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**The relationship between impulsivity, affect and a history of psychological
adversity: A cognitive-affective neuroscience approach**

Jonathan C. Ipser
Supervisor: Prof. Dan J. Stein

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in the Department of Psychiatry

Faculty of Health Science
UNIVERSITY OF CAPE TOWN
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University of Cape Town

DECLARATION

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ABSTRACT

Background: There is increasing evidence that trauma exposure is associated with impulsive behaviour and difficulties regulating affect. The findings of recent studies implicate the disruption of neurobiological mechanisms, particularly those involving the neurotransmitter serotonin, in both impulsivity and affect regulation.

Method: This thesis interrogated the link between maladaptive responses to childhood trauma, affect-regulation and impulsivity, using a four-pronged approach. Firstly, a systematic meta-analysis of pharmacotherapy for disorders associated with poor impulse control and aggression in children and adolescents provided a basis for the argument that developmental disruptions of the serotonergic system are common to both. The extent to which serotonin is involved in difficulties regulating emotion in traumatised adults was subsequently investigated via a meta-analysis of the efficacy of selective serotonin-reuptake inhibitors (SSRIs) in treating posttraumatic stress disorder (PTSD). The neural circuitry underlying behavioural impulsivity and affect regulation was identified by conducting an Activation Likelihood Estimation meta-analysis of fMRI data from 51 studies employing the Go/NoGo paradigm. Finally, an empirical investigation of the hypothesis that the relationship between childhood trauma exposure and subsequent difficulties in emotion regulation and impulsivity might be mediated by impaired opioid neurotransmission was conducted by comparing performance on an emotion recognition paradigm in 40 trauma-exposed and healthy students from the University of Cape Town who participated in a placebo-controlled study of the partial mu-opioid agonist buprenorphine.

Results: This thesis observed evidence that (a) the reduction of aggression symptoms in disruptive behaviour disorders might be mediated by serotonergic pathways, (b) that the SSRIs are effective in treating PTSD, (c), that the GNG paradigm reliably elicits neural activation associated with inhibition and emotion regulation, and (d), that adults with a history

of childhood trauma demonstrate impairments in affect regulation, including the avoidance of angry faces, and that buprenorphine was effective in normalising trauma-associated deficits in the recognition of fearful faces.

Conclusion: Collectively, the results obtained through a combination of multiple methodologies, including the analysis of data from a pharmacological challenge study as well as that collected through meta-analysis, point to possible clinical and research implications for the serotonergic manipulation of childhood-trauma associated impairments in impulsivity and affect regulation. Moreover, the GNG paradigm appears to be a suitable candidate measure for the effect of serotonergic agents on affective forms of impulsive behaviour.

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1. INTRODUCTION

As many as 80-100% of people will be exposed to a potentially traumatising event during their lifetimes (Breslau et al., 1998; Frans, Rimmö, Aberg, & Fredrikson, 2005). There is evidence of a robust relationship between psychological trauma incurred in childhood and deficits in emotion regulation. For example, childhood interpersonal traumas but not adult traumas were recognised in a large sample (N=620) of non-clinical subjects as representing a vulnerability factor for poor affect regulation (Briere & Rickards, 2007). Additionally, cumulative childhood trauma but not adult trauma predicted the likelihood of deficits in self-regulation (including affect dysregulation) and posttraumatic stress disorder (PTSD) symptoms in a sample of 582 women who presented at trauma clinics (Cloitre et al., 2009). The replication of this latter finding with respect to a sample of children suggests that it cannot be explained solely by the effects of mood in adults on retrospective self-reporting measures of child trauma (Cloitre et al., 2009). Finally, disordered eating and self-injurious behaviours in females, frequently associated with childhood maltreatment, has been theorised to be moderated by difficulties regulating emotions (Hund & Espelage, 2006; Paivio & McCulloch, 2004).

The majority of evidence for an association between trauma exposure, affect dysregulation and impulsivity can be found in the clinical literature on posttraumatic stress disorder (PTSD). PTSD is observed in approximately 5-9% of individuals who have been exposed to traumas (Breslau et al., 1998; Frans et al., 2005; Kessler et al., 2005), has been conceptualised as fundamentally involving deficits in affect regulation (Frewen & Lanius, 2006), and frequently presents with symptoms of impulsive aggression (Olatunji, Ciesielski, & Tolin, 2010; Orth & Wieland, 2006). PTSD is defined in the latest edition of the Diagnostic and Statistical Manual (DSM-IV) as the psychological sequelae of exposure to "actual or threatened death or serious injury, or threat to the physical integrity of self or others," and in

which "the person's response involved intense fear, helplessness or horror" (American Psychiatric Association, 1994). It is characterised by symptoms of intrusiveness/re-experiencing, avoidance/numbing, and hyperarousal, and results in enormous personal and societal costs (Brunello et al., 2001; S. D. Solomon & Davidson, 1997).

A substantial body of evidence implicates poor emotion regulation as a core component of PTSD (Chemtob, Novaco, Hamada, Gross, & Smith, 1997; Cloitre, Koenen, Cohen, & Han, 2002; Cloitre, Stovall-McClough, Miranda, & Chemtob, 2004; Frewen, Pain, Dozois, & Lanius, 2006). For instance, Frewen et al. (2006) conceptualised PTSD as essentially a disorder of poor affect regulation that is characterised by either a failure to inhibit a state of hyperarousal in response to traumatic memories, or the overly efficient inhibition of arousal (in the dissociative form of PTSD), with associated correlates in fear-related neurocircuitry (L. M. Shin & Handwerker, 2009). PTSD is particularly strongly associated with difficulties regulating anger. A meta-analysis of 39 studies of trauma exposed adults observed an overall association across traumatic events between anger and PTSD (Pearson $r = 0.48$), with the effect largest for military veterans (Orth & Wieland, 2006). In addition, a subsequent meta-analysis detected greater impairments amongst mostly treatment seeking veterans with PTSD in anger control and anger-out and anger-in dimensions, relative to a composite group of studies consisting of all other anxiety disorders (Olatunji et al., 2010)¹.

Characterising adverse trauma-responses in terms of poor emotion regulation is consistent with the emphasis in current diagnostic taxonomies of PTSD on the emotional response to

¹ It should be noted that a examination of US population-based survey data from the National Comorbidity Survey - Replication study (Kessler et al., 2005) found the association of anger expression and experience to be less robust for PTSD than the other anxiety disorders (Hawkins & Cogle, 2010). This may be due to differences between community and treatment-seeking samples, or differences in trauma type. For instance, the most common traumatic event associated with PTSD diagnosis in the NCS-R data was "death of a loved one", whereas the Olatunji et al. (2010) meta-analysis was composed primarily of war veteran samples.

the traumatic event rather than any inherent quality of the event itself (American Psychiatric Association, 1994). It also resonates with the proposal of a diagnostic category of Disorders of Extreme Stress-Not Otherwise Specified (DESNOS), which is frequently associated with early-life adversity, poor affect regulation and dissociative tendencies (Bessel A van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005).

Early childhood adversity has been associated with increases in impulsive behaviour. For instance, clinically depressed patients who had experienced child abuse were more likely to be impulsive and aggressive (Brodsky et al., 2001). In addition, early life trauma in a military sample was associated with the development of personality styles characterised by poor impulse control (Rademaker, Vermetten, Geuze, Mulwijk, & Kleber, 2008). The association between trauma exposure and poor impulse control extends to PTSD, with large-scale epidemiological studies reporting significant increases in patients with PTSD in the prevalence of comorbid substance abuse (Mills, Teesson, Ross, & Peters, 2006) and suicidality (Nock et al., 2009). Impulsivity has also been associated with the emergence of re-experiencing symptoms characteristic of maladaptive post-traumatic responses in adults (Aidman & Kollaras-Mitsinikos, 2006), and with PTSD symptoms more generally (Joseph, Dalgleish, Thrasher, & Yule, 1997). Finally, the observation that acts of impulsive aggression may predict a diagnosis of PTSD in veterans (Teten et al., 2010) provides an explicit link between trauma exposure, deficits in inhibiting impulsive behaviour, and emotion regulation difficulties.

1.1 Characterising the relationship between emotion regulation and impulsivity

Emotion regulation has been described as “the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions” (Gross, 1998, pg. 275). In a recent review and meta-analysis of the relationship between emotion regulation and psychopathology, Aldoa et al. (2009) described

6 emotion regulation strategies which have been consistently identified in the literature. Half of these are regarded as protective of psychopathology (re-appraisal, problem-solving and acceptance), whereas the remainder (suppression, avoidance, rumination) are regarded as vulnerability factors for the development of psychopathological states, including depression, eating and substance-related disorders. Although PTSD studies were excluded from this review, studies of community and clinical samples have generally found that suppression of emotional expression and cognitive re-appraisal are associated with increases and reductions in trauma-related symptoms, respectively (Amstadter & Vernon, 2008; Eftekhari, Zoellner, & Vigil, 2009; Moore, Zoellner, & Mollenholt, 2008).

There is a general consensus that understanding of the role of emotion regulation in psychopathology would be advanced by experimental studies using laboratory-based measures of behaviour. Gratz & Roemer (2004) provide a broad definition of emotion regulation that is well-suited for this purpose. They characterise emotion regulation as involving the monitoring and modulation of emotions in an adaptive fashion, particularly with respect to achieving particular goals whilst experiencing negative emotion. The emphasis in this conceptualisation is on the functional nature of emotions, and on managing emotions in the service of performing behaviour, rather than controlling the emotion itself. It also bypasses controversies in the literature regarding the distinction between emotion regulation and reactivity (Lewis, Zinbarg, & Durbin, 2010).

There is evidence suggesting that the functional schema of emotion regulation proposed by Gratz & Roemer (2004) has utility in describing maladaptive responses to psychological trauma. For instance, Tull and colleagues (2007) were able to detect significantly higher impairment in impulse-control, access to effective emotion regulation strategies, and emotional clarity amongst 108 University students with scores on the PTSD Checklist (PCL) consistent with a diagnosis of PTSD. These effects remained even after controlling for the

confounds of negative affect and difference in income. The importance of access to effective emotion regulation strategies in preventing trauma-related psychopathology (reviewed with respect to general psychopathology by Aldao et al. 2009) was recently illustrated by the finding that women who were exposed to traumatic events were more likely to experience symptoms of anxiety, depression and PTSD if they reported infrequently or ineffectively regulating their emotions (Eftekhari et al., 2009).

The literature on alexithymia provides further evidence of the association between trauma exposure and impairments in affect regulation. Alexithymia is most commonly defined operationally using the 20-item Toronto Alexithymia Scale (TAS-20) as being characterized by deficits in identifying and describing internal emotions (Bagby, Parker, & Taylor, 1994). There is ample evidence for a relationship between early life adversity and alexithymia, particularly with respect to emotional neglect/abuse and sexual abuse (Frewen, Lanius et al., 2008; McCaslin et al., 2006; McLean, Toner, Jackson, Desrocher, & Stuckless, 2006; Zlotnick, Mattia, & Zimmerman, 2001). Evidence of a relationship between childhood adversity and impaired emotion regulation is consistent with theoretical frameworks postulating that stressful interaction with caregivers during childhood impacts, via its effects on attachment relationships, on abilities to regulate affect and develop positive relationships in later life (Schorre, 2002; B. A. van der Kolk & Fislser, 1994).

A number of studies have also identified elevated symptoms of alexithymia in patients diagnosed with PTSD (Frewen et al., 2006; Fukunishi, Sasaki, Chishima, Anze, & Saijo, 1996; Yehuda et al., 1997). The association between PTSD symptoms and alexithymia was revealed in a meta-analysis as being relatively robust (Frewen, Dozois, Neufeld, & Lanius, 2008). Alexithymia has been conceptualised as most strongly related to avoidance and emotional "numbness" symptoms in PTSD (Badura, 2003), though empirical support for an exclusive relationship with this symptom cluster have been mixed (Badura, 2003; Frewen,

Lanius et al., 2008; Fukunishi et al., 1996). Nevertheless, these studies indicate that difficulties in recognising emotions may be one important aspect of poor affect regulation characterising maladaptive sequelae of exposure to psychological trauma.

The association of early life adversity and PTSD with alexithymia supports the use of a measure of affect regulation in populations exposed to trauma that tests the ability to recognise emotions. One such measure is the Difficulties in Emotion Regulation Scale (DERS), which contains two dimensions that are particularly relevant in this regard (“lack of clarity of emotions” and “emotional awareness”)(Gratz & Roemer, 2004). The DERS has demonstrated sensitivity to age-related differences in emotional control in healthy individuals (Orgeta, 2009), and has identified deficits in behavioural aspects of emotion regulation in clinical populations, including borderline personality disorder (Glenn & Klonsky, 2009) and substance abuse populations (Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007; Fox, Hong, & Sinha, 2008). The close link between emotion regulation and impulsivity is apparent in the observation that two of the six dimensions contained within the DERS relate to impulsivity: (1) difficulties engaging in goal-directed behaviours when experiencing negative emotions, and (2) impulse-control difficulties when experiencing negative emotions (Gratz & Roemer, 2004).

Conversely, poor affect regulation forms a core component of an influential conceptualisation of impulsivity proposed by Whiteside & Lynam (2001). Whiteside and Lynam (2001) provided an empirical formulation of impulsivity by factor analysing data collected from 437 undergraduates on a variety of impulsivity scales. This analysis identified four dimensions of impulsivity that were subsequently operationalised as the UPPS Impulsive Behaviour Scale; urgency, lack of perseverance, lack of planning and sensation seeking. The impulsivity dimension of urgency is most clearly related to affect regulation, describing as it does the “tendency to act rashly in response to distress” (Cyders & Smith, 2008, pg. 808).

Differences in scores on the urgency subscale of the UPPS have consistently predicted impulsive behaviours, including bulimia symptoms, cigarette craving and drinking alcohol to cope (Anestis, Selby, & Joiner, 2007; Billieux, der Linden, & Ceschi, 2007; Fischer, Smith, & Anderson, 2003). Further work has distinguished between negative urgency, which is identical to the original conceptualisation of urgency and positive urgency, where positive emotions contribute to the likelihood of engaging in rash behaviour (Cyders et al., 2007). Positive urgency has been shown to uniquely predict elevations in pathological gambling, as well as risky sexual behaviour, alcohol and drug use during the 1st year of college (Cyders & Smith, 2008a; Zanolski, Cyders, & Smith, 2009).

1.2 The neurobiology of emotion regulation and trauma exposure

Neural correlates of the regulation of emotional response have been obtained from studies employing brain imaging technologies, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). fMRI and PET provide measures of blood oxygenation and glucose metabolism, respectively, that are interpreted as indices of neural activity in response to task demands. fMRI studies have reported an inverse relationship between activation of the frontal cortex (ventrolateral and ventromedial PFC) and the amygdala in the context of the active regulation of emotion (Ochsner, Bunge, Gross, & Gabrieli, 2002; Urry et al., 2006). Emotion regulation paradigms employing the labelling of emotional expressions versus control conditions have documented the same inhibitory cortical-subcortical coupling in the emotion identification condition, both in normal controls (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman et al., 2007) and subjects who had been exposed to “harsh parenting” (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006).

The similarity between the findings from imaging studies of emotion regulation and models of functional neural pathology in PTSD are suggestive. A dominant model of the neurocircuitry of PTSD involves impaired inhibition of limbic activity by the prefrontal cortex (Rauch, Shin, & Phelps, 2006; L. Shin et al., 2004). Evidence for such abnormalities comes in the form of covariation in activity of the anterior cingulate cortex (ACC) and the amygdala in patients with PTSD on exposure to emotional facial expressions (L. Shin et al., 2005; Williams et al., 2006). Symptom severity also correlated positively with amygdala activation and negatively with activation of the medial prefrontal cortex in PTSD patients asked to imagine traumatic events while listening to a personalised script (L. Shin et al., 2004). Although the amygdala is a component of the fear circuitry that is engaged in healthy individuals as well as across a range of anxiety disorders, a meta-analysis of brain imaging studies of patients with social anxiety disorder, specific phobia or PTSD who had been exposed to affective stimuli detected frontal deactivation in the PTSD group only (Etkin & Wager, 2007).

