.17	.02	-	
11	F8 - F7: Low1	.13	.22	.00	.12	.29*	-
12	F8 - F7: Low2	.05	-.34*	.45**	-.03	.00	.27
13	F8 - F7: Total	.16	-.07	.12	.06	.66***	.76***
14	Fp2 - Fp1: High	.40**	-.09	-.03	-.08	.06	-.14
15	Fp2 - Fp1: Low1	.19	.41**	.05	.23	-.15	.51***
16	Fp2 - Fp1: Low2	.04	-.20	.60***	.22	-.11	.06
17	Fp2 - Fp1: Total	.38**	.09	.31*	.20	-.11	.25

	Variable	Depressivity	F8 - F7		Fp2 - Fp1		
			Low 2	Total	High	Low 1	Low 2
1	Depressivity	-					
12	F8 - F7: Low2	.05	-				
13	F8 - F7: Total	.16	.61***	-			
14	Fp2 - Fp1: High	.40**	.01	-.03	-		
15	Fp2 - Fp1: Low1	.19	-.01	.17	.10	-	
16	Fp2 - Fp1: Low2	.04	.36*	.14	-.17	.03	-
17	Fp2 - Fp1: Total	.38**	.18	.15	.60***	.69***	.41**

** p < .05, ** p < .01, *** p < .001*

Table 3.8

Zero order correlations between frontal alpha asymmetry fixed sub-bands and PID-5 depressivity in males.

	Variable	Depressivity	Af4 - Af3				F4 - F3
			High	Low 1	Low 2	Total	High
1	Depressivity	-					
2	Af4 - Af3: High	-.55**	-				
3	Af4 - Af3: Low1	-.11	.25	-			
4	Af4 - Af3: Low2	-.09	.32	.47*	-		
5	Af4 - Af3: Total	-.28	.63***	.76***	.85***	-	
6	F4 - F3: High	-.20	.59**	.44*	.20	.50**	-
7	F4 - F3: Low1	.00	.13	.87***	.28	.57**	.45*
8	F4 - F3: Low2	.02	.27	.53**	.77***	.73***	.29
9	F4 - F3: Total	-.07	.42*	.79***	.56**	.79***	.73***
10	F8 - F7: High	-.38*	.64***	.24	.28	.48**	.69***
11	F8 - F7: Low1	-.31	.43*	.78***	.49**	.74***	.41*
12	F8 - F7: Low2	-.29	.25	.36*	.60**	.56**	.13
13	F8 - F7: Total	-.46*	.62***	.66**	.66***	.85***	.58**
14	Fp2 - Fp1: High	-.47**	.73***	.26	.47**	.62***	.28
15	Fp2 - Fp1: Low1	-.08	.25	.69***	.62**	.72***	.32
16	Fp2 - Fp1: Low2	-.12	.24	.39*	.90***	.73***	.14
17	Fp2 - Fp1: Total	-.22	.42*	.56**	.83***	.83***	.28

	Variable	Depressivity	F4 - F3			F8 - F7	
			Low 1	Low 2	Total	High	Low 1
1	Depressivity	-					
7	F4 - F3: Low1	.00	-				
8	F4 - F3: Low2	.02	.42*	-			
9	F4 - F3: Total	-.07	.80***	.77***	-		
10	F8 - F7: High	-.38*	.24	.14	.45*	-	
11	F8 - F7: Low1	-.31	.62***	.39*	.61**	.32	-
12	F8 - F7: Low2	-.29	.19	.50**	.37*	.23	.17
13	F8 - F7: Total	-.46*	.51**	.49**	.68***	.72***	.72***
14	Fp2 - Fp1: High	-.47**	.08	.16	.22	.46*	.47**
15	Fp2 - Fp1: Low1	-.08	.41*	.30	.44*	.24	.59**
16	Fp2 - Fp1: Low2	-.12	.19	.56**	.40*	.26	.43*
17	Fp2 - Fp1: Total	-.22	.29	.45*	.45*	.35*	.59**

	Variable	Depressivity	F8 - F7		Fp2 - Fp1		
			Low 2	Total	High	Low 1	Low 2
1	Depressivity	-					
12	F8 - F7: Low2	-.29	-				
13	F8 - F7: Total	-.46*	.67***	-			
14	Fp2 - Fp1: High	-.47**	.36	.61**	-		
15	Fp2 - Fp1: Low1	-.08	.45*	.61**	.51**	-	
16	Fp2 - Fp1: Low2	-.12	.57**	.60**	.43*	.64***	-
17	Fp2 - Fp1: Total	-.22	.57**	.72***	.70***	.89***	.88***

** p < .05, ** p < .01, *** p < .001*

Parietal Alpha Asymmetry – Bands and Electrodes

Introduction

The Combined eye condition and fixed bandwidth used for FAA was also used for PAA. This keeps the measures as consistent as possible. PAA scores were calculated for parietal electrode channels P8 – P7 and P4 – P3 in the low 2, low 1, high and total sub-bands. Part correlations are displayed in Table 3.9. Correlation matrices for female participants are presented in Table 3.10, males in Table 3.11.

Table 3.9

PID-5 depressivity variance accounted for by the best parietal alpha asymmetry measures and each other sub-band within their electrode pair for female participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
P8 - P7					
Low 1	-13.8	-6.9			
Total	-7.0	0.0	6.9	6.9	-13.9
Low 1	-13.8	-11.6			
High	-2.3	0.0	11.6	2.2	-13.9
Low 1	-13.8	-13.6			
Low 2	-0.4	0.2	13.8	0.2	-14.0

Note. All values are correlations represented as signed percentage of variance.

[a] Calculated as the sum of part correlations.

[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.

[c] The R^2 of the model, converted to proportion of variance.

Table 3.10

Zero order correlations between parietal alpha asymmetry fixed sub-bands and depressivity in female participants.

