Neural Correlates of Inhibition in Children and Adolescents with Conduct Problems: An Exploration of Treatment Effects Following Multisystemic Therapy

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

Child and adolescent conduct problems are associated with considerable clinical and research interest and advances in technologies for measuring neural correlates of these difficulties present new opportunities for developing understanding and perhaps assessment and treatment options.

Part one of this thesis is a literature review of studies that employed two leading measures of functional brain activity, event related potential (ERP) and functional magnetic resonance imaging (fMRI), that examined neural correlates of inhibition in young people with conduct problems. Sixteen studies, nine which used ERP and 7 which used fMRI, were reviewed. Although the results were mixed, there is some support for the view that conduct problems, like other externalising disorders including attention deficit disorder and substance dependence, have abnormally reduced ERP amplitudes (specifically the N2 and P3 components) and reduced activation in areas of the ventrolateral and dorsolateral prefrontal cortex during inhibition tasks.

Part two is an empirical study using a social-competitive go/no-go task to examine the inhibitory N2 and P3 ERPs in adolescents with and without histories of antisocial behaviour problems. The study explores comparisons between clinical and control groups, and also explores whether completion of a course of Multi-Systemic Therapy is associated with differences in inhibitory ERPs compared to Management as Usual and control status. Finally, the study explores whether antisocial behaviour symptom improvement is associated with ERP differences.

Part three is a critical appraisal of the research process, including reflections on the experience of conducting the literature review and empirical study and consideration of the limitations and possible implications of the research.

This study was conducted as a joint project.

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Part 1: Literature Review

Neural Correlates of Inhibition in Children and Adolescents with Conduct Problems: A Systematic Review of ERP and fMRI studies

Abstract

Aim

Neural correlates of inhibition in childhood and adolescent conduct problems was systematically reviewed with a focus on Event Related Potential (ERP) and Functional Magnetic Resonance Imaging (fMRI) studies. The aim was to explore this subject and situate the findings in relation to other externalising conditions.

Method

A systematic search was conducted using PsycINFO and MEDLINE databases to identify relevant studies from peer reviewed journals.

Results

Sixteen peer reviewed studies were retrieved, nine of which used ERP and seven used fMRI. They provided a mixed picture of neural correlates of inhibition in conduct problems. Only three studies found reduced ERP amplitude, which is typically found in other externalising problems, to be related to conduct problems. Conduct problems were associated with reduced activation of regions related to inhibition, particularly the anterior cingulate cortex (ACC) and inferior frontal gyrus (IFG).

Conclusions

The review suggests that more research using both methods is required to establish a clear picture of the neural correlates of inhibition in young people with

conduct problems. The findings are discussed in relation to competing models of inhibition in externalising disorders.

Introduction

Conduct problems in children and adolescents are common and have serious social, psychological, and economic costs and consequences. Research into the mechanisms underpinning behavioural problems may enable more effective management of these difficulties, for example through the identification of diagnostic bio-makers (Krueger et al, 2002). Several research avenues suggest that deficits in inhibitory processes may be important features of behaviour disorders such as oppositional defiant disorder (ODD) and conduct disorder (CD). This systematic literature review explores the Event Related Potential (ERP) and fMRI research on three key types of inhibition in childhood and adolescent conduct problems.

Inhibition and Conduct Problems

Inhibition is the ability to actively suppress, interrupt, or delay a response and the concept is central to several developmental and psychopathological theories (Nigg, 2000; Barkley, 1997; Quay, 1997). It is an essential requirement for a range of everyday functions, since without it we would be unable to avoid inappropriate behavioural responses, we would lack the delay required to evaluate options for purposeful decision making, and it would be impossible to ignore distractions (Cragg, Fox, Nation, Reid, & Anderson, 2009).

Inhibition deficits have been suggested to be a core deficit in a range of behaviour disorders, including Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder, and substance dependence disorders. In fact, the high levels of covariance in the symptomatology of the above mentioned disorders, characterised by high levels of

impulsivity and disinhibited behaviour has been shown through factor analysis to load on a single factor which has been named the “externalising factor” or “externalising spectrum” (Krueger et al, 2002).

Conduct disorder (CD) is diagnostically defined by violations of social rules and the rights of others and by persistent display of antisocial behaviours, over a six to twelve month period before the age of eighteen (DSM-IV). Oppositional Defiant Disorder (ODD) is characterised by persistent patterns of argumentative, negativistic, disobedient behaviour towards figures of authority, though it lacks the aggressive behaviour typical in conduct disorder, and is only applied to children up to the age of ten. There is debate over whether these disorders have a core deficit in inhibition mechanisms, as has been shown in ADHD. It has been suggested that theoretical models applied to ADHD may also apply to ODD/CD (Albrecht et al, 2005), such as Barkley’s (1997) influential model which posits deficits in three types of inhibition: inhibition of the initial prepotent response to an event; stopping of an ongoing response; and interference control. There is some evidence that young people with ODD/CD also demonstrate these deficits (Oosterlaan, Logan, & Sergeant, 1998), but the research is mixed, with some researchers suggesting that the relationship between inhibitory deficits and ODD/CD is eliminated when adjusted for comorbid ADHD symptoms (Zhu et al, 2014). While reviews of behavioural studies of response inhibition have been conducted (Oosterlaan et al, 1998) these have not systematically reviewed the literature on neural correlates of inhibition of conduct problems. An influential model with applicability to ODD and CD is proposed by Blair (2005) who suggests that conduct disorders have impairments in a response inhibition circuit, situated in the ventrolateral frontal cortex, which is implicated in the loss of temper

and exaggerated aggression in ODD/CD. Blair (2005) suggests that there are also impairments in a second circuit involved in emotional processing, situated in brain areas around the amygdala, and is implicated in increased antisocial behaviour (Nordermeer, Luman, and Oosterlaan, 2016). Blair's (2005) model is derived primarily from studies of psychopathy in adults displaying severe antisocial and aggressive behaviour (Nordermeer, Luman, and Oosterlaan, 2016) but may also be relevant to children and adolescents. The following section describes the two leading approaches to measuring functional neural correlates of inhibition and key findings from recent reviews of externalising conditions.

Measuring the Neural Correlates of Inhibition

Electroencephalography (EEG) is a noninvasive, painless, approach to recording brain electrical activity with electrodes placed on the scalp (Luck, 2005). A particular functional method of EEG is the Event Related Potential Technique (ERP), which measures brain electrical activity in response to particular sensory, motor, or cognitive events or stimuli (Luck, 2005). Since the transmission to electrical potentials within the brain to the recording electrodes is effectively instantaneous, so ERPs provides excellent fine grained temporal resolution (De Haan & Thomas, 2002). While ERP research provides safe, relatively inexpensive good temporal information about neural processes, its spatial resolution is not very precise. Functional Magnetic Resonance Imaging (fMRI), measures a blood-oxygenation-level-dependent (BOLD) response to show changes in blood flow related to energy use in brain cells and is therefore used a measure of neural activity (De Haan & Thomas, 2002). Whereas ERP has excellent temporal resolution, fMRI has good

spatial resolution. Use of both approaches together, and pooling of studies from both methodologies for comprehensive reviews has been recommended for developmental and clinical research (De Haan & Thomas, 2002).

Two ERP components have been consistently reported as neural correlates of response inhibition in a range of behavioural tasks (Jonkman, 2006). Firstly, the N2 is a negative wave component emerging 150 to 400ms following stimulus presentation. In response inhibition tasks such as the go/no-go and stop-signal tasks, the N2 ERP associated with the inhibition response is accordingly named "no-go N2" and "stop N2", and is differentiated from the "go N2" with a significantly enhanced wave amplitude. This enhanced N2 has been viewed as a "red flag" (Kok et al, 2003) in that it appears to index a top-down mechanism required to inhibit response tendencies and corresponds with behavioural outcomes of inhibitory control (Falkenstein et al 1999; Jodo & Koyama, 1992). Inverse modeling techniques have shown that the primary neural generator of N2 is the anterior cingulate cortex (ACC) (Nguyun, Moyle, & Fox, 2016), a region associated with response inhibition, interference inhibition (Bush et al, 1998), and conflict monitoring (Laird et al, 2005; Van Veen & Carter, 2002). In addition to ACC, the N2 is also generated by the right ventral prefrontal cortex, dorsolateral prefrontal cortex, and pre-supplementary motor area, which are all areas that have also been related to response inhibition (Nguyun, Moyle & Fox, 2016). While the precise functional significance of N2 is debated, it is agreed that it indexes processes related to early stages of inhibition (Luijten et al, 2014). The second ERP component associated with inhibition is the slightly later P3, a positive wave emerging 300 to 500ms following stimulus presentation, with fronto-central neural generators close to the motor and premotor cortices (Kok et al, 2003).

As with the no-go N2, P3 is enhanced in inhibitory trials (Bokura et al, 2001). While the N2 is connected to early stages of inhibition, the P3 appears to index a later stage that relates more closely to the actual inhibition of the motor network in the premotor cortex (Luijten et al, 2014; Kok et al, 2003). Importantly, the inhibitory P3 effect is seen in tasks requiring both overt (withholding a button press) and covert (not counting number of stimuli) inhibition, suggesting that P3 is related to inhibition and not only to movement related potentials (Smith, Johnstone and Barry, 2008). Another perspective is that the later inhibition process that P3 relates to is monitoring or evaluating the outcome of the inhibition (Bruin et al, 2001). The N2 appears to index a process that anticipates inhibition whereas P3 reflects the inhibitory break itself (Luijten et al, 2014).

FMRI research with healthy participants has highlighted several regions associated with response inhibition and interference inhibition. Several regions have been implicated across inhibition tasks, while others appear more task specific (Simmonds, Pekar, & Mostofky, 2008). Research using tasks that require inhibition of a prepotent response (eg. go/no-go task), have shown the involvement of the right ventrolateral prefrontal cortex (VLPFC), the dorsolateral prefrontal cortex (DLPFC) and the pre-supplementary motor cortex (pre-SMA) (Chikazoe, 2010). Within the VLPFC, the inferior frontal gyrus (IFG) and its border with the insula are commonly activated in inhibition tasks, but their role is contentious (Zhu et al, 2014), with some suggesting they play a major role in response inhibition (Garavan et al, 1999; Konishi et al, 2002; Li et al, 2006; Rubia et al, 2003) while others argue they are part of the ventral attention system (Chao et al, 2009). Tasks requiring stopping of an initiated response (eg. Stop-signal task) also show involvement of these regions

(Chikazoe, Konishi, & Asari, 2007), and also the medial frontal gyrus (MFG) and basal ganglia, suggesting a stop-inhibition fronto-basal-ganglia circuit (Simmonds, Pekar, & Mostofky, 2008). Interference inhibition tasks, (eg. Stroop tasks) have shown the activation of ACC, which is suggested to reflect its role in mediating response selection or allocating attentional resources when presented with conflicting information processing demands (Bush et al, 1998). The DLPFC, and MFG have also been shown to be related to interference inhibition. (Leung, Skudlarski, Gatenby, et al, 2000; MacDonald, Cohen, Stenger, et al, 2000; Milham, Banich, Webb, et al, 2001).

Neural Correlates of Response Inhibition in Externalising Disorders

Several systematic reviews of inhibition processes in clinical populations have included studies using ERP, fMRI, or both, including reviews of Attention Deficit Hyperactivity Disorder (ADHD) (Johnstone, Barry, & Clarke, 2013; Barry, Johnstone, & Clarke, 2003) and substance dependence (Luijten et al, 2014). While there have been several ERP/fMRI reviews of conduct problems, these have not focussed on response inhibition (Noordermeer, Luman, & Oosterlaan, 2016) and have mostly used a selective rather than systematic review approach (Mathys, Vanderschuren, & Schutter, 2013; Rubia, 2011; Cappadocia, Desrocher, Pepler, & Schroeder, 2009; Patrick, 2008).

Reviews of ADHD and substance dependence suggest that deficits in response inhibition correlate with ERP activity. In ADHD, reduced N2 and P3 amplitudes are relatively consistently associated with response deficits (Johnstone, Barry, & Clarke, 2013). In a review of a wide range of substance abuse disorders,

reduced N2 was associated with inhibition problems, while the results were more mixed for P3 (Luijten et al, 2014). In developments of the research on the externalising spectrum of disorders, ERP research using oddball tasks have identified that the highly heritable (Krueger et al, 2002) externalising factor is associated with reduced P3 amplitudes in oddball tasks (Patrick, Bernat, Malone, Iacono, Kreuger, & McGue, 2006) and this has been suggested as a potential biomarker for the vulnerability to externalising disorders. While oddball tasks involve both sustained attention and inhibition to a degree, they are not the best method for eliciting explicit response inhibition. Nonetheless, the most influential theory of P3 is that it reflects inhibitory processes necessary for various other executive functions including sustained attention and effective working memory operation (Polich, 2007). Patrick (2008) argues that reduced P3 indicates a dispositional vulnerability towards impulse control problems and may be particularly helpful for understanding impulsive aggressive behaviour. FMRI reviews suggest that ADHD and substance abuse are associated with abnormally reduced BOLD activation in most of the areas highlighted above as involved in response inhibition, particularly the anterior cingulated cortex (ACC), inferior frontal gyrus (IFG), and dorsolateral prefrontal cortex (Luijten et al, 2014). Rubia (2011) reviewed fMRI studies of ADHD and CD and argued that while ADHD is characterised by abnormal activation of the inferior frontal, striatal, parietotemporal, and cerebellar regions associated with the so called "cool executive functions" of inhibition, attention, and timing functions associated with the disorder, conduct disorder was rather associated with abnormal activation of the ventromedial orbitofrontal-limbic areas that relate to "hot" emotion regulation and motivational functions.

The current Review

The current systematic review aims to describe the ERP and fMRI correlates of response inhibition in child and adolescent conduct problems. It aims to determine how the correlates of inhibition in conduct problems compare with non-clinical populations, as well as other externalising problems, particularly ADHD and substance dependence. Evidence of reduced N2 and P3 ERPs, and reduced activation of inhibition related regions such as DLPFC would be consistent with Blair's (2005) model and would challenge Rubia (2011).

Method

Inclusion/exclusion criteria

The studies in the present review met the following criteria:

- *Published in a peer review journal*- this criterion was used to guarantee that the studies were of a high standard. Dissertations were excluded.
- *"Child and adolescent" age range*- this was defined as covering an age range of 8 to 20. Previous developmental ERP and fMRI studies (Jonkman et al, 2006) have found a pattern of more diffuse neural activation related to inhibition in children below age 10 and a more distinct region-specific pattern over 10 which appears to correspond with the development of effective mature inhibition and impulse control. The decision to include a younger age range was pragmatic to enable inclusion of studies which straddled this late-childhood/early adolescence stage of development.
- *Focus on oppositional defiant and conduct disorders*- ADHD and conduct problems are highly comorbid, however because ADHD has been shown to be associated with inhibition deficits and to have ERP and fMRI correlates of this, it presents a confounding variable. Initially, a review of only studies without ADHD comorbidity was considered, however this produced a very small sample size so a pragmatic decision was made to include studies where conduct problems was the primary presenting issue, or in studies with a focus on ADHD inclusion was accepted if separate analysis of participants with and without comorbid conduct problems was conducted.

- *No substance related problems*- studies suggest that substance dependence is associated with inhibition related deficits and would therefore present a confound to the current investigation.
- *Use of standardised measure of conduct problems*- to ensure that the participants met clinical thresholds to be considered to have oppositional defiant disorder or conduct disorder.
- *Inclusion of control group or correlational design comparing high and low scorers on a measure of conduct problems*- in the first instance studies with control groups were preferred, however because of the small number of studies in this area, correlational studies were accepted as a secondary course.
- *Use of an inhibition experimental task*- only studies with explicit inhibition tasks were included to allow for exploration of neural correlates of response inhibition processes. Thus while oddball tasks have been associated with the externalising spectrum and the neural biomarker appears to be related to inhibitory processes, the task itself is not primarily inhibitory. Oddball tasks have been shown to involve micro-saccadic inhibitions which are associated with P300 amplitude (Valsecchi, Dimigen, Kliegl, & Turrato, 2009) however this is primarily seen as relating to sustained attention and furthermore has not yet been examined in young people with externalising problems.
- *Use of Event Related Potential and/or Functional Magnetic Resonance Imaging*- these are viewed as the best methodologies for gaining temporal and visual/topographic information on neural correlates relating to behavioural and psychological processes.

Search Strategy

A systematic search was conducted using keyword searches of titles and abstracts of studies in PsycINFO and MEDLINE databases. Search terms were chosen to reflect the key areas of interest, and were adapted from existing comparable reviews of neural correlates of behavioural inhibition in clinical populations (Noordermeer, Luman, & Oosterlann, 2016; Luijten et al, 2014; Johnstone, Barry, & Clarke, 2013; Cappadocia et al, 2009; Patrick, 2009).

The following terms were combined:

1. Relating to fMRI and ERPs: fMRI or magnetic resonance imaging or ERP or ERPs or EEG or electroenc* or electrophys* or N2 or nogo-n2 or P3 or nogo-p3 or P300 or p3a or p3b or event-related potential or evoked potential.
2. Relating to inhibition tasks: inhib* or nogo or no-go or gng or oddball or stop signal or SST or continuous performance or CPT or flanker or stroop.
3. Relating to children and adolescents: child* or adolesc* or youth* or teen
4. Relating to behaviour problems: conduct problem or conduct disorder or oppositiona* or behavior problems or behaviour problems or aggressi* or offending or offender or delinquen* or externali* or antisocial or anti-social or violen*.

Sixteen papers were found to meet the inclusion criteria, including 13 papers retrieved from PsycINFO and MEDLINE, and 3 additional papers found in the references of these studies. Figure 1 displays the search process.

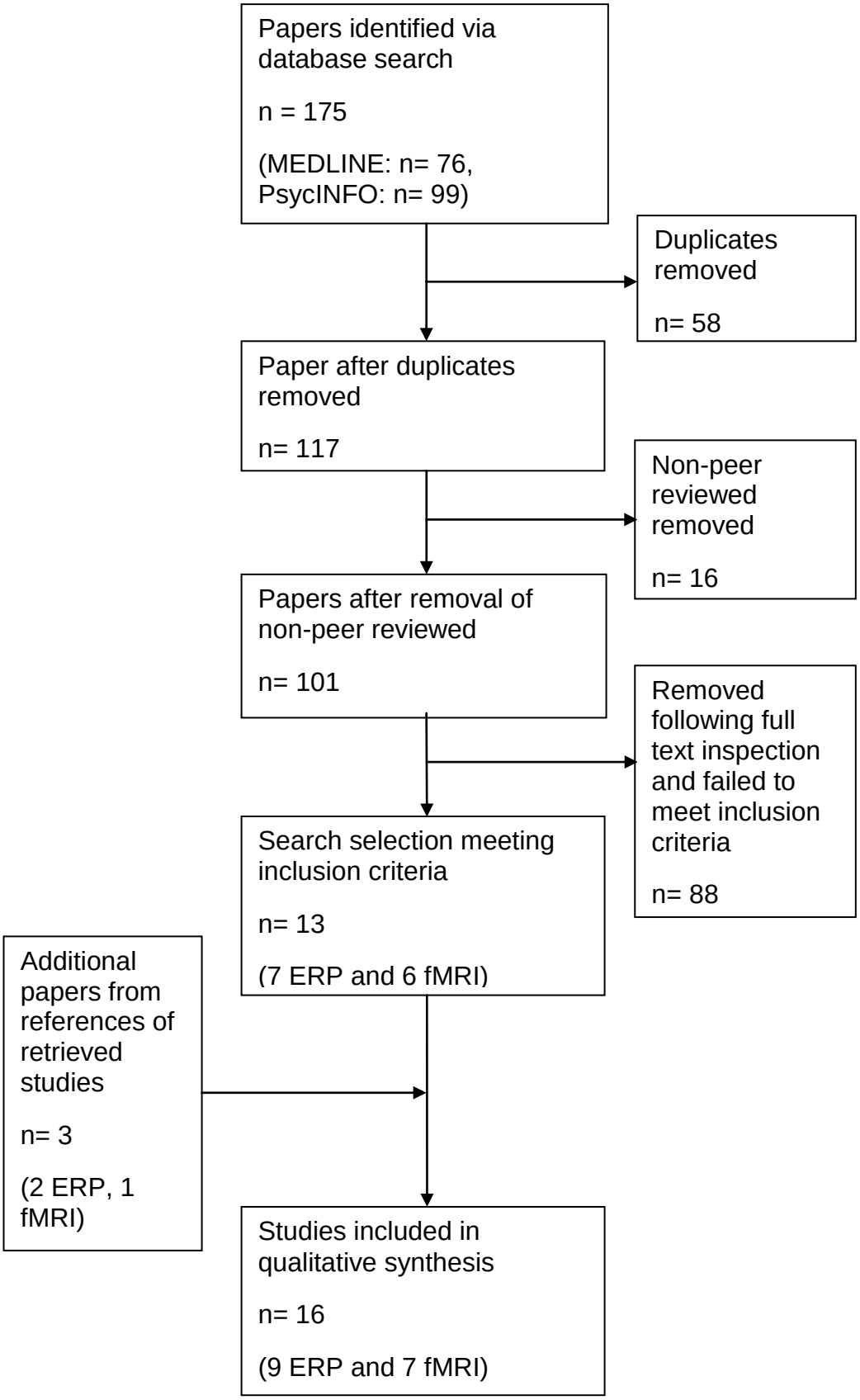

Figure 1: Paper selection and screening process

Results

The results section begins with a descriptive summary of key study characteristics, including sample features, experimental tasks and their relation to inhibition types and concepts of "hot" and "cool" executive functions. This is followed by a diagrammatic summary of the studies (Table 1) and a narrative review of the empirical findings.