Studies of particular genetic polymorphisms have also implicated frontal-limbic pathology in emotion regulation. Hariri (2002) found increased activation of the amygdala of carriers of the short variant (S) of the serotonin transporter gene, associated with less efficient transcription of serotonin, within an emotion induction paradigm, relative to people homozygous for the long variant (L) of this gene (Hariri et al., 2002). This finding has subsequently been replicated in a larger sample (Hariri et al., 2005). Indeed, the association between 5HTTLPR polymorphisms and amygdala activation to a variety of aversive stimuli has been confirmed in a recent meta-analysis of 14 studies (Munafò, Brown, & Hariri, 2008). Although functional or structural measures of the amygdala alone has not always been strongly predictive of an S allele effect on emotional behaviour, one study found that functional coupling between the pregenual anterior cingulate cortex (pACC) and the amygdala accounted for almost 30% of the variance in anxious temperament (Pezawas et al., 2005). Notably, functional connectivity between these regions was significantly reduced

in carriers of the short allele. This finding mirrors the coupling detected during the presentation of aversive pictures between activity in the ventral medial prefrontal cortex and bilateral amygdala for healthy participants homologous for the L allele (Heinz et al., 2005).

1.3 Involvement of neurotransmitters in the relationship between trauma and affect dysregulation

There is growing evidence for rather specific dysregulations of neurotransmitter systems (including the serotonin, noradrenaline, and dopamine systems) and neuroendocrine systems (including the hypothalamus-pituitary-adrenal axis) in PTSD (Charney, Deutch, Krystal, Southwick, & Davis, 1993; Connor & Davidson, 1998; Ravindran & Stein, 2009). A large body of clinical evidence suggests that medications that selectively block the reuptake of serotonin at synapse terminals, collectively known as selective serotonin reuptake inhibitors (SSRIs), are particularly effective in treating PTSD symptoms. This has been confirmed in meta-analyses (Mooney, Oakley, Ferriter, & Travers, 2004; D. J. Stein, Ipser, & Seedat, 2006), and the use of SSRIs as first line agents in treating PTSD has been incorporated into clinical practice guidelines (Asnis, Kohn, Henderson, & Brown, 2004; Bandelow et al., 2008).

Low serotonergic activity is also associated with maladaptive acts of aggression in naturalistic studies of people and non-human primates. In a review of studies investigating the relationship between violence and serotonin, Krakowski et al. (2003) describes studies that have experimentally manipulated serotonin availability via tryptophan precursor dosing, and demonstrated an increase in prosocial behaviour with increasing serotonin and increases in hostility/aggression with reduced levels of serotonin. This effect was especially pronounced in individuals who are predisposed to aggression, suggesting that serotonergic manipulation may be affecting the tendency of individuals to act out on their impulses.

Indeed, van Honk and colleagues argue in their Triple Imbalance Hypothesis of reactive aggression that an imbalance between testosterone and cortisol results in acts of impulsive aggression, but only against the background of lower levels of serotonin (van Honk, Harmon-Jones, Morgan, & Schutter, 2010).

Similarly, the association of abnormal dopamine levels with emotion regulation and impulsivity has been considered in the context of its interaction with serotonin. For instance, Cyders et al. (2008b) suggest that serotonin inhibits the risky, approach behaviours associated with high levels of dopamine, such that individuals with high levels of dopamine and low serotonin levels might be particularly likely to behave impulsively in response to negative emotional state. The high density of dopamine and serotonin receptors in the amygdala and the prefrontal cortex suggest that one mechanism by which this might take place is via the PFC-amygdala pathway.

Conceptualising certain forms of impulsivity, such as negative urgency, as arising within the context of negative affect, suggests that other neurotransmitters besides serotonin that may mediate the relationship between childhood trauma and affect regulation might also have implications with regards to impulsive behaviour. As described below there are both theoretical and empirical grounds for believing that one such class of neurotransmitters are represented by the opioids. There is accumulating evidence that mu-opioids in particular are involved in regulating negative emotions.

From a neurodevelopmental perspective, animal research has demonstrated that mu-opioids are secreted endogenously in circumstances in which social attachments such as infant-mother bond are formed, and that they may have a role in regulating separation distress (“social pain”)(Panksepp, 2003). The effects of opioids on social pain may be mediated by

the evolutionary co-opting of neural circuits involved in pain regulation, as suggested by evidence that endogenous and exogenous opioids reduce activation in areas implicated in pain sensitivity, emotion regulation and reward sensitivity, including the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), insula, amygdala, caudate and periaqueductal gray (see Stein et al. 2007, and Bruehl et al. 2009 for reviews). Further support for this theory comes in the form of evidence that opioid dysregulation appears to mediate the relationship between the tendency to “act out” feelings of anger and increased sensitivity to pain (Bruehl et al., 2009).

Dysregulation of the opioid system may also characterise pathological responses to psychological trauma. Heat and cold pain thresholds were significantly increased in both combat veterans with and without PTSD, with subjective reports of pain as more intense in PTSD populations once the threshold is achieved (Kraus et al., 2009). Additional research suggests that PTSD may be associated with the failure of a compensatory response in the opioid system to trauma. In a PET study employing the mu-opioid receptor radioligand [11C] carfentanil, significant down-regulation of mu-opioid receptor binding potential was observed in regions implicated in emotion regulation in both PTSD patients and combat exposed controls relative to normal controls (insula, nucleus accumbens, anterior cingulate cortex and extended amygdala) (Liberzon et al., 2007). Reductions in opioid binding were observed in the orbitofrontal cortex (OFC) and subgenual ACC in the combat-exposed groups, relative to the healthy controls. Interestingly, these differences were more apparent in the OFC in the combat controls than the PTSD patients, suggesting a compensatory mechanism in response to neural changes induced by trauma-exposure that was not harnessed in the clinical population.

1.4 The behavioural measurement of impulsivity and affect regulation

Both impulsivity and affect regulation are multi-dimensional constructs (Fineberg et al., 2010). Investigations of the relationship between these constructs are complicated by the plethora of mostly self-rated questionnaires to select from in their measurement. The validity of these questionnaires is also frequently questionable, especially given the continuing debates regarding how to define impulsivity and affect regulation (Lewis et al., 2010).

An alternative approach to using self-report questionnaires to assess emotion regulation and impulsivity is to use performance on a behavioural measure as a proxy for these constructs, with the advantage that brain regions involved in the performance of affect-drive impulses can also be identified. One such task that may be particularly suitable in this respect is the Go-NoGo (GNG) task. The GNG task is one of the most extensively validated motor inhibition tasks, and is frequently employed as a behavioural proxy for impulsivity in both research and clinical settings. There is also some evidence that performance and neural activation on the GNG correlates with self-rating measures of impulsivity in healthy subjects (Brown, Goltz, Vilis, Ford, & Everling, 2006; though see Horn, Dolan, Elliott, Deakin, & Woodruff, 2003), and in measures related to impulsivity, such as absent-mindedness, assessed using the Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006),.

In the traditional GNG task, participants are presented with a series of distinct stimuli on a computer screen, one or more of which are designated as targets ('Go' trials). Subjects are instructed to press a response button as quickly as possible when presented with the 'Go' stimuli, and to withhold responding on presentation of other distractor stimuli ('NoGo' trials). The number of commission errors, or responses to NoGo trials provides an indication of

ability to inhibit motor responses. This paradigm has been successfully adapted for brain imaging studies, suggesting that it might have utility in investigating the neural correlates of impulsivity. Prior meta-analyses of response inhibition that have incorporated GNG studies reported reliable patterns of activation in cortical and subcortical brain structures, including the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), sensory motor association areas, the parietal cortex, basal ganglia (putamen, caudate) and insula (see Buchsbaum et al. 2005, Nee et al. 2007, Simmonds et al. 2008, Swick et al. 2011 and Levy et al. 2011 for reviews).

The conceptual and empirical overlap between impulsivity and emotion regulation suggests that behavioural measures of response inhibition might be more sensitive to impulsivity following trauma exposure if they include an affective component. This seems plausible given the observation that the same genes involved in affect regulation are also implicated in impulse control (5HTT & MAO-A) (Passamonti et al., 2006; Passamonti et al., 2008). A similar conclusion was reached by Gay and colleagues (2008) in their discovery that (negative) urgency was specifically related to errors in prepotent response inhibition using a Go/NoGo paradigm, leading the authors to suggest that urgency may be even more strongly related to inhibition of automatic motor responses in conditions in which emotional stimuli are used.

A number of research teams have modified the GNG to include affective stimuli, in efforts to distinguish between subjects suffering from clinical disorders characterised by impaired affect regulation and healthy controls. This approach has been validated, with the affective GNG (AGNG) revealing differences in performance in a range of clinical populations, including patients diagnosed with borderline personality disorder and premenstrual dysphoric disorder. For example, borderline personality disorder was associated with a greater number

of errors on negative NoGo trials (Silbersweig et al., 2007) while healthy female subjects demonstrated faster reaction times to neutral as opposed to negative or positive target words, an effect that was not observed for subjects with premenstrual dysphoric disorder (Protopopescu et al., 2008). The affective version of the GNG has also been successfully employed in separating clinical from normal populations in terms of brain activity, even in cases where behavioural performances in the two groups were equivalent. For instance, Wessa et al. (2007) detected increased BOLD signal in the right medial and left superior OFC, the right precuneus (extending to the posterior cingulate cortex), the left insula and the caudate (bilaterally) in euthymic bipolar disorder patients relative to normal controls on the comparison of emotional versus neutral distracters (despite comparable performance in these two groups).

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2. OBJECTIVES

The literature reviewed provides evidence that increased impulsivity and affect dysregulation, as well as associated neurobiological abnormalities, may characterise the long-term negative sequelae experienced by some individuals who have been exposed to psychological trauma, both in childhood and later in life. It also suggests that the GNG paradigm might be usefully employed in investigating neural correlates of impulsivity and affect regulation. This evidence forms the basis of the four-fold strategy in investigating the relationship between trauma, impulsivity and affect regulation outlined below.

The first two components of this thesis will attempt to use systematically compiled evidence for the efficacy of serotonergic agents to gauge the extent to which serotonergic pathways are involved in impaired impulse control and affect regulation, as well as pathological responses to psychological trauma. This strategy takes the converse approach to that employed recently by Serretti et al. (2007), who were able to confirm from a meta-analysis of pharmacogenetic studies that polymorphisms of the serotonin transporter predict response to antidepressants (Serretti et al., 2007).

In the first part of this dissertation, the importance, from a developmental perspective, of the serotonergic system in affect regulation and impulse control will be identified by conducting a systematic review and meta-analysis of pharmacotherapy for disruptive behaviour disorders (DBDs) in children and adolescents. The DBD group of disorders includes oppositional defiant disorder (ODD) and conduct disorder (CD), and was selected as it is relatively well-characterised, and represent a form of psychopathology that involves aspects of both impulsive behaviour and poor affect regulation. Moreover, paediatric patients presenting with DBD's frequently have a history of maltreatment (Ford et al., 2000), suggesting a role for psychological trauma and/or neglect in the difficulties that they have in regulating negative emotions.

The second part of the dissertation will involve an investigation of the neurobiological systems that mediate the relationship between trauma and impulsivity/affect regulation. This will be achieved through a systematic comparison of the efficacy of serotonergic agents in not only reducing global PTSD symptom severity, but also the intrusion, hyperarousal and numbing/avoidance symptom clusters from which this disorder is constituted. It is anticipated that this will provide insight into the extent to which serotonin mediates disruptions in affect following trauma exposure. The hyperarousal and avoidance/numbing clusters are likely to be particularly informative in this regard, given their centrality in the characterisation of PTSD as a disorder of affect regulation (Frewen & Lanius, 2006).

The third component of this dissertation will investigate the utility of a laboratory measure of response inhibition in identifying regions of the brain that subserve impulsivity and affect regulation. Brain regions that are involved in inhibition of motor responses, with and without the requirement to regulate affect, will be identified by synthesising data from functional magnetic resonance imaging (fMRI) studies of the Go/NoGo paradigm. This will be achieved through conducting an Activation Likelihood Estimation (ALE) meta-analysis of coordinates corresponding to regions of the brain that are activated in healthy adults while correctly inhibiting motor responses (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002). A formal statistical comparison of data from versions of this task that employ affective stimuli versus versions that do not will help pinpoint potential sites of impairment in disorders characterised by affective impulsivity.

Finally, the hypothesis that a history of childhood trauma will impact negatively on the regulation of aversive emotions, and that these effects are mediated by the opioid system, will be investigated within the context of a pharmacological challenge study. Specifically, evidence of an association between trauma exposure and affect dysregulation in general,

and childhood trauma and alexithymia in particular, leads to the prediction that University students with a history of childhood adversity will be poorer in recognising the emotions displayed in fearful and angry faces. The extent to which the modulation of particular biological systems can normalise these deficits will be investigated through the placebo-controlled administration of the partial mu-opioid agonist, buprenorphine.

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3. SYSTEMATIC REVIEW OF PHARMACOTHERAPY OF DISRUPTIVE BEHAVIOUR DISORDERS IN CHILDREN AND ADOLESCENTS

3.1 Preface

The disruptive behaviour disorders consist of the diagnoses of conduct disorder (CD) and oppositional defiant disorders (ODD). The DSM-IV-TR defines ODD as a pattern of negativistic, hostile and defiant behaviour, often directed towards authority figures (American Psychiatric Association, 1994). Conduct disorder, on the other hand, is described as a persistent and recurrent pattern of behaviour in which age-appropriate social norms and the rights of others are violated. Disruptive behaviour disorders (DBDs) are often characterised by the poor control of impulsive behaviour (Hollander, Baker, Kahn, & Stein, 2006), with impulsivity being demonstrated as highly predictive of conduct disorder in adolescents (Askenazy et al., 2003; Vitacco & Rogers, 2001).

Although disruptive behavioural disorders have been characterised by some as primarily involving premeditated aggressive acts (Fahim et al., 2011), this may be more true of CD than ODD, for which 3 of the 8 DSM-IV symptom criteria for the diagnosis of this condition are more closely allied to impulsive forms of aggression (“often loses temper”, “is often touchy or easily annoyed by others”, “is often angry and resentful”)(American Psychiatric Association, 1994). A comparison of grey matter density in 8 year old children with disruptive behavioural disorders revealed differences between those diagnosed with conduct disorders and/or ODD, relative to healthy controls (Fahim et al., 2011). Interestingly, a specific effect was observed for ODD in the left OFC, a region that has been identified as a major site in the brain for the control of anger (Blair, 2003).

The following chapter reviews pharmacotherapy for DBDs with the intent of determining the relative efficacy of different agents in treating this class of disorders. It will be re-examined with the intent of extracting information on the underlying serotonergic abnormalities that may characterise these disorders.

3.2 Introduction

This paper provides a systematic review of the pharmacotherapy of disruptive behaviour disorders (DBDs) in children and adolescents. Disruptive behaviour disorders are prevalent in the community, and result in significant personal impairment and socio-economic costs. In the National Comorbidity Survey Replication, impulse control disorders (including both disruptive behaviour disorders and intermittent explosive disorder) had a higher lifetime prevalence than mood or substance abuse disorders at 24.8%, with a median initial age-of-onset of 11 years (Kessler et al. 2005). Public service utilisation costs were 10 times as large in the UK in 1998 in patients with conduct disorder than those without (Scott et al. 2001).

Pediatric DBDs are likely to be particularly disruptive, as they impair academic and social performance during a period of mental and behavioural maturation (Burke et al. 2002). It has been estimated that disruptive behaviour problems (including Attention Deficit/Hyperactivity Disorder (ADHD)) account for over 50% of pediatric referrals to mental health practices (Waschbusch et al. 2002).

Disruptive behaviour disorders are composed of conduct disorder (CD), oppositional defiance disorder (ODD), and disruptive behavior disorders not otherwise specified (DBD-NOS). While oppositional defiance disorder is defined by the DSM-IV-TR as a pattern of antisocial behaviour that is frequently directed towards authority figures, conduct disorder refers to a pattern of behaviour in which age-appropriate social norms and the rights of

others are repeatedly violated (American Psychiatric Association, 1994). In the case of conduct disorder these behaviours have been categorised in the DSM-IV-TR as aggression to people and animals, destruction of property, deceitfulness or theft, and the serious violation of rules. The criteria for the diagnosis of oppositional defiance disorder and conduct disorder are provided in Tables 1 & 2.

Table 1. DSM-IV-TR behavioural criteria for oppositional defiant disorder

-
- 1) often loses temper
 - 2) often argues with adults
 - 3) often actively defies or refuses to comply with adults' requests or rules
 - 4) often deliberately annoys people
 - 5) often blames others for his or her mistakes or misbehavior
 - 6) is often touchy or easily annoyed by others
 - 7) is often angry and resentful
 - 8) is often spiteful or vindictive
-

A minimum of 4 of the behaviours listed must have been performed for a period of at least 6 months before a diagnosis of oppositional defiant disorders can be made.