	Variables	Depressivity	P4 - P3				P8 - P7		
			High	Low 1	Low 2	Total	High	Low 1	Low 2
1	Depressivity	-							
2	P4 - P3: High	-.05	-						
3	P4 - P3: Low 1	-.22	.22	-					
4	P4 - P3: Low 2	.01	-.02	.23	-				
5	P4 - P3: Total	-.13	.66***	.75***	.54***	-			
6	P8 - P7: High	-.15	.56***	-.03	-.02	.29*	-		
7	P8 - P7: Low 1	-.37**	.15	.39**	.28*	.41**	.36*	-	
8	P8 - P7: Low 2	-.06	-.09	.06	.54***	.22	.02	.29*	-
9	P8 - P7: Total	-.26	.33*	.17	.37**	.43**	.71***	.74***	.62***

** p < .05, ** p < .01, *** p < .001*

Table 3.11

Zero order correlations between parietal alpha asymmetry fixed sub-bands and depressivity in male participants.

	Variables	Depressivity	P4 - P3				P8 - P7		
			High	Low 1	Low 2	Total	High	Low 1	Low 2
	PID-5								
1	Depressivity	-							
2	P4 - P3: High	-.13	-						
3	P4 - P3: Low 1	.03	.39*	-					
4	P4 - P3: Low 2	-.02	.44*	.53**	-				
5	P4 - P3: Total	-.05	.74***	.80***	.85***	-			
6	P8 - P7: High	-.09	.41*	.24	.07	.28	-		
7	P8 - P7: Low 1	.06	.36*	.53**	.11	.40*	.40*	-	
8	P8 - P7: Low 2	.17	.36*	.15	.62***	.49**	-.04	.29	-
9	P8 - P7: Total	.07	.55**	.43*	.40*	.57**	.66***	.80***	.62***

** p < .05, ** p < .01, *** p < .001*

Results

Female. Almost all correlations were negative in direction, the sole measure that was positive accounted for less than .01% of depressivity variance (see Table 3.10). In both parietal pairs the low 1 sub-band accounted for the most variance with the total band trailing behind. Only the finding in the lateral pair was reliable. P8 – $P7_{low\ 1}$ accounted for the most variance of all variables, with none of the other variables showing a part correlation greater than 1% (see Table 3.9).

Male. Males did not follow the same pattern as their female counterparts. The strongest correlate was P8 – $P7_{low\ 2}$ which was positive, but only accounted for 2.9% of depressivity's variance. The high sub-band in both pairs provided the next best measures, which were both negative and accounted for less than 2% of variance.

Discussion

In female participants P8 – $P7_{low\ 1}$ accounted for the most proportional variance. Part correlations showed P8 – $P7_{low\ 1}$ accounted for all useful variance in other bands. Therefore, P8 – $P7_{low\ 1}$ was chosen as the optimal PAA measure for females. P8 – $P7_{low\ 2}$ accounted for the most proportional variance in male participants, however this finding was not reliable.

Higuchi Fractal Dimension – Bandwidth

Introduction

The combined eye condition was used for HFD. However, as discussed in Chapter 2 HFD analyses the spatial content of the signal, which is lost in the FFT used to select the fixed bandwidth. Instead two different sets of bandwidths were compared. An MRA dataset obtained via a 4-level multiresolution analysis containing an approximate alpha band (8 – 16Hz) and the artefact-free full channel data containing the full bandwidth of the raw data. Signed proportional variance between HFD and PID-5 depressivity were calculated for each channel and bandwidth. The bandwidths were then compared using a one-way, repeated-measures ANOVA. The means and standard deviations of each are displayed in Table 3.12.

Table 3.12

Mean and standard deviation of HFD signed proportion of variance by bandwidth and gender.

Gender	Mean (SD)		N
	MRA	Full Channel	
Female	11.330(.833)	15.576(.891)	12
Male	.709(.112)	1.804(.499)	12

Results

Female. The full channel bandwidth accounted for a higher proportion of variance than the MRA bandwidth. This difference was reliable ($F(1,11) = 9.380$, $p = .011$, $\eta^2 = .460$).

Male. The full channel bandwidth accounted for a higher proportion of variance than the MRA bandwidth. This difference was also reliable ($F(1,11) = 5.117$, $p = .045$, $\eta^2 = .317$). However, proportion of variance was low, less than 2% in both bandwidths.

Discussion

In both male and female participants, the full channel bandwidth reliably accounted for more variance than the MRA HFD. Due to these findings, the full channel HFD was identified as the best HFD measure to analyse.

Higuchi Fractal Dimension – Electrodes

Introduction

The HFD of each channel in the FC bandwidth was calculated. The correlation matrix for female and male participants can be seen in Table 3.15 and 3.16 respectively. To keep the method like those used in our AA analyses, the strongest correlate in each homologous electrode pairs was selected to move forwards. These correlates are displayed in Table 3.13. Partial and part correlations are displayed in Table 3.14.

Table 3.13

Proportion of PID-5 depressivity accounted for by best HFD measure at each homologous pair.

Channel Pair	Females			Males		
	Strongest Channel	%	p	Strongest Channel	%	p
Fp2 - Fp1	Fp1	13.2	.020	Fp1	1.3	.588
Af4 - Af3	Af3	16.4	.009	Af3	0.7	.688
F4 - F3	F4	18.5	.005	F4	1.4	.574
F8 - F7	F8	17.6	.006	F8	3.6	.364
P4 - P3	P3	19.4	.004	P3	5.4	.264
P8 - P7	P7	19.4	.004	P8	2.5	.454

Note: All values are correlations represented as percentage of variance, there were no negative correlations for HFD.