Study characteristics

Samples

The included samples met the specifications of the inclusion and exclusion criteria.

Diagnoses

The systematic search identified only four studies (three fMRI) that focus primarily on comparing young people with conduct problems and healthy controls. One of these studies had the additional grouping variable of paternal substance abuse history, two studies specified conduct problems with aggressive features, and one study described a "pure ODD" sample. Five of the studies compared children with ADHD to children with conduct problems and controls. Three of these were ERP studies, and one of these was primarily comparing ADHD to controls but included a separate analysis of comorbid ADHD and ODD. The literature search identified other ADHD studies with participants comorbid for conduct problems, however no other studies provided separate analyses of these participants so were not included in the current study.

Five ERP studies had clinical samples with primary diagnoses of externalising conduct problems, but also comorbid internalising symptoms. In two of these (Stieben et al, 2007; Lamm et al, 2011), anxious and non-anxious aggressive children were compared with each other and with controls, and one correlational study related externalising and internalising symptoms to ERP correlates of inhibition (Moadab et al, 2010). In two of the ERP studies with comorbid participants, (Lewis et al, 2008; Woltering et al, 2011) no separate analyses for externalising and internalising were conducted. In the other studies, presence of anxiety disorders, major depression, and other psychiatric disorders were exclusion criteria, as were histories of substance abuse, serious head injuries, IQ of below 80, uncorrected vision problems, and colour blindness. The two correlation studies included mainly subclinical participants but which had a range of symptomatology and therefore allowed for analysis of relationship between conduct problem severity and neural correlates of inhibition. One was an ERP study and the other fMRI. The limited focus on "pure" conduct problems, and the overlap with research on ADHD and internalising problems, means that conclusions about how conduct problems relate to neural correlates of inhibition must be made cautiously. However, it can be argued that the scarcity of "pure" CD or ODD reflects the reality of how these difficulties present in the general population (Zhu et al, 2014).

Sample sizes

The samples sizes for the studies varied widely. For the group comparison studies, samples ranged from 21 (11 ODD and 10 control) (Zhu et al, 2014) to 210 (95 CD/ODD and 115 control) (Bauer & Hesselbrock, 1999). None of the studies

reported *a priori* sample size or power calculations, nor commented on expected effect sizes. This is a common weakness in neurophysiological research (Larson & Carbine, 2016 for a review of sample size calculation in ERP studies) and creates a challenge for determining if adequate sample sizes were used. Several of the studies reported that measures were taken to increase statistical power, but this was typically post hoc. Two studies (Albrecht et al, 2005; Stieben et al, 2007) identified their small samples, across multiple comparison groups, (n=40 and n=44 respectively) were potential study limitations, and this can be applied to the other studies with similar sample sizes and comparisons (Lamm et al, 2011; Lewis et al, 2008; Overtoom et al, 1998). Significant differences were found for the studies with small samples, suggesting they were adequate to capture effects. The correlational studies differed greatly from each other, with one including 75 participants and the other 1778. The studies reflect the norm of ERP and fMRI samples being 15 to 40 participants (Robbins, Fraley, & Krueger, 2010).

Age and gender

Participant ages ranged from 6 to 20. In the ERP studies, a range from late childhood (8-9 years) to mid adolescence (14-15) was most common, while in fMRI studies more of the studies were in the early to late adolescent range (9-18). Most of the studies had more male participants than females, including six studies with only males. Five studies had roughly even distribution of male and female participants across groups.

Recruitment route

In the majority of studies, clinical participants were recruited from child and adolescent outpatient mental health services, six of which were specialised treatment programs for behavioural difficulties. Other routes for clinical participants included referrals by private mental health practitioners. Non-clinical participants were mostly recruited via adverts in local newspapers and posters in schools and community youth organisations.

Measurement tools for conduct problems

In most of the studies using clinical samples, diagnoses were confirmed by a psychiatrist or clinical psychologist. DSM-IV diagnostic criteria was used for 14 out of 16 studies, and DSM-III-R was used for the remaining 2 studies.

A range of self-report and other (parent,teachers, clinician) measures were used to assess behavioural problems. The most commonly used tool was the Child Behaviour Checklist (CBCL, Achenbach, 1991), a parent completed measure that assesses externalising (aggressive, hyperactive, noncompliant, and undercontrolled behaviours) and internalising (anxious, depressed, overcontrolled) symptoms (used in 7 out of 8 clinical ERP studies but in none of the fMRI studies). Other measures used were the Development and Wellbeing Assessment Interview, the Behaviour Disorders module of the K-SADS, the Adolescent Symptoms Inventory, and several studies counted number of items for conduct disorder.

Neurophysiological Approaches

Nine of the retrieved studies used ERPs as the neurophysiological measure. Five studies measured N2 only, one measured P3 only, and three measured both N2 and P3. All ERP studied identified N2 and P3 by peak amplitude within set time windows. N2 windows ranged from 170 to 400ms and 200 to 500ms following stimulus presentation, while P3 windows ranged from 300 to 700 and 250 to 900ms following stimulus presentation. Seven studies used fMRI and all employed whole-brain BOLD analysis. No studies combined ERP and fMRI.

Tasks

The experimental tasks used in the retrieved studies are described in the following section, organised according to the three types of inhibition identified by Barkley (1997):

1. *Inhibition of the initial prepotent response to an event;*

- The go/no-go task (GNG)
- Cued continuous performance task (CPT-A-X)

2. *Stopping of an ongoing response;*

- The Stop-signal Task
- The GoStop Task

3. *Interference control.*

- The Stroop Task

- The Simon Task

Another widely used task for interference inhibition research is the flanker task (Johnstone, Barry, & Clarke, 2013). The term was specifically included in the search strategy and this revealed that the task has not been used in ERP/fMRI studies of inhibition in conduct disorders.

1. Inhibition of the initial prepotent response to an event- tasks

The Go/No-go Task (GNG)

The GNG is one of the most commonly used behavioural tasks in response inhibition research. In the standard version of the task, "go stimuli", are presented frequently (eg. 66% of presentations) to build up an automatic or "prepotent" response tendency. Participants must respond as quickly as possible to "go" stimuli, for example by pressing a particular keypad, but withhold the response for infrequent "no-go" stimuli. The standard version is viewed as a "cool executive function task" since it provides a relatively pure measure of prepotent response inhibition. Interestingly, all of the studies retrieved in the literature search were ERP studies, and all of them used a variation on the GNG designed by Lewis, Lamm, Segalowitz, Stieben, and Zelazo (2006). This version is best viewed as a "hot executive function task" because in addition to the standard GNG comparison, the task introduces a frustrating "emotional" condition by manipulating the response success rates and altering the reward and punishment points system. Children were told they needed to amass points to win a "good prize" and in the first and third blocks of the experiment, high performance was ensured by keeping a 50% fixed error rate

(achieved by altering stimulus duration in response to inhibition performance) and rewarding correct response with +50 "points" and punishing incorrect response with -10 points. In the second block however, error rate was fixed so that children lost more rounds and the reward and punishment rates were changed to +15 for correct responses and -55 points for incorrect responses. The paradigm is useful for examining how response inhibition and its neural correlates are affected by frustrating task conditions. The five studies using this paradigm (Lamm et al, 2011; Woltering et al, 2011; Moadab et al, 2010; Lewis et al, 2008; Stieben et al, 2007) used samples with clinical levels of both externalising and internalising symptoms, and this raises the possibility of examining how these difficulties relate to response inhibition. Unfortunately, as noted above, only three of the five studies compared different levels of internalising and externalising symptomatology (Lamm et al, 2011; Moadab et al, 2010; Stieben et al, 2007). The four clinical vs control group studies (Lamm et al, 2011; Woltering et al, 2011; Lewis et al, 2008; Stieben et al, 2007) were conducted by the same research team, but using different samples. Woltering et al (2011) and Lewis et al (2008) tested participants before and after a cognitive behavioural and parent skills intervention to test whether treatment effects were seen in the neural correlates of inhibition, which they views in terms of self-regulation. Moadab et al (2010) applied used the emotional GNG with a subclinical sample and a correlational approach to analysis.

The Cued Continuous Performance Task (CPT-A-X)

Two studies used a cued continuous performance test (or CPT-A-X) (Banaschewsi et al, 2004; Overtoom et al, 1998), both of which were ERP studies. The CPT-A-X is viewed as advantageous as it measures both attention (as in the typical CPT task) and response inhibition (Johnstone, Barry, & Clarke, 2013). A sequence of letters is presented on a computer screen and the participants must press a button if the letter "A" is followed by the letter "X" (go condition) but must withhold a response if the letter A is followed by any other letter (no-go condition). In both retrieved studies, go and no-go targets were presented at 10% rates. Whereas in the GNG task the "initiated" prepotent response comes from its higher occurrence probability, in the CPT-A-X the response is initiated by the cue stimuli.

2. Stopping of an ongoing response- tasks

The Stop-signal Task

The SST is another much used task in response inhibition research. It is based on a well-established theory of response inhibition called the "race model" (Logan, 1994) which suggests that response inhibition depends on a race between processes underlying response execution and the inhibitory process (Oosterlaan et al, 1998). In the SST, participants must quickly and accurately complete a primary visual task, and must inhibit that behaviour as quickly as possible when a stop-stimulus (visual or auditory) is presented. The primary behavioural measures are the stop-signal reaction time (SSRT), and successful and failed stops. Castellanos-Ryan (2014) and Rubia et al (2008) presented simple left and right arrow images as go stimuli and participants

had to press corresponding directional keys, and inhibited the response when an upwards facing arrow was presented. Albrecht et al (2005) used an equivalent visual task in which images of an aeroplane moved left or right across a computer display screen and children had to press a corresponding directional key, and stopped the response whenever a "little man" with hands raised appeared on the screen.

The GoStop Task

Zhu et al (2014) used a variety of stop task called the GoStop task (Dougherty et al, 2003) in which a series of go trials (a five digit number identical to the previous number that remained black) are presented to establish a pre-potent response tendency, followed by stop trials (identical number to previous one but changed from black to red) that require response inhibition. In addition to go and stop trials, Novel trials were different numbers which remained black, and participants were told not to respond to these. The proportion of go to stop trials was 50%.

3. Interference control- tasks

Five studies were retrieved that used interference tasks. One of these was an ERP study using a traditional "cool EF" version of the Stroop task (Bauer & Hesselbrock, 1999), comparing children with and without conduct problems. The four fMRI interference tasks included a "cool EF" Stroop study (Mathews et al, 2005) comparing children with conduct problems with aggressive features to controls, and two "hot EF" Emotional Stroop tasks (Kalnin et al, 2011; Hwang et al, 2016). Kalnin et al (2011) compared children with aggressive conduct problems to controls and Hwang et al (2016) compared ODD/CD to controls. The fourth fMRI interference

inhibition study used a cool EF Simon Task (Rubia et al, 2009) in which children with pure CD were compared with boys with pure ADHD, and healthy controls.

The Stroop Tasks

In the "cool EF" Stroop studies, Bauer & Hesselbrock (1999) used the standard colour-word interference task in which participants had to indicate the colour of word stimuli which were either compatible (RED appears in colour red), incompatible (RED appears in blue), or unrelated (TOWN in blue or red). Incompatible trials are regarded as inhibition trials. Mathews et al (2005) used the Counting Stroop task (Bush et al, 1998), during which participants report the number of words (1 to 4) that appear on screen irrespective of word meaning. Interference trials present number words that are incongruent with the number of words presented (Three copies of TWO). Congruent trials have agreement between the word and the number of words presented (two TWOs), and neutral trials contain nouns from a single semantic category, such as animals.

The two studies with "hot EF" tasks were variations on Emotional Stroop tasks. Kalnin et al (2011) used a colour-word Stroop, in which participants had to indicate the colour of presented words. Rather than using names of colours, the word stimuli were violent (HIT, KILL) and non-violent (RUN, WALK) verbs presented in three colours. Kalnin et al (2011) compared ODD/CD with controls, and also analysed the effect of high and low levels of exposure to violent media on interference inhibition processes. Hwang et al (2016) compared young people with ODD/CD who were also rated high or low in callous-unemotional (HCU and LCU) traits with controls on a numerical stroop task. Participants had to indicate how many

numbers were displayed. In congruent trials the number of digits matched the digits displayed (three 3s), while in incongruent trials they did not (two 3s). The emotional aspect came in the form of positive, negative, or neutral images that were shown between response trials. In emotional stroop tasks it is assumed that the same type of semantic interference inhibition is required as in the standard stroop (Nigg, 2000), however psychopathology studies also suggest that participants with anxiety disorders have greater interference for anxiety words, possibly implicating a role of limbic based systems moderating interference control for affective stimuli (Nigg, 2000).

The Simon Task

Rubia et al (2009) used a Simon Task in which participants must use direction keys to indicate whether an arrow appears on the left or right side of the screen. In congruent trials the arrow points in the same direction as it is located spatially on the screen. Low probability (12%) interference inhibition trials are those where arrow direction and location are incongruent.

Table 1: Studies included in the review: characteristics and results

Study	Measures	Inhibition Type	Task	Hot or Cold EF	Groups	Participants	Outcome
Stieben et al (2007)	ERP (N2)	Inhibit prepotent response	GNG	Hot	ODD/CD, ODD/CD with anxiety, Control	44 males 0 f (aged 8 to 12)	No N2 difference between ODD/CD and controls. Enhanced N2 for ODD/CD with anxiety during and after emotion induction block relative to comparison groups.
Lewis et al (2008)	ERP (N2)	Inhibit prepotent response	GNG	Hot	ODD/CD (with some internalising symptoms), Control	42 males 0 females (aged 8 to 12)	No N2 difference between clinical and control. Improvers showed reduced activation in ventrolateral prefrontal cortex compared to non-improvers.
Lamm et al (2011)	ERP (N2)	Inhibit prepotent response	GNG	Hot	ODD/CD, ODD/CD with anxiety, Control	23 males 18 females (aged 8 to 12)	No difference between ODD/CD and controls. Enhanced N2 in ODD/CD with anxiety relative to comparison groups.
Moadab et al (2010)	ERP (N2)	Inhibit prepotent response	GNG	Hot	Correlational community sample range of low-high conduct symptoms	37 males 38 females (aged 9 to 13)	Greater conduct disorder symptoms associated with reduced N2.
Woltering et al (2011)	ERP (N2, P3)	Inhibit prepotent response	GNG	Hot	ODD/CD (with some internalising symptoms), Control	68 males 27 females (aged 8 to 12)	Enhanced N2 and reduced P3 in clinical group compared to controls at pre-treatment. After treatment, improvement associated with smaller N2 compared to non-improvers but no change in P3.

Banaschewski et al (2004)	ERP (N2, P3)	Inhibit prepotent response	CPT-A-X	Cool	ODD/CD, HD, HCD, Control	59 males 5 females (aged 8 to 14)	No N2 difference between groups. Reduced P3 in hyperkinetic group only.
Overtoom et al (1998)	ERP (N2, P3)	Inhibit prepotent response	CPT-A-X	Cool	ADHD (6 ODD), Control	32 males 0 females (aged 6 to 14)	No N2 difference between ADHD and control but subset ADHD/ODD had reduced N2 compared to control. P3 larger for ADHD group but no difference for ADHD/ODD.
Albrecht et al (2005)	ERP (N2)	Stop initiated response	SST	Cool	ADHD, ODD/CD, ADHD/ODD/CD, Control	40 males 0 females (aged 8 to 14)	Reduced N2 for ODD/CD and ADHD groups, effect at trend level for ADHD/ODD/CD.
Bauer & Hesselbrock (1999)	ERP (P3)	Interference inhibition	Stroop	Cool	ODD/CD and Controls	95 males 115 females (aged 15 to 20)	Greater number of conduct problem behaviours associated with reduced P3 (specific to "Rule Violation" conduct problems).
Rubia et al (2008)	fMRI (BOLD)	Stop initiated response	SST	Cool	ODD/CD, ADHD, Control	53 males 0 females (aged 9 to 17)	During failed stops, ODD/CD had reduced activation in temporal-parietal regions in compared to other groups. ODD/CD and ADHD both showed reduced posterior cingulate activation. In successful stops, ODD/CD did not show reduced activation of dorsolateral prefrontal cortex while ADHD did.
Castellanos-	fMRI	Stop	SST	Cool	Correlational	866 males	Structural equation model CD/ADHD factor

Ryan et al (2014)	(BOLD)	initiated response			community sample range of low-high conduct symptoms	912 females (aged 14)	correlated with reduced activation of frontal cortex (anterior cingulate cortex, rostral caudate, inferior frontal gyrus).
Zhu et al (2014)	fMRI (BOLD)	Stop initiated response	StopGo	Cool	ODD, Control	21 males 0 females (aged 10 to 12)	Reduced activation of inferior frontal gyrus in ODD compared with control.
Mathews et al (2005)	fMRI (BOLD)	Interference inhibition	Stroop	Cool	ODD/CD, Control	28 males 10 females (aged 13 to 17)	Reduced activation of anterior cingulate cortex, medial frontal cortex, and inferior frontal gyrus in ODD/CD compared to control.
Kalnin et al (2011)	fMRI (BOLD)	Interference inhibition	Emotional Stroop	Hot	ODD/CD, Control	26 males 18 females (13 to 17)	No whole group differences, but ODD/CD who also reported high exposure to violent media showed reduced activation in amygdala, anterior cingulate cortex, and premotor cortex.
Hwang et al (2016)	fMRI (BOLD)	Interference inhibition	Emotional Stroop	Hot	ODD/CD, Control	37 males 26 females (aged 10 to 18)	ODD/CD showed reduced anterior insular cortex activation relative to controls.
Rubia et al (2009)	fMRI (BOLD)	Interference inhibition	Simon Task	Cool	CD, ADHD, Control	53 males 0 females (9 to 17)	ADHD and CD both showed reduced activation in temporal and parietal regions, and precuneus. CD also showed reduced activation in superior temporal lobe.

Study Findings

1. Inhibition of the initial prepotent response to an event findings

GNG Results

All five studies measured N2 amplitudes for successful inhibitions (no-go) trials, and Woltering et al (2011) also measured no-go P3. The ERP results of the GNG studies were somewhat mixed. Stieben (2007) and Lamm (2011) compared anxious-aggressive children with non-anxious aggressive children and controls. Neither study found significant differences between the non-anxious aggressive participants and controls, although Stieben et al (2007) found trend level reduced N2 for aggressive children during and after the frustrating block. In contrast, both studies found enhanced N2 for the anxious-aggressive children, with this effect present in all three trial blocks for Lamm et al (2011), but only during and after the frustrating points-loss trial for Stieben et al (2007). The authors suggested that this indicated that anxious-aggressive children recruit more cortical resources to self-regulate and complete inhibition tasks, and this was partially supported by source-space analysis that showed enhanced activation of ventral prefrontal areas (associated with negative emotion regulation) (Lamm et al, 2011). However they did not find differences in the dorsal anterior cingulated cortex, which they noted is typically linked to individual differences in self-regulation (Lamm et al, 2011) and is a known generator of N2.

Moadab et al (2010), using a correlational design, reported the expected reduced N2 to be significantly associated with conduct problems. High levels of externalising problems were associated with reduced N2 when compared with low

levels of externalising. Interestingly, the relationship between conduct problems and reduced N2 was seen during the first and third trial blocks, but not during the frustrating second block.