Table 2. DSM-IV-TR behavioural criteria for conduct disorder

-
- 1) often bullies, threatens, or intimidates others
 - 2) often initiates physical fights
 - 3) has used a weapon that can cause serious physical harm to others
 - 4) has been physically cruel to people
 - 5) has been physically cruel to animals
 - 6) has stolen while confronting a victim
 - 7) has forced someone into sexual activity
 - 8) has deliberately engaged in fire setting with the intention of causing serious damage
 - 9) has deliberately destroyed others' property (other than by fire setting)
 - 10) has broken into someone else's house, building, or car
 - 11) often lies to obtain goods or favors or to avoid obligations
 - 12) has stolen items of nontrivial value without confronting a victim
 - 13) often stays out at night despite parental prohibitions, beginning before age 13 years
 - 14) has run away from home overnight at least twice while living in parental or parental surrogate home
 - 15) is often truant from school, beginning before age 13 years
-

A minimum of 3 of behaviours listed must have been performed over the previous year, with at least 1 criterion present over the past 6 months, before a diagnosis of conduct disorder can be made.

Disruptive behaviour disorders are associated with a high degree of comorbidity, with depression, substance abuse and ADHD frequently co-occurring in patients with conduct disorder (Loeber et al. 2000). As many as 50% of children referred to clinics with ADHD are also diagnosed with conduct disorder (Newcorn et al. 2001), a pattern of comorbidity associated with a poorer outcome (Lahey et al. 2002; Satterfield and Schell 1997), as well as an earlier onset of conduct disorder (Biederman et al. 1996; Loeber et al. 1995). The odds that children and adolescents with conduct disorder also present with comorbid impulse control disorders during their lifetimes were found in the National Comorbidity Survey Replication to be over 7 times greater than for those participants without conduct disorder (Nock et al. 2006). This is consistent with evidence that impulsivity is highly predictive of conduct disorder in adolescents (Askenazy et al. 2003; Vitacco and Rogers 2001).

The negative behavioural and criminal sequelae of conduct disorder have been well established (Fergusson et al. 2005; Foley et al. 1996). Oppositional defiant disorders feature prominently in the developmental trajectory of conduct disorder, which, in turn, has been associated with the subsequent development of antisocial personality disorder (APD). Risk factors identified by Burke (2002) as implicated in the development of disruptive behaviour disorders include (a) biological factors, such as a genetic predisposition (suggested by family and twin studies), impaired neuroanatomy and functioning (specifically deficits in the functioning of the frontal lobes and the amygdala), underarousal of the autonomic system, low levels of serotonin, and the presence of neurotoxins, (b) childhood functional factors, such as temperament, poor maternal attachment, reading problems, impulsivity/behavioural inhibition, and poor social skills, and (c) psychosocial factors, such as poor parenting, selective mating, child abuse, peer interaction (including peer rejection and association with deviant peers), socio-economically disadvantaged neighbourhoods, and poor coping skills.

Most children's first contact with clinicians is through their referral for disruptive and aggressive behaviour (Steiner and Karnik 2003). Many of these children are subsequently diagnosed with conduct disorder. The exact diagnosis assigned depends on the classification system employed. The DSM-IV-TR subsumes conduct disorder and oppositional defiant disorder as distinct entities within the broader classification of disruptive behaviour disorders, with sub-clinical presentations of these disorders diagnosable as disruptive behaviour not otherwise specified. The most recent version of the International Classification of Diseases (ICD-10), on the other hand, defines oppositional defiant disorder as a milder form of conduct disorder. In addition, while the DSM-IV-TR allows concurrent diagnoses of ADHD and conduct disorder, the ICD-10 defines hyperkinetic disorder (which is analogous to the DSM-IV diagnosis of ADHD) as a disruptive behaviour disorder, and hence as an exclusionary criteria for the diagnosis of CD.

3.2.1 Treatment

There are to date no registered medications for the treatment of disruptive behaviour disorders. Children with disruptive behaviours represent a difficult to treat population, as they are non-compliant almost by definition. The frequent co-occurrence of a number of biological, functional and psychosocial risk factors for the development of CD suggests a need for multi-modal interventions (Burke et al. 2002). A recent clinical practice guideline on the treatment of ADHD with or without comorbid conduct disorder recommended that psychotherapy be employed as first line treatment for conduct disorder, and that concurrent pharmacotherapy be reserved for severe or treatment resistant cases (Kutcher et al. 2004).

The presence of comorbidity in disruptive behaviour disorders also has treatment implications. Although stimulants such as methylphenidate are commonly employed agents

for treating ADHD, the presence of CD symptoms has typically been regarded as a contraindication for this medication, given the greater perceived risk of abuse by children with conduct disorder (Fischer and Barkley 2003). The efficacy of stimulants in treating ADHD with comorbid conduct disorder also needs to be determined, as there is evidence that the combination of these disorders is physiologically distinct from either diagnosis on its own (Banaschewski et al. 2003).

In this paper we will focus on the role of pharmacotherapy in pediatric disruptive behaviour disorders. We systematically retrieved randomised controlled trials (RCTs) in this area for review and conducted a meta-analysis of trials meeting strict inclusion criteria to determine the efficacy and tolerability of pharmacotherapy in treating these disorders. A narrative review of those RCTs which were not included in the meta-analysis was also conducted. To our knowledge, this is the first systematic review of pharmacotherapy for pediatric disruptive behaviour disorders.

3.3 Method

The electronic databases, PubMed (1966 - May 2006), psycINFO (1972-2006 PART A) and the Cochrane Library (2006, Issue 1) were searched for all randomised controlled trials of disruptive behaviour disorders. The search query included the following terms: "Conduct Disorder", "Attention Deficit and Disruptive Behavior Disorders", "Disruptive behaviour", "Oppositional defiant disorder", "aggression", "adolescent", and "child" (contact author for full search strategy). These terms were appended to a sensitive search strategy for PubMed devised by Robinson and Dickersin (2002) for the retrieval of RCTs. Similar search strategies were devised for the psycINFO and Cochrane Library databases. Unpublished trials were retrieved through the Controlled-trials database (<http://www.controlled-trials.com>)

and through contacting pharmaceutical companies and experts in the field.

All randomised controlled trials of children (0-10 years) and adolescents (11-18 years) who have been diagnosed with disruptive behaviour disorders according to DSM or ICD criteria were considered for inclusion in the review. With regards to the meta-analysis, only trials published after the release of the DSM-III (1980) (American Psychiatric Association 1980) were included, in order to ensure homogenous diagnostic criteria. The presence of comorbid substance use, depression, hyperkinetic conduct disorder (in which features of both hyperkinetic disorder and conduct disorder are present) or ADHD were not used as exclusion criteria, given the high co-occurrence of these disorders with disruptive behaviour disorders. Publication in other languages besides English and the failure to report outcome data were also not grounds for excluding studies from the meta-analysis. Trials including pediatric patients with sub-average IQs were included, provided the majority of the sample was not diagnosed with mental retardation ($IQ \leq 70$). Trials of participants with a diagnosis of hyperkinetic disorder were excluded from the meta-analysis, as were trials in which an augmenting medication was used in addition to the medication under study.

Treatment response and reduction in global symptom severity were the primary outcomes of interest. Treatment response was determined by calculating the relative risk of difference (RR) for outcome, as assessed on the improvement item of the Clinical Global Impressions (CGI-I) or related scale. The number needed to treat (NNT) was also calculated. This provides an indication of the number of patients who require treatment with medication before a single additional patient in the medication group responds to treatment, relative to the control group. Reduction in global symptom severity was assessed by means of computing standardised mean difference (SMD) scores on the severity item of the Clinical Global Impressions (CGI-S) scale.

SMD scores were calculated using Hedges adjusted g , a variant of the Cohen d estimate of effect size that controls for small group bias (Rosenthal and Rosnow 1991). Cohen's d is calculated by dividing the difference between the mean summary score at trial endpoint for the medication and comparison groups by the pooled standard deviation of the means (Cohen 1988). Summary statistics for categorical and continuous measures were obtained using the DerSimonian and Laird random effects model (DerSimonian and Laird 1986). The random effects model includes both within-study sampling error and between-studies variation in determining the precision of the overall effect size. The contribution of each of the trials to the overall effect size was weighed by the inverse of the variance of each trial.

Secondary outcomes included the efficacy of medication in reducing aggression on scales validated for this purpose (such as the modified Overt Aggression Scale (Malone et al. 1994a)), as well as the number of patients who discontinued treatment due to drug-related adverse events. The chi-square test was also used to calculate whether there were differences in the proportion of such events reported for the medication and comparison groups. All drug-related adverse events occurring in more than 10% of patients in the trials included in the meta-analysis, or which were significantly more frequent following medication treatment in these trials, are described in the narrative review.

The order of preference for the retrieval of summary statistics in trials utilising multiple sources of information (teachers, parents and clinicians) was to select clinician rating outcomes first, followed by teacher and parent ratings. This strategy was adopted on the basis of evidence for the greater validity of teacher to parent ratings in assessing impairment due to disruptive behaviour disorders (Hart et al. 1994). In the case of data from trials employing multiple fixed doses of medication, the bias introduced through comparing the

summary statistics for multiple groups against the same placebo control was avoided by pooling the means and standard deviations across all of the treatment arms as a function of the number of participants in each arm.

The extent of differences in treatment response across studies was determined by means of the chi-square test of heterogeneity, with a significance level of less than 0.10 interpreted as evidence of heterogeneity, given the low power of the chi squared statistic when the number of trials is small (Deeks et al. 2005). A specially designed data collection form was used for data abstraction, with analyses conducted using the RevMan software (The Cochrane Collaboration 2005).

Studies were stratified by medication class (stimulants, antipsychotics, anticonvulsants and other medications), with a separate category created for lithium. All summary statistics were expressed in terms of an average effect size and 95% confidence intervals (CIs). The small number of trials included in the quantitative comparisons have been supplemented with a qualitative description of all of the RCTs retrieved in the literature search.

We also decided to conduct a brief review of pediatric impulse control disorders, given the observation that both DBDs and impulse control disorders may be characterised by the poor control of impulsive behaviour (Hollander et al. 2006). A similar search strategy to that described above was employed, with the queries modified to retrieve all clinical trials of pediatric intermittent explosive disorder, kleptomania, pathological gambling, pyromania and trichotillomania.

3.4 Results

3.4.1 Meta-analysis

A total of 14 (823 participants) of the 30 short-term trials identified as eligible for inclusion in the review were included in the meta-analysis. Twelve of the trials were placebo-controlled. A flow diagram of the trial selection procedure is provided in Figure 1, with descriptive data for the RCTs considered for inclusion presented in Table 3. Two ongoing studies were also identified from the controlled-trials database: a trial of divalproex in the treatment of disruptive behaviour disorder and explosive tempers in adolescents and adults (ID: NCT00218114), and a relapse prevention trial of children and adolescents with conduct and other disruptive behaviour disorders who responded to initial open-label treatment of risperidone (ID: NCT00236444).

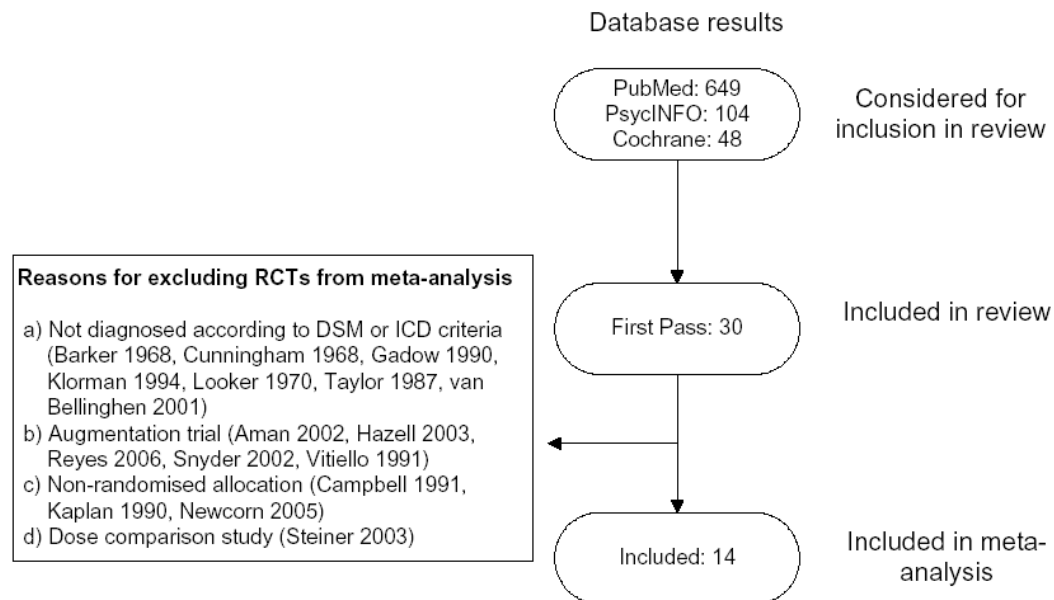


Figure 1. Flowchart of trial selection procedure

Table 3. Descriptive data for pediatric RCTs included in the review

Principal Author	Year	Medication	Duration	Dosage ^b (mean or range)	Primary outcomes	Treatment response ^c
Anticonvulsants						
Steiner	2003	divalproex Patients: 71 with CD (14-18 years)	7	1000 vs 125 mg/d (mode)	CGI-I	high dose > low dose
Donovan ^a	2000	divalproex Patients: 20 with DBDs (10-18 years)	12	750-1500 mg/d	MOAS & SCL-90 (6 items)	med > placebo
Cueva ^a	1996	carbamazepine Patients: 24 with CD (5-12 years)	6	683 mg/d	GCJS	med = placebo
Looker	1970	diphenylhydantoin Patients: 17 with temper tantrums (6-15 years)	4	100 - 200 mg/d	CTRS	med = placebo
Antipsychotics						
Reyes	2006	risperidone Patients: 235 with CD or ODD or ODD (NOS), comorbid ADHD in 68% (5-17 years)	6 mo	<50kg: 0.25-0.75 mg/d >=50kg: 0.5-1.5 mg/d	time to remission	med > placebo
Aman	2002	risperidone Patients: 119 (sub-average IQs) with DBDs (5-12 years)	6	1.16 mg/d	NCBRF	med > placebo
Snyder	2002	risperidone Patients: 110 (sub-average IQs) with DBDs (5-12 years)	6	0.98 mg/d	NCBRF	med > placebo
van Bellinghen	2001	risperidone Patients: 13 (sub-average IQs) disruptive behaviour (6-14 years)	4	0.01 - 0.09 mg/kg/d	CGI-I	med = placebo
Buitelaar ^a	2001	risperidone Patients: 38 (sub-average IQs) with DBDs and comorbid ADHD (6-14 years)	6	2.9 mg/d	CGI-S	med > placebo
Findling ^a	2000	risperidone Patients: 20 with CD (6-14 years)	10	0.75-1.5 mg/d	RAAPP	med > placebo
Greenhill ^a	1985	molindone & thioridazine Patients: 31 with CD (6-11 years)	4	26.8 mg/d & 169.9 mg/d	CRS	(mol = thi) > placebo
Campbell ^a	1984	haloperidol & lithium	4	2.95 mg/d & 1166 mg/d	GCJS	(hal = lit) > placebo