Results

Female. HFD correlated with depressivity reliably in every channel (see Table 3.15). The level of intercorrelation was high across all channels. Parietal channels accounted for the most variance, with the lateral and medial frontal channels close behind (see Table 3.13). P7 displayed higher part correlations than all other identified correlates. When paired with P7 no other variable's part correlation accounted for more than 2% variance (see Table 3.14).

Male. HFD was not reliably correlated with depressivity in any channel. Intercorrelation between the HFD's of every channel was apparent (see Table 3.16), mimicking the intercorrelation observed in female participants. Frontopolar and anterior frontal channels accounted for less variance than other frontal and parietal channels (Table 3.13).

Table 3.14

Proportion of PID-5 depressivity accounted for by the best HFD measure paired with best HFD at each homologous pair in females.

Channels	Correlations			Combined Variances		
	Zero-order	Partial	Part	Unique	Shared	Total
P7	19.57	1.51	1.21			
P3	19.56	1.49	1.20	2.4	18.4	20.8
P7	19.57	2.72	2.22			
F8	18.13	.97	.78	3.0	17.3	20.4
P7	19.57	3.68	3.00			
F4	18.51	2.41	1.93	4.9	16.6	21.5
P7	19.57	7.69	6.67			
Fp1	13.18	.35	.28	7.0	12.9	19.8
P7	19.57	4.81	4.02			
Af3	16.39	1.05	.84	4.9	15.5	20.4

Note: All values are correlations represented as percentage of variance, there were no negative correlations for HFD.

Discussion

In females HFD was significant at every electrode, with the parietal channels accounting for the most proportional variance. There was a very high level of intercorrelation between all variables and a similar R value with most variables sitting at around .40. This level of intercorrelation suggests that the choice of electrode is somewhat arbitrary as differences are small. In this experiment, P3 and P7 had virtually identical correlations. P7 was identified by stepwise regression as the better of the two, due to a very small difference in p-value so P7 was chosen as the best predictor. There were no significant HFD variables in male participants, showing a stark contrast between genders.

Table 3.15

Zero order correlations between full channel fractal dimension and PID-5 depressivity in female participants.

	Variables	Depressivity	Af3	Af4	F3	F4	F7	F8
1	Depressivity	-						
2	Af3	.40**	-					
3	Af4	.40*	.94***	-				
4	F3	.36*	.97***	.90***	-			
5	F4	.43**	.96***	.96***	.95***	-		
6	F7	.31*	.87***	.87***	.87***	.85***	-	
7	F8	.43**	.89***	.92***	.88***	.91***	.96***	-
8	Fp1	.36*	.95***	.91***	.93***	.92***	.85***	.87***
9	Fp2	.35*	.80***	.92***	.77***	.84***	.78***	.83***
10	P3	.44**	.88***	.85***	.87***	.85***	.87***	.88***
11	P4	.39*	.84***	.83***	.81***	.82***	.84***	.84***
12	P7	.44**	.79***	.81***	.75***	.77***	.85***	.86***
13	P8	.40**	.73***	.72***	.68***	.68***	.81***	.79***

	Variables	Depressivity	Fp1	Fp2	P3	P4	P7	P8
1	Depressivity	-						
8	Fp1	.36*	-					
9	Fp2	.35*	.84***	-				
10	P3	.44**	.78***	.70***	-			
11	P4	.39*	.75***	.67***	.97***	-		
12	P7	.44**	.74***	.78***	.88***	.87***	-	
13	P8	.40**	.66***	.61***	.85***	.90***	.89***	-

** $p < .05$, ** $p < .01$, *** $p < .001$*

Table 3.16

Zero order correlations between full channel fractal dimension and PID-5 depressivity in male participants.

	Variables	Depressivity	Af3	Af4	F3	F4	F7	F8
1	Depressivity	-						
2	Af3	.08	-					
3	Af4	.07	.95***	-				
4	F3	.10	.99***	.95***	-			
5	F4	.12	.96***	.98***	.96***	-		
6	F7	.10	.93***	.94***	.94***	.94***	-	
7	F8	.19	.91***	.93***	.92***	.94***	.94***	-
8	Fp1	.11	.96***	.92***	.93***	.95***	.90***	.87***
9	Fp2	.03	.81***	.94***	.81***	.90***	.84***	.82***
10	P3	.23	.79***	.77***	.80***	.80***	.85***	.85***
11	P4	.20	.78***	.78***	.78***	.80***	.84***	.84***
12	P7	.01	.48**	.44*	.49**	.46*	.60**	.52**
13	P8	.16	.73***	.76***	.71***	.78***	.82***	.82***
	Variables	Depressivity	Fp1	Fp2	P3	P4	P7	P8
1	Depressivity	-						
8	Fp1	.11	-					
9	Fp2	.03	.84***	-				
10	P3	.23	.74***	.64***	-			
11	P4	.20	.73***	.67***	.97***	-		
12	P7	.01	.46*	.38*	.56**	.58**	-	
13	P8	.16	.75***	.72***	.81***	.86***	.65***	-

** p < .05, ** p < .01, *** p < .001*

Effect of Combining Measures.

Introduction

FAA is the primary measure of interest in this study. PAA and HFD were identified as measures that may supplement or replace FAA. PAA is calculated from a completely different region from FAA. HFD analyses a different aspect of the signal altogether. If both PAA and HFD are measuring different mechanisms to FAA, then they should contribute a large amount of unique variance to the FAA - depressivity model. To test this, the best FAA, PAA and HFD measures were each included in a stepwise linear regression. Zero order and part correlations are displayed in Table 3.17.