Lewis et al (2008) and Woltering et al (2011) used clinical participants who had primary externalising problems, but also comorbid internalising symptoms. A limitation of these studies, compared to Stieben et al (2007) and Lamm et al (2011) is the absence of non-anxious externalising children, which means the effect of these symptoms on ERPs cannot be fully disentangled. The studies are notable because they compared the ERPs for the GNG task before and after a cognitive behavioural intervention aiming at improving self-regulation strategies, and hence more effective inhibition and ability to manage difficult emotions. Lewis et al (2008) found no differences in N2 between clinical and control groups and no effect of trial block. No N2 differences were found between improvers and non-improvers, however, like Lamm et al (2011) a source space analysis was to estimate activation levels of the neural generators of the N2. Consistent with Lamm et al (2011) improver status was associated with decreased ventral prefrontal activation, but no difference was found for dorsal ACC (Lewis et al, 2008). Woltering et al (2011) found differences in the ERP profiles of their clinical and control groups. Importantly, they did not include data from the frustrating block condition in their analysis due to low amount of usable trials retrieved. Prior to treatment, the clinical group had larger N2 amplitudes and smaller P3 amplitudes. Following treatment, children who improved on measures of externalising and internalising showed reduced N2, but no change to P3. A source-space analysis showed that improvers had reduced activity in the dorsal ACC while non-improvers showed no differences. No changes in activation

estimates were found for ventral prefrontal areas. The use of source-space analyses in these studies to measure activation of areas in the windows of the ERPs seems a questionable methodological approach, given that estimation of spatial configuration and activation of neural generators from scalp electrical activity is unreliable (Urbach & Kutus, 2002) and fMRI would be a preferred method to test activation of brain regions.

CPT-A-X Results

The CPT-A-X studies provide mixed results. Overtoom et al (1998) primarily compared an ADHD sample with a control sample and at that level of analysis found no difference in no-go N2 amplitude. However, when a small subsample of the clinical group that was comorbid for ADHD and ODD (n=6) was analysed, this group showed significantly reduced N2 compared to the control group. P3 amplitude was larger for the ADHD group compared with control, but no difference was found for the comorbid group. While interesting, these results are taken cautiously given the extremely small sample and the problem of co-morbidity. Banaschewski et al (2004), compared children with hyperkinetic ADHD, hyperkinetic conduct disorder, ODD/CD, and controls. Unlike Overtoom et al (1998) no group differences were found in N2 amplitude, and only hyperkinetic children showed reduced P3.

2. Stopping of an ongoing response findings

Stop-signal Results

Three studies used the SST, one of which used ERP (Albrecht et al, 2005) and two used fMRI (Castellanos-Ryan, 2014; Rubia et al, 2008). Rubia et al (2008)

compared children with ADHD to children with ODD/CD and controls, and Albrecht et al (2005) similarly compared ADHD, ODD/CD, and also co-morbid ADHD/CD to controls. Castellanos-Ryan (2014) used a large mostly subclinical sample to conduct a correlational analysis.

SST ERP Results

In their comparison of children with ADHD, ODD/CD, ADHD+ODD/CD, and controls, Albrecht et al (2005) reported that only the ADHD and OCC/CD groups had deficits in behavioural measures of inhibition, namely more stop-failures and longer SSRT. Interestingly, the comorbid group had faster SSRT than the other clinical groups. With regard to ERP results, the behavioural evidence of inhibition deficits was paralleled by both ADHD and ODD/CD groups showing significantly reduced stop-N2 amplitudes compared with controls. The comorbid group showed a trend level reduced stop-N2. The results were interpreted by Albrecht et al (2005) as suggesting that both ADHD and conduct problems involve response inhibition deficits, but that the combined ADHD/CD did not show evidence of an additive effect of these difficulties, raising the possibility that it should be viewed as a separate disorder distinct from ADHD and ODD/CD. The authors suggest that the results argue against Quay's (1997) theory that the behavioural inhibition system (BIS) is underactive in ADHD but unimpaired in ODD/CD.

SST fMRI Results

Rubia et al (2008) reported that participants with "pure" ADHD and pure conduct disorder showed different types of brain abnormality during the stop trials,

although they did not find differences in the behavioural measures. During successful compared with failed inhibitions, only children with ADHD problems showed abnormally reduced activation of the left dorsolateral prefrontal cortex. This is an area associated with "stopping" inhibition (Verbruggan & Logan, 2008), and the apparent normal level of activation in this area for children with conduct problems was viewed by Rubia et al (2008) as suggesting that children with conduct problems do not have deficits in stopping. However, children with conduct problems did show abnormally reduced posterior cingulate activation during failed stop trials compared with go trials, as did children with ADHD. Unlike children with ADHD, those with conduct disorder also had reduced parietal-temporal activation in the left hemisphere up to superior temporal cortex, precentral gyrus and insula. The parietal-temporal and cingulate areas are viewed as related to error detection following failed responses and subsequent reallocation of attention to minimise further mistakes. Rubia et al (2008) hypothesise that since both areas are abnormally reduced in children with conduct problems, this may indicate a more severe performance monitoring deficit in conduct disorder than in ADHD. This view would support the idea that reduced inhibitory N2 indicates deficits in conflict monitoring rather than inhibitory processes per se.

Castellanos-Ryan et al (2014) used structural equation modelling to examine how externalising symptoms in a mainly sub-clinical sample related to neural correlates of inhibition during an SST. They reported that a latent factor previously identified by the researchers (Castellanos-Ryan & Conrod, 2011) as representing variance unique to conduct disorder, also included ADHD symptoms. The combined ADHD/CD factor correlated significantly with self-reported impulsivity, poor

response inhibition, and reduced BOLD activation in the frontal cortex bilaterally (including the anterior cingulate cortex, rostral caudate, and inferior frontal gyrus) during failed stop trials. The anterior cingulate, as noted above is associated with performance monitoring (Verbruggan & Logan, 2008), while the inferior frontal gyrus has been suggested to be part of a frontal-basal-ganglia circuit, along with the dorsolateral prefrontal gyrus and basal ganglia, involved in suppression of motor output (Verbruggan & Logan, 2008).

GoStop Results

Boys with ODD showed poorer accuracy on inhibition trials than controls and also took longer to inhibit the already initiated responses (Zhu et al, 2014). With regard to fMRI results, both clinical and control groups showed task related activation in the inferior frontal gyrus. The ODD groups had reduced BOLD activation of this area compared with the control sample suggesting it is a correlate of an inhibition deficit.

3. Interference control findings

Stroop Results

Stroop ERP Results

Bauer and Hesselbrock's (1999) cool EF stroop study compared children with and without conduct problems, and also the effect of paternal substance abuse history. They reported that higher numbers of conduct problems were associated with reduced P3 amplitude during the Stroop task. Interestingly, "rule violation" types of conduct problems were associated with reduced P3 amplitude, but aggression,

deceitfulness, and theft types of behaviour problems were not. The study found reduced P300 was associated with conduct problems, equally, on unrelated, compatible, and incompatible trials, raising the possibility that the difference in P300 was not specifically related to interference inhibition , but perhaps a more general problem with attention or resource allocation. The study did not find any significant effect of paternal substance abuse history on P3 amplitude. The authors speculate that this suggests that conduct problems rather than family substance abuse history may better explain reduced P3.

Stroop task fMRI results

Mathews et al (2005), in their cool EF counting Stroop study, reported that participants with ODD/CD with aggressive features showed significant deficits in behavioural measures of interference inhibition (longer reaction times and more errors) and showed reduced frontal lobe activation during interference inhibition compared with control participants. Specifically, while control participants showed significant activity in ACC, left MFG, and left IFG, the clinical participants did not show activity in these regions, suggesting inhibition deficits, although the ACC and IFG have also been implicated in attentional control and emotional regulation.

In the hot EF Stroop tasks, Kalnin et al (2011) found that ODD/CD participants did not differ from controls on reaction time or accuracy for interference trials and the groups did not differ in fMRI activation. However, they reported that participants who self-reported high violent media exposure had slower reaction times to both violent and non-violent words, and high exposure to media violence was associated with increased activity in bilateral frontal gyri and the left cuneus

compared with low exposure, a pattern that has been linked to efforts to maintain attention during distracting stimuli presentation (Kalnin et al, 2011). High exposure was also associated with reduced activity in the right fusiform, an area associated with word recognition. Taken together this suggests that high violent media exposure causes interference in stimuli processing, and hence reduced interference inhibition. Of particular interest to the current review, was a significant interaction between diagnosis and media exposure, whereby in the ODD/CD group, high violent media exposure was associated with decreased BOLD activation in right amygdala, rostral anterior cingulate cortex (rACC) and premotor cortex, while low exposure was associated with increased activation in these areas. In the control group the opposite pattern of media exposure-amygdala activation was found. Decreased activation of amygdala along with enhanced right rACC is associated with high emotional conflict resolution in the Stroop task. The authors suggest that young people with conduct problems and high exposure to violence may struggle to ignore violent words due to priming effects of aggressive tendencies, and therefore experience greater colour-word interference. Control subjects may be affected with low exposure may have experience greater interference due to the relative novelty of the stimuli. This study suggests that emotional contexts impact on interference inhibition and fMRI can highlight the interacting hot and cool executive function systems.

Hwang et al (2016) used a counting stroop task with positive, negative, and neutral pictures between trials. When ODD/CD were compared to control participants, there were no whole group differences on behavioural measures, however when levels of callous-unemotional traits were analysed, ODD/CD with low callous-unemotional (LCU) traits had lower accuracy on incongruent trials than those

with high callous-unemotional traits (HCU) and controls. The most relevant fMRI comparison for the current review is the comparison of activations during inhibition between clinical and control groups, and this showed that ODD/CD had reduced bilateral anterior insular cortex (AIC) activity relative to controls. The AIC is typically co-activated with the ACC and is implicated in inhibition, but also emotional awareness (Gu, Hof, Friston, & Fan, 2014). This supported the authors prediction that conduct problems would be associated with reduced activation of interference inhibition related regions (Hwang et al, 2016). However, the authors did not find any group by task by emotional stimuli interactions to support emotional context having an impact of interference inhibition in any group comparisons (Hwang et al, 2016). The researchers did report evidence of decreased connectivity between amygdala and bilateral insula and inferior frontal cortex, in participants with ODD/CD and LCU, suggesting deficits in emotion regulation. The authors suggest that overall the results indicate that ODD/CD youth show an inhibition deficit that is separate from callous-unemotional traits and that is likely more related to impulsiveness and would exacerbate antisocial and risky behaviour (Hwang et al, 2016).

Simon Task fMRI Results

On the behavioural measures, clinical groups were unimpaired on the specific conflict (interference) measures, although CD participants made more errors overall and ADHD participants were more variable on congruent trials relative to controls, which the authors suggest may indicate that the clinical groups both showed sub-optimal performance.

During interference inhibition trials, both groups showed reduced activation in temporal and parietal areas and the precuneus. These areas are typically reduced in ADHD compared to controls during interference inhibition tasks, but the authors noted that their study was the first to show this pattern was also found in conduct disorder. These areas are related to inhibition processes, and the precuneus in associated with the conflict error effect in the Simon task in controls, which suggests its role in attentional/inhibition processes (Rubia et al, 2009). The temporal lobes have been associated with aggression, so the underactivation of these areas is particularly interesting with respect to conduct disorder's aggressive features. Conduct disorder was also found to show reduced activation in the superior temporal lobe, compared to ADHD and controls. This region is implicated in attention problems (Rubia et al, 2009).

Discussion

A systematic review was conducted to explore the literature on neural correlates of inhibition in young people with conduct problems. The search focussed on studies that employed the event related potential (ERP) electrophysiological approach and functional magnetic resonance imaging (fMRI) methodology. The discussion session will first cover the study characteristics, then focus on the study findings, then consider possible limitations as well as potential future directions.

Study characteristics

The systematic search revealed that the current body of literature in this area is limited. Only sixteen studies in total were retrieved from the two major research databases, with just nine ERP studies and seven fMRI studies. None of the studies

employed the combined ERP and fMRI approach advocated by De Haan & Thomas (2002), and while it is beneficial to pool findings from different ERP and fMRI research, as modelled by Luijten et al (2014), it would be preferable to compare the two types of data retrieved from the same samples and undertaking the same tasks. This raises a further clear feature of the study sample; range of tasks employed in the studies. The tasks were disproportionately spread across the ERP and fMRI methodologies, with the ERP sample dominated by the emotional GNG task designed by Lewis et al (2006), while the fMRI had a higher proportion of Stroop-type tasks. This imbalance is important since the different tasks tested distinct types of inhibition. The ERP sample only had one study tapping interference inhibition, while this type of inhibition made up more than half of the fMRI studies. While there is evidence that the ERP and fMRI indices are common across inhibition types, a more balanced distribution of studies would allow for more meaningful comparison of findings across task, inhibition type, and neurophysiological measurement approach.

Another feature of the study samples was the mix of hot and cold EF inhibition tasks. Although all of the studies included in the review involved a response inhibition task, there was variation in whether or not they included emotionally salient stimuli, context, or manipulation. Unfortunately, these task variations were not evenly distributed across ERP and fMRI studies so it was not possible to compare how these different measures of inhibition neural correlates varied according to hot or cold designs. Several of the GNG studies attempted to provide two types of activation information through their use of source-space analysis to explore activation of generators of ERPs (even when no differences were

found for ERPs), however such methods are not reliable and fMRI would provide a much superior approach for examining spatial/locational activation differences.

The small number of studies, particular when divided between ERP and fMRI approaches, severely limits the validity of comparing results within and between hot and cold inhibition tasks. Previous reviews, such as Noordermeer et al (2016) and Rubia (2011) compared hot and cold executive functions in conduct disorder and ADHD but covered a much broader range of processes (such as attention, working memory, reward and punishment processing, etc). Again, in the ERP studies the GNG designs involved "Hot" EF elements through the frustrating points loss blocks. On the one hand these studies provided an interesting opportunity to look at how emotionally challenging task manipulations may impact inhibition/ self-regulation processes. An advantage of this sort of design is that it presents a situation which is arguably more ecologically valid for studying inhibition in children with conduct problems, since problematic behaviour will often occur in moments when young people feel upset or provoked. On the other hand, the GNG studies did not provide an ecologically valid context of explanation for the points loss block and future research could build on this by proving more realistic contexts, for example by using social-competitive tasks such as researchers using the Taylor Aggression Paradigm (Taylor, 1967) have used, whereby participants believe they are competing against another young person, and their responses to "winning" (and being rewarded) and "losing" (and being punished) can be studied (Wiswede et al, 2011). These studies have not focussed on inhibition related ERPs and this could be a direction for future research.

A number of the studies had participants who presented with the commonly comorbid externalising (conduct problems) and internalising (anxiety) symptoms, or ADHD symptoms. Unfortunately, for the purpose of the current review, only two of these studies compared groups with and without the comorbid anxiety symptoms, while two named the groups as characterised by a primary externalising diagnosis but also with some level of anxiety symptoms. This means conclusions about how the results of these studies generalise to conduct disorder may be limited. On the other hand, these are very common comorbidities so it could be argued that the studies used realistic samples.

With respect to the participant characteristics, the studies used predominantly male young people, which tended to reflect the difficulty of recruiting female clinical participants. Conduct problems are more common in males, however the makeup of the samples meant that analysis of gender effects were largely absent from the studies. Another notable characteristic of the samples was that most of the studies used participants in the late childhood and early adolescence age range. This was particularly true of the ERP studies. Interestingly, age effects were largely unanalysed in the studies. Although developmental ERP studies are scarce (Jonkman, 2006), previous research suggests that inhibitory P3 is not detected prior to ten years of age (Jonkman et al, 2003), while no-go N2 is typically larger in young children than adults (Ciesieski et al, 2004). Further research that compares ERP and fMRI activation across different age ranges is required.

Discussion of Study Findings

The current review explored whether young people with conduct problems show abnormal neural correlates of inhibition processes. This is a perspective suggested by several theories, perhaps most influentially in the cognitive neuroscience presented by Blair (2005) which posits a deficit inhibition network and a deficient emotional regulation network in conduct disorder (Noordermeer et al, 2016). Abnormal neural correlates on inhibition would also be consistent with the theory that the broad range of externalising disorders are characterised by behavioural disinhibition and impulsivity, and that this may be reflected in common biomarkers (Krueger et al, 2002; Gilmore, Malone, & Iacano, 2010). Recent systematic reviews of ADHD (Johnstone, Barry, & Clarke, 2013) and substance dependence (Luijten et al, 2014), which are disorders on the externalising spectrum (Kruger et al, 2002), showed that these problems were associated with deficits in inhibition, and associated with reduced amplitude of N2 and P3 ERPs, and reduced activation of inhibition related areas, particularly the anterior cingulated cortex, inferior frontal gyrus, and dorsolateral prefrontal cortex (Luijten et al, 2014). The current review aimed to determine whether a similar pattern of ERP and fMRI results characterised young people with conduct problems.

The results of the ERP and fMRI studies are mixed. The ERP studies alone present an inconsistent picture. Of the eight studies measuring N2, three found the expected association of conduct problems with reduced N2 amplitude (Moadab et al, 2012; Albrecht et al, 2015; Overtoom et al, 1998). These three studies used different tasks (GNG, SST, and CPT-A-X), covering two types of inhibition (inhibition of

prepotent response and stopping an initiated response). Of these studies, the one with the strongest methodology was Albrecht et al (2015), which compared ADHD, ODD/CD and comorbid groups with controls and showed clear impairments and related reduced N2 in both ODD/CD and ADHD. Conclusions from Overtoom et al (1998) must be more limited since the finding of ODD related reduction in N2 came from analysis of a small subgroup that was comorbid for ADHD and ODD, and although the authors suggest the reduced N2 was led by the ODD symptoms, this was not found for the larger comorbid sample in the Albrecht et al (2005) study. The Moadab et al (2012) study provides an interesting comparison since they used a correlational design and showed a significant relationship between conduct symptoms and reduced N2, and they did so using the emotional GNG task that provided contrasting results for the group comparison studies. However Moadab et al's (2012) correlational design has the important limitation of not comparing clinical participants with healthy controls so their sample of mainly subclinical young people probably does not accurately represent clinical features. Unfortunately only two of the GNG group comparison studies (Stieben et al, 2007, Lamm et al, 2011) compared "pure" conduct problems with combined conduct and anxiety problems. Neither of these found differences in N2 amplitude between those with pure conduct disorder and controls, while they did show enhanced N2 in those with combined internalising and externalising symptoms. The authors suggested that those with anxiety problems showed greater N2 amplitudes due to inefficient self-regulation, a view which contradicts the usual interpretation of enhanced N2 amplitudes during inhibition as associated with successful inhibition (and therefore efficient regulation). The other two group comparison GNG studies also did not find differences between

their clinical and control groups on N2 amplitude, however some caution must be taken with these groups as although they were primarily defined as having externalising problems, they also had some anxiety symptoms. The fact that they did not show enhanced N2 like the comorbid groups used by the Stieben et al (2007) and Lamm et al (2011) may perhaps be seen as confirming that they were primarily externalising groups. Another perspective is that the groups did not show the expected reduced N2 because of something about the task used, for example, although the first block was effectively a cool inhibition task (it preceded the frustrating block) it is possible that the promise of a performance dependent prize was itself anxiety provoking, or otherwise impacted on the direction of the ERP component. For example, some authors have suggested that N2 and P3 may be enhanced to factors such as participant motivation and engagement (Polich, 2007; Boksem, Mejman, & Lorist, 2005, Polich & Kok, 1995), and reduced due to factors such as fatigue (Boksem, Mejman, & Lorist, 2005).

The studies that measured P3 also did not provide strong support for the expected reduced amplitude. Bauer & Hesselbrock (1999) showed reduced P3 related to conduct problems, and interestingly, their analysis specified that these were only "rule violation" behaviour problems. Woltering et al (2011) also showed reduced P3 in their externalising group. This finding is intriguing since they also reported enhanced N2 for the externalising group. While N2 and P3 are thought of as reflecting different aspects of inhibition, they do not typically respond in opposite directions.

Two of the GNG ERP studies (Woltering et al, 2011; Lewis et al, 2008) included pre and post treatment comparisons. While treatment effects was not the focus of the current review, the suggestion that neural correlates are responsive to treatment is an interesting idea and might suggest that correlates of inhibition may be used to track symptom change or could even be used to identify mechanisms of change in treatments. This is another area for further research.