						Patients: 61 with CD (5-13 years)
Cunningham	1968	haloperidol	4	0.5 - 3 mg/d	behav. ratings	med > placebo
						Patients: 12 with disruptive behaviour (8-13 years)
Barker	1968	haloperidol	3	0.05 mg/kg/d		med > placebo
						Patients: 16 with disruptive behaviour (4-15 years)
Lithium						
Malone ^a	2000	lithium	4	900 - 2100 mg/d	GCJCS	med > placebo
						Patients: 40 with CD (10-17 years)
Rifkin ^a	1997	lithium	2	--	OAS	med = placebo
						Patients: 33 with CD (12-17 years)
Campbell ^a	1995	lithium	4	1,248 mg/d	GCJS	med > placebo
						Patients: 50 with CD (5-12 years)
Stimulants						
Spencer ^a	2006	MAS XR ^d	4	10 - 40 mg/d	CGI-I	med > placebo
						Patients: 308 with ODD or ODD & ADHD (6-17 years)
Riggs ^a	2004	pemoline	12	37.5 - 112.5 mg/d	CGI-I	med > placebo
						Patients: 69 with ADHD, SUD ^e & CD (13-19 years)
Kolko ^a	1999	low & high dose methyl-phenidate	6	0.3 vs 0.6 mg/kg	IOWA O/D	med > placebo
						Patients: 22 with ADHD & DBDs (6-13 years)
Klein ^a	1997	methyl-phenidate	5	41.3 mg/d	CPRS & QRBC	med > placebo
						Patients: 83 with CD (6-15 years; 51/74 completers with ADHD)
Klorman	1994	methyl-phenidate	3	22.3 mg/d	IOWA A/O	med > placebo (ADD/O)
						Patients: 107 with ADD or ADD + aggression/oppositionality (5-12 years)
Vitiello	1991	diphenhydramine	as needed	25 or 50 mg p.r.n.	CGI-I	med = placebo
						Patients: 21 with ADHD and/or CD or MD (5-13 years)
Kaplan	1990	methyl-phenidate	3	0.47 mg/kg	AABC	med > placebo
						Patients: 6 with ADHD & CD (13-16 years)
Gadow	1990	methyl-phenidate	4	0.3 vs 0.6 mg/kg	IOWA I-O	(high = low dose) > placebo
						Patients: 11 with ADHD & aggression (5-12 years)
Taylor	1987	methyl-phenidate	7	5 - 30 mg/d	global CD severity	med > placebo
						Patients: 39 with disruptive behaviour (6-10 years)

Other medications

Newcorn	2005	atomoxetine	8	1.2 & 1.8 mg/kg/d	CPRS-RS	med (all doses) > placebo (ADHD + ODD)
Patients: 293 with ADHD & ODD (8-18 years)						
Hazell	2003	clonidine	6	--	Cr-PTRC	med > placebo
Patients: 67 with ADHD & DBDs (6-14 years)						
Connor ^a	2000	clonidine, methyl-phenidate	12	0.17 & 32.5 mg/d	DBS	clon = methyl = placebo
Patients: 24 with ADHD & DBDs (6-16 years)						

^aTrials included in meta-analysis

^bDosages are provided as ranges or means, depending on the availability of the information

^cWhere categorical treatment response not defined, indicates efficacy on primary outcome measure

^dMAS XR = mixed amphetamine salts extended release

^eSUD = substance use disorder

Acronyms for primary outcomes: AABC: Adolescent Antisocial Behavior Checklist; CGI-I: Clinical Global Impressions - Improvement item; CPRS: Children's Psychiatric Rating Scale; CPRS-RS: Connor's Parent Rating Scale - Revised Short form; CrPTRC: Connor's revised Parent and Teacher Rating Checklist; CRS: Connor's Rating Scale; DBS: Disruptive Behavior Scale; GCJS: Global Clinical Judgements Scale; IOWA A/O: IOWA Conners Aggression/Oppositionality subscale; IOWA O/D: IOWA Conners Oppositional/Defiant subscale; NCBRF: Nisonger Child Behavior Rating Form (conduct problem subscale); MOAS: Modified Overt Aggression Scale; OAS: Overt Aggression Scale; RAAPP: Rating of Aggression Against People and/or Property Scale; SCL-90: Symptom Checklist - 90 item scale

The majority of the trials (8/14) in the meta-analysis were restricted to participants with conduct disorder. Comorbid ADHD was present in 5 of the studies, one of which contained patients diagnosed with substance abuse disorder (Riggs et al. 2004). Only one trial investigated pharmacotherapy for pediatric oppositional defiant disorder (Spencer et al. 2006). The most common reason for excluding trials from the meta-analysis was failure to diagnose disruptive behaviour disorders according the relevant diagnostic criteria (see Figure 1). The trials included in the meta-analysis tested the following medications: stimulants (3 methylphenidate, 1 mixed amphetamine salts extended release, 1 pemoline), antipsychotics (1 haloperidol, 1 molindone, 2 risperidone), lithium (4 trials), the anticonvulsants (1 carbamazepine, 1 divalproex), the selective adrenergic agonist clonidine and the dopamine antagonist thioridazine (1 trial each). Only one trial included a comparison of medication with psychotherapy (Kolko et al. 1999).

Treatment response was significantly greater following treatment with medication than placebo across the 4 trials of disruptive behaviour disorders that provided data on the CGI-I and the Global Clinical Judgements Scale (relative risk (RR) of response = 2.39, 95%CI = 1.1 to 5.21, n = 136) (see Figure 2). Approximately 3 patients with DBDs would have to be treated with medication before one could expect to witness an additional response, relative to placebo (NNT = 3.1). A significantly larger proportion of patients responded to lithium than placebo (N = 2, RR = 4.22, 95%CI = 1.83 to 9.74, n = 90). Risperidone was effective in reducing overall symptom severity by 2.19 points on the CGI-S (N = 2, 95%CI = -3.07 to -1.31, n = 58)(Figure 3).

There was limited evidence for the effectiveness of medication in reducing aggression (N=4, SMD = -1.93, 95%CI = -3.88 to 0.02, n = 172), despite significant variation in the efficacy of the different agents (Figure 4). The tendency of medication to reduce aggression was largely attributable to the reduction of aggression scores in the single trial of methylphenidate (Klein et al. 1997). Differences were also apparent for the two trials of risperidone (Chi = 10.59, p < 0.01), with significantly less reduction of aggression observed in the trial of adolescents with sub-average IQs (Buitelaar et al. 2001).

Review: Pharmacotherapy for impulse control and disruptive behavior disorders in children and adolescents
 Comparison: 01 Primary outcomes
 Outcome: 01 Treatment response (CGI-I or similar)

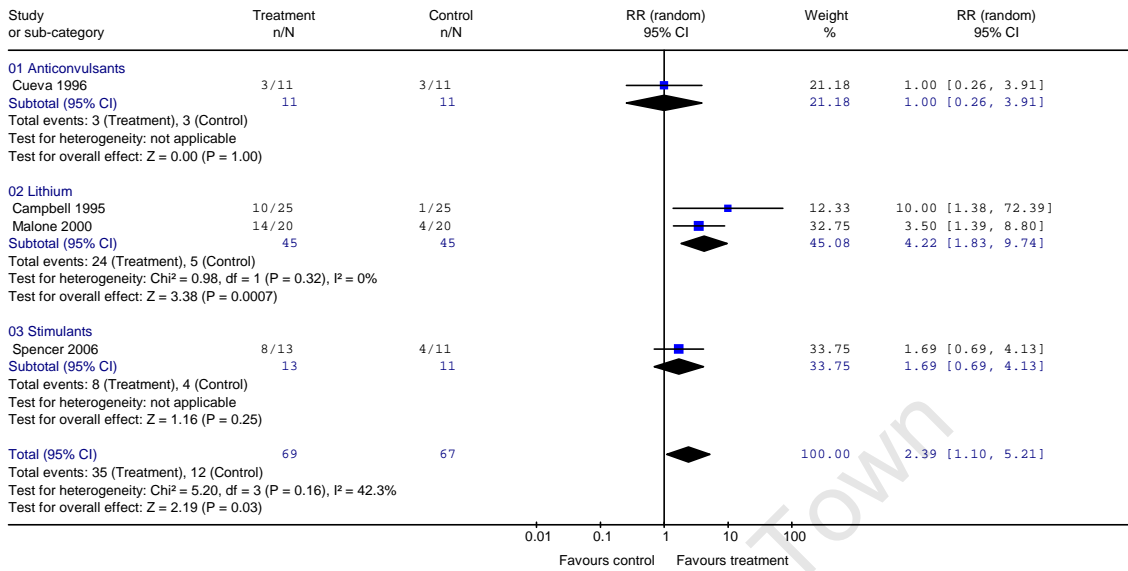


Figure 2. Response to pharmacotherapy treatment on the CGI-I

Review: Pharmacotherapy for impulse control and disruptive behavior disorders in children and adolescents
 Comparison: 01 Primary outcomes
 Outcome: 02 Clinical global impressions symptom severity

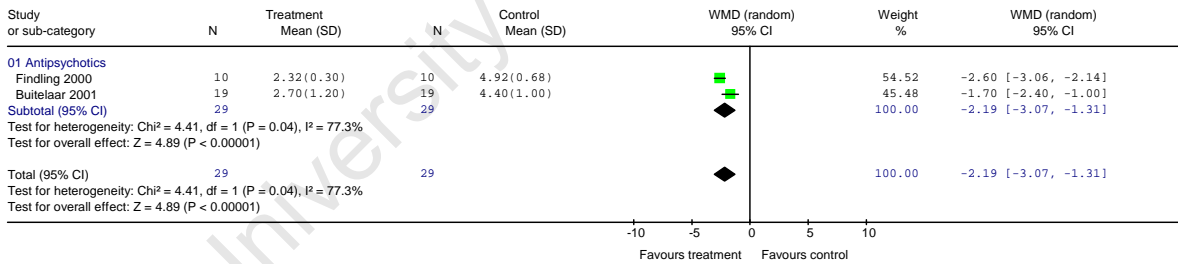


Figure 3. Reduction of ODD symptom severity on the CGI-S

Review: Pharmacotherapy for impulse control and disruptive behavior disorders in children and adolescents
 Comparison: 02 Secondary outcomes
 Outcome: 01 Aggression scales

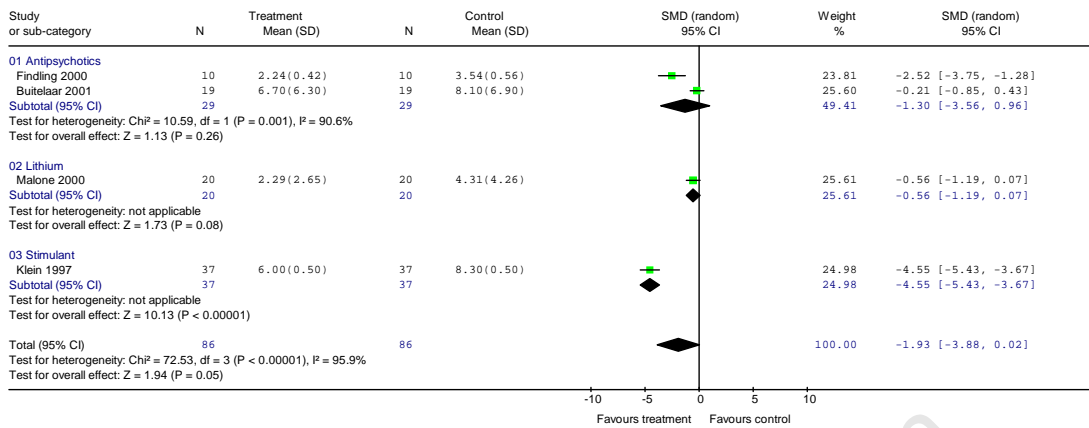


Figure 4. Reduction of symptoms of aggression following treatment with medication

Although it was originally the intention of the authors to conduct an a priori comparison of patient withdrawals due to drug-related adverse events, there were insufficient data for this purpose. Instead, overall dropout rates in the medication and placebo groups were calculated as a proxy measure of medication tolerability. Total patient dropout for trials included in the meta-analysis was equivalent in the placebo and medication groups across the 8 studies for which dropout data was available ($RR = 0.97$, $95\%CI = 0.60$ to 1.55 , $n = 631$). Dropout rates were not significantly higher following treatment for any of the medication groups. It was not possible to conduct an a priori subgroup analysis to test for the differential effect of medication in early versus late-onset CD due to lack of data on the breakdown of patient samples by age-group.

3.4.2 Narrative review

Efficacy of medication in treating disruptive behaviour disorders

There have been several open-label studies providing preliminary evidence of the efficacy of medication in the treatment of disruptive behaviour disorders, including bupropion (Riggs et

al. 1998), lithium (Malone et al. 1994b), reboxetine (Mozes et al. 2005) and trazodone (Zubieta and Alessi 1992). The psychostimulant, methylphenidate, has been particularly well studied, with both open label (Serra-Pinheiro et al. 2004) and controlled studies (Gadow et al. 1990; Kaplan et al. 1990; Klein et al. 1997; Klorman et al. 1994; Kolko et al. 1999; Taylor et al. 1987) supporting the usefulness of this agent.

In the first placebo-controlled trial of methylphenidate for behaviour problems, approximately a third of the boys who were treated were classified as "much improved" after 3 weeks of treatment (Taylor et al. 1987). Behavioural hyperactivity, younger age and the absence of affective symptoms were better predictors of treatment response than a diagnosis of ADHD. Children diagnosed with attention deficit disorder and high levels of aggression/oppositionality demonstrated decreased symptoms of oppositionality, as well as improved performance on cognitive tasks after 3 weeks of treatment with methylphenidate (Klorman et al. 1994). Methylphenidate was also successful in reducing aggression in a crossover study of 6 patients with conduct disorder and comorbid ADHD (Kaplan et al. 1990). Ratings of antisocial behaviour were reduced in a similar population following treatment with methylphenidate, even after controlling for the severity of comorbid ADHD (Klein et al. 1997).

There is little evidence of the effectiveness of other stimulants besides methylphenidate in treating disruptive behaviour disorders. A recent 12 week placebo-controlled trial of pemoline failed to detect a reduction in symptoms of CD in 69 adolescents with comorbid ADHD and substance abuse (Riggs et al. 2004). In addition, the use of pemoline is not generally recommended, as it carries a risk of hepatotoxicity and thus requires frequent monitoring of liver enzyme levels. Negative results were also obtained in a small controlled trial of the antihistamine stimulant diphenhydramine for a range of childhood psychiatric disorders

(Vitiello et al. 1991), including conduct disorder. Nevertheless, a recent large multicentre RCT of mixed amphetamine salts extended release (MAS XR) in treating oppositional defiant disorder demonstrated efficacy and tolerability for higher doses of this medication (30 and 40 mg/d) in the pediatric population (Spencer et al. 2006). Despite this finding, evidence of treatment response was not observed when the analysis was limited to the minority of patients (21%) without comorbid ADHD.

Lithium has well-known anti-aggressive properties, and has been used extensively in treating pediatric aggression. Lithium and haloperidol demonstrated equivalent efficacy in reducing symptom severity in a placebo-controlled trial for 61 treatment-resistant hospitalised children with CD (Campbell et al. 1984). Lithium performed better than haloperidol on a global scale of improvement and in reducing explosiveness in conduct disorder. It was also more effective in reducing CGI side effect scores and resulted in less cognitive impairment (Platt et al. 1984). The efficacy of lithium on measures of global improvement and aggressivity has been confirmed in subsequent placebo-controlled trials (Campbell et al. 1995; Malone et al. 2000). The findings of the only controlled trial to date to report that lithium was not more effective than placebo in reducing conduct disorder symptoms may be attributable to the short duration of this trial (2 weeks) (Rifkin et al. 1997).

Antipsychotics have also been used in clinical practice for the treatment of childhood aggressivity (Kaplan et al. 1994). Children treated with haloperidol displayed significantly less disobedience and aggression towards adults than when they were provided with placebo, both when used as monotherapy (Barker and Fraser 1968) and in adjunction with behavioural treatment (Cunningham et al. 1968). The antipsychotic molindone hydrochloride and the dopamine antagonist thioridazine were equally effective in reducing aggression and disruptive behaviour in hospitalised children with conduct disorder (Greenhill et al. 1985).

Low doses of the atypical antipsychotic risperidone (0.5 mg/d - 3 mg/d) resulted in significantly greater reductions on a scale assessing aggression against people and/or property than placebo for children and adolescents diagnosed with CD, many of whom had previously failed community-based treatment with methylphenidate (Findling et al. 2000). A double-blind trial of children and adolescents with disruptive behaviour disorders detected significantly lower relapse rates in the medication than placebo group after 6 months of maintenance treatment with risperidone (Reyes et al. 2006).

The effectiveness of risperidone in treating disruptive behaviour in the mentally-impaired pediatric population has also been assessed. At the end of a trial comparing 6 weeks of double-blind risperidone and placebo treatment for 38 mentally impaired children with aggression-related psychiatric disorders (CD, ODD or ADHD) (Buitelaar et al. 2001), 21% of those receiving risperidone were rated as "markedly" or "severely" disturbed on the CGI-S, compared to 84% of the placebo control group. Equivalent magnitudes of response were observed in a placebo-controlled pilot study of risperidone for low IQ children with persistent behavioural disturbances (Van Bellinghen and De Troch 2001). Reductions in symptom severity were also demonstrated in two large multi-centre placebo-controlled trials of risperidone for disruptive behavior disorders in low IQ children, even after controlling for the sedative effect induced by the medication (Aman et al. 2002a; Snyder et al. 2002). Significant improvements in behaviour were detected as early as 1 week after treatment initiation. The interpretation of these findings is complicated, however, by that fact that many of children were receiving concurrent psychotropic medication.