Table 3.17
Proportion of PID-5 depressivity accounted for by the best FAA, PAA and HFD measures when paired and combined in female participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
Paired					
$P7_{FC}$	19.6	15.7			
Fp2 - $Fp1_{high}$	16.1	12.2	27.9	3.9	31.8
$P7_{FC}$	19.6	17			
P8 - $P7_{low\ 1}$	-13.8	-11.3	28.2	2.6	30.8
Fp2 - $Fp1_{high}$	16.1	14.8			
P8 - $P7_{low\ 1}$	-13.8	-12.6	27.4	1.3	28.7
Combined					
$P7_{FC}$	19.6	13.6			
P8 - $P7_{low\ 1}$	-13.8	-10.5			
Fp2 - $Fp1_{high}$	16.1	11.5	35.6	6.7	42.3

Note. All values are correlations represented as signed percentage of variance.
[a] Calculated as the sum of part correlations.
[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.
[c] The R^2 of the model, converted to proportion of variance.

Results

Female. The stepwise regression included all 3 predictors. $P7_{FC}$ was the first variable included ($F(1,39) = 9.490$, $p = .004$, $R = .442$), followed by $Fp2 – Fp1_{high}$ ($F(2,38) = 8.864$, $p = .001$, $R = .564$) and finally $P8 – P7_{low\ 1}$ was added to the model ($F(3,37) = 9.035$, $p < .000$, $R = .650$).

Part correlations (see Table 3.17) show that the proportion of variance accounted for by each measure is primarily independent. Only 6.7% of the model's 42.3% variance was shared between the measures, the remaining 35.6% was unique and divided amongst the measures equally. The measure contributing the highest proportion of unique variance was $P7_{FC}$ (13.6%) but this only contributed 2.1% more than the lowest, $P8 – P7_{low\ 1}$ (10.5%).

Table 3.18
Proportion of PID-5 depressivity accounted for by the best FAA, PAA and HFD measures when paired and combined in male participants.

Band	Correlations		Combined Variances		Model[c]
	Zero-order	Part	Unique[a]	Shared[b]	
Paired					
$P3_{FC}$	5.4	3.9			
$Fp2 - Fp1_{high}$	-21.8	-20.4	24.3	1.5	25.8
$P3_{FC}$	2.9	2.4			
$P8 - P7_{low\ 2}$	5.4	4.9	7.3	0.5	7.8
$Fp2 - Fp1_{high}$	-21.8	-21.3			
$P8 - P7_{low\ 2}$	2.9	2.3	23.6	0.6	24.2
Combined					
$P3_{FC}$	5.4	3.5			
$P8 - P7_{low\ 2}$	2.9	1.9			
$Fp2 - Fp1_{high}$	-21.8	-19.9	25.4	2.3	27.7

Note. All values are correlations represented as signed percentage of variance.
[a] Calculated as the sum of part correlations.
[b] The difference between the sum of part correlations and the proportion of the model is the variance shared between variables.
[c] The R^2 of the model, converted to proportion of variance.

Male. Neither PAA nor HFD were reliable in male participants. In the interest of comparing the part correlations of male and female participants a combined model was tested (see Table 3.18). The part correlations display a similar pattern to those seen in the female model; the majority of variance is unique to each measure with a minor amount being shared between them. However, there

were no increases in overall variance explained that would suggest that the low initial correlations of PAA nor HFD were due to some form of suppression effect.

Discussion

FAA, PAA and HFD all contribute primarily unique variance, in roughly equal quantities. The amount of variance shared between these measures is a minority. FAA is the primary focus of this research, but these findings suggest that PAA and HFD are worth investigating in greater detail as they each appear to be independent of each other. HFD appears to be a stronger predictor of depressivity in females than FAA.

CHAPTER 4: DISCUSSION

Overview

In Chapter 1, the literature on FAA, PAA, HFD and their relationship to depression suggested three hypotheses: (1) Alpha asymmetry at F4 – F3 will account for the greatest proportion of PID-5 depressivity variance in the frontal region; (2) The strongest PAA measure will contribute significant unique variance when included in a model with FAA; and (3) HFD will contribute significant unique variance when paired with FAA or PAA and when FAA, PAA and HFD are all included in a single model.

Hypothesis 1 was not supported. F4 – F3 did not account for the most PID-5 depressivity variance, instead it accounted for the least. $Fp2 – Fp1_{high}$ was the optimal measure of FAA and the only FAA measure that was reliable in both male and female participants. Hypothesis 2 was partially supported. The optimal PAA measure was $P8 – P7_{low\ 1}$ in female participants. $P8 – P7_{low\ 1}$ shared very little variance with $Fp2 – Fp1_{high}$, the contribution of each measure remained almost completely unique. However, PAA effects were not reliable in males. Hypothesis 3 was also partially supported. $P7_{FC}$ was the optimal HFD measure in female participants. When paired with FAA and PAA the variance contributed by HFD remained primarily unique. However, HFD effects were not reliable in males. A combined model of all three optimised measures in females showed that the majority of PID-5 depressivity accounted for was unique to each measure, with a minor amount shared between them. Although there were no reliable PAA or HFD findings for male participants a combined model appeared structurally similar to that for females but with no increase in the explanatory power of PAA or HFD of the type that could have resulted from suppression effects reducing their simple correlations with depressivity.

The results for FAA, PAA and HFD are discussed in greater detail in the subsequent sections, followed by a discussion of the combined effects. In each section, an overview of the results, interpretation of the results in relation to prior literature and any implications for future research are discussed. After these sections, the limitations of this thesis are discussed and conclusions provided.

Frontal Alpha Asymmetry

Overview of results

The strongest correlations for each electrode pair were seen in either the high sub-band, or the total band. In cases where the total band was the strongest, the high sub-band was always the next strongest. In female participants, Fp2 – $Fp1_{high}$ accounted for the largest proportion of variance. The total band was the only other band that accounted for a non-trivial proportion of variance, but this was almost entirely shared with the high sub-band. No other homologous pair displayed reliable correlations. In male participants, reliable correlations occurred at Fp2 – $Fp1_{high}$, Af4 – $Af3_{high}$ and F8 – $F7_{total}$, and all were negative. Part correlations showed that the proportion of variance accounted for within and between electrode pairs was primarily shared, with the part correlations of weaker variables reducing to irrelevance when the strongest correlations were included. As Fp2 – $Fp1_{high}$ was the only correlate to reach significance in both genders it is the best single FAA measure in this experiment.