The fMRI results, though mixed, were broadly in agreement with the expected pattern on activation suggested by the previous externalising condition reviews in regards to areas related to inhibition. While the one SST study (Rubia et al,2008) did not find evidence of abnormal activation of response inhibition related brain regions for conduct disorder, three interference inhibition studies did (Mathews et al, 2005; Rubia et al, 2009; Zhu et al, 2014), particularly highlighting reduced BOLD activation of the anterior cingulated cortex and inferior frontal gyrus. It is important to note that although these areas have been related to response inhibition, they have also been implicated to have roles in attentional control, performance monitoring, and emotional processing. This pattern of reduced activation in inhibition related areas in the cool EF tasks, and reduced emotional processing areas in the hot EF tasks (along with reduced ACC/AIC) broadly fits the predictions of Blair's (2005) model which argues that children with conduct problems have deficits in these two neural systems.

Caution must be taken when interpreting these results since the sample of fMRI studies was very small, revealing the limited research so far conducted on response inhibition in children and adolescents with conduct problems. The lack of

any GNG studies was particularly notable given that this is one of the most widely used inhibition tasks, and also compared to the ERP sample which was dominated by the emotional GNG task. The sample had disproportionately high number of interference inhibition tasks. Given the small sample size and limited representation of different types of inhibition, it was not possible to make meaningful comparisons of fMRI activation across tasks types or inhibition types.

It was also notable that the fMRI study tasks involved a variety of secondary comparisons. These provide limited glimpses at several factors that may impact on inhibition processes in children with conduct problems. For example Hwang et al (2016) highlight that different levels of callous-unemotional traits may influence the degree to which emotional stimuli may cause differences in interference inhibition, while Kalnin et al (2011) provide evidence that past exposure to violent media such as video games and films can interact with ODD/CD in relation to interference inhibition relating to violent words. While interesting, and certainly worthy of further research, these studies also highlight that requirements of the tasks, even within the inhibition types, were quite variable. It is perhaps questionable as to how valid comparisons of interference inhibition with violent verbal stimuli is when compared to interference relating to differences in number of digits presented and names of those digits. Nigg (2000) suggests that different varieties of Stroop task do tap shared interference inhibition mechanisms, and it is also arguably reflective of everyday life in the sense that people face inhibition challenges in a variety of different situations and with differently valenced stimuli presented in a variety of mediums.

Because of the small number of studies available, a pragmatic flexible approach was required for study inclusion. While it might have been preferable to include only between group comparison studies, the decision was made to also include correlational studies. Castellanos-Ryan et al (2014) present an interesting approach using structural equation modelling. Again, it has the advantage of ecological validity because rather than trying to compare theoretical diagnostically "pure" samples, which may actually be very rare in reality (note for example that Zhu et al, 2014 found only 70 boys out of a total of more than 2500 Chinese students who were viewed as "relatively pure ODD") they instead examined how different symptoms clustered together and found high rates of shared variance between conduct disorder symptoms and ADHD. The chief limitation with this approach however is that it is not clear which symptoms related to which activations.

This systematic literature review found some support for the view that conduct disorder has recognisable abnormalities in neural correlates of inhibition, as measured by ERP and fMRI approaches. The findings were mixed however and certainly this area requires further research before firm conclusions can be made. Areas for further research include development of hot EF task approaches to test response inhibition in ecologically valid social-competitive situations, and further exploration of whether treatment effects can be indexed with ERP or fMRI in externalising populations.

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Part 2: Empirical Paper

Neural Correlates of Inhibition in Children and Adolescents with Conduct Problems: An Exploration of Treatment Effects Following Multi-Systematic Therapy

Abstract

Aims

This study aimed to explore the neural correlates of inhibition in children and adolescents with histories of behaviour problems using Event Related Potentials (ERPs). Comparisons were made between clinical and control groups and between Multisystemic Therapy (MST) and Treatment as Usual (TAU) treatment groups. Finally, treatment improvers were compared with non-improvers to determine whether inhibitory ERPs reflect treatment effects. Additionally, the study examined how different levels of a social provocation condition influenced the inhibitory ERPS.

Methods

Two clinical groups, MST (n=30) and TAU (n=30), and a control group (n=33), completed a go/no-go task while ERPs were recorded. The go/no-go task involved a social-competitive aspect whereby they played against other young people (actually a computer program) and the impact of being provoked (financially punished) harshly or leniently was explored. Clinical participants completed a self report delinquency measure and this was used to determine improver status.

Results

No main effects group differences were found for clinical versus control, or MST vs TAU, or improvers vs improvers. There was however a significant interaction between gender, group, and go-no go that was seen in both clinical/control and MST/TAU comparisons. Male clinical (and male TAU) participants were found to have a larger difference between no-go and go P3 amplitudes.

Conclusions

No evidence was found to support the idea that ERPs of inhibition can distinguish childhood conduct disorder or index treatment related changes. This finding is discussed in relation to research on other externalising conditions. The finding that P3 showed an interaction for gender, group, and go/nogo was suggested to reflect motivational/engagement factors that may have resulted from the task design.

Introduction

Child and adolescent antisocial behaviour is associated with serious and wide ranging psychological, as well as economic, costs to individuals, families, and society at large (Fonagy et al, 2013). Children who present with such behaviour commonly experience peer rejection, risk school exclusion (Taylor & Biglan, 1998), and in severe cases, where their behaviour cannot be managed by caregivers, are at risk of being taken into care (National Institute for Health and Clinical Excellence, 2013). Longitudinal research shows that such young people are at increased risk of mental and physical health problems, substance abuse, poor educational and employment outcomes, significant relationship problems, and criminality, into adulthood (Hill & Maughan, 2001). Youth anti-social behaviour also represents a significant burden on education, health and social care services, and the criminal justice system (Barrett, Byford, Chitsabesan, & Kenning, 2006). Conduct problems are the most common reason for referral to Child and Adolescent Mental Health Services in the UK and represent 30% of a typical General Practitioners' consultations, 45% of community health care referrals, and are a factor in 28% of all paediatric outpatient referrals (National Institute for Health and Clinical Excellence, 2013). Likewise, conduct problems represent a significant proportion of referrals to social services, with the most vulnerable and disturbed young people often being placed in foster placement, or more rarely, in residential care homes (National Institute for Health and Clinical Excellence, 2013), placements that are associated with high financial costs (Romeo, Knapp, & Scott, 2006). Anti-social behaviour is associated with significant economic costs, with individuals with persistent antisocial behaviour at ten years of age are estimated to cost society ten times as much as their

non-delinquent peers by the time they are 28 years old (Scott, Knapp, Henderson, & Maughan, 2001), and based on longitudinal research over a seven year period in the United States, the costs attributed to young people with conduct disorder have been estimated to be around ten times those attributed to individuals with other mental health problems (Foster & Jones, 2005). These severe behavioural problems tend to persist into adulthood, with conversion rates from childhood Conduct Disorder to adult Anti-Social Personality Disorder estimated to be between 40 and 70% (National Institute for Health and Clinical Excellence, 2009). Given that the costs associated with youth anti-social behaviour and offending are so considerable, development of effective treatments for this population is an important policy priority (Cary, Butler, Baruch, Hickey, & Byford, 2013). One example is Multisystemic Therapy (MST).

MST is an intensive family focussed approach based on social-ecological (Bronfenbrenner, 1979) and family systems theories (Henggeler, Schoenwald, Borduin, Rowland & Cunningham, 1998; Henggeler, Schoenwald, Rowland & Cunningham, 2002, Littell, 2006). A central idea is that since the causes of offending behaviour are in young people's social ecology (family, school, peer group, neighbourhood), effective treatment must intervene at these different levels, not just with the individual (Henggeler, et al 1998). This is based on research that has identified that the keys risk factors for youth anti-social behaviour are impulsivity in the young people; low levels of parental involvement and harsh critical parenting; high levels of family conflict; and young people's involvement with deviant peers (Fonagy et al, 2013; Lipsey & Derzon, 1998). MST therapists work on each of these issues with families, borrowing from a range of treatment models including strategic

family therapy, structural family therapy, and cognitive behaviour therapy (Henggeler, 2009).

Recent guidelines from the National Institute for Health and Clinical Excellence (NICE) have identified MST as potentially the most promising intervention for reducing youth antisocial behaviour (National Institute for Health and Clinical Excellence, 2013), and several studies suggested that MST can be extremely effective in managing severe antisocial behaviour and reducing out of home placement (Schaeffer & Borduin, 2005; Henggeler, Halliday-Boykins, Cunningham, Randall, Shapiro, & Chapman, 2006). However this has not been shown consistently across all studies, with trials in Sweden (Sundell, Hansson, Lofholm, Olsson, Gustle, Kadesio, 2008) and Canada (Leschied, 2002) failing to show differences in treatment effects between MST and a treatment as usual condition. Fonagy et al (2013) argued that for MST to be considered valuable it must demonstrate superior effectiveness in care systems outside of the US where there is a stronger evidence base for TAU than the earlier studies initiated by the developers of MST, that the therapists delivering MST should be independent from the developers of MST, and the sentencing policy within the justice system does not result in a comparison with alternatives such as incarceration. These conditions were met by the first RCT of MST in the UK conducted at the Brandon Centre (Butler, Baruch, Hickey, & Fonagy, 2011) which compared MST plus usual services from youth offending teams (YOT)(n=56) with the services offered by youth offending teams alone (n=52). Reductions were seen in offending for both groups, but were greater in the MST+YOT intervention, with the MST+YOT group showing reduced likelihood of non-violent offending after 18 months. The clinical trial (Butler et al, 2011) and

subsequent economic evaluation (Cary et al, 2013) suggest that MST could be an effective and cost saving treatment in the UK.

Deficits in inhibition processes have been suggested to play a key role in conduct disorders and youth antisocial behaviour (Oosterlaan et al, 1998). Inhibition deficits may manifest in a wide range of ways in children with conduct problems, reflecting the heterogeneous nature of the disorder (Klahr & Burt, 2014). For example, Klahr & Burt (2014) note the associations between impulsivity and non-aggressive antisocial behaviours, such as theft and vandalism, while Patrick (2008) suggests that inhibition deficits may help explain impulsive aggression in young people with conduct disorder, as opposed to more deliberate instrumental aggression. There is debate over whether children with such conduct problems show recognisable neural correlates of inhibition problems such as have been shown for ADHD (Rubia, 2011). Several neurological models of conduct problems suggest that conduct problems are associated with deficits in inhibitory systems. Blair's (2005) model suggests two deficit neural systems in conduct disorder, one relating to response inhibition and the other to emotion regulation. Quay (1997) draws on Gray (1991) to suggest that children with conduct disorder have an over active behavioural activation system (BAS) but unimpaired behavioural inhibition system (BIS). Rubia (2011) suggests that the impulsivity seen in conduct problems results from impaired "hot" emotional regulation systems rather than "cool" executive function (e.g. inhibition and attention) systems. Recently, a range of electroencephalography (EEG) studies have provided evidence that certain Event Related Potentials (ERPs) may be viewed as biomarkers for inhibition problems in a range of disorders that are characterised by disinhibition, impulsivity, aggression, and negative emotionality

(Hicks, Bernat, Malone, Iacono, Patrick, Kreuger, & McGue, 2007). These conditions, which include Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder, and Substance Dependence, have been shown to share a highly heritable latent factor that accounts for the systematic high rates of symptom covariance and this has been labelled the "externalising factor" (Kreuger et al, 2002). The externalising factor is consistently related to reduced amplitudes of the P3 ERP in oddball tasks and this "Reduced P3" has been suggested to be a biomarker for the broad vulnerability towards developing externalising problems (Hicks et al, 2007). The P3 ERP is typically regarded as relating to inhibitory processes (Polich, 2007) however the oddball task is not the most ideal paradigm for assessing neural correlates of inhibition, since it is primarily an attentional task.

Behavioural inhibition tasks are better suited to exploring neural correlates of inhibition since they explicitly require inhibition of a prepotent response (eg. the Go/No-Go task), the stopping of an initiated response (eg. the Stop-Signal Task), or test interference control (eg. Flanker and Stroop tasks). ERP studies using these experimental paradigms have shown that two ERP components are reliably associated with behavioural aspects of inhibition (Johnstone, Barry, & Clarke, 2013). In non-clinical populations, one of the most widely used behavioural inhibition tasks is the Go/No-Go (GNG) task and its use has identified two ERPs that are consistently associated with inhibition of responses. Firstly, the N2 is a negative ERP component that occurs 150 to 400ms following stimulus onset, has its maximal amplitude at frontal electrode sites. The primary evidence for the association between N2 and behavioural aspects of inhibition is the consistent finding that it shows enhanced amplitude for no-go (inhibitory trials) compared to go trials and enhanced N2 is

associated with fewer errors on No-go trials (Jodo & Kayama, 1992; Falkenstein, Hoormann, & Hornsbein, 1999). The "No-go N2" is thought to reflect early stages of the inhibition process and has been described as a "red flag" marking the start of inhibition (Kok et al, 2003). The increased N2 in response to no-go trials compared to go trials has been suggested to reflect increased efforts to activate the response inhibition system and to interrupt preparations for response activation (Géczy et al., 1999). An alternative, though arguably related view of the N2 is that enhanced no-go N2 reflects "conflict monitoring" rather than response inhibition per se (Jonkman, 2006), given that as the relative frequency of go to no-go trials is varied, N2 amplitude is enhanced for whichever response is less frequent (Niewenhuis et al, 2003; Donkers & van Boxtel, 2004). Following the N2, the P3 is also consistently seen in response inhibition tasks (Bokura et al, 2001). The P3 is a positive ERP component emerging 300 to 500ms following stimulus onset and has maximal amplitudes in midline electrode sites. Like the N2, P3 is also enhanced for no-go trials (Bruin et al, 2001; Donkers & Van Boxtel,2004) and larger P3 amplitude is associated with fewer errors on inhibition trials (Jonkman, 2006), and is enhanced for successful compared to partial and failed inhibitions (Cragg, Fox, Nation, Reid, & Anderson, 2009). Unlike N2, which is associated with early inhibition stages, the no-go P3 is thought to index a later stage of inhibition, being suggested to relate to the inhibitory response itself (Dimoska, Johnstone, & Barry, 2006; Ramautar, Kok, & Ridderinkof, 2006). An alternative view is that the late stage of inhibition that P3 relates to is monitoring/evaluating the outcome of the inhibitory response (Bruin, Wijers, & Staveren, 2001). The relationship between externalising conditions and N2 and P3 in inhibitory tasks has been most thoroughly investigated in ADHD

(Johnstone, Barry, & Clarke, 2013; Barry, Johnstone, & Clarke, 2003) and substance dependence (Luijten et al, 2014). Systematic reviews in these areas report that the inhibitory N2 and P3 are typically reduced in clinical groups compared to controls, and while this is not true of every study reviewed (Groom et al, 2008; Wiersema et al, 2006), the overall picture supports the view that that reduced N2 and P3 are reliable correlates of inhibition problems in these conditions. In contrast, relatively few studies have used ERPs to measure neural correlates of inhibition in children with conduct problems. The systematic review in Part One of the current thesis identified only nine such studies and the pattern of results was mixed, with only three studies (Moadab et al, 2012; Albrecht et al, 2005; & Overtoom et al, 1998) out of eight that measured N2 showing the expected reduced amplitude in clinical groups, and only two studies (Woltering er al, 2011; Bauer & Hesselbrock, 1999) out of four that measured P3 showing reduced amplitude in children with conduct problems. While this is currently an area in need of further research, it appears that reduced N2 and P3 may be viewed as biomarkers for inhibitory problems, and one potential clinical and research implication for such biomarkers is the possibility of using them not only diagnostically identify those at risk of developing externalising problems, but perhaps also to index treatment related changes.

Only a few studies have used inhibitory N2 and P3 to investigate treatment effects in clinical populations (Hum and Lewis, 2013; Woltering, Granic, Lamm, & Lewis, 2011; Lewis, Granic, Lamm, Zelazo, Steiben, & Todd, 2008). Before describing the findings of these studies it is important to outline how the researchers used a variation on the standard GNG task, and how such variations raise issues about interpretation of N2 and P3. In typical GNG tasks, participants are presented

with “go” stimuli and must make a response, for example pressing a key pad, whereas for “no go” stimuli they must inhibit the response. Most of the trials, typically 66%, are go trials so a prepotent response is established. In the “emotional GNG” Lewis, Lamm, Segalowitz, Stieben, and Zelazo (2006) told participants they would earn a “good prize” if they scored enough points (gained for successful inhibitions and lost for failed inhibitions), and in the second of three blocks of trials ensured that participants lost most of their points in order to provoke frustration and anxiety. They found enhanced N2 amplitudes during the frustrating block which they related to self-regulation processes and suggested that inhibition may be impacted by emotional contexts and events. An alternative explanation, supported by other studies, is that the enhanced N2 in this task may have reflected another factor such as increased response conflict or increased effortful attention (Donkers and van Boxtel, 2004; Niewenhuis et al, 2003). Indeed, research also suggests that N2 and P3 may be enhanced by factors such as motivation and engagement (Polich, 2007; Boksem, Mejman, & Lorist, 2005, Polich & Kok, 1995), and reduced due to factors such as fatigue (Boksem, Mejman, & Lorist, 2005). While N2 and P3 are viewed as reliable correlates of inhibition, it is apparent that other factors may influence them, and this should be considered when considering their use in indexing treatment effects.

The treatment studies showed mixed results. Two studies used inhibitory ERPs to index treatment change in children (aged 8 to 12) with externalising problems. In both studies the primary diagnoses were ODD/CD and the children also had some secondary anxiety symptoms. Lewis et al (2008) compared inhibitory N2 activation between clinical and control groups before and after a treatment that included Parent Management Training and Cognitive Behaviour Therapy which was

focussed on helping children and their parents manage the children's aggressive behaviour. They also compared improvers with non-improvers and the treatment groups. No group differences were found for N2 amplitude, however additional analyses of activation in the neural generators of N2 suggested that improvers showed an overall reduction in ventral prefrontal activation during the N2 time window, suggesting that there were changes in neural correlates of inhibition but that these were not reflected at the level of N2 amplitude. These results should perhaps be viewed cautiously given that source-space analysis from ERP activity is not viewed as accurate or reliable (Urbach & Kutus, 2002). Woltering et al (2011), however, reported that inhibitory N2 amplitudes were higher for the clinical group than the control group before treatment, they suggested that higher N2 amplitude reflected inefficient inhibition processes, which is contrary to the typical interpretation of inhibitory ERPs in previous literature which tends to associated larger ERP with more efficient and successful inhibitory responses (Cragg, Fox, Nation, Reid, & Anderson, 2009). It is also difficult to explain the enhanced N2 in relation to the frustrating points-loss task, because although the block was completed, the authors note that they were unable to report on the results due to inadequate usable trials. They also reported that clinical children had reduced inhibitory P3 amplitude compared to controls, which is more consistent with previous findings (Johnstone, Barry, & Clarke, 2013; Luijten et al, 2014). They reported that children whose externalising behaviour improved with treatment showed reductions in N2 amplitude relative to non-improvers, while P3 was not shown to be responsive to treatment. These results are clearly inconclusive about whether N2 and P3 can be used to index treatment effects, and further research is needed.

Building on Lewis et al (2008) and Woltering et al (2011), the current study will attempt to investigate how a provocative, frustrating situation impacts on neural correlates of inhibition. The theoretical relevance of this aspect of the research is that although so called "cold executive function" tasks (those that tap functions like inhibition, attention, and working memory but not emotional processes or factors like motivation) can provide a picture of individual important executive functions, it is likely that they are put under strain during emotional or frustrating circumstances, thus using so called "hot executive functions". It is more ecologically valid to explore deficits in inhibition in children with conduct problems in situations that are highly provocative/frustrating compared with situations that are not. Also, rather than simply having an unexplained decontextualised frustrating situation, as used by Lewis et al (2008) and Woltering et al (2011), the current study will situate the provocation in a realistic and ecologically valid social competitive task, using the Taylor Aggression Paradigm (Taylor, 1967) in which participants play a GNG reaction time game against a computer opponent (whom they believe is a real person).

The current study will explore whether clinical and control participants differ with respect to N2 and P3 amplitudes during an inhibition task where levels of social provocation are varied. It will also build on the previous treatment investigations by exploring how treatment group relates to the measures of inhibition, comparing MST and TAU. Furthermore, the relationship between improvement status will also be explored to add to the research on treatment effects. Given the mixed results of the scarce previous studies in this area, no firm directional hypotheses are made with regard to these comparisons.