Although anticonvulsants are increasingly being used to treat affective disorders, mixed results have been obtained in placebo-controlled trials of their use to treat disruptive behaviour disorders. An early controlled trial of diphenylhydantoin in treating children and

adolescents with disruptive behaviour (tantrums), failed to detect a significant difference in parent and teacher ratings between medication and placebo (Looker and Conners 1970). Carbamazepine also failed to demonstrate effectiveness on any of the outcomes measures employed in a study of children with conduct disorder (Cueva et al. 1996). On the other hand, greater response to divalproex than placebo was observed in participants diagnosed with explosive tempers, mood lability, and disruptive behaviour disorders (Donovan et al. 2000), as well as in adolescents with conduct disorders who had at least one criminal conviction (Steiner and Karnik 2003). In the latter study, symptom severity and global improvement ratings were more favourable after administration of high doses (500 - 1500 mg/d) than low doses (up to 250 mg/d) of divalproex.

The selective adrenergic agonist clonidine has shown some promise in augmenting pharmacotherapy for disruptive behaviour disorders with comorbid ADHD. Clonidine is implemented widely in clinical practice as an add-on to treatment for psychostimulants (Hazell et al. 1996). In a controlled trial over half (21/37) of patients receiving clonidine as augmentation improved on a conduct scale compared to 21% (6/29) of those receiving placebo (Hazell and Stuart 2003). Interestingly, in this trial clonidine seemed to reduce some of the side effects associated with psychostimulants, but not insomnia, a common indication for its prescription. A comparison of clonidine and methylphenidate monotherapy and treatment combining both agents revealed few differences in the efficacy and tolerability of these medications for a group of children and adolescents (Connor et al. 2000). Preliminary data on newer agents, such as atomoxetine, are promising. A recent placebo-controlled trial of this selective noradrenaline uptake inhibitor in children with ADHD found that symptom reductions occurred in children with ADHD and comorbid oppositional defiance at higher (1.8 mg/kg/d), but not lower (1.2 mg/kg/d), doses (Newcorn et al. 2005).

Drug-related adverse events in trials included in meta-analysis

Treatment of conduct disorder with lithium resulted in significantly more nausea (Campbell et al. 1995) and vomiting (Malone et al. 2000) than placebo. Of the anticonvulsants included in the meta-analysis, carbamazepine (Cueva et al. 1996) and divalproex (Donovan et al. 2000) resulted in increased levels of dizziness and appetite, respectively. Four out of 13 of the patients receiving carbamazepine experienced moderate, but transient leukopenia, with 2 children experiencing marked symptoms of this condition. Equivalent levels of subjective distress and mild side effects were reported in one of the excluded trials for both high (500 - 1500 mg/d) and low dose (up to 250 mg/d) divalproex (Steiner and Karnik 2003).

Few of the trials of stimulants included in the meta-analysis provided information on side effects. In the escalated dose placebo-controlled trial of mixed amphetamine salts extended release (MAS XR) (Spencer et al. 2006), anorexia/decreased appetite, insomnia, headache and abdominal pain were relatively common in all dosage groups (10, 20, 30 & 40 mg/d). Anorexia/decreased appetite and insomnia occurred significantly more frequently in those patients given 20, 30 or 40 mg/d of MAS XR than placebo, and led more often than other side effects to trial discontinuation. In the study of pemoline (Riggs et al. 2004), stomach-aches, insomnia and skin-picking were significantly more common in the medication than the placebo group. Higher rates of drowsiness and dizziness were observed relative to placebo following augmentation of stimulants with clonidine (Hazell and Stuart 2003). Prescription of this medication requires careful monitoring, as it is associated with adverse cardiovascular events, self-poisoning, and sudden death in children.

A significantly greater number of patients receiving the neuroleptic haloperidol experienced sedation than those receiving lithium or placebo (Campbell et al. 1984), with medication also resulting in a higher incidence of dystonia than placebo. Treatment with the dopamine

antagonist thioridazine resulted in elevated levels of sedation and dizziness (Greenhill et al. 1985). There was, however, no difference in the overall tolerability of thioridazine when compared to molindone, despite high levels of dystonia following treatment with the antipsychotic.

Significant increases in drowsiness, vomiting, weight gain, and the extrapyramidal symptom of parkinsonism were observed following double-blind treatment with risperidone (Buitelaar et al. 2001). Amongst the trials excluded from the meta-analysis, somnolence was reported as significantly more frequent in two trials of risperidone for children with sub-average IQs (Aman et al. 2002a; Snyder et al. 2002; Aman et al. 2002b). Adverse events in the acute phase of a large augmentation trial of risperidone for children with oppositional defiant disorders (Reyes et al. 2006) had largely subsided by the end of the 6 month double-blinded maintenance component of this trial. Nevertheless, adverse events resulting from treatment with risperidone suggest caution in its use for pediatric DBDs, especially given the absence of efficacy comparisons between risperidone and other more established treatment modalities (Keenan 2005).

Impulse control disorders

We were not able to find any clinical trials of pharmacotherapy for pediatric impulse control disorders. Although the SSRIs and mood stabilizers have been recognised as first line agents in the treatment of intermittent explosive disorder in adults (Coccaro and Danehy 2006), there is little controlled evidence for the efficacy of these agents in other impulse control disorders in either pediatric or adult populations.

3.5 Discussion

The meta-analysis detected an overall effect of short-term pharmacotherapy on treatment response in patients diagnosed with conduct disorder. The similar number of dropouts in the medication and placebo groups, both overall, and when stratified by medication class, suggests that the medications employed in these studies were relatively well tolerated. Nevertheless, certain side effects, such as sedation, dizziness and nausea are common. The potential emergence of serious drug-related adverse events, such as extrapyramidal symptoms with antipsychotics, are particularly worrisome.

There are a number of factors limiting the conclusions that can be drawn from this review. Firstly, few of the trials of disruptive behavior disorders that were retrieved provided sufficient data for inclusion in the meta-analysis, with many employing ad-hoc, non-standardised rating scales. As a result, the meta-analysis possessed limited power to detect treatment effects, a problem compounded by the small sample sizes employed in the individual studies. In addition, although efforts were made to be as inclusive as possible, the requirement that trials included in the meta-analysis examine comparable patient populations places constraints on the applicability of its findings to the complex cases that typically present within clinical practice.

Despite these shortcomings, this review found lithium and risperidone to be effective in treating CD on global measures of treatment response and symptom severity, respectively. Lithium treatment has the drawback of requiring constant monitoring to prevent the emergence of serious side effects. The effectiveness of low-dose risperidone, on the other hand, is consistent with the recommendation in a recent consensus statement that low doses of risperidone be provided to patients with CD who do not respond to an initial

psychosocial intervention (Kutcher et al. 2004).²

The new generation of atypical antipsychotics are regarded as possessing a more favourable side effect profile than traditional neuroleptics (Connor et al. 2001). Nevertheless, substantial increases in somnolence and weight gain have been observed in the trials of risperidone in pediatric DBDs conducted to date. There also remain significant concerns about the possibility of extrapyramidal symptoms, with low rates of parkinsonism observed in a few of the trials (Buitelaar et al. 2001; Reyes et al. 2006). In the light of the serious nature of these adverse events, and evidence that low doses of risperidone present a stimulant effect (Alcantara and Barcia 1999), additional trials comparing risperidone with more established psychostimulants would be useful (Keenan 2005).³ Further, although treatment with risperidone over longer periods was well tolerated in the only long-term trial included in this review (Reyes et al. 2006) long-term effectiveness data are needed in order to comprehensively evaluate the risk-benefit ratio for this medication.

The presence of aggressive behaviour in youth with primary conduct disorder has been recognised as indicating augmentation of psychosocial treatment with medication (Kutcher et al. 2004). This review revealed a great deal of variability between trials of pediatric disruptive behaviour disorders in the effectiveness of medication in treating aggression. Despite this, aggressive behaviour was significantly reduced in patients with normal intellectual functioning in single trials of methylphenidate (Klein et al. 1997) and risperidone (Findling et al. 2000).

Psychostimulants, and in particular, methylphenidate, appear effective in treating children

² A consensus statement sponsored by Johnson & Johnson, the manufacturers of risperidone

³ though see Aman et al. (2004) for evidence that combined risperidone/stimulant treatment may be more effective than stimulant monotherapy for DBDs in children with sub-average IQs

and adolescents with disruptive behaviour disorders. The majority of the controlled trials of this medication are for children and adolescents diagnosed with CD and comorbid ADHD. Nevertheless, a meta-analysis of 28 studies of ADHD with aggression found a dissociation between the effects of stimulants on aggression-related behaviours and ADHD symptoms (Connor et al. 2002). Methylphenidate was also effective in reducing antisocial behaviour in a trial of children and adolescents with conduct disorders, after controlling for the severity of comorbid ADHD symptoms (Klein et al. 1997). The optimum dosage of this medication still needs to be determined, however, with dose control trials demonstrating effects of dosage in some trials (eg. Kolko et al 1999), but not in others (eg. Gadow et al. 1990). Evidence for the efficacy of anticonvulsants in treating disruptive behaviour disorders is mixed, with the most evidence for efficacy being observed for divalproex (Donovan et al. 2000; Steiner and Karnik 2003).

The role of serotonin in behaviour inhibition, and the reduction of impulsive and aggressive behaviour with the administration of serotonin reuptake inhibitors (Cherek et al. 2002) suggests that serotonin dysregulation plays a role in disruptive behaviour disorders. There is a need for more controlled trials of SSRIs in treating impulse control and disruptive behaviour disorders in pediatric patients, despite the favourable side-effect profile of the SSRIs relative to older antidepressants.

The presence of comorbid psychiatric diagnoses has implications for the pharmacotherapy of pediatric disruptive behaviour disorders. This is particularly the case for patients with comorbid ADHD, which is not only prevalent in children and adolescents with conduct disorder, but is also associated with early onset CD, a particularly severe and treatment-resistant form of the disorder. A recent consensus statement (Kutcher et al. 2004) recommended that first line psychosocial interventions for pediatric conduct disorder be

combined with pharmacotherapy in the treatment of ADHD with comorbid CD. This patient subgroup also appears to respond preferentially to higher doses of medication such as stimulants (Gadow et al. 1990) and atomoxetine (Newcorn et al. 2005). The development of slow-release formulations of medication should increase the effectiveness of pharmacotherapy for this difficult-to-treat population (Kutcher et al. 2004).

In clinical practice different modalities of treatment are often combined. However, only a few trials incorporating psychotherapy and pharmacotherapy have been conducted to date. A controlled trial of pediatric ADHD and comorbid ODD or CD found main effects for methylphenidate and behaviour modification on their own, but little evidence for an incremental increase in effectiveness through combining these interventions (Kolko et al. 1999). Analyses of data from the NIMH Collaborative Multisite Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder suggests that the addition of psychosocial to medication therapy increases response rates in children with ADHD and comorbid ODD by up to 21% (Swanson et al. 2001).

We were only able to find one controlled trial of the long-term treatment of disruptive behaviour disorders. The finding of reduced relapse rates after 6 months of maintenance therapy amongst responders to acute risperidone treatment (Reyes et al. 2006) is consistent with the suggestion that children with conduct disorder should receive pharmacotherapy for a minimum of half a year before discontinuing treatment (Buitelaar et al. 2003). Little research has been conducted on pharmacotherapy for pediatric ODD. The high proportion of patients with ODD and comorbid ADHD in the trial demonstrating the efficacy and tolerability of mixed amphetamine salts (Spencer et al. 2006) supports the recommendation that medication only be used for ODD comorbid with other psychiatric diagnoses that are responsive to medication (Rey and Walter 1999).

Further research should be conducted into promising medications for the treatment of disruptive behaviour disorders, such as naltrexone (Kim et al. 2001). The influence of gender on the effectiveness of medication in treating disruptive behaviour disorders should also be assessed, as there is some evidence to suggest that females who are diagnosed with CD have a poorer prognosis than males (Dalsgaard et al. 2002). Finally, studies of resilience to risk factors associated with the subsequent development of DBDs, including trials investigating genetic predisposition for antisocial behaviour (Caspi et al. 2002; Jaffee et al. 2005), would provide valuable information for the design of treatment programmes in the future.

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4. EVIDENCE-BASED PHARMACOTHERAPY OF POSTTRAUMATIC STRESS DISORDER

4.1 Preface

Data provided by randomised controlled trials (RCTs) on differences in the efficacy of medication agents for treating PTSD provides one way to interrogate the involvement of serotonin in difficulties with regulating emotion following psychological trauma. Frewen et al.'s (2006) conceptualisation of PTSD draws attention to the arousal and numbing symptom clusters as particularly pertinent in this regard. Indeed, Davidson predicted that tricyclic antidepressants that target the serotonergic system would be more effective in treating numbing symptoms, and noradrenergic agents intrusion symptoms (Davidson 1992). This is consistent with the findings from an early trial of the SSRI fluoxetine, in which a reduction was observed after 5 weeks in hyperarousal and numbing symptoms, but not re-experiencing or active avoidance symptoms (B. van der Kolk et al., 1994).

The feasibility of using symptom cluster response profiles to infer the involvement of particular biochemical pathways in pathological responses to trauma is also suggested by findings from a meta-analysis that the effects of treating PTSD with atypical antipsychotic agents (employed as monotherapy or augmentation agents in randomised controlled trials) were restricted to intrusion symptoms (Pae et al., 2008). The following chapter describes a systematic review and meta-analysis of the effects of pharmacotherapy in treating PTSD. In line with the emphasis of this thesis, the focus of the review was not only on the reduction of overall PTSD symptom severity, but also on comparing the effects of serotonergic agents on particular symptom clusters.

4.2 Introduction

It is estimated that as many as 80% to 100% of all people are exposed to traumatic events during their lifetimes (Breslau et al., 2005; Frans et al., 2005). Depending on the nature of the trauma, approximately 5-9% of the general population go on to develop posttraumatic stress disorder (PTSD), a condition characterised by the experience of persistent flashbacks of the event (re-experiencing/intrusion symptoms), a state of high arousal when exposed to reminders of the trauma (hyperarousal symptoms), and concomitant avoidance/emotional numbing in response to these reminders (avoidance/emotional numbing symptoms) (Breslau et al., 1998; Frans et al., 2005; Kessler et al., 2005). This constellation of symptoms satisfy the criteria for PTSD when they extend beyond a month after exposure to the trauma and cause clinically significant functional disability, as conceptualised in current psychiatry diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994).

PTSD is frequently chronic and associated with significant morbidity, poor quality of life, and high personal, social and economic costs. It additionally represents a risk factor for developing other mood and anxiety disorders, as well as substance use disorders. It has been estimated that the US economy alone loses in the region of 3 billion dollars annually due to PTSD-related loss in productivity (Brunello et al., 2001).

PTSD is characterised by a range of neurobiological disruptions, including changes in the hypothalamus-pituitary-adrenal axis, as well as alterations in the serotonergic, and noradrenergic neurotransmitter systems. Chemical modulation of these systems by means of medication therefore holds promise as a treatment for this disorder. Conversely, reports of the efficacy of the selective serotonin reuptake inhibitors, or SSRIs, in treating PTSD implicates involvement of the serotonin system in its aetiology. Indeed, on the basis of both open-label and controlled trials of these agents the majority of clinical practice guidelines

have recommended the SSRIs as first line agents in treating PTSD. The SSRIs paroxetine and sertraline are currently the only medications approved by the Federal Drug Agency in the United States for the treatment of PTSD.

Despite the general acceptance of SSRIs as first-line medication interventions for treating PTSD, a recent analysis of clinical practice treatment guidelines revealed considerable variability in conclusions regarding their efficacy (Stein et al., 2009). This is reflected in a review conducted by the Institute of Medicine, in which it was concluded that there is insufficient evidence that any of the SSRIs reduce PTSD symptom severity (Institute of Medicine (IOM), 2009). In addition, there is recognition that not all patients with PTSD respond to the SSRIs, leading to the need for augmentation or combination treatment strategies, and to interest in agents such as tiagabine that employ novel mechanisms of action. A comprehensive review of the efficacy of medication in treating PTSD is therefore warranted.