Hypothesis 1

These results did not support our literature-based hypothesis that the F4 – F3 pair would display the best correlations. The results instead show the exact opposite: that F4 – F3 provides the worst AA correlations in both genders.

FAA literature

The main aim of this thesis was to identify the best FAA measure to use in neurofeedback protocols targeting depression. The results show that Fp2 – $Fp1_{high}$ is the best FAA measure for that purpose. It was the only measure that reached significance in both males and females. This area has been identified in EEG studies of depression and anxiety as significant, although results are mixed with some positive (Hinrikus et al., 2009; Liao et al., 2013) and others finding null results (Carvalho et al., 2011; Gold et al., 2013). In the wider AA literature, significant effects have been found in the frontopolar region, particularly in relation to anxiety (Demerdzieva & Pop-Jordanova, 2015; Papousek & Schulter, 2002; Smith, Zambrano-Vazquez, & Allen, 2016). Anxiety and depression exhibit a very high rate of comorbidity (Lamers et al., 2011) so significant findings for both disorders in the same location is not unexpected.

In support of our frontopolar findings is a wealth of neuroscientific research showing relationships between depression and the frontopolar region. The frontopolar electrodes (Fp1, Fp2, Fpz) are located over Brodmann area 10, a subsection of the ventromedial prefrontal cortex (vmPFC). Studies of lesions in the vmPFC suggest that it may be causally involved in depression (Koenigs & Grafman, 2009; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). Other findings include reduced oligodendroglial activity (Hayashi et al., 2011), decreased activity during conversation (Takei et al., 2014) and abnormal fatty acid composition (Tatebayashi et al., 2012) in the frontopolar area of depressed individuals. These findings all point to the frontopolar region as playing a significant role in depression and reduce the odds of our finding being spurious. Our F3 – F4 results may be due in part to our use of the statistically refined PID-5 depressivity trait measure and it is possible that other measures (e.g. PID-5 anxiety, clinically assessed depression) might show stronger relationships with F3 – F4.

The direction of correlation observed in the frontopolar region was not expected. Previous research has displayed negative correlations between alpha asymmetry and depression, indicating hypoactivity in the left hemisphere. Male participants followed this pattern, but female participants in this study displayed positive correlations between asymmetry and depressivity. Interpreting this is difficult as the frontopolar area is under-investigated. The simplest explanation is that it's positive

because there is a true positive correlation there. The main area from which negative correlations are reported in the literature is F4 – F3, which was also negative in the current study. However, the strongest sub-band in F4 – F3 only accounted for 1.1% of PID-5 depressivity variance, which makes the finding high unreliable. Differing directionality has also been observed between genders in other studies (Miller et al., 2002). With the midfrontal area following the direction of previous studies and differential effects observed in genders previously, it is reasonable to take the positive correlation at face value.

Implications for future research

There are several important implications for frontal alpha asymmetry stemming from this thesis. The difference between sub-bands was quite distinct in our findings, suggesting that the use of total alpha band analysis is likely to miss key features. The electrode search conducted here has shown that important results may be found in areas not often analysed, implying that the individual analysis of a wider range of homologous pairs is warranted as is comparison of their relations among different well-constructed trait measures and/or distinct diagnostic categories. The opposing direction signs between genders strongly back the *a priori* separation of genders when it comes to data analysis, combining both genders could result in gender-specific effects being cancelled out by the inversion of signs.

Parietal Alpha Asymmetry

Overview

In females, the strongest measures for each pair were found in the low 1 sub-band. Of those, only P8 – $P7_{low\ 1}$ was reliable. Part correlations showed that P8 – $P7_{low\ 1}$ contributed high unique variance compared to other sub-bands whose part correlations reduced to trivial values. Therefore P8 – $P7_{low\ 1}$ was chosen as the best correlate for females. There were no reliable correlates for male participants, so none moved forwards.

PAA literature

These findings fit in with previous AA literature and wider neuroimaging literature. PAA has previously been linked to depression status (Kentgen et al., 2000; Tement et al., 2016) and also to lifetime depression status (Stewart et al., 2011). Gender and comorbid anxiety also appear to have considerable influence (Bruder et al., 1997; Kentgen et al., 2000; Tement et al., 2016). In the wider literature, functional connectivity models of depression have found the temporoparietal area to be important (Zeng et al., 2012). This area is also thought to be involved in emotional arousal with depressed patients exhibiting right lateralised hypofunction (Moratti, Rubio, Campo, Keil, & Ortiz, 2008).

Implications for future research

Prior studies have focused primarily on FAA. The present results support the claims made by Stewart et al. (2011) that the parietal region is understudied. Although PAA findings were not as strong as those in the frontal region, they were reliable. The correlations occurred in the opposite direction to those seen in FAA, in a different sub-band, and only in females. These differences indicate that the parietal region is worth researching in the future. Furthermore, with reliable correlations observed in both frontal and parietal regions, research targeting occipital and temporal areas may well

be worth undertaking. As with FAA, PAA produced quite different results between females and males.

Higuchi's Fractal Dimension

Overview of results

There was a high level of intercorrelation between HFD scores across all electrode sites, meaning that HFD at one electrode was very similar to HFD at any other electrode. This indicates that HFD may be a global phenomenon, with little heterogeneity between electrode sites. Given that complexity is likely to arise from interactions between multiple areas, this is not surprising. In female participants HFD reliably accounted for a sizable proportion of depressivity variance at every electrode site. HFD at P7 was selected as the best electrode, though P3 had an almost identical level of correlation. Part correlations revealed that the majority of variance was shared, further reinforcing the plausibility of HFD as a global change. As with PAA, HFD was not significant in male participants.