Method

Participants

Clinical Sample

A clinical group of 60 participants was recruited from the larger (n= 684) Systematic Therapy for At Risk Teens (START) clinical trial of MST. These young people were recruited to the START trial at ages 11 to 19, and had severe conduct problems and were at risk of being placed into care. The current study took place two years after initial recruitment so the participant age range is higher, from 13 up to 19. This clinical group included 30 young people who received MST and 30 who were in a TAU comparison group. They were recruited at one of the six month follow up sessions by Research Assistants who informed the young people about the EEG study. Participants were given a full Information Sheet, Letter (a summarised bullet point version of the Information Sheet) and Consent to Contact form to sign. A minimum of a week was left after signing the consent to contact form so participants had time to think about taking part and to ask questions. They were then contacted by phone to book an appointment and a further reminder phone call was offered. At the time of testing, the researchers were blind to whether the participants received MST or TAU, to minimise performance expectation effects. Two participants in the clinical group were found to have faulty data and were removed from analysis, thus 58 clinical participants (33 males, 57%) with an average age of 16.34 years (SD= 1.72 years) had usable data following the testing session.

In the clinical group, neural correlates of improvement were tested using subgroups (defined below). The Improvers consisted of 13 participants (6 male; M =

16.21 years, S.D. = 1.73) and the Non-improvers consisted of 14 participants (8 male; M = 16.86 years, S.D. = 1.70).

Control Sample

A control group of young people, who were matched for age and gender but had no history of conduct problems, was recruited. Most of these participants were recruited from schools and sixth-forms in the same geographic areas of London as the clinical participants. The researchers visited the schools and gave short presentations describing the project. Young people who were interested signed consent to contact forms, those under sixteen took consent to contact form for their parents or guardians to sign and return. After three days they were then sent the Information Sheets and an appointment was made. Two of the control participants were recruited via a sibling who attended one of the schools and three participants were recruited through a drama group attended by one of the students who had attended the study and recommended that it would be of interest. Thirty-nine control participants completed testing, but due to faults in recording on 6 sessions, 33 participants had usable data (17 male) with a mean age of 16.21 (SD=1.73).

Power calculation:

In the previous study by Woltering (2011), a large effect size was found (d = .90) so for the current study to have 80% power to detect an effect size of this magnitude a sample size of 33 is required at alpha = .05 using standard regression, with 3 covariates. We estimated that approximately 60% of the START sample would be classified as improvers (from both arms of the trial), so a final sample size

of 55 would be required in the treatment groups. Our aim was to collect 30 participants from each arm of the treatment study to meet the requirements for sufficient power to test the contrast between improvers and non improvers, and also to achieve 80% power to detect clinical versus control differences for effect sizes of d = .56 or higher. This sample size was achieved.

Inclusion and Exclusion Criteria

All participants had normal, or corrected to normal, hearing and vision. Young people with generalised learning problems (as indicated by an IQ below 65) and/or history of severe brain injury or neurological disorders were excluded from participating.

The inclusion criteria for the original START trial, from which participants were drawn, varied according to recruitment source. The inclusion criteria are therefore listed separately by referral source below:

Recruitment via Children's services:

1) Young person aged 11−17 years;

2) Sufficient family involvement for MST to be applied, excluding adolescents already in local authority care or foster accommodation,

3) No existing agency involvement (e.g. the family is already engaged with a therapist) which would interfere with MST;

4) Adolescent designated as 'Child in Need' where this is associated with antisocial behaviour on the part of the adolescent;

5) Exhibiting extremely challenging behaviour by EITHER Persistent (weekly) and enduring (6 months or longer) violent and aggressive interpersonal behaviour AND/OR a significant risk of harm to self or to others e.g. self-harming, substance misuse, sexual exploitation, absconding.

Recruitment via Forensic services:

1) At least one conviction within the last twelve months, or referral via a supervision order with MST as specified activity,

2) A warning, reprimand and/or conviction on at least three occasions in the 18 months.

Recruitment via Child Mental Health services could have the following specific criteria:

1) Current diagnosis of conduct disorder, substance misuse, major depression or anxiety;

2) History of at least one unsuccessful outpatient intervention;

3) EITHER history of school exclusion OR assessment as child in need.

Recruitment from Educational services:

1) Currently permanently excluded from School,

2) History of having been excluded from at least one other school for aggressive conduct.

Exclusion Criteria for the START study were:

1) History or current diagnosis of psychosis

2) Generalised learning problems (clinical diagnosis) as indicated by IQ below 65,

3) Risk of injury or harm to a worker,

4) Presenting issues for which MST has not been empirically validated, in particular substance abuse in the absence of criminal conduct or sex offending as the sole presenting issue.

For the control group, participants had to be in the same age range of 13 to 19, have no generalised learning problems, and have no current or historical behavioural problems.

The Intervention

MST

Young people in the clinical group received multi-systemic therapy for a period of between 3 to 5 months. This involved the young people and their families being allocated an MST therapist who provided behavioural support to the parents to help manage the young person's challenging behaviour, set boundaries, and improve relationships. The therapist also worked with the young person to help them improve other important relationships in different systems of their lives, such as at school/college, within the local community, with peers. In contrast, those in the TAU condition did not receive a specialist intervention on top of more standard support through existing systems such as mentorship at school or contact with Youth Offending workers.

Procedure

When the young people arrived at the testing centre (accompanied by a parent or guardian if under 16) they were given the opportunity to ask any questions about the study and then sign a consent form to participate. After obtaining informed consent, participants were fitted with an EEG net. First, head circumference was measured and the central vertex point (Cz) located between the nasion and inion points and the preauricular notches to enable the EEG net to be located in the correct position. A Hydrocel high-density array of 128 Ag/AgCl electrode net (Geodesic Sensor Net, EGI Inc.) was soaked in a solution of water, potassium chloride (KCl which acts as an electrolyte) and baby shampoo (which breaks up grease on the scalp) and was then placed on the participants head.

EEG data was collected with the Netstation v.4.4.2 software package (EGI, Inc) and EGI high impedance amplifiers (EGI, Inc. Series 300 amplifier), sampling at 250Hz. Online filters were set to .1-100 Hz. We ensured that impedances for all electrodes were below 100 KΩ throughout the tasks and checked this with the inbuilt Netstation impedance tool before and after the experimental tasks.

Taylor Aggression Paradigm

The third task participants completed was the GNG task. The participants were given verbal instructions and taken through a step-by-step practice of the task. They then completed a short quiz to ensure they understood the task. The researchers then introduced the participants to their "opponents" via webcam, though in fact the

participants were shown a video recording of a young person of the same sex and age, since the participants were actually playing against a computer program.

The GNG task involved the participant seeing a large green or red arrow on the computer screen, surrounded by smaller grey "flanker" arrows pointing in either the same direction (congruent) or opposite direction (incongruent) as the large arrow. When the green arrow was displayed participants had to press a key that corresponded with the direction it faced (L for right and A for left). When the arrow was red participants had to press no buttons at all. Green "go" arrows appeared approximately 66% of the trials so that a pre-potent response was established and red "no-go" arrows required inhibition of the response. The "flanker" stimuli were not of interest to the current study, thus analysis only considered congruent trials.

Participants were told that they had to "beat" the opponent by being the fastest and most accurate in their responses. They were informed that they were playing for money and that they would begin with £3.50 "in the bank". For every won round they gained 20p, but for every loss they would be punished an amount chosen by their opponent. The opponent was likewise punished an amount chosen by the participant.

The task was organized into four blocks, with the participant playing the first opponent and then a second, then taking a break which they were told was required for the two opponents to play each other. They then played each opponent again. Each block contained 120 trials, grouped into sub-blocks (rounds) of 20 trials which always began with a slide asking them to "choose a punishment" for their opponent. They were then required to press a key to indicate a monetary punishment of 10p,

20p, 30p, 40p, 50p, or 60p. In the middle of each sub-block, participants saw a "Blink" screen when they were encouraged to blink, in order to minimise blinking during the experiment. At the end of each sub-block a screen informed the participant "you win!" or "you lose!" If the participant lost the round they would also be informed of the amount of money they lost and heard an irritating buzzing noise, which was louder at the higher levels of punishment, emphasising the loss.

The "opponents" were set to impose either a high punishment (high provocation) (average of 50p per trial) or a low punishment (low provocation) (average of 20p per trial). The trials were fixed so that the participants won roughly 50% of the trials, thus they experienced both levels of punishment. It also meant that all participants won approximately £5.00 in the game.

Participants had an average of 32.88 (SD=2.33) Low Provocation No-Go trials, 75.35 (SD=7.27) Low Provocation Go trials, 32.95 (SD=2.73) High Provocation No-Go trials, and 76.01 (SD=5.45) and High Provocation Go trials (which maintained the desired proportion of approximately 66% Go trials).

Measures

The *Self-Report of Delinquency* (SRD) is a questionnaire regarding antisocial behaviour, which was developed as part of a major longitudinal study in Scotland exploring relationships between developmental transitions in adolescence and criminal behaviour (Smith & McVie, 2003). The questionnaire was developed using a systematic analysis of existing relevant instruments and a review of questions used in similar research (Smith and McVie, 2003). The measure does not have clinical

thresholds and has not been referenced to normative data. Its use is therefore limited to comparing the clinical and non-clinical samples, the MST and TAU samples, and can suggest improvement status to a limited degree. The questionnaire asks respondents about the frequency that they have engaged in different types of antisocial behaviour and produces metrics of Variety and Volume of behaviours. The delinquent behaviours included in the measure include property damage, theft, assault, carrying weapons, truancy, drug selling and drug use. Respondents are asked to answer for the period of the last six months. In the current study, only the Volume scores were used as a metric of delinquency. 21 items composed of descriptions of a behavior (eg. "During the last 6 months did you damage or destroy property that did not belong to you on purpose") followed by option of answering "Yes or No", followed by 7 frequency options (1= Once, 2= twice, 3=3 times, 4 =4 time, 5 =5 times, 6=between 6 and 10, 7=more than 10 times). The range of scores was therefore between 0 and 147, with a high score indicating higher levels of delinquency. At the time of EEG testing, the clinical population had a volume score of 8.43 (sd 9.14) (ranging from 0 to 38) while controls had 1.06 (sd 2.14) (ranging from 0 to 7). The SRD was found to have a Cronbach alpha coefficient of internal consistency of .89.

Analysis

Design

A mixed between and within subjects design was used. The between subjects independent variables were the Groups (clinical vs control, MST vs TAU, and Improver vs Non-Improvers) and within subjects factors were Provocation (high and

low) and Go/No-go Trial (Go and No go). Sex was added as a covariate. Each of the group variables were analysed separately from each other (i.e. Only one group variable was included in any one analysis). The dependent variables were N2 and P3 amplitudes and GNG error rates.

Group Comparisons

Three main analyses were conducted in this study. Firstly, clinical participants were compared against the control group. Secondly, MST and TAU groups were compared against each other to determine if there were differences according to treatment. Finally, treatment response across both clinical groups was tested by comparing "improvers" and "non-improvers". Because the time between the baseline and testing date varied (mean = 27.15, sd= 7.08, range from 18 to 48 months), a linear rate of change was calculated by subtracting the current score (at the EEG testing date) from the baseline score and dividing by the time elapsed from the baseline (mean rate of change= .25, sd= .59, range from -.83 to 3.22). The participants from the upper and lower quartiles on the rate of change for volume of delinquent behaviours were taken as "improvers" (n=13) and "non-improvers" respectively (n=14).

Behavioural Data Analysis

The main metric of interest for behavioural performance relating to inhibition is the error rate on no-go trials. This was defined as the number of key presses during the no-go trials (errors of commission) divided by number of no-go trials. SPSS (version 21) was used to compute mixed ANOVAs with provocation as a within

subject factor (high versus low), and the above named groups as between subject factors (clinical and control, MST and TAU, and Improvers and Non-improvers), and sex as a covariate.

EEG Data Analysis

The EEG was recorded with a 128-channel Geodesic Sensor Net and sampled at 250Hz, using Netstation software. Data were band-pass filtered with cut-offs of 0.3 and 40Hz. The EEG was segmented around participants' responses between -100ms (before stimulus presentation) to 750ms after stimulus presentation, with a baseline set at 100ms pre-stimulus. Participants had an average of 32.88 (SD=2.33) Low Provocation No-Go trials, 75.35 (SD=7.27) Low Provocation Go trials, 32.95 (SD=2.73) High Provocation No-Go trials, and 76.01 (SD=5.45) and High Provocation Go trials (which maintained the desired proportion of approximately 66% Go trials).

The analysis of the ERP data was conducted using the EEGlab toolbox (version 13.4.4b; Delorme & Makeig, 2004). This included visual inspection of all participants ERP waves to identify any faulty data, and computation of ERP averages by specifying electrodes and time windows of interest for statistical analysis and for plotting ERP graphs. Following past research (eg. Woltering et al 2011; Munro, Dywan, Harris, McKee, Unsal, & Segalowitz, 2007), the N2 and P3 were both measured at medial-frontocentral electrodes centred around FCz (electrodes 5, 6, 7, 12, 13, 106, 112,) as the mean amplitude in the windows of 200ms to 350ms and 350ms to 500ms after stimulus presentation, respectively.

SPSS was used to compute repeated-measures ANOVAs to test for group differences in the ERP components. Group was therefore entered as a between subjects factor, Go Versus No-NoGo and Provocation as within subjects factors and sex as a covariate. Separate ANOVAs were run for each ERP component (N2 and P3) and for each Group variable (clinical vs control, MST vs TAU, and Improvers Vs Non-Improvers)) across each group comparison (clinical vs control, MST vs TAU, and Improvers Vs Non-Improvers as between subject factors), for the within-subjects factors of Provocation (two levels of high and low) and GNG (two levels of go and no-go), with sex as a covariate.

Results

The results section is divided into four sections. In the first section the EEG grand averages across all participants are presented in order to confirm the presence of the N2 and P3 components in the sample as a whole and to describe their topography. The second section compares the N2 and P3 between clinical and control groups as well as scores on the self rated delinquency scale (SRD) and behavioural performance (error rates) between these groups. The third section repeats the comparisons of ERP components, SRD scores, and error rates for MST and TAU groups. The final section repeats the above comparisons for treatment improvers and non-improvers.

Grand Average ERP Components Across all Groups

For descriptive purposes the topographical distribution of the EEG activity for the electrode sites is displayed in figures 1a and 1b. As expected the N2 shows maximal activity in frontal central area at around 260ms post stimulus and P3 shows

maximal activity at around 420ms. For simplicity, only the scalp maps for activity in the high provocation conditions are presented, since the pattern of activity is almost identical in the low provocation condition.

When mean amplitudes were compared between go and no-go conditions and high and low provocation, the N2 showed a large go versus no-go difference ($F(1,90)= 60.1$ $p < .001$; *fig 2.*), but no significant effect of provocation ($F(1,90) = 2.41$, $p = .12$) nor provocation by GNG interaction ($F(1,90) = .01$, $p = .30$). Likewise, the P3 showed a large go versus no-go difference ($F(1,90) = 183.5$, $p < .001$) but there was no significant effect of provocation ($F(1,90) = .35$, $p = .56$) nor was there a provocation by GNG interaction ($F(1,90) = 0.12$, $p = .90$).

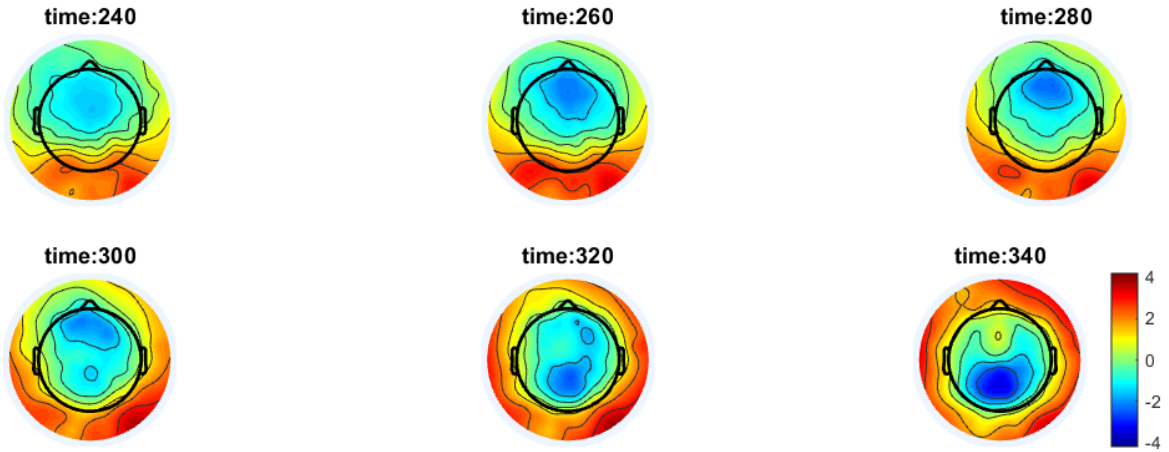

Figure 1a: Scalp maps showing N2 peak amplitude (dark blue) at about 260ms in frontal area, in a window of 240 to 340ms.

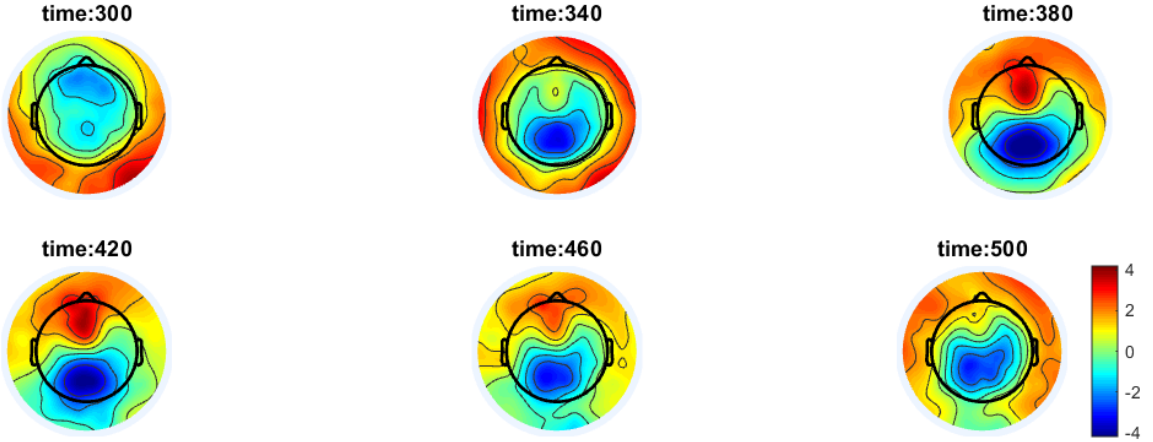

Figure 1b: Scalp maps showing P3 peak activation (dark red) at about 420ms, in a window of 300 to 500ms.