Accordingly, a narrative review was conducted of the effectiveness of medication in reducing PTSD symptoms, as reported by randomised controlled trials (RCTs) of pharmacotherapy for PTSD. Efficacy data was synthesised across trials as part of an update of a prior meta-analysis of PTSD pharmacotherapy, using the guidelines established by the Cochrane Collaboration (Higgins and Altman, 2008). Finally, a review of pharmacotherapy RCTs for treatment resistant patients was also conducted.

This review addresses the following questions:

- 1) is medication effective in treating PTSD?
- 2) are some agents more effective than others?
- 3) how long should medications be administered?
- 4) are augmentation strategies effective in treating resistant PTSD?

4.3 Method

Inclusion of studies in this review was restricted to all placebo-controlled randomised controlled trials (both published and unpublished) of pharmacotherapy for adults (18 – 64 years) diagnosed with PTSD, according to DSM-III+ or ICD-9+ criteria. Assessment of RCTs for inclusion in this review was conducted independently by 2 raters. Concurrent treatment of the majority of patients with medication (\Rightarrow 50%) as part of standard care were grounds for exclusion. Concurrent psychotherapy was permitted, on the condition that it was (a) not trauma-focused, or (b) had been initiated at least 3 months prior to the beginning of the trial. RCTs of medication prophylaxis for PTSD were not eligible. Finally, studies were restricted to those in which the objective was to treat all symptom clusters defining PTSD, rather than specific subsets, such as sleep disturbances.

Eligible RCTs were identified in February, 2010 by systematically searching the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and the National PTSD Center Pilots database. Database-specific search queries were designed (see the supplementary material for full syntax), and included the terms "posttraumatic stress disorder" and "randomized controlled trial". Additional unpublished studies were located by searching the bibliographies of published articles and contacting experts in the field. Where study data was missing, or in cases in which there was concern regarding publication of multiple reports on the same trial, the reviewers contacted investigators by email in an attempt to obtain more information. The selection procedure for trials that were eligible for inclusion in the review is presented in Figure 1. Study characteristics and outcomes are provided in a separate table (Table 1).

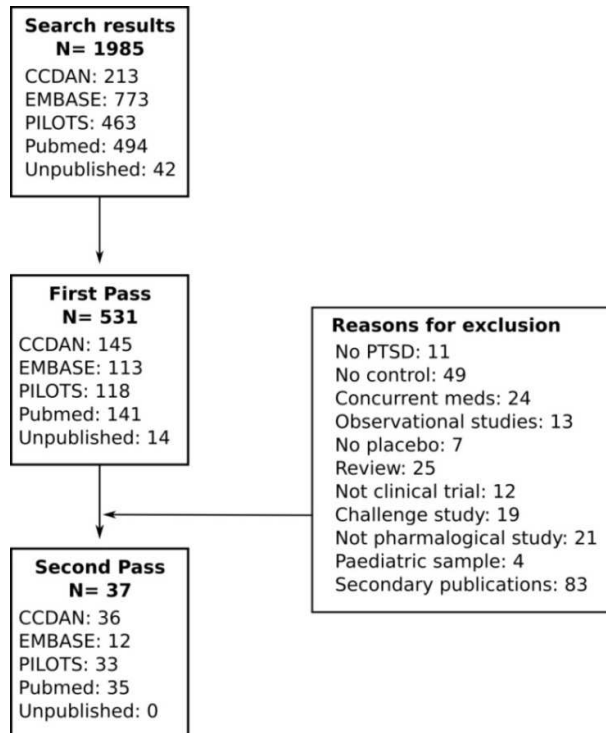


Figure 1. Selection flowchart for RCTs included in the review

4.4 Narrative review of the findings of RCTs of pharmacotherapy for PTSD

4.4.1 Mono-amine oxidase inhibitors

The Mono-amine oxidase inhibitors (MAO-I) were one of the first class of agents to be tested in RCTs for treating PTSD. The mono-amine oxidase A enzyme is a deaminater of both norepinephrine and serotonin, neurotransmitters that have been implicated in PTSD (Baker et al., 1995). Two RCTs of phenelzine, a mono-amine oxidase inhibitor (MAO-I), provide mixed evidence for its efficacy in treating this patient population. No differences were detected in a 5 week cross-over RCT (Shestatzky et al., 1988), with over half of the participants (7/13) withdrawing during the course of the study while receiving phenelzine. A placebo-controlled comparison of phenelzine and the tricyclic antidepressant imipramine in

60 male combat veterans reported a significant decrease after 3 weeks of treatment with phenelzine in the score on the primary PTSD symptom severity scale, the self-rated Impact of Event Scale (IES) (Horowitz et al., 1979; Kosten et al., 1991).

4.4.2 Reversible inhibitors of monoamine oxidase A (RIMAs)

The clinical utility of the MAO-Is is limited by the potential for serious drug-related adverse events, such as hypertensive crises, and stringent dietary restrictions that reduce the likelihood of compliance. These shortcomings have been largely overcome in the case of the reversible inhibitors of monoamine oxidase A (RIMAs) a class of agents that temporarily inhibit the functioning of the monoamine oxidase A enzyme.

Nevertheless, results from two placebo-controlled trials of the RIMA brofaromine have been disappointing. In the first, Katz et al (1994) observed no evidence of reductions in the total score of the gold-standard observer-rated measure of symptom severity, the Clinician Administered PTSD scale (CAPS)(Blake et al., 1995), following 14 weeks of treatment. A significant treatment effect did emerge, however, when restricting the sample of 60 patients to those diagnosed for at least one year. A larger 12 week study of 118 patients failed to detect difference on the CAPS following a similar dosing regimen (Baker et al., 1995). Moreover, although RIMAs are relatively safe compared to the MAO-Is, their potential for harmful interactions with other medications suggests care should be taken in their use in treating refractory patients.

4.4.3 Selective Serotonin Reuptake Inhibitors

The SSRIs represent the medication class that has been most frequently investigated in placebo-controlled trials, with a total of 18 RCTs conducted to date. It is primarily on the basis of these studies that these agents are regarded as first line treatments for PTSD.

Paroxetine

Paroxetine is registered by the FDA for the short-term treatment of PTSD. All 3 published randomised placebo-controlled trials of this medication have reported favourable results. In the first two trials, improvements in symptom severity on the CAPS were detected after 4 weeks of paroxetine, with medication effective for all 3 symptom clusters (Marshall et al., 2001; Tucker et al., 2001). In one of these trials, almost a third of patients on paroxetine (29.4%) went into remission after 12 weeks of treatment (Tucker et al., 2001). A large placebo-controlled comparison of fixed doses of paroxetine (20 mg/d versus 40 mg/d) failed to detect a difference in treatment response as a function of dosage or comorbid depression (Marshall et al., 2001). Marshall et al. (2007) reported significant differences in treatment response on the improvement item of the Clinical Global Impressions scale (CGI-I) after 10 weeks, with a third (14/21) of patients in a sample of 52 mostly Hispanic adults responding to treatment (Guy, 1976).

Fluoxetine

Six RCTs of fluoxetine have been conducted to date. This includes the first published placebo-controlled trial of an SSRI for the treatment of PTSD, a 5 week trial in which significant reductions in PTSD symptom severity were observed in a sample of 64 patients on the CAPS (van der Kolk et al., 1994). This effect was not observed in a subsample from a VA site, however.

In a second trial in civilian subjects (N = 54) differences in treatment response between the placebo and medication groups only reached significance for subjects classified as very much improved (Connor et al., 1999). Using a composite measure, almost half of the subjects on fluoxetine (41%) were regarded as displaying minimal levels of symptoms and non-disability by study endpoint. No differences were observed on any of the self or clinician-rated symptom severity measures after 12 weeks of fluoxetine treatment in a small sample (N = 12) of combat veterans with high levels of comorbid depression (Hertzberg et al., 2000). In a larger sample of 54 predominantly male participants a statistically significant effect of medication emerged after 6 weeks on the observer-rated TOP-8 symptom severity scale (Connor et al., 1999; Martenyi et al., 2002b).

A subsequent trial comparing treatment with 20 or 40 mg/d of fluoxetine in a sample composed primarily of women did not detect superiority of medication after 12 weeks between any of the comparison groups (N = 411)(Martenyi et al., 2007). Similar results were reported for a 8 week comparison of treatment with fluoxetine or eye movement desensitization and reprocessing (EMDR) (van der Kolk et al., 2007). No patients in the fluoxetine arm of this study (N = 30) were asymptomatic (CAPS score < 20) at 6 month follow-up.

Sertraline

Sertraline is licensed by the FDA for the short and long-term treatment of PTSD. There have been a total of 7 published placebo-controlled RCTs of sertraline conducted to date.

Evidence for the efficacy of sertraline has been mixed, with negative results reported for under-powered studies, or typically treatment-resistance populations (veterans). Significant differences in symptom severity were observed in two 12 week RCTs employing similar

designs. Brady and colleagues (Brady et al., 2000) detected differences on the CAPS after only 2 weeks of sertraline in 187 outpatients, with 70% of the reductions on the CAPS and the IES apparent after 4 weeks. Davidson et al. (2001b) reported significant differences on all primary severity measures after 12 weeks in an intent-to-treat sample of 202 outpatients.

In contrast, however, two small 10 week sertraline, one in a sample of Israeli military veterans (N = 42) and the other in predominantly female outpatients (N = 35), both failed to detect an effect of medication on the total CAPS score (Tucker et al., 2003; Zohar et al., 2002). Moreover, Tucker and colleagues (2003) also observed negative effects in the citalopram arm of their study, casting doubt on the power of the study to detect treatment effects. No differences on intent-to-treat analyses were observed for either drinking or PTSD severity outcomes in a 12 week fixed dose study of sertraline in 94 subjects with comorbid PTSD and alcohol abuse/dependence (Brady et al., 2005). Additionally, a 12 week placebo-controlled comparison of sertraline and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine in 538 mixed-trauma subjects did not detect differences between sertraline and placebo on the CAPS-SX, the primary outcome measure (Davidson et al., 2006b).

In the final RCT of sertraline for PTSD, an equivalent number of treatment responders on the CGI-I were observed in the sertraline (36.9%) and placebo (41.5%) groups in a sample of 169 combat veterans after 12 weeks (Friedman et al., 2007). The majority of patients treated with sertraline experienced treatment-emergent adverse events (86%), with diarrhoea and headaches being most common. Combat trauma was associated with a significantly smaller placebo response than non-combat traumas.

Citalopram

A single published RCT of citalopram (described above), failed to demonstrate an effect on PTSD symptom severity after 10 weeks compared to either sertraline or placebo in 33 outpatients (Tucker et al., 2003).

4.4.4 Tricyclic antidepressants (TCAs)

Despite being one of the most established classes of antidepressants, only 3 relatively small controlled trials of TCAs for PTSD have been published to date. In the earliest (cross-over) study, the TCA desipramine did not reduce PTSD symptom severity after 4 weeks of treatment in 18 male US war veterans with high levels of comorbid psychopathology, including affective disorder and substance abuse (Reist et al., 1989).

This cross-over study was followed by a flexible-dose parallel group study of amitriptyline in 46 veterans, in which medication demonstrated superiority over placebo after 8 weeks of treatment. These effects of medication were restricted to self-rated PTSD severity scales, however (Davidson et al., 1990). Finally, an 8 week comparison of the TCA imipramine and phenelzine detected a significant reduction on the IES after 5 weeks of imipramine (Kosten et al., 1991). However, a relatively larger proportion of patients on imipramine than phenelzine dropped out due to treatment-related side effects (17.4% versus 5.3%, respectively).

4.4.5 Anticonvulsants

The possibility that limbic hypersensitisation or kindling might underlie increased arousal to traumatic stimuli in PTSD suggests that anticonvulsants might be effective in treating this disorder (Post et al., 2003). A 10-week RCT of lamotrigine was conducted in war veterans to

test this hypothesis (Hertzberg et al., 1999). Although a larger proportion of participants responded to treatment in the medication than placebo group (2/5 versus 1/4, respectively), the small sample (N = 15) precluded estimation of a treatment effect size.

More recently, 232 patients from 38 centres in the US were treated for 12 weeks with the selective GABA reuptake inhibitor tiagabine (Davidson et al., 2007). No differences were observed in any of the efficacy outcomes assessed. Similar lack of efficacy was observed in 40 outpatients on most outcomes after 12 weeks of treatment with topiramate (Tucker et al., 2007). A reduction in overall PTSD symptom severity was detected on the self-rated TOPS-8 following medication treatment, however. No effect of treatment was detected on any outcome measure after 8 weeks of placebo-controlled treatment with the selective GABA inhibitor divalproex in 85 US military veterans with PTSD (Davis et al., 2008).

4.4.6 Antipsychotics

Three small randomized controlled trials have evaluated the effectiveness of antipsychotic medication as monotherapy in treating PTSD. An initial trial of the atypical antipsychotic olanzapine was unable to detect a treatment response in 15 mostly female patients with non-combat PTSD over 10 weeks (Butterfield et al., 2001). Patients treated with olanzapine gained significantly more weight than those given placebo by study end (11.5 lb versus 0.9 lb, respectively).

Two small studies provide preliminary evidence that risperidone may be effective in treating PTSD in female patients, however. In a trial of 21 women with PTSD from childhood physical, sexual, verbal and emotional abuse, 8 weeks of risperidone resulted in a significant reduction of symptom severity on the CAPS-2 (Reich et al., 2004). Almost half of the subjects were receiving concurrent antidepressants or benzodiazepines. A similar superiority of

risperidone over placebo was detected on the CAPS after 10 weeks of treatment in 20 women exposed to domestic violence and sexual assault (Padala et al., 2006).

4.4.7 Benzodiazepines

Our search strategy retrieved a single RCT testing the effectiveness of benzodiazepine in treating PTSD. In a small controlled trial, sixteen outpatients were administered alprazolam or placebo for two 5 week periods in a cross-over fashion, separated by a 2 week placebo-substitution washout period (Braun et al., 1990). Analysis of data from the 10 patients who completed the study revealed a significant reduction in depression symptoms only.

4.4.8 Other medications

A total of 5 placebo-controlled RCTs of medications with novel mechanisms of action have been conducted. In the first placebo-controlled trial inositol, a glucose isomer, was administered over four weeks in a cross-over fashion to 17 outpatients with mixed trauma, with no discernable effect of medication on the primary outcome (IES) amongst the 13 subjects who completed the trial (Kaplan et al., 1996).

The second trial compared the effectiveness of 8 weeks of treatment with mirtazapine or placebo in 26 subjects with PTSD, the majority of whom had comorbid depression (Davidson et al., 2003). A greater number of treatment responders were observed in the medication group, with mirtazapine also demonstrating an antidepressant effect. Davis et al. (2004) detected superiority of 12 weeks of nefazodone to placebo in 42 combat veterans on the continuous total CAPS score. The high dropout rate amongst those treated with medication (46%) raises questions regarding the tolerability of this agent, however.

A 6 month study of the serotonin norepinephrine reuptake inhibitor venlafaxine assessed its effectiveness in patients sampled from 56 outpatient centres outside of the US (Davidson et al., 2006a). An improvement was observed on the CAPS-SX total score, as well as on measures of quality of life, functional disability, resilience to stress and comorbid depression. A subsequent trial by the same group detected significant reductions in symptom severity following venlafaxine treatment in 538 outpatients on the CAPS-SX total score. Differences were observed as early as 2 weeks following the initiation of treatment (Davidson et al., 2006b).

4.5 Meta-analysis of pharmacotherapy for PTSD

This brief review highlights the inconsistency of the evidence for the efficacy of medication in treating PTSD. Of the 37 short-term studies included in this review that conducted between-group comparisons, only 12 detected a significant reduction in PTSD symptom severity on the CAPS or an alternate primary outcome measure (see Table 1). This divergence in findings was detected even amongst first line agents, with 9 of the 15 SSRI trials employing the CAPS unable to distinguish statistically between the effects of medication and placebo.

Poor sensitivity to treatment effects may be partially due to variation in study methodology and the clinical characteristics of patient groups, as well as insufficient power to detect a treatment effect in small studies. The quantitative synthesis or meta-analysis of treatment outcome data allows one to maximise power in detecting an effect. Overall treatment effects are typically summarised in the form of a mean difference (MD) or effect size estimate that can be standardised to accommodate the use of different outcome scales (Cohen, 1988).