HFD literature

The findings of this thesis fit well with other studies, which have found full channel HFD to reliable correlate with depression (Akar et al., 2015; Bachmann et al., 2013; Hosseinifard et al., 2013). Unlike the chequered findings for alpha asymmetry, HFD has seen consistent correlations with depression.

Implications for future research

The elevated level of intercorrelation observed between HFD at all electrodes is of high interest because it implies that HFD is a global measure. If HFD at one electrode is roughly equivalent to HFD at any other electrode it would be very useful for neurofeedback protocols as specificity of

location would be unimportant. It also brings up the possibility of a global increase in EEG complexity in females that correlates with depressive symptomology, the neural mechanisms underpinning that complexity could be useful clinically. However, our data provide no reason to assume that HFD could be used for neurofeedback in males.

Additivity of FAA, PAA and HFD

Overview of results

The strongest measures from FAA, PAA and HFD contributed high levels of unique variance to the combined model in females. Comparatively little variance was shared. These findings indicate that each of the measures is identifying distinctive features and they are not all just different measures analysing the same mechanisms. Of the three, HFD ($P7_{FC}$) was the strongest individually, follow by FAA ($Fp2 - Fp1_{high}$) and then PAA ($P8 - P7_{low\ 1}$). However, FAA was the only measure, which was reliable at a single site in both genders, while PAA and HFD were specific to females.

A male combined model was tested to see if the pattern of part correlations seen in female participants (primarily unique variance contributed by each measure) would also be present in male participants. The same pattern was seen in male participants. The finding is unreliable as both PAA and HFD were weak. There was no evidence that the low values for either PAA or HFD in males were due to a suppression effect and so, although weak, the additivity in males appears to be qualitatively the same as in females.

Hypothesis 2

The hypothesis for PAA predicted that the majority of variance accounted for by PAA would be unique from that accounted for by FAA. The results supported this hypothesis. When $P8 - P7_{low\ 1}$ was paired with $Fp2 - Fp1_{high}$, very little variance was shared between them and the clear majority was unique to each measure. However, this only applies to females.

Hypothesis 3

The hypothesis for HFD predicted additivity with both PAA and FAA. The results support this hypothesis. When paired with either measure only a negligible portion of depressivity variance was shared, with the vast majority remaining unique to the individual measures. However, this only applies to females.

Literature

To my knowledge these measures have not been directly compared before. The findings of this thesis suggest that the relationship between alpha asymmetry and depressive symptomology is likely more localised than often suggested in the literature. While some researchers analyse homologous pairs on their own merits (Gold et al., 2013; Jaworska et al., 2012; Segrave et al., 2011), others collapse scores across homologous pairs (Blackhart et al., 2006; Nelson et al., 2012). The present results suggest that there are localised effects that may be missed if electrodes are averaged hemispherically.

The additivity seen between the optimised measures is of interest. FAA, PAA and HFD shared very little variance between them, the majority of variance accounted for by each measure was unique. If these measures were all representing the same underlying mechanisms we would expect them to share a lot of variance. The lack of shared variance instead suggests that the mechanisms involved are different for each measure. Additivity between FAA and PAA is further evidence against the practice of collapsing data hemispherically mentioned in the preceding paragraph; these are two localised measures conveying almost entirely unique information. Unlike the localised effects seen in the AA measures, changes in HFD appear to be global and unique from the other measures. Overall it seems that all three measures are unique, alpha asymmetry has localised effects while HFD is more global.

Implications for future research

The additivity seen between measures is particularly interesting. Previous studies have focused on the notion of differences at the hemispheric level, but the findings of this research suggest otherwise. Frontal and parietal findings exhibited opposite direction in correlation, showing that hemispheric differences are not consistent across the entire brain. The additivity of FAA and PAA provide further evidence the link between alpha asymmetry and depression is more localised than suggested in the literature. Future research would likely benefit from including both frontal and parietal asymmetry due to their distinct relationships with depressivity.

Unlike alpha asymmetry these results suggest that increases in depressivity involve an increase in HFD at every electrode in females. While alpha asymmetry appears to be localised, this does not appear to be the case with HFD. The additivity of FAA, PAA and HFD measures is evidence that both global and localised electrophysiological changes occur with depressive symptomology, suggesting that there may be several different biological mechanisms at play. Future research investigating these mechanisms, the relationships between them and the role of other electrophysiological measures would be invaluable to the understanding of depression.

Implications of the Current Results for Neurofeedback

The findings of this thesis challenge the methodology used in neurofeedback protocols. Recent neurofeedback experiments targeting depression have used scores obtained from the midfrontal (F4 – F3) region (Jesulola, Sharpley, Bitsika, Agnew, & Wilson, 2015; Mennella, Patron, & Palomba, 2017; Peeters, Oehlen, et al., 2014; Quaedflieg et al., 2016; Wang et al., 2016). The results of this thesis (albeit with a low number of participants) failed to find a reliable correlation between the midfrontal pair and depressivity, suggesting that the F4 – F3 pair may not be an ideal target.

The identification of Fp2 – $Fp1_{high}$ as the best FAA measure carries several implications for neurofeedback. The use of frontopolar electrodes can allow for simplified equipment, easier application and increase accessibility of neurofeedback. An EEG headset specifically designed for neurofeedback could be streamlined to only record from the relevant electrodes, heavily reducing the

number of electrodes needed. These reductions would reduce the cost of such a headset. The frontopolar region is not covered in hair, making it the most readily accessible EEG area. Dry electrodes are easier to design when hair is not an issue, eliminating the need for electrode gel and simplifying the application procedure. Use of dry electrodes would also improve the plausibility of self-administration. Cheaper, easier to use equipment is already available for small numbers of frontal sites and opens the possibility of wide-scale commercialisation and therefore greatly improved accessibility. The application of this kind of neurofeedback is possible now and is not dependent on future technological developments.