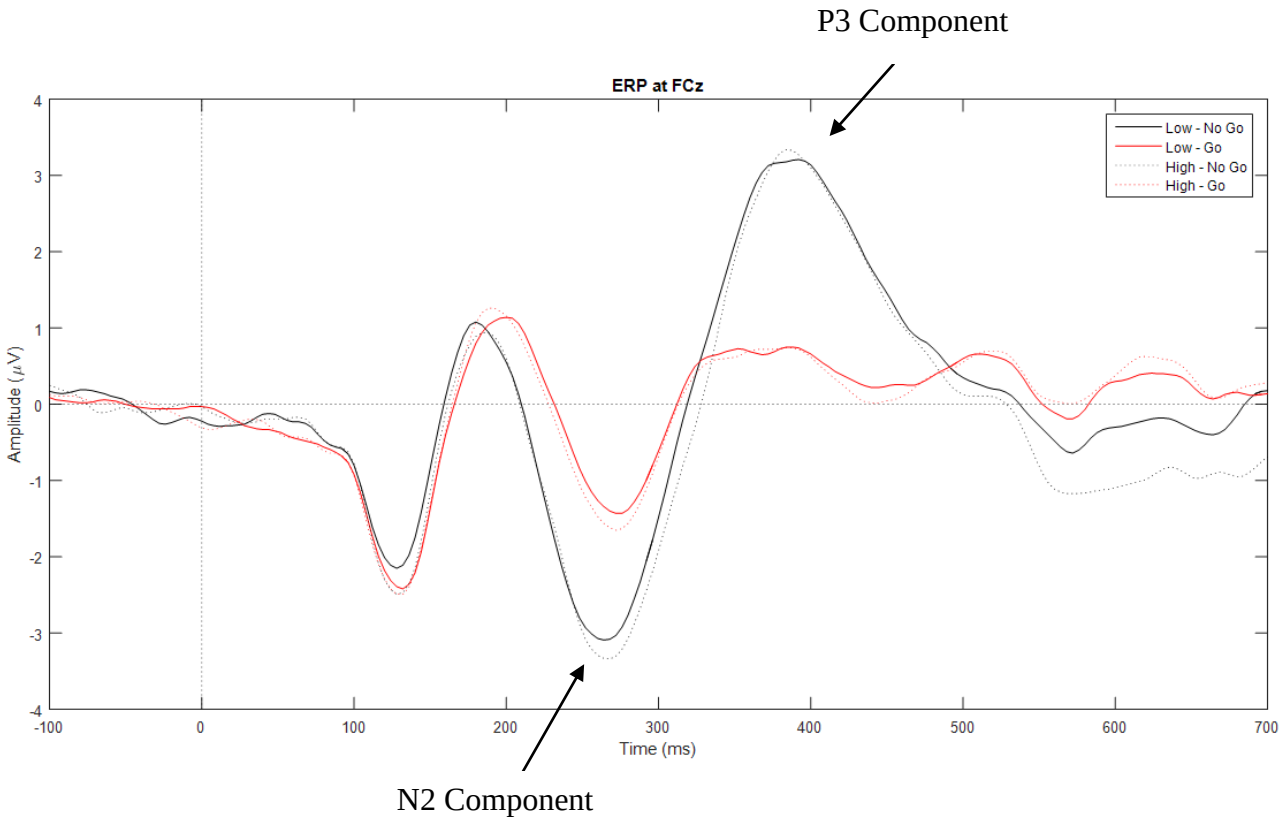

Figure 2: Grand Average ERPs for frontal N2 and P3 for high and low provocation and go and no-go trials

Clinical vs. control comparisons

Self-reported delinquency scores

Self-reported delinquency (volume) at the date of EEG testing were compared between clinical and control groups. Shapiro-Wilk tests of normality found that the distributions of scores for clinical ($D(58) = 1.78$, $p < .05$) and control ($D(33) = .42$, $p < .001$) were significantly non-normal, therefore an independent samples Mann-Whitney U test was used to compare group medians and as expected, found significantly higher number of delinquent behaviours reported by clinical (*Mdn*=7) compared to control participants (*Mdn*=0), ($U = 421.50$, $p < .001$, $r = 0.49$).

Behavioural data

Prior to examining the EEG data we tested whether there were differences in the error rates on no-go trials between clinical participants and controls. The mean error rates are shown in table 1, separately by group, provocation and gender.

Table 1: Means and standard deviations for no-go error rates for clinical and control participants across provocation level and gender.

	Male				Female			
	Low No-Go error rate		High No-Go error rate		Low No-Go error rate		High No-Go error rate	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Clinical	0.03	0.04	0.03	0.06	0.03	0.04	0.04	0.06
Controls	0.04	0.08	0.06	0.22	0.04	0.04	0.02	0.02

As can be seen in the table, there were only small differences in no-go error rates between conditions or groups with none reaching significance at the $p < 0.05$ level.

ERPs

N2: There was no main effect for group, and no significant interactions between group and GNG. However there was a 3-way interaction that approached significance between GNG, group, and sex (F(1,87)=3.78, *p*=.055). As seen in figure 3, clinical males showed a smaller difference between the no-go N2 (-1.74 µV, sd=3.18) and the go N2 (-1.13 µV, sd= 2.63) than was seen for other groups. When the genders were analysed separately, for males the interaction between GNG and group was not significant but was at trend level (F(1, 48)= 2.96, *p*=.09) and non-significant for females (F(1, 39)= 39.0 *p*=.31). A plot of the N2 for males showed that the clinical males had a smaller difference in the N2 than the control males (see Figure 3 below, note that post-hoc tests revealed that both groups showed a significant difference between go-and no-go (clinical males, *p*= .008; control males i <.001).

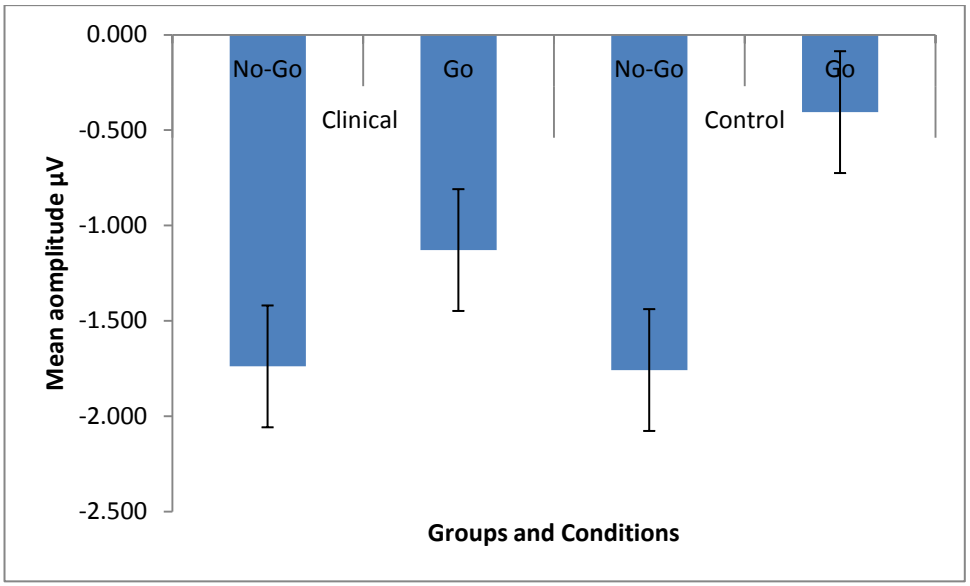

Figure 3: Mean (SE) N2 amplitudes in go and no-go trials for clinical and control male participants.

A significant interaction was found between provocation and sex ($F(1,87)=6.24$, $p=.014$), with females showing a significantly greater difference in magnitude of N2 amplitudes between low and high provocation conditions than males, with the females showing larger N2s under high provocation. Furthermore, there was a significant interaction between provocation, clinical/control groups, and sex ($F(1,87)= 8.14$, $p=.005$). When analysed separately by gender, for males, there was a trend-level interaction between provocation and group ($F(1,48)= 3.75$, $p= .059$). For females, the same interaction was significant ($F(1,39)= 4.94$, $p = .032$). Post-hoc tests indicated that only the control females showed a significant difference between provocation conditions, with enhanced N2 for high provocation (-1.06 µV, sd=2.64) compared to low (-.21 µV, sd=2.07). There were no other significant effects or interactions.

P3

There was a significant interaction between GNG, group and sex (F(1, 87)= 7.95, *p*=.006). Running the analysis separately by gender revealed a strong Group by GNG interaction for the males (F(1,48)= 8.65, *p*= .005), but no such interaction for the females. As the graph below shows males in the clinical group showed a large difference between go and no-go trials in the P3, whereas control boys showed a very small difference. Post-hoc tests showed that the go-no-go difference in the P3 was significant for the clinical males (*p*<.001) but not for the control males (*p*= .44).

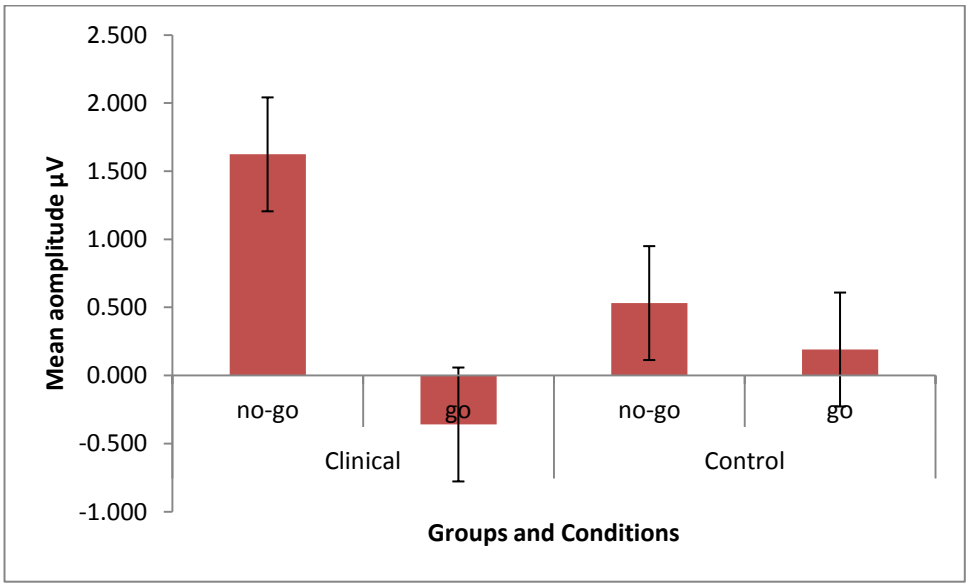

Figure 4: Mean (SE) P3 amplitudes in go and no-go trials for clinical and control male participants.

There was also a significant interaction between provocation, group, and sex (F(1, 87)= 4.81, *p*=.031, with post-hoc Sidak comparisons finding that only female control participants had significant differences in P3 amplitudes between low

(.83 µV, sd=2.75) and high (.12 µV, sd=2.82) provocation conditions. No other main effects or interactions were significant.

MST versus TAU comparisons

Self report delinquency scores

Shapiro-Wilk tests found the distributions of SRD scores reported by MST (D(30)=.77, p<.001) to be significantly non-normal while those for TAU (D(28)=.90, p=.13), were normally distributed. As above, a non-parametric Mann-Whitney U test was used, and found significantly higher volume of delinquent behaviours for TAU participants (*Mdn*=9), compared with MST (*Mdn=2), (U*=284.00, p=.032, r= -.28).

The SRD rate of change scores for MST and TAU were also compared. Shapiro-Wilk found the rate of change scores to be significantly non-normal for both MST (D(30)=.81, p<.001) and TAU (D(28)=.86, p< .001), so a Mann-Whitney U test was conducted and found no significant difference between rate of change SRD volume score for MST (*Mdn*=.30*)* and TAU (*Mdn= .33), (U*=393.50, p=.68, r=-.05)

Behavioural Data

Prior to analysis of the EEG data, error rates for the MST and TAU groups were examined, and are presented Table 2. As with the clinical and control conditions, the differences in error rates between MST and TAU groups were very small, and repeated measures ANOVA found no significant differences for gender, provocation, or treatment.

Table 2: Means and standard deviations for no-go error rates for MST and TAU participants across provocation level and gender.

	Male				Female			
	Low NoGo error rate		High NoGo error rate		Low NoGo error rate		High NoGo error rate	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Clinical	0.02	-0.02	0.02	-0.03	0.02	-0.03	0.05	-0.05
Controls	0.05	-0.06	0.05	-0.08	0.05	-0.05	0.03	-0.07

ERP Components

N2: The ANOVA revealed no significant main effects or interactions involving treatment group on the N2.

P3: A significant interaction was found between treatment group (MST vs TAU), GNG and sex ($F(1, 54)= 5.77$, $p=.02$). We found a significant treatment x GNG interaction in the males ($F(1,31)= 4.41$, $p=.044$; *fig. 5*), but not the females, with TAU males showing a larger difference in the P3 between go and no-go than the MST males (though post-hoc tests showed that the GNG differences was significant in both groups [MST, $p=.003$; TAU, $p < .001$]). No other significant main effects or interactions involving treatment were found for the P3.

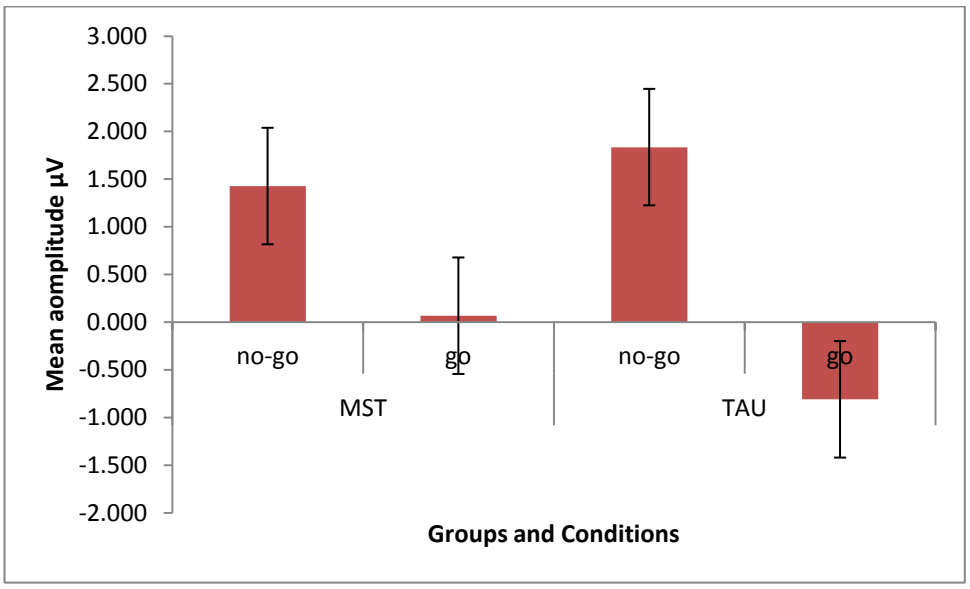

Figure 5: Mean (SE) P3 amplitudes in go and no-go trials for males in MST and TAU treatment groups.

Improvers and Non-improvers

Self report delinquency scores

Shapiro-Wilk tests found that improvers (D(13)=8.70, *p*=.053) and non-improvers (D(14)=.95, *p*=.58) were normally distributed, so a t-test (t(25) =-2.38, *p*=.025) was used to compare these scores and as expected, non-improvers were found to have significantly higher self-reported volume of delinquent behaviour (*M*= 12.79, sd= 8.65) compared with improvers (*M*=6.31, sd=4.80).

Behavioural Data

Prior to examining the EEG data we tested whether there were differences in the error rates between clinical participants and controls. The mean error rates are shown in table 1, separately by group, provocation, and gender.

Table 3: Means and standard deviations for no-go error rates for improvers and non-improvers across provocation level and gender.

	Male				Female			
	Low NoGo error rate		High NoGo error rate		Low NoGo error rate		High NoGo error rate	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Clinical	0.03	0.03	0.05	0.09	0.04	0.04	0.02	0.03
Controls	0.04	0.06	0.02	0.03	0.04	0.07	0.07	0.10

Again, error rates were extremely low, and repeated measures ANOVA found no significant effects or interactions.

ERPs

N2: The ANOVA revealed no main effect for improvement status. An interaction between improvement status and GNG trials approached significance (F(1,23)= 5.20, *p*=.055; *fig. 7*). Post-hoc tests showed that the go-no-go difference was highly significant in the improvers (*p* = .002) but not in the non-improvers (*p* = .50).

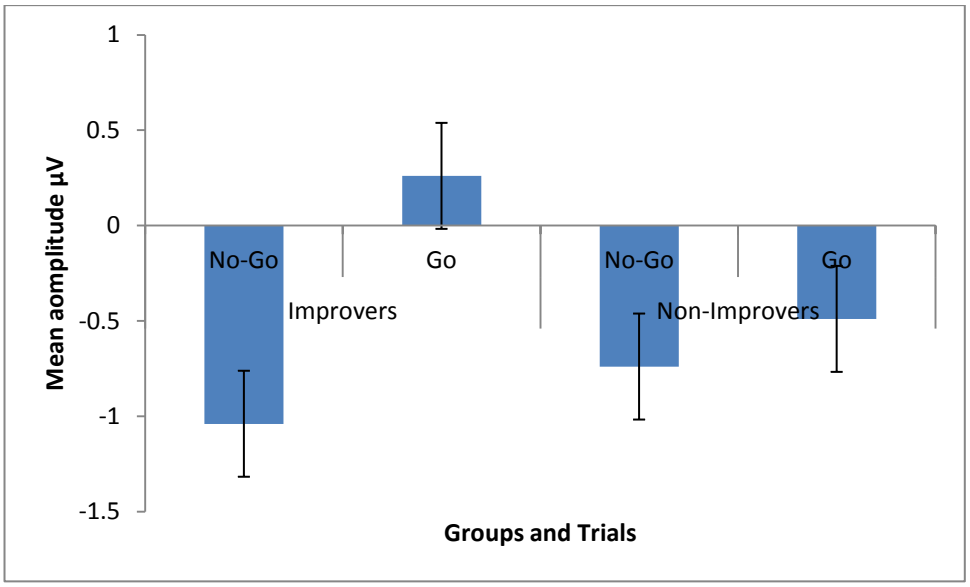

Figure 6: Mean (SE) N2 amplitudes for improvers and non-improvers for go and no-go trials.

An interaction between GNG, improvement status, and sex was also close to significance (F(1,23)=5.37, *p*=.051). Separate ANOVAs for males and females revealed a significant improver x go-no-go interaction for males (F(1,12)= 6.15, *p*=.029), but not females, with male improvers demonstrating a larger difference in

the N2 than male non-improvers (*fig. 8*). Post-hoc tests showed that the difference between go and no-go was significant for the male improvers but not the male non-improvers (improvers, $p = .025$; non-improvers, $p = .10$). There were no other significant main effects or interactions involving improvement status for the N2.

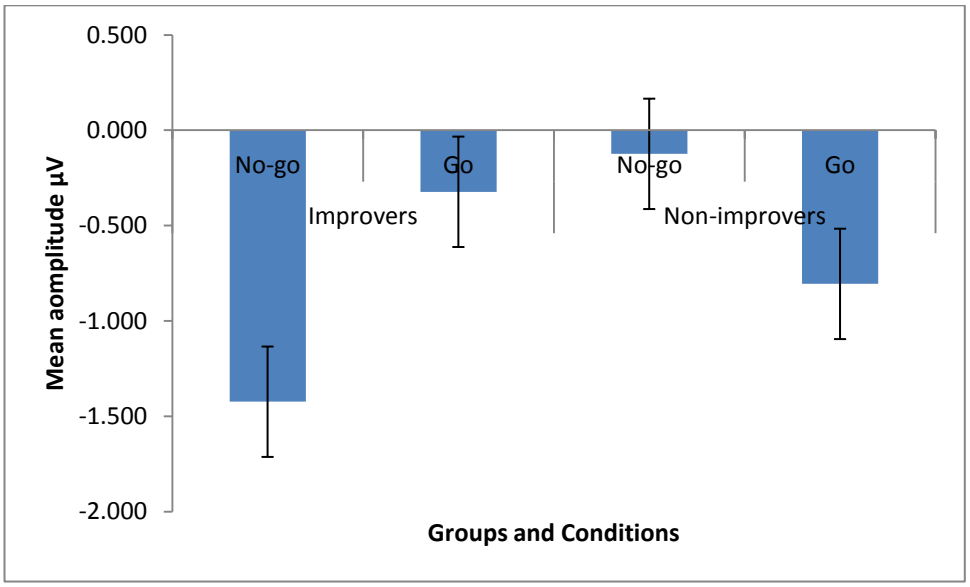

Figure 7: Mean (SE) N2 amplitudes in go and no-go trials for improver and non-improver male participants.

P3: The ANOVA for the P3 revealed no main effects or interactions involving improver status.

Discussion

Externalising disorders are characterised by impulsive behaviours and difficulties in inhibiting inappropriate responses (Kreuger et al, 2002). Previous behavioural studies suggest that children and adolescents with oppositional defiant disorder and conduct disorder exhibit deficits in response inhibition tasks (Oosterlaan et al, 1998). Blair (2005) theorised that children with conduct problems have both an

abnormally functioning inhibitory neural network and an abnormal emotional regulation network, and consistent with this a limited number of ERP studies have shown both deficits in behavioural inhibition performance and abnormal inhibitory N2 and P3 amplitudes (Moadab et al, 2012; Albrecht et al, 2005; & Overtoom et al, 1998). Rubia (2011) on the other hand, suggests that the impulsivity seen in conduct disorder may results from deficits in "hot" ventromedial-orbitofrontal-limbic regions and more related to emotional regulation problems than inhibition problems per se. Two previous studies explored how therapeutic treatment effects in children with histories of behaviour problems related to these neural correlates of inhibition, however they provided unconvincing results (Lewis et al, 2008; Woltering et al, 2011) and their frustrating situation/ mood induction blocks were not presented in ecologically valid or interesting contexts. The current study aimed to build on these previous studies, examining whether N2 and P3 amplitudes differed between clinical and control groups, between MST and TAU treatment groups, and between improvers and non-improvers, and in each comparison exploring how high or low levels of social-competitive provocation influenced the results.

Consistent with past GNG research, no-go trials produced significantly larger N2 and P3 amplitudes than go trials. This was found for both the clinical groups and the control groups, which is also consistent with previous research (Falkenstein, Hoorman, & Hohnsbein, 1999; Bokura et al, 2001). The very low levels of errors on no-go trials suggest that the clear enhanced N2s and P3 are associated with effective early and late inhibitory processes.