A number of meta-analyses of medication treatment for PTSD have been conducted to date, synthesising data from trials of individual agents (Adamou et al., 2007; Mooney et al., 2004),

as well as comparing treatment efficacy across agents (Penava et al., 1996; Stein et al., 2006; Stewart and Wrobel, 2009; Van Etten and Taylor, 1998). Although the findings of these meta-analyses have in general supported the use of pharmacotherapy, and SSRIs in particular, in treating PTSD, their conclusions have been weakened by methodological shortcomings (listed in Table 3). Accordingly, we conducted a meta-analysis of placebo-controlled RCTs of PTSD in adults that was restricted to between-group comparisons of outcome data from validated scales.

4.5.1 Methods of meta-analysis

Primary outcomes included the reduction in total symptom severity on the Clinician Administered PTSD Scale and the number of subjects rated as “much improved” or “very much improved” on the improvement item of the Clinical Global Impressions scale (CGI-I) (or closely related measure). Secondary outcomes included the efficacy of medication in alleviating the severity of PTSD symptom clusters, as assessed by the respective subscales of the observer-rated CAPS and the self-rated DTS. Medication acceptability was estimated by calculating the total proportion of participants who withdrew from the RCTs due to treatment emergent adverse events.

Weighted mean differences (WMD) for continuous measures and relative risks for categorical outcomes were obtained from a random effects model and were expressed in terms of the average and 95% confidence interval of the effect size for each subgroup. Treatment response on the CGI-I was converted into a number needed to treat (NNT) for each medication agent (see footnotes in Table 3 for the exact procedure).

Efficacy analyses (detailed below) were conducted using the metafor package in the R statistical software, and employing the DerSimonian-Laird estimator of heterogeneity

(DerSimonian and Laird, 1986; Viechtbauer, 2010). Differences in the efficacy of classes of medication were assessed by means of Deeks' stratified test of heterogeneity (2001). Egger's regression test of funnel plot asymmetry was employed in order to determine whether there was evidence of possible publication bias (Egger et al., 1997). A mixed-model meta-regression was conducted to determine the degree to which methodological (gender distribution and proportion of patients with combat-trauma) and clinical (duration of trial in weeks, number of sites, year of publication, and pharmaceutical funding) differences between trials might have systematically influenced variation in the reduction of PTSD symptom severity.

4.5.2 Results of meta-analysis

A total of 37 short-term RCTs (4 – 24 weeks), containing data for 5008 patients treated with medication for an average of 10 weeks, were included in the review (Table 1). These included data from unpublished industry-funded short-term RCTs of paroxetine (SKB627) and sertraline (Pfizer588), published in the National Institute of Clinical Excellence PTSD guidelines (NICE, 2005). In addition, 5 published (Connor et al., 2006; Davidson et al., 2001a; Davidson et al., 2005; Marshall et al., 2007; Martenyi et al., 2002a) and 1 unpublished RCTs (SKB650) included a maintenance component. The greatest number of trials assessed the effectiveness of the SSRIs (N = 20). There was little evidence from an Egger regression plot of publication bias across the 23 studies that were included in the meta-analysis ($z = 1.12$, $p = 0.27$; see supplementary material for regression plot).

Medication treatment resulted in a significant reduction in PTSD symptom severity, with a reduction of about 6 points on the CAPS total score relative to placebo (N = 23, MD = -6.10, 95%CI = -7.98, -4.23, n = 4112)(see Figure 1.). A moderate degree of variation was evident in the results of the SSRI ($I^2 = 35\%$) and brofaromine trials ($I^2 = 31\%$). Of the 4 SSRI agents

for which there was data (citalopram, fluoxetine, paroxetine and sertraline), evidence of efficacy was only available for paroxetine (N = 4, MD = -10.65, 95%CI = -14.16, -7.14, n = 1100) and sertraline (N = 8, MD = -4.35, 95%CI = -6.76, -1.93, n = 1260). Paroxetine was significantly more effective than sertraline and fluoxetine in reducing symptom severity using a fixed effects model (chi-squared=10.37, p = 0.001 and chi-squared=3.08, p = 0.08, respectively).

Pharmacotherapy was more likely to result in a global clinical response on the CGI-I than placebo (N = 16, RR = 1.4, 95%CI = 1.17, 1.66, n = 1821). A larger proportion of patients were responders on this scale in the medication (57.2%) than placebo (40.2%) groups. The corresponding NNT indicates that, relative to patients in the placebo groups, approximately 7 to 10 patients have to be treated for an average of 11 weeks with medication in order for an additional patient to respond to treatment.

Significant treatment effects were observed for the intrusion/re-experiencing, avoidance/numbing and hyperarousal symptoms on the CAPS. Comorbid depression but not anxiety were reduced following medication treatment (HAM-D: N = 10, MD = -2.31, 95%CI = -3.6, -1.02, n = 930). Significant improvements were also observed in functional disability following medication treatment (N = 10, MD = -1.87, 95%CI = -2.72, -1.02, n = 1852). Finally, a larger number of patients on medication withdrew from treatment due to adverse events than on placebo (N = 29, relative risk = 1.38, 95%CI = 1.10, 1.72, n = 4045), though the absolute proportion that withdrew was relatively small (9.5%).

More recently published trials were more likely to report smaller reductions in symptom severity than older trials (coef = 1.32, z = 3.28, p = 0.001). Although the placebo response on the CAPS was relatively marked across trials (mean reduction of 26.8 points), there was little evidence of an increase in placebo response over time that could explain this pattern.

Instead, it is more likely a result of the fact that the more recent studies are small trials of novel psychotropics, for which there is limited evidence of effectiveness, and which are under-powered to detect treatment effects.

A strong positive relationship was observed between response on the CAPS and number of centres at which a trial was conducted. The high correspondence between number of centres and sample size ($\rho = 0.92$), suggests this finding may also result from increased power in the larger samples employed in multi-centre studies. Surprisingly, no effect on outcome was detected for the source of funding, duration of trial, or proportion of females or veterans comprising the study sample.

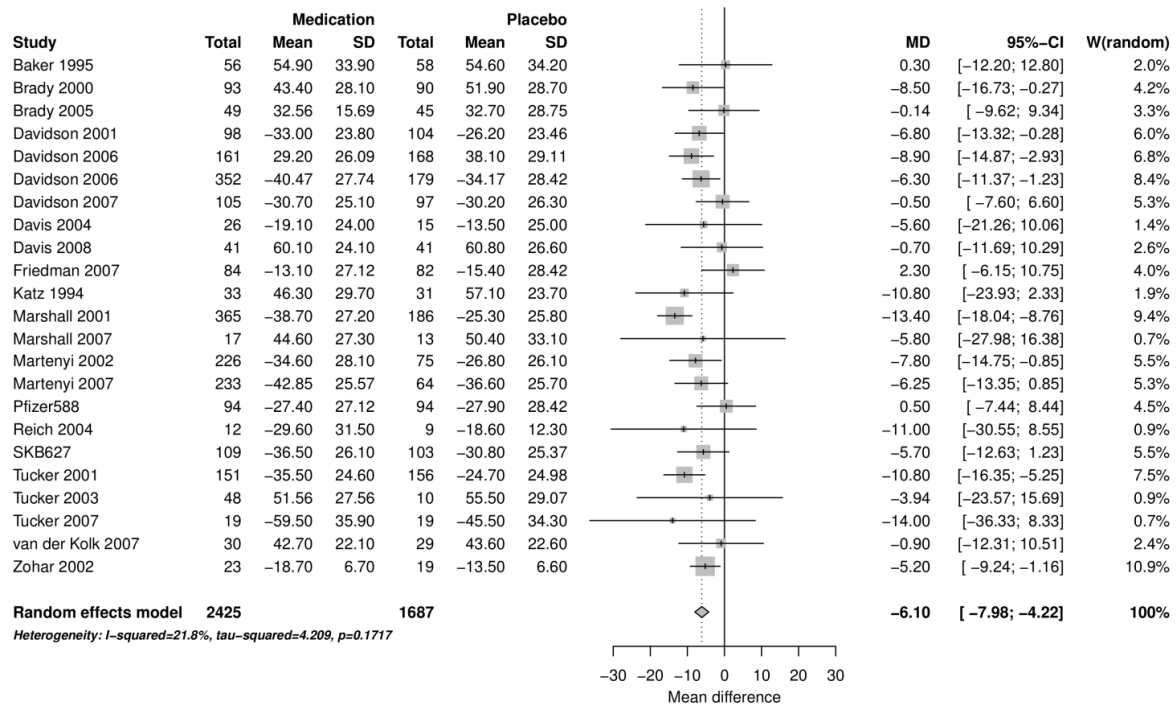


Figure 1. Forest plot of response on the CAPS in PTSD pharmacotherapy RCTs

4.6 Length of treatment

The available pharmacotherapy evidence base suggests that treatment effects may emerge as early as 2 to 4 weeks for the SSRIs and the SNRI venlafaxine. Less is known about how long patients should be treated to achieve a maximal response, and when it is safe to discontinue pharmacotherapy without risking relapse.

Davidson and colleagues administered 28 weeks of placebo or sertraline to patients who completed a 12 week placebo controlled trial of sertraline, and who responded to a subsequent 24 weeks of open-label treatment with this agent (50 – 200 mg/d) (Davidson et al., 2001a). Response to acute-treatment with sertraline was maintained in the majority of patients during open-label continuation, with more than half of the non-responders to sertraline (54%) during the acute phase responding during the continuation phase (Londborg et al., 2001). Relapse, defined as a composite measure consisting of reductions in clinical improvement scores, increasing PTSD symptom severity and investigators opinion of clinical deterioration, was 6.4 times as frequent in responders to continuation treatment who were subsequently randomised to placebo (26%) than sertraline (5%).

Responders to medication in 12 week double-blind placebo-controlled trial of fluoxetine for PTSD were randomised to another 24 weeks of treatment with fluoxetine or placebo (Martenyi et al., 2002a). Relapse was defined as an increase from baseline at week 12 of acute treatment by 40% on the TOP-8 score and an increase ≥ 2 on the CGI-S. Time to relapse was significantly longer in the medication than the placebo group, with a lower proportion of the 131 responders to acute-phase fluoxetine treatment relapsing (5.8%) after continuation with medication than placebo (16.1%). Patients who were randomised to fluoxetine continued to improve significantly on the clinical and PTSD severity scores, as well as in anxiety and depression symptoms.

Davidson et al. (2005), randomized 62 subjects to 6 months continuation treatment with fluoxetine or placebo after the same period of open-label treatment (max: 60 mg/d) with fluoxetine. Relapse was defined as either an untoward clinical event (eg. psychiatric hospitalization) during the randomisation phase, or an increase of at least 2 points on the CGI since randomisation, or as no improvement or worsening of symptoms on the CGI relative to open-label baseline. Although a relatively strong effect of medication was observed in preventing relapse during the maintenance phase of the study, relapse rates were high for both participants who continued receiving a stable dose of fluoxetine (22%) as well as for those whom medication was discontinued medication (50%).

The efficacy of maintenance treatment with the selective GABA reuptake inhibitor tiagabine was tested by randomising 18 completers of 12 weeks of open-label treatment with tiagabine (max dose: 16 mg) to ongoing medication treatment or placebo for an additional 12 weeks (Connor et al., 2006). No differences in clinical response were detected.

The limited evidence reviewed above suggests that treatment with SSRIs may be beneficial over the long term. These agents also appear to be well-tolerated amongst those patients who have achieved stable doses, with no drug-related adverse events reported for more than 20% of subjects in any of the relapse prevention studies reviewed.

4.7 Treatment refractory cases

A large proportion of patients with PTSD fail to respond to treatment with pharmacotherapy. For example, close to half of the patients (44.2%) in the 23 RCTs that provided information on treatment response were non-responders (Table 1).

Despite the relatively high rates of treatment resistance, few rigorous trials of pharmacotherapy in non-responders to first-line treatments for PTSD have been conducted (Table 4). In a recent review, Ipser et al. (2006) identified only 4 RCTs that assessed augmentation strategies for treating PTSD in populations who were currently receiving psychotropic medication, and who could be defined as treatment resistant according to lack of response on the CGI-I or a validated measure of symptom severity (Bartzokis et al., 2005; Hamner et al., 2003; Raskind et al., 2003; Stein et al., 2002). These trials are briefly described below, as well as a subsequently published study of the antipsychotic risperidone that satisfied the inclusion criteria employed by Ipser et al. (2006)(Rothbaum et al., 2008).

Dysregulation of the sympathetic system and the centrality of hyperarousal symptoms in PTSD suggest that agonists of adrenergic receptors might be effective treating refractory patients. A small 20 week double-blinded cross-over study of the efficacy of the alpha 1 adrenergic antagonist prazosin in treating sleep disturbances in 10 patients with chronic PTSD reported clinically significant improvement following medication treatment in PTSD and sleep symptoms (Raskind et al., 2003).

Antipsychotic agents may be indicated as augmentation agents in treating PTSD, given the presence of psychotic symptoms in complicated cases of PTSD, and the possibility that the disorder is characterised by dysregulation of the dopaminergic system (Seedat et al. 2003). The first antipsychotic tested in an RCT for PTSD as part of an augmentation strategy was olanzapine (Stein et al., 2002). This agent was administered for the treatment of chronic PTSD in 21 war veterans who did not respond to a minimum of 12 weeks of prior treatment with an SSRI. Olanzapine significantly reduced symptom severity on the CAPS and sleep disturbance after 8 weeks of double-blind treatment, despite the absence of psychotic symptoms in any of the patients.

The efficacy of risperidone in treating PTSD has been assessed in three RCTs. No effect of medication was observed on the CAPS following 5-weeks of treatment with risperidone in 37 Vietnam veterans diagnosed with PTSD and psychotic symptoms (Hamner et al., 2003). However, a greater reduction was observed in the medication group in severity of psychotic symptoms, as measured using the PANSS (Kay et al., 1987). A subsequent placebo-controlled trial of risperidone was conducted in 65 veterans with PTSD who were participating in a 5 week psychotherapy residential program (Bartzokis et al., 2005). Patients with psychotic symptoms were excluded, and most of the study participants were being treated with antidepressants (88%). Superiority of medication was observed after 16 weeks in reducing PTSD symptoms on the total CAPS score, as well as anxiety and negative and positive psychotic symptoms.

In one of the few trials to assess pharmacotherapy for treatment-resistant PTSD in a non-veteran population, Rothbaum and colleagues (2008) administered add-on risperidone for 8 weeks to 20 patients who failed to achieve a 75% reduction in total score on the CAPS after 8 weeks of open-label treatment with sertraline. Many of the patients were reported as displaying psychotic symptoms. Virtually identical differences were observed on the CAPS at endpoint in the placebo and medication groups. Approximately a third of the patients treated with risperidone (4/11) dropped out due to possibly treatment-related adverse events.

The majority of controlled trials of pharmacotherapy in combating anxiety disorders add a course of antipsychotics to ongoing treatment with SSRIs (Ipser et al., 2006). In general, findings from trials of PTSD appear to support the efficacy of this strategy, at least with respect to combat-related traumas. There is less evidence regarding the management of PTSD in civilian populations. Paradoxically, antipsychotic agents have thus far only demonstrated effectiveness in reducing PTSD symptoms in patients without psychotic symptoms. Evidence that prazosin is effective in treating sleep disturbances associated with

refractory PTSD is consistent with findings from an RCT of this agent when used as monotherapy in treating sleep-related symptoms in PTSD patients (Taylor et al., 2008).

4.8 Conclusion

The results of a meta-analysis are only as valid as the quality of the individual trials from which they are composed. With this in mind the authors conducted an exhaustive search for eligible trials, and restricted the results of this review to RCTs, widely regarded as the most rigorous study design. Moreover, the test of publication bias provided little evidence that articles that reported positive results were disproportionately represented in the meta-analysis.

The results of our review support the effectiveness of medication in treating PTSD over the short-term, with the largest body of evidence of efficacy for the SSRIs and venlafaxine. The agents appear relatively fast-acting, with response reported as early as the first 2 to 4 weeks of treatment. Nevertheless, maximising response to medication might require treatment for substantially longer, with RCTs of paroxetine and fluoxetine observing substantial improvements in clinical response beyond 12 weeks of treatment (Martenyi et al., 2002a). No evidence of efficacy was available for the benzodiazepines, despite their continued popularity in clinical practice (Cloos and Ferreira, 2009).