There are some negatives to the use of Fp2 – Fp1. Any neurofeedback protocol using that region needs be processing in real time. The frontopolar electrodes are the electrodes most affected by eye blinks, introducing the possibility of eyeblink artefacts polluting data. This necessitates the use of an automated process that can filter eye blinks effectively. Such a procedure has recently been developed in our laboratory but not yet tested in the context of neurofeedback (McNaughton, Personal Communication). Another comes from the gender differences seen. As male and female participants exhibited opposite sign correlations in the same area (and differ in relation to PAA and HFD) neurofeedback protocols using Fp2 – $Fp1_{high}$ may need to be gender specific or even tailored to the individual based on some form of pre-test.

Limitations

Multiple testing issues

This research took a broad approach to address current issues in AA literature. While it was necessary to investigate the differences in eye condition, bandwidth calculation and sub-bands, this breadth came at the cost of an increased number of variables. With more variables comes a corresponding increase in the chances of false positives and an increase in type 1 error rate. Therefore, there is a clear possibility that the results found here are spurious and so replication is needed.

Although there are methods that aim to correct for increase type 1 error rate, no such method was applied in this study. Corrections, such as the Bonferroni correction, help reduce type 1 error rate, but also increase the odds of discarding a true positive (increase type 2 error rate). The level of significance typically seen in AA experiments is low enough that a true positive would almost certainly be ruled out if corrections were applied to this study. Even if correction was applied and findings remained significant, the need for replication would not be diminished due to the inconsistency of findings in the literature. Therefore, correction was not applied as it would cause an unacceptable increase in type 2 error and would do little to improve the strength of the study. Replication in a completely new larger sample of participants and using focussed hypotheses based on the current results, not altered p-values, is needed to fortify these findings.

Sample size and homogeneity

The demographics of our sample, as well as the sample size are also limiting factors. The participants are relatively homogenous: young university students. As with any restricted sample it would be unwise to assume that the findings generalise to other populations. Further, a narrowing of the variance range may have suppressed detection of correlations (and so potentially account for the poor F3 – F4 results). The small sample size further compounds these issues. This thesis used a large number of variables and split the participants by gender which further reduces the power of the findings.

This thesis aims to identify something that is practically useful in the future. To be useful it must have a reliable effect size in small sample sizes, ideally at the individual level. If the effect is not observable at our sample size (66) then it's unlikely to be clinically useful. The most effective way of addressing the limitations of this study is replication in future research. No single study is likely to provide insurmountable evidence, especially not in a field with a history of inconsistent results. However, if these effects are practically useful they will also need to be robust enough to be seen in other samples. Replication is essential for validating these results and is absolutely required if this is to ever be clinically useful.

Specificity to depression

This study only analysed the relationship between the various measures and PID-5 depressivity. It is possible that these measures are not depression specific, but are more generalised in nature. Anxiety, neuroticism, clinical depression scales, or some underlying trait that affects all three may better correlate with these measures. While the results of the present study demonstrate a correlation, future research is needed to determine the specificity of the relationships identified here if the measures were to be used as biomarkers. However, it should be noted that a lack of specificity would be more an advantage than a problem for use in neurofeedback.

Conclusions

Neurofeedback protocols targeting depression have used alpha asymmetry in the midfrontal electrodes (F4 – F3) as an index of depression, seeking to alleviate symptomology through manipulation of this asymmetry. This is based on a body of work which identifies left frontal hypoactivity (greater relative left alpha power) as a correlate of depression, primarily in the midfrontal area. However, research linking alpha asymmetry to depression has not always been consistent. This inconsistency prompted the research in this thesis, aiming to identify the optimal alpha asymmetry index for a neurofeedback protocol.

The results of this present experiment suggest that the best frontal alpha asymmetry measure to use in a neurofeedback protocol is Fp2 – $Fp1_{high}$. The findings show mixed support for the theory of left hypoactivity (relatively greater left alpha power) being linked to depressive symptomology. Correlations were generally positive in female participants and negative in male participants. This suggests right hypoactivity in females, and left hypoactivity in males. However, the midfrontal electrode did display negative correlations in both genders though these did not reach significance. This may indicate that the left hypoactivity observed in other research is localised, varying across the frontal region.

Further support for the possibility of localised effects in alpha asymmetry were the findings regarding parietal alpha asymmetry. Lateral parietal asymmetries typically displayed an inverse direction of correlation to their frontal counterparts, a finding observed previously by Stewart et al. (2010). The majority of variance accounted for by parietal asymmetry was unique and not shared with frontal asymmetry in females. If AA effects were global, we would expect that asymmetry in any pair would display primarily shared variance with other pairs. Instead we have mainly unique variance, with differing signs and different sub-bands by region within the same participants, a pattern of findings more consistent with localised effects occurring in different regions within the alpha bandwidth.

In addition to alpha asymmetry, HFD was also analysed in this study. HFD had previously been found to correlate significantly with depression across several different studies and has also been applied to neurofeedback protocols before. Our findings support previous studies correlating HFD with depression. Results also suggest that, unlike alpha asymmetry, HFD is a global phenomenon with all channels demonstrating high levels of intercorrelation and shared variance. The variance contributed by HFD is distinct from both FAA and PAA, supporting our original speculation that because it analyses a different kind of information HFD would be additive to alpha asymmetry.

To summarise: $Fp2 - Fp1_{high}$ is the frontal AA measure that best correlates with PID-5 depressivity. As it is the best AA measure it is also the measure best suited for neurofeedback due to its consistency across genders. $P8 - P7_{low\ 1}$ was the strongest parietal AA measure in females, though there was no significance in any parietal channels for males. HFD was likewise significant only in females, but was significant in every channel with $P7_{FC}$ being marginally stronger than others. All 3 measures are additive, with most of their variance being unique and this pattern was also present in male participants.