With respect to clinical versus control groups, no significant differences were found in N2 or P3 amplitudes. This is consistent with the majority of the studies reviewed in the systematic literature review of conduct disorders in Part One of the thesis including Lewis et al (2008), but contrasts with the pattern of reduced N2 and P3 in reported in systematic reviews of ADHD (Johnstone, Barry, & Clarke, 2013) and substance dependence (Luijten et al, 2014), and also suggested by the finding of reduced P3 in the behavioural genetic studies of the externalising factor (Hicks, Bernat, Malone, Iacono, Patrick, Kreuger, & McGue, 2007). This may indicate that conduct disorders do not have the same abnormal activation of response inhibition related brain areas as these other externalising disorders. This would fit more closely with Rubia's (2011) review of fMRI studies of ADHD and ODD/CDD which suggested that the deficits in cool executive functions regions characterise ADHD but not conduct problems. This is potentially an important finding in respect of how the externalising factor has been linked to the reduced P3 in oddball tasks (Hicks et al, 2007)), since the research on conduct disorder specifically suggests that the inhibitory P3, as seen in explicitly inhibitory tasks, may not show the characteristic reduced amplitude. This may suggest that although the reduced P3 tends to be spoken about having a relationship to impulsivity and disinhibition, its connection to these symptoms in conduct disorder may be indirect. It is possible that the oddball P3, although viewed as having an inhibitory function (see Polich, 2007 for extensive review of how P3 indexes inhibitory functions required for efficient transmission of information and inhibition of extraneous information to support working memory), this may be separate from the "no-go P3" as an index of response inhibition. Of course it is also possible that the current sample would not show the reduced P3 on

an oddball task, and this might be a good way to determine whether these P3s are different, or whether there is something unusual about this sample compared to other externalising samples.

For P3, there was a 3-way interaction between gender, group, and GNG, but interestingly this was in the opposite direction to what might be expected, with the clinical males showing a larger difference between go and no-go P3, an effect not seen in the control males. The result is curious since studies where differences have been seen between groups have tended to show a relationship between externalising, inhibition problems, and reduced no-go P3. In this case, it appears that the clinical males, who would be expected to show the reduced P3, are showing the opposite. Previous research has shown that other factors can influence P3 amplitude, and participant motivation and engagement has been linked to enhanced P3 amplitude (Polich, 2007; Boksem, Mejman, & Lorist, 2005, Polich & Kok, 1995). It is possible that something about the task specifically engaged or motivated the clinical males. One possibility is that the overall social-competitive nature of the task, and the financial reward was particularly appealing to these participants and they may have overcome inhibition deficits through effort and attentiveness. The idea that they were particularly responsive to competition or reward also evokes Quay's (1993) application of Gray's (1991) theoretical behavioural activation system (BAS) and behavioural inhibition system (BIS) to conduct disorder. Quay (1993) argued that while ADHD appears characterised by underactive BIS but intact BAS, children with ODD/CD have an overactive BAS, which is sensitive to rewards, and an unimpaired BIS, sensitive to punishment (Albrecht et al, 2005). One might speculate that clinical males were particularly engaged by the potential rewards, perhaps reflecting BAS

over-arousal. This would perhaps also help account for the lack of interactions with provocation level as clinical males may have been less responsive to different levels of punishment. Another ERP that has been related to punishment is the Error Related Negativity (ERN) which has been shown to be reduced in response to punishment conditions in participants with externalising conditions including substance abuse (Franken, Van Strien, Franzek, & van de Wetering, 2007) and externalising factor (Hall et al., 2007). Interestingly, like N2 and P3, ERN is generated by the ACC and is suggested to play a role in error monitoring (Weinberg et al., 2012). ERN responses to punishment in conduct disorder have not been reported in peer reviewed journals, however my research collaborator, Michael Eisen, has studied the ERN in the current sample. A valuable future project would be a comparison of the ERN, N2 and P3 ERPs as this may provide insight into the clinical samples responsiveness to punishment.

There were no differences in N2 and P3 response between those who received MST versus those who received TAU, however, there was another gender by GNG interaction in which TAU males demonstrated a larger difference between go and no-go P3 than the MST males. It is possible that the TAU participants show this enhanced P3 no-go>go effect due to higher task engagement than their MST counterparts. It seems more likely that they are working harder, able to engage more resources to successfully inhibit, rather than that they have actually shown greater improvement than the active treatment group.

It is noteworthy that a very different picture emerged for the improvers versus non-improvers. In contrast to the previous comparisons, there were no effects for P3

at all. This is somewhat in line with the findings of Woltering et al. (2011), who reported reduced inhibitory P3 was associated with clinical status but that P3 was not responsive to treatment effects. No main effects were found for N2, but there was an interaction that was close to significance between improvement status and GNG whereby non-improvers did not show a difference between no-go and go N2s, while improvers did. This trend fits the hypothesised outcomes. This result was seen also in interaction between gender, improvement status, and GNG that was also at trend level, with only male improvers showing a significant difference in N2 go vs no-go. Although it is tempting to suggest that these results better fit the hypotheses, it is important not to read too much into trends. It is important to note that the sample sizes for the improvers and non-improvers were necessarily smaller because only the upper and lower quartiles of the clinical groups were used in the analysis, and this reduces statistical power. On the other hand, it might also be expected that these more extreme ends of the spectrum do better represent the picture suggested by the literature. The finding that male participants had a particular interaction with improvement and GNG is worthy of further research.

This study replicated the well-established finding of enhanced no-go versus go N2 and P3 across all participants. However, the comparisons of clinical/control, MST/TAU, and improver/non-improver groups provided unexpected results which are not easy to explain only with reference to the literature. The findings raise some interesting questions for further research on the neural correlates of inhibition and treatment effects. Firstly, the finding that male clinical participants, and particularly those who were in the TAU group, appear to have to have responded to the experimental task in a different way to other participants, possibly because of greater

engagement or motivation is worth further investigation. A possible direction for this research would be include a non-competitive "cold" inhibition task to compare with the social-competitive "hot" task. Other potentially motivating features might also be manipulated, such as varying the level of reward that participants are told they can achieve.

The study does not clarify whether ERPs are helpful for tracking treatment outcomes, which was also true of the previous studies which compared children pre and post CBT/parent management training (Lewis et al, 2008; Woltering et al, 2011). This is suggested to still be an area where further research could be helpful since this if ERPs can be shown to reliably index and predict treatment outcomes this could have clinical implications in terms of development of diagnostic and prognostic tools.

With regards to investigating neural correlates of treatment, the study demonstrates that there were differences between the MST and TAU group however this was not in the expected direction, although as noted this is cautiously interpreted in the context of possible influences of the experimental task on the engagement of the clinical males. As such it is not possible to make strong conclusions about the importance of improved response inhibition to the success of MST, or indeed the role of MST in improving response inhibition. The study was not intended as an evaluation of the effectiveness of MST, but rather made use of an opportunity sample to explore treatment effects.

There are several limitations to the current study. Firstly, although we found some gender interactions, it is worth bearing in mind that the statistical power to

detect interactions would have been limited due to the small sub-group sizes. While the comparisons of clinical versus control groups likely had sufficient power, the MST versus TAU, and particularly the improvers versus non-improvers comparisons involved much small samples, and the ability to detect real effects is therefore limited.

A further limitation was the absence of baseline measurement of EEG and some other baseline measure of inhibition (for example a standardized inhibition/impulsivity self report scale). Such baselines would have been a helpful means to establish if there were no differences in EEG (ERPs) measure of inhibition and inhibitory capacities before the treatment (which was assumed to be the case). We relied on randomisation as the means to manage this issue. It is possible that with the somewhat small sample that randomisation could not guarantee control for such differences. Measuring the ERPs at pre and post treatment, following the method used by Woltering et al (2011) would have been preferable, but unfortunately this was not an option since the main study was underway when the current study was designed.

Similarly, the approach to identifying treatment effects and particularly choosing the improvers and non-improvers was not ideal. The SRD is not a standardised measure and is not particularly well suited to measuring outcome change. Of the instruments available that had baseline and at EEG testing date data it was considered the most relevant to measurement of delinquent behaviours, but it was limited in not allowing a meaningful interpretation of symptom severity. Future research would benefit from using a widely used standardised measure such as the

Child Behaviour Check List (CBCL). The SRD showed a significant difference between the clinical and control participants however it was not clear how severe either group was and in fact the clinical group had a relatively low score considering the large range of possible scores. It is possible that no ERP differences were found because these while the scores were significantly different statistically, they may not have been significantly different clinically. A limitation of taking only upper and lower quartiles is that although this gives the more extreme ends of the ranges, the loss of the middle section of participants would reduce statistical power for analysis.

It is possible that the clinical group had participants who were comorbid for conduct problems and ADHD since unfortunately we were unable to administer a measure of ADHD symptoms to rule this out. Such comorbidity could have influenced the ERP results, for example Albrecht et al (2005) found that while ADHD only and ODD/CD only groups had reduced N2, this was only at trend level for participants with combined ADHD/ODD/CD, whereas Overtoom et al (1998) found that participants who were comorbid for ADHD /ODD had significantly reduced N2 compared to controls, while those with ADHD alone did not. Rubia (2011) suggests that the two disorders have deficits in different circuits, with ADHD showing impairments in cool inhibition related regions conduct disorder showing impairments in emotion regulation, so if there were significant levels of ADHD in the clinical group, this might have been shown in significantly reduced N2 and P3 amplitudes.

Similarly, we did not conduct an analysis of current and past internalising symptoms, which in respect to the mixed results reported in the emotional GNG

tasks (Lewis et al, 2008; Woltering et al, 2011) may be valuable. Given that Woltering reported enhanced N2 in their externalising group, who were found to have a degree of comorbid anxiety, it is possible that this enhanced N2 effect might hide a more typical reduced N2 effect. On the other hand, this result (Woltering et al, 2011) was unusual among the other emotional GNG studies and more recent research (Hum, Manassis, & Lewis, 2013) has reported reduced N2 in relation to internalising symptoms. It is apparent that this area of research has yet to reach a consensus on the patterns and meaning of N2 and P3.

Other limitations relate to the design of the task. The current study made use of an existing experimental design which was employed by another research project. Part of this original design included features such as go and no-go stimuli with flankers, and while this was managed in the current study by only using congruent trials, an improvement would be using stimuli without distracting flankers.

A possible limitation was the length of the testing sessions. The session included two ERP tasks and last around 2.5 hours. It is possible that participants would have shown fatigue effects by the later stages of the session. This was managed by the researchers through maintaining their engagement and we did not detect signs of fatigue effects between start and end of the session. However, an improvement for future research would be to shorten the testing session, perhaps by only using one task.

Professional and Clinical Implications

One of the potential professional and clinical issues explored by the study is whether the N2 and P3 are reliable biomarkers for deficits in inhibition in children and adolescents with conduct problems, and whether these markers are sensitive to treatment related changes. The study did not find evidence to support this idea and therefore caution is recommended in regards to using the inhibitory N2 or P3 diagnostically, or to track or predict treatment outcomes in this population. Interestingly, Hum, Manassis, & Lewis, (2013) have reported that in children with primary diagnoses of anxiety disorders, the inhibitory N2 appears to be an indicator of treatment response, and another ERP, P1 which is believed to reflect attention and/or arousal may serve as a predictor of treatment outcome. This suggests that further research into the use relationship between ERPs and treatment effects would be beneficial.

The issue of whether the inhibitory P3 is separate from the oddball P3 is also worthy of further research. The finding that reduced P3 in oddball tasks is strongly associated with externalising has typically also corresponded with individual externalising disorders showing reduced P3 in inhibitory tasks. This may not be the case for conduct disorders. Care should perhaps be taken when thinking about what the externalising conditions have in common (apparently impulsive and disinhibited behaviour) to explore in more depth what may surprisingly differentiate them (different responses on explicit tests of response inhibition).

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Part 3: Critical Appraisal

The following section presents my critical reflections on the research process. I begin by briefly outlining my interest in the topic and approach, then discuss some of the challenges and advantages of conducting a study that was part of an existing research project. I then consider how the literature review connects with the empirical study.

Topics, Approaches, and Assumptions.

My interest in the topic of the research derived from a number of factors. My pre-training experience was primarily in work with children and adolescents with severe conduct problems, both in the community when I worked as an Assistant Psychologist in a service that was partly inspired by the Multi-Systemic Therapy approach, and prior to this as a care worker in children's homes with young people who had been placed in care because of their behaviour. I was keen to continue to develop my understanding about this population of young people, whom I have found extremely engaging and rewarding to work with. Secondly, my previous research experience, during an MSc in Health Psychology, utilised a qualitative approach to understand the experiences of staff on a neurorehabilitation ward in their work with adolescent males who had suffered traumatic brain injury, and in particular how they constructed meaning in regards to the challenging behaviour they encountered. While I enjoyed the qualitative approach, I was drawn to the opportunity to approach understanding behaviour difficulties in from a quantitative experimental perspective, and particularly the chance to work with a psychophysiological approach such as the Event Related Potential technique to actually study the neural processes underlying behaviour. The experience has given me a new insight into this approach to research and a respect for the time and hard

work required to undertake such a project. While I had previously assumed that wrestling with an individual's subjective constructions of meaning was not only more enjoyable, but also more challenging, I have realised that conducting and analysing an experimental study can be equally as fascinating, but also unexpectedly enjoyable and certainly challenging.

The Research Process

Design issues

While in my previous experience of research I had thought about a question I wanted to answer and had then chosen an approach and designed a protocol to answer that question, the experience of conducting my doctoral thesis research was somewhat different. This was largely because the opportunity to take part in an ERP study was afforded to me because another larger project was already underway and was using an experimental protocol that was adaptable enough to allow for multiple research projects. This meant that a significant challenge was choosing a research question that I could approach given the experiment that was already in progress. The experiment consisted of an number of different components, including an "imitation inhibition" task which involved following instructions to press a button with either the first of second finger while viewing a hand on screen that made either congruent on incongruent movements and therefore provided a novel interference inhibition task, and the go/no-go (GNG) task. The GNG task itself had a number of elements including flanker stimuli, different levels of punishment (financial) that were administered and received by the participants, and virtual opponents that punished at high or low levels. In addition to these task parameters, a number of

questionnaires measured facets such as callous-unemotional traits and self reports of delinquent behaviour. These factors suggested that the most appropriate research questions would be around response inhibition, which the GNG is classically used for response inhibition trials (eg. Bokura, 2001), response to flanker interference, response to reward and punishment, aggressive responsiveness, etc. It would have been difficult to have used all the aspects of the experiment without replicating the experiment being run by Jamie, so when I decided to focus on inhibition, using the N2 and P3, this required a number of task elements to become redundant to my research question. Although this was not hugely problematic, there were probably unintended (from my perspective) effects going on in the task. An example was the flanker stimuli which may have influenced attention, or led participants to think about irrelevant (from my perspective) aspects of the task, or perhaps increased fatigue due to additional cognitive processes. The interference effect was controlled for by only using congruent trials. The disadvantage of reducing the number of trials is that it reduces the reliability of the recorded ERPs, since the effects are typically small but can also vary between trials (Luck, 2005).

Because the experiment had already been designed and set up, we were in the fortunate position of not having to spend time and effort designing the protocol ourselves or creating the materials needed for the experiment. We were lucky to have a complex computer based task to use, although it would have been a good learning experience to have developed skills in using Eprime.

An important aspect of the study that was particularly appealing in terms of relating the research to clinical interests was the fact that a clinical sample had been

recruited, and furthermore, that they were part of a large and important national trial of MST. I was particularly interested in seeing whether the ERP technique could be used to distinguish the clinical and non-clinical participants, and particularly whether the ERPs could be used to identify treatment effects. Unfortunately, because we did not have the opportunity to measure ERPs of clinical participants before the start of treatment, since the project started after the START MST trial, we had to improvise an alternative way to identify improvers and non-improvers, using change in the self-report of delinquency scores. This approach is not ideal since the self-report measure relies on honest reporting by the participants, and since this is an indirect measure, while testing before and after a treatment is a much more direct approach.

Although having to fit a research question to an existing experiment raised some limitations in terms of what sort of research was possible, I did not find this overly restrictive and was pleased to be able to investigate inhibition in young people with behaviour problems. Furthermore, my sense is that the advantages of joining the project far outweighed any disadvantages. An early benefit was that we were not required to submit a study proposal to a Regional Ethics Committee since the main experiment had already been granted this. We were able to have minor amendments accepted swiftly. Based on previous experiences of applying for ethics in the NHS I was aware of how lengthy a process this could be. Instead we were able to begin data collection relatively quickly, which was important given how long this actually took.

Data Collection

I was jointly responsible for recruiting the healthy control sample, since the clinical samples (those having Multi-Systemic Therapy and those receiving

Treatment as Usual) had already been recruited. For me the recruitment process was one of the more stressful parts of the research process as there were phases when we struggled to get through to the schools we had identified as in the appropriate geographical areas, or did not hear back from them despite having been told they were interested in the project. We discovered that a good strategy was to speak directly to the heads of science or available science teachers and to offer to visit the school or colleges to give presentations on the project. We explained that participation in the project was an experience that we thought the pupils would find enjoyable and educational, and that we thought that it would particularly appeal to students interested in science subjects. We were fortunate to get in contact with a number of enthusiastic science teachers who helped promote the project and encouraged students to get involved. We were able to recruit the required number of students and matched the clinical samples in regards to age and gender. While the recruitment of participants was successful, it made clear the importance of starting this process early and being flexible and creative in our approach. Having identified participants who registered their interest in the study, we faced high levels of attrition throughout the testing phase. This may partly have been due to the length of time between initial recruitment and the date of the actual testing session, as we were told by a number of the young people or their parents that they had been interested at the time but had lost their enthusiasm. We had much greater success when we were able to contact students and quickly book them in to attend at testing session within a couple of weeks, and we stressed the importance of either attending letting us know if they needed to cancel. However, we still found that a large number of potential

participants simply failed to attend sessions, or more rarely, cancelled at the last moment.

I was quite surprised at the high level of attrition and non-attendance because in addition to thinking that the project would be interesting to the young people, I also believed that the financial compensation was quite substantial and I expected the young people to be keen to claim this. This might suggest that the participants who attended were particularly interested in the project, or thought that it would be fun, or indeed that they were particularly motivated by the financial incentive. One of the interesting findings of the research was the unexpected finding that clinical male participants showed a bigger difference between no-go P3 (which was enhanced) and go P3. One possible explanation for this was that they were particularly motivated to focus and attend during the task, and this may have led to the enhanced no-go P3 effect. It is perhaps possible that this was partially an effect of the recruitment process in the sense that young men who were particularly motivate by rewards were the ones who attended, and those who did not attend may have shown a different pattern of results. This is just speculation and does not explain why the males who attended showed the effect relative to the females, and relative to the control group.

The running of the sessions themselves was also challenging at times. We benefited greatly from having substantial training from Jamie Sheffield, our PhD research collaborator, in how to apply the EEG net and how to run the relatively complex experimental protocol, but we nonetheless made a number of mistakes over the course of the data collection phase. On one occasion for example, a broken electrode net was applied to a participant and we only realised this after they had

completed the approximately two and a half hours testing session and we had congratulated ourselves on another successful session. This was certainly frustrating, but also a significant waste of our time and resources. On several occasions in the early part stages of the project we attempted to apply nets that were the wrong size leading to wasted time and quite probably discomfort for the participants, thought they were typically too polite to complain. A quick application of the net was one of the most important and challenging aspects of the process since taking too long would like mean we would lose the interest and attention of the participants, which be likely to affect their performance on the task (Luck, 2005).

Maintaining the engagement of the young people was an important aspect of the procedure since fatigue, motivation, and attention affect ERP recording (Luck, 2005). This was something we prioritised in our division of labour, such that when one of the researchers was applying the net and then making sure each of the 128 individual electrodes had a good conductance level which was a process that could take around 25 minutes on average, the other researcher chatted to the participant to keep them awake and engaged. A number of the participants asked at these points, and during brief breaks in the testing if they could drink coffee or have a cigarette, but unfortunately this had to be refused since both can influence ERPs. The testing sessions lasted around three hours and although attending the session was perhaps initially exciting and interesting for the participants, the tasks required a large number of trials to gather reliable data (Luck, 2005) and the simple tasks quickly became repetitive. Nonetheless, for the most part we found that the participants remained engaged. I am very grateful to the patience and enthusiasm of the participants.