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APPENDIX A: Participant Information & Consent Sheet

Stop Signal EEG and Personality

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

INFORMATION SHEET FOR PARTICIPANTS

Introduction

Thank you for showing an interest in this project. Please read this information sheet carefully. Take time to consider and, if you wish, talk with relatives or friends, before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the aim of this research project?

This project investigates how the electrical activity of your brain varies when you are trying to stop a response once you have started making one. We are particularly interested in how one specific brain rhythm (which appears when stopping and going are in conflict with each other) relates to current questionnaires that measure anxiety-related traits. The results should show how the various personality trait measures relate to trait variation in the conflict response and should also provide a basis for developing a new conflict response scale, extreme responses on which could potentially be used to diagnose a specific kind of anxiety disorder. The brain rhythm data will also provide a reference population against which clinical groups can be compared in future.

Who is funding this project?

This project is part of the work funded by a grant to Professor Neil McNaughton and collaborators at the University of Otago and the University of Auckland from the Health Research Council of New Zealand.

Who are we seeking to participate in this project?

We are seeking participants who are 18-40 years old, healthy (with no major illness in the previous 30 days), with no regular use of psychotropic medication in the last 6 months and no use of alcohol in the 24 hours before testing. You should be willing to receive medical and psychiatric screening interviews and undergo a urine test for psychotropic compounds.

<u>You will NOT be able to participate</u> **in the project because it may involve an unacceptable risk to you if have:**

1. Susceptibility to photosensitivity.
2. A history of seizure.
3. A history of allergic skin reactions to chemical agents including detergents.

If you participate, what will you be asked to do?

For the main part of the test, we will record the electrical activity from your scalp, heart and a finger during a ten minute rest period and in a "stop signal" task with stimuli delivered on a computer screen and through earphones and to which you will make responses using a computer mouse. You will be interviewed about your physical and mental health and also be asked to complete several questionnaires that measure aspects of your mood and personality. The whole experiment will take about three hours. In recognition of the time, inconvenience, and travel costs in attending for testing, you will be compensated at a rate of $15 for each hour of attendance.

Preparation for the experiment

Hair products and natural oils on our scalp make it difficult to record your brain activities. It is important to us that you come with a clean scalp. ***Please avoid using any hair products on the day of the experiment.*** We recommend that you wash your hair on the day or the day before and avoid using a hair conditioner. For participants with glasses, we also recommend that you wear contact lenses if possible for your own comfort.

Electrical recording procedure

You will put on an electro-cap as shown in the picture. We will fill the electrodes (small metal discs) attached to the cap with a gel that conducts brain signals from your scalp to our recording system. To achieve good recordings, we will abrade your skin gently before applying the gel. The electrodes are then connected to an amplifier that allows us to record your brain rhythms (EEG). We will also attach stick-on electrodes to your body to record your heart activity (ECG) and a clip on electrode to an index finger to measures your skin resistance/perspiration (GSR). The whole system is regularly tested and passes the current standards for connecting electrical equipment to people.

Is there any risk of discomfort or harm from participation?

There is a risk of allergic skin reaction to the electrode gel and of minor discomfort from the abrasion of the skin surface during gel application. Exposure to stimuli on a computer screen has a rare risk of inducing seizures in those with or without a history of seizure. If you have a history either of photosensitivity or of any form of seizure you should not take part. The person running your electrical testing is required to be trained in the procedures for connecting you to the equipment and to have a current First Aid Certificate (with training renewed every two years by the New Zealand Red Cross) so that they can respond appropriately to any unexpected adverse events that occur during testing.

What data will be collected, and how will they be used?

Your physical and mental health status, questionnaire scores, and elecgtrical recordings will be stored in secure computer databases and will be identified only with your participant number. Any paper

records will be stored securely in locked filing cabinets. Health status will be assessed only to exclude participants who do not meant the entry criteria. Questionnaire and electrical data will be subjected to group statistical analysis to determine general group-wide personality trait relationships and reference data. Urine samples, identified only by participant number, will be disposed of by the analysing laboratory using their usual procedures and only the qualitative, present/absent, result returned by the laboratory will be used for inclusion/exclusion. Data will be stored for 10 years and then deleted.

What about anonymity and confidentiality?

No identifying data will be recorded. All collected data will be linked only to your participant number. All data will be stored securely and accessed only by study personnel. Reporting of the completed research will be of aggregated data over all participants and no data will be reported linked to an individual participant number.

Can Participants Change their Mind and Withdraw from the Project?

You may withdraw from participation in the project at any time and without any disadvantage to yourself of any kind.

What if Participants have any Questions?

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Shabah Shadli (Telephone: 03 479 5835) or Professor Neil McNaughton (Telephone: 03 479 7634)
shabah.shadli@otago.ac.nz nmcn@psy.otago.ac.nz

This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.n). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

Stop Signal EEG and Personality

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

CONSENT FORM FOR PARTICIPANTS

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage.
6. I am aware that undergraduate students will be present and will carry out some parts of the experiment.
7. I know that as a participant I will undergo electrical (EEG/ECG/GSR) testing, physical and mental health screening, and a qualitative urine test for psychotropic drugs and complete questionnaires assessing emotion, as listed in the information sheet. I understand that I may decline to answer any interview or questionnaire question without disadvantage of any kind.
8. I know that no personal identifying information will be included in the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
9. I understand the nature and size of the risks of discomfort or harm that are explained in the Information Sheet, including the rare risk of computer screen-induced seizures.
10. I understand that the results of the project may be published but my anonymity will be preserved and only group data reported.

I agree to take part in this project.

……

(Full name)

....

(Signature of participant) (Date)

This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.n). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.