ERP Analysis

The primary challenge relating to the analysis was learning how to use various software required to process the data for analysis. These tools appeared relatively esoteric and took some time to became familiar and somewhat competent with. The analysis itself was conducted using SPSS. Statistical analysis is one of my strengths as a researcher and I am grateful for the advice and support that Professor Pasco Fearon provided for this.

The Writing Process

The most challenging part of the research process was by a long way the writing up of the thesis. This was in part a reflection of difficulties that I had in effectively managing time between clinical placement commitments and the research process. One significant error that contributed to my difficulty in writing and indeed getting to grips with the topic was that I delayed starting the literature review on multiple occasions. Initially this was because I struggled to settle on one topic. There have actually been a number of iterations of the literature review, including a focus on the range of behavioural studies used to measure different types of response inhibition, a review of psychophysiological indices of psychological treatment outcomes, and the eventual topic of ERP and fMRI correlates of inhibition in conduct disorders. I have recognised the importance of choosing a topic for a given piece of work, and sticking with it, and also the importance of simply completing a task that needs to be completed. My experience was that the longer the delays went on, the more difficult it became to pick up the task again. This became particularly difficult when I was also doing full time clinical work. While I greatly enjoyed the practical aspects of conducting an experiment, the writing process has been a

significant challenge. It is something that I hope to get better at because there have also been times when I greatly getting into the results and writing about them. I will certainly endeavour to learn from the experience and to better organise my time, allow myself to commit to one idea, and to then get the work done as efficiently as I can.

Conclusions

The empirical research process was an enjoyable process for the most part. It was particularly good to be part of a research team which felt supportive and enabled me to develop new skills. The importance of preparing contingencies from the earliest stages was made apparent through this process, particularly is respect to the high attrition rates.

Reflections on the Findings

The literature review revealed a much more mixed picture of the neural correlates of inhibition in childhood and adolescent conduct problems than I had expected. The behaviour-genetic literature on externalising problems showed reduced P3 in oddball tasks as a biomarker for impulsivity and disinhibition problems (Hicks et al, 2007), and the reviews of ADHD (Johnstone, Barry, & Clarke, 2013) and substance dependence (Luijten et al, 2014) showed reduced N2 and P3 associated in the clinical groups during inhibition relative to controls. These findings appeared consistent, and I expected conduct problems to show a similar pattern. The mixed results made me more cautious about the results of my own empirical study and rather than state a directional hypothesis, for example that conduct problems would be associated with reduced N2 and P3 I remained open minded. Similarly, the

two studies that used N2 and P3 to reflect treatment effects (Lewis et al, 2008; Woltering et al, 2011) provided somewhat contradictory results, with Woltering et al (2011) finding the clinical group had enhanced reduced P3, but enhanced N2 compared to the clinical group, and Lewis et al (2008) finding no difference in N2 between clinical and control groups and also no change in N2 relative to treatment effects. Woltering et al (2011) on the other hand reported reduced N2 amplitude for improvement but no change in P3. My results similarly lacked the clarity that appeared to have been seen in ADHD and substance dependence reviews. While the mixed results of the literature review may be more of a reflection of the limited research conducted in the area, and the wide range of variations of tasks and samples used, my own study used quite clearly distinguishable participant groups and used a relatively simple task. The absence of main effects for N2 and P3 in the inhibitory task in conduct problems may indicate that as a disorder it does is not as defined by inhibition deficits as those other externalising problems.

Our finding that clinical male participants had larger differences between P3 amplitudes for go and no-go trials is intriguing, as described above, and is worth further exploration.

The lack of effect for different levels of provocation may suggest that the participants were not worried by higher punishments, but perhaps a more plausible explanation is that N2 and P3 were not responsive to these factors. The ERN may be a better ERP to pick up these effects and it may be valuable to analyse ERN alongside N2 and P3 in future studies.

Clinical/Professional Implications

One clinical area that I was hopeful might see developments from research in this area is the use of ERPs, which are a relatively inexpensive and non-invasive measure, to help track treatment effects and perhaps be used as diagnostic and prognostic tools. It would appear that more research is needed and indices of inhibition may not be the most appropriate for this purpose.

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Appendix A: Information Sheet (Participant)

Information Sheet

The Neurobiological Correlates of Aggression and Empathy in Adolescence.

Version 1.1, 17.02.2014

London Queens Square REC reference Number : 12/LO/0733

We would like to invite you to take part in this research study. However, before you make your decision, we want to make sure you understand why the research is being done, and what your involvement means. Please take some time to read the following information about the study, and talk it through with anyone you wish. If there is anything that you don't understand, or if you would like to ask some more questions, please feel free to contact one of the researchers (contact details can be found at the end of this sheet).

What is the purpose of this study?

This study is looking at how problems with self-control and aggression might be related to activity in the brain. Part of this project involves studying a group of teenagers who have had significant difficulties in these areas, such as breaking the law or repeatedly getting into fights. We also need a group of teenagers that have not had these difficulties so that we can compare them. We are contacting you to be part of this second group of adolescents who have not experienced these difficulties. This study will be looking at brain activity that

occurs when young people are dealing with several common situations, like winning or losing, dealing with stress and with situations requiring empathy. This will be done by looking at brain activity and behaviour whilst teenagers play two computer-based games. Ultimately, we hope this project will help us to find better ways of supporting teenagers that get into trouble in the future.

We measure brain activity using a completely safe and harmless net that is worn on your head. This net measures the tiny electrical changes (called EEG) that your brain naturally makes when you are thinking, perceiving, or responding. We are not looking to see if there is anything wrong with you, or to see if there is anything abnormal about your brain activity, and it is not possible for us to determine this. We are only interested in how brain activity relates to behaviour during the games, and comparing this between the two groups of teenagers.

Why have I been invited?

You have been invited because you are a teenager between the ages of 13 and 20.

Do I have to take part?

No, it's up to you. After reading this information sheet, we will go over all the tasks that you will be asked to complete, and you may ask any questions to help you decide whether you would like to participate. If you do, you will be asked to sign a consent form before the session begins. If at any point you want to stop, you can stop without giving us a reason. If you wish your data to be removed from the study upon your withdrawal, then we will do so. Any data that we do store will be kept strictly confidential.

What will I have to do if I take part?

We will invite you to a testing session at the Developmental Neuroscience Unit in the Anna Freud Centre, which is in North London, close to Finchley Road and Swiss Cottage Underground stations.

The study session is around two and a half hours long, and in that time you will complete 2 tasks on a computer whilst having an EEG recording. The first task, called the mirror neuron task, is a computer based reaction time game where you will be copying, or ignoring, hand movements as quickly as you can. This task helps us understand how teenagers are influenced by others and how they understand the actions of other people.

The second game is another reaction time game, which you will play against two other people, where you have a chance to win money. The player who is fastest will receive a small amount of money, and get to decide the punishment for the other player (how much money they lose). Depending on what you (or your opponent) chooses, the punishment will be accompanied by either a relatively loud or a quiet blast of white noise. The loud blast of white noise will not be painful, but it will be slightly uncomfortable. It is not loud enough to do any harm. This task helps us to see how children manage mildly challenging situations and competitive situations.

Finally, between the tasks, you will also be asked to complete a short questionnaire pack about your behaviour and how you get on with other people. This will take roughly 45 minutes to complete.

Description of the EEG recording

While you are doing the computer tasks, you will be wearing an EEG sensor net. The brain gives off small amounts of electricity at all times, and the EEG net lets us monitor and measure changes in these electrical signals, which can indicate changes in brain activity as you think of feel different things. However, you cannot tell *what* you are thinking!

The sensor net is made up of soft sponges sitting in small plastic tubes, which are held in place using an elastic net that stretches over your head. These

sponges are placed in contact with your scalp and are what pick up the changes in electrical activity in the brain.

To place the net on you, we will not have to anything to your hair, but we will have to soak the net in a saline (salt water) and shampoo solution. This will help conduct the electrical signals across the scalp, letting us get a good reading of the brain's electrical activity. The whole process should take around 15 minutes.

The EEG itself is very safe and the net that we are using has been approved for safe use with human participants. Given that the net needs to be soaked in saline and shampoo solution before it is applied to your head, you will feel a mild dampness while it is there. Occasionally, some people report a mild itchiness whilst the solution dries, but this will tends to disappear quickly.

Expenses and Payment

You will receive £30 for coming in and taking part, as well keeping the money you win in the competitive reaction time game. We will also refund your travel expenses, as long as you provide us with a receipt of travel.

What are the disadvantages of taking part?

As far as we can foresee, there shouldn't be any disadvantages from participating this study. The reaction game against another person may involve some mildly unpleasant sounds if you lose, which may be briefly uncomfortable, but will be played at a safe volume and won't be painful.

Will my participation in the study be confidential?

Yes. All the data that we collect will be kept completely anonymous and will only be used for research purposes. We will not store it with your name or any of your contact details, and once you have participated in the study, your

data will be given an anonymous identification number and your name and contact details will be deleted. No one will be able to identify you based on the data you give us.

If you decide that you want to be contactable for future studies, your contact information will be stored completely separately from any data we gathered in relation to this study, and will be stored in a secure location (either a locked filing cabinet or a secure server).

Some study documents may also be looked at by authorised representatives from University College London (UCL) Research & Development Unit to check that the study is being carried out correctly. Professional standards of confidentiality will be followed by the authorised representatives. The handling, processing, storage and destruction of data will be in accordance with the UK Data Protection Act 1998.

What will happen to collected data?

All data that we collect during the study will be made anonymous, and will be stored securely, only accessible to the research staff who are working on the study. Once we have collected all the data, we hope to report our findings in academic journals, and present the findings at conferences. There will be no way of identifying you in any of the reports or publications that result from this study.

If you would like to be informed of what the research team finds from the study, we would be more than happy to contact you with the findings. You will be asked to put your name and contact details on a list of those who would like to be contacted about the results of the study. This will be securely stored and then once the information has been sent to everyone, the list will be destroyed.

What happens if I want to make a complaint?

If you wish to complain, or have any concerns about any aspect of the way you and/or your child have been approached or treated by members of staff due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask the researchers if you would like more information on this.

If you still have concerns after you leave, or you wish to make a formal complaint, you may contact the principle investigator, Peter Fonagy, or the UCL Head of the Division of Psychology and Language science, David Shanks, all of whose details can be found at the bottom of this sheet.

Who is funding the research?

The research is being organised and funded by the Anna Freud Centre, a University College London affiliated research centre, and University College London.

Who has reviewed this study?

All research is reviewed by an ethics committee to ensure the protection and proper treatment of all who participate in the study. This study has been reviewed by the London Queen Square REC.

If you have any questions about the study or your participation in the study, please feel free to contact:

Vicki Chow, James Hanley, Michael Eisen

To make a formal complaint, please contact one of the people

below:

Professor Peter Fonagy

[redacted]

Professor David Shanks

[redacted]

Appendix B: Information Sheet (Parent/Guardian)

Information Sheet - Parents and Guardians

The Neurobiological Correlates of Aggression and Empathy in Adolescence.

Version 1.1, 17.02.2014

London Queens Square REC reference Number: 12/LO/0733

We would like to invite your child to take part in this research study. However, before you decide, we want to make sure you both understand why the research is being done and what your child's involvement means. Please take some time to read the following information about the study, and talk it through between the two of you, and anyone else you want. If there is anything that you don't understand, or if you would like to ask some more questions, please feel free to contact one of the researchers (contact details can be found at the end of this sheet).

What is the purpose of this study?

This study is looking at how problems with self-control and aggression might be related to activity in the brain. Part of this project involves studying a group of teenagers who have had significant difficulties in these areas, such as breaking the law or repeatedly getting into fights. We also need to see a group of teenagers that have not had these difficulties so that we can compare them. We are contacting you and your child to be part of this second group of adolescents who have not had these difficulties. The study will be looking at brain activity

that occurs when young people are dealing with several common situations, like winning or losing, dealing with stress and with situations requiring empathy. This will be done by looking at brain activity and behaviour while teenagers play two computer-based games. Ultimately, we hope this project will help us to find better ways of supporting teenagers that get into trouble in the future.

We measure brain activity using a completely safe and harmless net that is worn on your head. This net measures the tiny electrical changes (called EEG) that your brain naturally makes when you are thinking, perceiving, or responding. We are not looking to see if there is anything wrong with your child, or to see if there is anything abnormal about their brain activity, and it would not be possible for us to determine this. We are only interested in how brain activity relates to behaviour during the games, and comparing this between the two groups of teenagers.

Why has my child been invited?

Your child has been invited because they are a teenager between the ages of 13 and 20.

Do they have to take part?

Not at all. Their participation is up to the two of you. After reading this information sheet, we will go over all the tasks that your child will be asked to complete with both of you, and you can ask any questions to help both of you decide whether your child will participate or not. If you are both happy with the answers to your questions and would like to take part in the study, you will be asked to sign a consent form before the session begins. If at any point you or your child wants the session to stop, you can stop it without having to give any reason. If you want your child's data to be removed from the study upon your withdrawal, then we will do so. All your child's answers will be kept completely anonymous and will only be used for research purposes. Any data that we do store will be kept strictly confidential.

What will my child have to do if they take part?

We will invite you and your child to a session at the Developmental Neuroscience Unit in the Anna Freud Centre, which is in North London, close to Finchley Road and Swiss Cottage Tube stations.

The study session is around two and half hours long, and in that time your child will complete 2 tasks on a computer whilst having an EEG recording being taken. The first task is called the mirror neurone task. All that will be required of your child is to copy or ignore the action of a hand on a screen. This task helps us understand how teenagers are influenced by others and how they understand the actions of other people.

The second task is a reaction time game where they will be playing against two other people, and the first one to press a correct key will get to decide how what kind of punishment the other player will get. Depending on what your child (or their opponent chooses) it will either be a relatively loud or quiet blast of white noise. The loud blast of white noise will not be painful, but it will be slightly uncomfortable. It is not loud enough to do any harm. This task helps us to see how children manage mildly challenging situations and competitive situations.

Between the behavioural tasks, we will also ask your child to complete a short questionnaire pack about their behaviour and how they get on with other people. These should take roughly 45 minutes to complete.

Description of the EEG recording

While they are doing the computer tasks, they will be wearing an EEG sensor net. The brain gives off small amounts of electricity at all times, and the EEG net lets us monitor and measure changes in these electrical signals, which can indicate changes in thoughts or in feelings. However, you cannot tell *what* they are thinking.

The sensor net is made up of soft sponges sitting in plastic tubes, which are held in place using an elastic net that stretches over your child's head. These sponges are placed in contact with your child's scalp and are what pick up the changes in electrical activity in the brain.

To place the net on them, we will not have to do anything to their hair, but we will have to soak the net in a saline (salt water) and shampoo solution. This helps us get a good reading of the brain's electrical activity. The whole process of applying the net should take around 15 minutes.

The EEG itself is very safe and the net that we are using has been approved for safe use with human participants. Given that the net needs to be soaked in a saline and shampoo solution before it is applied to your child's head, they will feel a mild dampness while it is there. Occasionally, some people report a mild itchiness while the solution dries, but this disappears quickly.

Expenses and Payment

Your child will receive £30 for their participation in this study, as well as the money they win on the second reaction time game. We will also refund both of your travel costs to get here, as long as you provide us with a receipt of travel.

What are the disadvantages of taking part?

As far as we can foresee, there should not be any disadvantages for either of you from participating in this study. The reaction game against another person involves some mildly unpleasant noise if your child loses, which may be briefly uncomfortable, but will be played at a safe volume and will not be painful.

Will my child's part in the study be confidential?

Yes. All the data that we collect will be kept anonymous (stored with just

a numerical code) and will only be used for research purposes. All your personally identifying information (e.g. name, address, telephone number) will be kept securely, not passed on to anyone else, and will be kept separate from the rest of the data that we collect as part of the study. Please note however that by law we are required to inform relevant authorities if we were to become extremely concerned about a child's safety. We would always endeavour to talk to you about this before taking any action.

Some study documents may also be looked at by authorised representatives from University College London (UCL) Research & Development Unit to check that the study is being carried out correctly. Professional standards of confidentiality will be followed by the authorised representatives. The handling, processing, storage and destruction of their data will be in accordance with the UK Data Protection Act 1998.

What will happen to collected data?

All data that we collect during the study will be made anonymous, and will be stored securely, only accessible to the research staff that are working on the study. Once we have collected all the data, we hope to report our findings in academic journals, and present the findings at conferences. There will be no way of identifying either of you in any of the reports or publications that result from this study.

If you, or your child, would look to be informed of what the research team found from the study, we would be more than happy to contact you both with a summary of the findings. You will be asked to put your name and contact details on a list of those who would like to be contacted about the results of the study. This will be securely stored and then once the information has been sent to everyone, the list will be destroyed.

What happens if something goes wrong?

If you wish to complain, or have any concerns about any aspect of the way you and/or your child have been approached or treated by members of staff due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this.

If you still have concerns after you leave, or you wish to make a formal complaint, you may contact the principle investigator, Peter Fonagy or the UCL Head of Division of Psychology and Language science, David Shanks, all of whose details can be found at the bottom of this sheet.

Who is funding the research?

The research is being organised and funded by the Anna Freud centre, a University College London affiliated research centre, and University College London.

Who has reviewed this study?

All research is reviewed by an ethics committee to ensure the protection and well treatment of all people who participate in the study. This study has been reviewed and given a favourable opinion by the London Queens Square REC.

If you have any questions about the study or your child's participation in the study, please feel free to contact:

James Sheffield

[redacted]

To make a formal complaint, please contact one of the people below:

Professor Peter Fonagy

[redacted]

Professor David Shanks

[redacted]

Appendix C: Consent Form (Participant)

Consent Form – Confidential

Project Title

The Neurobiological Correlates of Aggression and Empathy in Adolescence.

Researcher(s): Prof. Peter Fonagy, Prof. Pasco Fearon, James Sheffield, Chia Chi Chow, James Hanley, Michael Eisen.

Version 1.1, 17.02.2014

REC reference number: 12/LO/0733

Participant Identification number: _____

Please tick the box in front of each statement to indicate consent.

- ☐ I confirm that I have read and understood the information for the above study.
- ☐ I confirm that I have had time to think about and ask any questions about my participation in the above study.
- ☐ I understand that my participation in this study is voluntary and it's completely in my rights to withdraw any at point without needing to give a reason.
- ☐ I agree that the anonymous findings from this study can be used in scientific publications and reports. I understand that my identity will not be revealed, nor will I be identifiable from the data I provide.
- ☐ I agree to take part in the above study.

Please circle Yes or No for the following statements

1. I would like to be contacted in the future about opportunities to participate in research **Yes / No**

2. I would like to be contacted with information regarding the findings of this study **Yes / No**

_____	_____	_____
Participants name	**Participants signature**	**Date**

_____	_____	_____
Researchers name	**Researchers signature**	**Date**

Appendix D: Consent Form (Parent/Guardian)

Parental Consent Form – Confidential

Project Title

The Neurobiological Correlates of Aggression and Empathy in Adolescence.

Researcher(s): Prof. Peter Fonagy, Prof. Pasco Fearon, James Sheffield, Chia Chi Chow, James Hanley, Michael Eisen.

Version 1.1, 17.02.2014

REC reference number: 12/LO/0733

Participant Identification number: _____

Please tick the box in front of each statement to indicate consent.

- ☐ I confirm that I have read and understood the information sheet provided for the above study.

- ☐ I confirm that I have had time to think about and ask any questions about my child's participation in the above study.

- ☐ I understand that my child's participation in this study is voluntary and it's completely in my and my child's rights to withdraw at any point without needing to give a reason.

- ☐ I agree that the anonymous findings from this study can be used in scientific publications and reports. I understand that my child's identity will not be revealed, nor will they be identifiable from the data they provide.

- ☐ I agree for my child to take part in the above study.

Please circle Yes or No for the following statements

3. It is ok for the researchers to contact me in the future about research opportunities my child could take part in. **Yes / No**

4. I would like to be contacted with information regarding the findings of this study **Yes / No**

_____	_____	_____
Parents name	**Parents signature**	**Date**

_____	_____	_____
Researchers name	**Researchers signature**	**Date**

Appendix E: Statement of Contribution to a Joint Research Project

I jointly contributed running experimental sessions with roughly two thirds of the total of 99 participants who took part in the study. I jointly recruited control group participants which involved identifying and contacting appropriate schools/colleges, visiting them to deliver a presentation about the project, collecting contact details for interested students/ their parents, contacting them to arrange a testing session, and gaining their informed consent to take part. I conducted all the analyses in the study, with some assistance from the supervisor of the project.