The current evidence-base supports the efficacy and tolerability of treatment with the SSRI's over the longer-term. The finding that over a quarter of patients relapsed after discontinuation of fluoxetine treatment after up to 26 weeks of treatment (Davidson et al., 2001a) provides some support to the consensus that treatment of chronic PTSD with medication should be continued for at least a year. Of the two FDA approved agents for the treatment of PTSD, stronger support is available for the efficacy of paroxetine than sertraline. This calls into

question the usefulness of including sertraline as the gold-standard comparator in RCTs comparing the efficacy of different medications (Chung et al., 2004; McRae et al., 2004; Saygin et al., 2002; Smajkic et al., 2001).

War-trauma is commonly perceived as being prognostic of a poorer response to treatment, with 9 of the 11 trials that included a majority of trauma veterans failing to demonstrate efficacy for pharmacotherapy. The finding in a 12 week trial of fluoxetine of increased response in patients recently exposed to combat suggests that the salient characteristic with regards to medication response might be duration of PTSD, rather than combat trauma or gender, per se (Martenyi et al., 2002b). Although inadequate information prevented a quantitative test of this hypothesis, the suggestion that combat trauma or gender are not influential determinants of study outcome is consistent with the results of the meta-regression analyses reported in this paper. Indeed, our analyses suggest that certain study design features, such as sample size, might be more important in determining the size of the treatment effects observed.

Neither of the dose-comparison studies of fluoxetine or paroxetine were able to detect significant differences in efficacy between higher and lower doses (Marshall et al., 2001; Martenyi et al., 2007). This is consistent with the general observation of a flat response curve for the SSRIs, and suggests that it might be prudent to initiate medication treatment at the low end of the recommended dose range, with the aim of minimising potential treatment-related adverse events. Future research should address the comparative efficacy of doses of venlafaxine, as there is evidence in studies of depression that the efficacy of venlafaxine is dose-dependent (Stahl et al., 2005). It is notable that the maximum dose of venlafaxine in both of the RCTs of this agent in PTSD conducted to date were higher than the FDA guidelines for the licensed prescription of this medication for depression (Davidson et al., 2006a; Davidson et al., 2006b).

There has recently been interest shown in the treatment of PTSD with medications that employ extra-serotonergic mechanisms of action, including the anticonvulsants, atypical antipsychotics and venlafaxine. With the exception of risperidone and venlafaxine, the results of these trials have been disappointing. Positive results from small underpowered studies of risperidone need to be followed up with larger placebo-controlled trials. Similarly, although medications such as prazosin and the atypical antipsychotics appear to hold promise as augmenting agents, much additional work is needed to determine how best to manage PTSD symptoms in treatment-refractory patients. Investigators are encouraged to design their clinical trials according to best-practice guidelines, and using gold-standard outcomes, such as the CAPS, in order to facilitate future meta-analyses of the efficacy of particular agents.

University of Cape Town

Table 1. Placebo-controlled randomised studies included in the review

Medication agents	P.I.	Year	Duration (weeks)	Sample size	% Males	Dose (mg/d)	Response Rates (%)		Response criteria‡	Efficacy*	Tx-related dropouts (%)
							Drug	Control			
MAOIs											
phenelzine	Shestatzky	1988	5	13	--	30-75	--	--		↔	44
phenelzine	Kosten	1991	8	37	100	15-75	68	28	CGI-I < 4	↔	17
RIMAs											
brofaromine	Katz	1995	14	60	76	50-150	55	26	no PTSD diagnosis	↔	5
brofaromine	Baker	1995	12	114	81	150 (max)	--	--		↔	18
SSRIs											
citalopram	Tucker	2003	10	35	29	20 - 50	--	--		↔	--
fluoxetine	v.d. Kolk	1994	5	64	66	20 - 60	--	--		↑	--
fluoxetine	Connor	1999	12	54	9	10-60	85	62	DGRP-I < 3	↑	0
fluoxetine	Hertzberg	2000	12	12	100	10-60	17	33	DGRP-I < 3	↔	17
fluoxetine	Martenyi†	2002	12/24	301	81	20-80	60	44	CGI < 3, TOP-8 <= 50%	↑	3
fluoxetine	Davidson†	2005	24/24	62	50	--	--	--			3
fluoxetine	Martenyi	2007	12	411	29	20, 20-40	41,39	38	CGI < 3, TOP-8 <= 50%, no PTSD diag.	↔	4 & 13
fluoxetine	v.d. Kolk	2007	8	59	14	10-60	81	65	no PTSD diag.	↔	--
paroxetine	Marshall	2001	12	376	32	20, 20-40	62,54	37	CGI-I < 3	↑	11 & 15
paroxetine	Tucker	2001	12	323	34	20-50	59	38	CGI-I < 3	↑	11
paroxetine	SKB627		12	322	46	20-50	--	--	--	--	--
paroxetine	SKB650†ms		36	176	34	--	--	--	--	--	--
paroxetine	Marshall†	2007	10/12	52	33	20-60	67	27	CGI-I < 3	↔	0
sertraline	Brady†	2000	12/24/28	187	27	25-200	53	32	CGI-I < 3, CAPS < 20	↑	5
sertraline	Davidson†	2001	12/24/28	208	22	25-200	60	38	CGI < 3	↑	9
sertraline	Zohar	2002	10	42	88	50-200	53	20	CGI < 3	↔	13
sertraline	Tucker	2003	10	33	29	50-200	--	--		↔	--
sertraline	Pfizer588		11	193	25	156 (mean)	--	--	--	--	--
sertraline	Brady	2005	12	94	54	150	--	--		↔	0
sertraline	Davidson	2006	12	352	--	25-200	--	--		↔	13

sertraline	Friedman	2007	10	169	80	25-200	37	42	CGI-I < 3	↔	13
TCAs											
desipramine	Reist	1989	4	18	100	50-200	--	--		↔	7
amitriptyline	Davidson	1990	8	46	100	50-300	50	17	CGI-I < 3	↔	12
imipramine	Kosten	1991	8	41	100	50-300	65	28	CGI-I < 4	↔	17
ANTICONVULSANTS											
divalproex	Davis	2008	8	85	98	500-3000	--	--		↔	7
lamotrigine	Hertzberg	1999	12	15	64	25-500	50	25	DGRP-I < 3	--	18
tiagabine	Connor†	2006	12/12	18	--	2 (BID) - 16	--	--			0
tiagabine	Davidson	2007	12	232	34	4-16	49	54	CGI < 3	↔	8
topiramate	Tucker	2007	12	40	21	25-400	42	21	CAPS < 20	↔	20
ANTIPSYCHOTICS											
olanzapine	Butterfield	2001	10	15	7	5-20	60	60	CGI < 3	↔	8
risperidone	Reich	2004	8	21	0	0.5-8	--	--		↑	9
risperidone	Padala	2006	10	20	0	0.5-6	--	--		↑	
BENZODIAZEPINE											
alprazolam	Braun	1990	5	16	--	1.5-6	--	--		↔	0
OTHER											
inositol	Kaplan	1996	4	13	62	12000	--	--		↔	--
mirtazapine	Davidson	2003	8	26	--	15-45	65	22	SPRINT-I < 3	↔	18
nefazodone	Davis	2004	12	42	98	200-600	47	42	CAPS >= 30% improvement	↑	19
venlafaxine	Davidson	2006	12	358	--	37.5-300	--	--		↑	10
venlafaxine	Davidson	2006	24	329	46	37.5-300	78	64	CAPS-SX >= 30% improvement at 12 wks	↑	9

*: significant differences in PTSD symptom severity in favour of medication is indicated by an upward pointing arrow (↑) and non-significant differences by a double-headed horizontal arrow (↔). Symptom severity data was collected for the CAPS, or from another primary efficacy measures where the CAPS was not employed.

†: sample included in maintenance trial

‡: CGI-I = Clinical Global Impressions Scale – Improvement item, DGRP-I – Duke Global Rating of PTSD – Improvement item, SPRINT-I = Short PTSD Rating Interview – Improvement item, CAPS = Clinician Administered PTSD Scale, SPRINT-I = -- = no data provided

Table 2. Meta-analyses of pharmacotherapy for PTSD

Study	Year	Intervention	Databases*	Date range	Trials†	PTSD Outcomes‡	ES§	Limitations
Penava	1996	All controlled trials of medication	psycINFO, MEDLINE	1974-July 1996	6	PTSD effect, or the “best overall measure of specific PTSD symptomatology”.	0.41(--) ^a	small number of studies; no explicit criteria for “best” measure of PTSD; variability of effect sizes not reported; combination of data from self and observer-rated scales; multiple data points for different studies
Van Etten	1998	All medication and psychological studies	MEDLINE, PILOTS, Psychological Abstracts, Current Contents library	1984-1996	16(19)	(1) observer-rated PTSD scales (2) self-rated PTSD scales	(1) 1.05 ^a , (2) 0.69 ^a	meta-analysis included open-label trials without controls; combination of wait-list, supportive psychotherapy and pill placebo as primary control group; likelihood of false positive findings increased through setting statistical threshold to 0.1; analyses limited to data from trial completers
Stein	2006	All medication RCTs	MEDLINE, psycINFO, PILOTS, CCDAN-TR, Controlled Trials metaregister	Up till December, 2004	35(17)	CAPS-2	-5.76 ^b (-8.16, -3.36)	possible publication bias in the funnel plot for the CAPS
Stewart	2009	All medication & psychotherapy	psycINFO	1988-2006	13(10)	Clinician and self-rated PTSD scales	1 ^a	included open-label studies that did not control for placebo effect; pre-post treatment within group analyses; two

trials for
combat-
related PTSD
(except case
studies)

of the studies employed the
medication as adjunctive agents to
existing pharmacotherapy; multiple
studies reporting on the same sample
included

*: AMED = Allied and Complementary Medicine Database, CCDAN-TR = Cochrane Collaboration Depression, Anxiety and Neurosis Trial Registry, CINAHL = Cumulative Index to Nursing and Allied Health Literature, PILOTS = Published International Literature on Traumatic Stress, SIGLE = System for Information on Grey Literature in Europe
†: Total number of pharmacotherapy trials included in study, with the specific number of trials included in meta-analysis in parentheses
‡: CAPS = Clinician Administered PTSD Scale, IES = Impact of Events Scale, DTS = Davidson Trauma Scale,
§: effect size estimates and 95% confidence intervals reported using standardised (a) or non-standardised (b) mean difference metrics

Table 3. Summary measures of effect size and statistical heterogeneity across medication agents

Medication	Studies	Sample	CAPS Effect & 95% CI*	Heterogeneity†	NNT‡
SSRIs	13	2642	-6.64 (-9.11, -4.16)	Moderate	6-9
Sertraline	7	1072	-4.84 (-7.37, -2.31)	Minimal	7-11
Paroxetine	3	888	-12.17 (-15.68, -8.65)	Minimal	4-7
Fluoxetine	2	356	-4.76 (-10.79, 1.27)	Minimal	8-12
Citalopram	1	33	-13.41 (-34.73, 7.91)	na	--
Brofaromine	2	178	-5.06 (-15.93, 5.81)	Moderate	16-25
Venlafaxine	2	687	-8.11 (-12.30, -3.92)	Minimal	--
Divalproex	1	82	-0.70 (-11.69, 10.29)	na	--
Nefazodone	1	41	-5.60 (-21.26, 10.06)	na	--
Risperidone	1	21	-11.00 (-30.55, 8.55)	na	--
Tiagabine	1	202	-0.50 (-7.60, 6.60)	na	25-40
Topiramate	1	38	-14.00 (-36.33, 8.33)	na	--

*: effect sizes reported as (non-standardised) mean differences

†: Heterogeneity classified as minimal, moderate and large, based on an I^2 statistic of less than 30%, between 30% and 50%, and over 50%, respectively.

‡: The number needed to treat (NNT) was calculated from the risk ratio estimates of treatment response, defined as "much improved" or "very much improved" on the Clinical Global Impressions Improvement item (or related scale). The NNT is based on a high and low estimate of response in the control group of 0.25 and 0.4, respectively, calculated by rounding the limits of the interquartile range for the placebo group response rate in the included studies to the nearest 5 percentage points. Baseline risk was calculated using the metannt command of the Metan package in Stata 11 (www.stata.com)

Table 4. Randomised placebo-controlled augmentation studies

Medication agents	P.I.	Year	Duration (weeks)	Sample size	Dose† (mg/d)	% Males	% War trauma	% other meds	Min. Severity	Outcome scales*
Alpha adrenergic agonists prazosin	Raskind	2003	10	10	9.5	100	100	70	CAPS distressing dreams item => 6	CAPS, CGI-I
Antipsychotics olanzapine	Stein	2002	8	21	15	100	100	100	--	CAPS, CGI-I, CES-D PSQI
risperidone	Hamner	2003	5	40	2.5	100	100	54	PANSS >= 60	PANSS, CAPS
	Bartzokis	2005	16	65	1-3	100	100	92	CAPS => 65	CAPS, HAM-D, HAM-A, PANSS-P
	Rothbaum	2008	8	20	.05-2	20	0	100	CAPS => 50	CAPS, DTS, PANSS, BDI, CGI-I

* CAPS: Clinician Administered PTSD Scale; BDI: Becks Depression Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; CGI-I: Clinical Global Impression scale – Improvement item; DTS: Davidson Trauma Scale; HAM-A: Hamilton Anxiety scale; HAM-D: Hamilton Depression scale; PANSS: Positive and Negative Syndrome Scale ; PANSS-P: Positive and Negative Syndrome Scale; PSQI: Pittsburgh Sleep Quality Index

† Doses reported as mean daily doses or dose ranges

4.9 Supplementary Material

4.9.1 Inclusion criteria for meta-analysis

Inclusion of studies in this review was restricted to all placebo-controlled randomised controlled trials (both published and unpublished) of pharmacotherapy for adults (18 – 64 years) diagnosed with PTSD, according to DSM-III+ or ICD-9+ criteria.

Assessment of RCTs for inclusion in this review was conducted independently by 2 raters. Concurrent treatment of the majority of patients with medication (\Rightarrow 50%) as part of standard care were grounds for exclusion. Concurrent psychotherapy was permitted, on the condition that it was (a) not trauma-focused, or (b) had been initiated at least 3 months prior to the beginning of the trial. RCTs of medication prophylaxis for PTSD were not eligible. Finally, studies were restricted to those in which the objective was to treat all symptom clusters defining PTSD, rather than specific subsets, such as sleep disturbances.

Eligible RCTs were identified in February, 2010 by systematically searching the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and the National PTSD Center Pilots database. Database-specific search queries were designed, and included the terms "posttraumatic stress disorder" and "randomized controlled trial" (see the supplementary material for full syntax). Unpublished studies were located by searching the bibliographies of published articles, and by contacting experts in the field. Where study data was missing, or in cases in which there was concern regarding publication of multiple

reports on the same trial, the reviewers contacted investigators by email in an attempt to obtain more information.

4.9.2 Electronic database search queries

CCDAN:

Searched on 11 February, 2010

1. ((serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj (uptake or reuptake or re-uptake)).mp.
2. (5-hydroxytryptophan or Acetylcarnitine or Alaproclate or alprazolam or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or anticonvulsant* or Antidepress* or antipsychotic* or anxiolytic*).mp.
3. (Befloxatone or Benactyzine or benzodiazepine* or Brofaromine or Bupropion or Butriptyline).mp.
4. (Caroxazone or cck-4 or Chlorimipramine or Chlorphenamidine or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or clonidine or Clorgyline or Clovoxamine or cyproheptadine or d-cycloserine).mp.
5. (Deanol or Demexiptiline or Deprenyl or Desipramine or Desvenlafaxine or Dibenzipin or Diclofensine or divalproex or dopamin* or Dosulepin or Dothiepin or Doxepin or Duloxetine).mp.
6. (Escitalopram or Etoferidone or Femoxetine or Fenfluramine or flumazenil or Fluotracen or fluoxetine or Fluparoxan or fluphenazine or Fluvoxamine or Furazolidone).mp.
7. (haloperidol or Harmaline or Harmine or hydrocortisone or Idazoxan or Imipramine or inositol or Iprindole or Iproniazid or Isocarboxazid or lamotrigine).mp.
8. (Lithium carbonate or Lithium compounds or Litoxetine or Lofepramine).mp.
9. (MAOI* or Maprotiline or medicat* or Medifoxamine or Melitracen or Metapramine or metyrapone or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monoamine Oxidase Inhibitor* or monocrotophos).mp.
10. (naloxone or naltrexone or Nefazodone or Nialamide or Nomifensine or noradrenerg* or norfenfluramine or Nortriptyline or Noxiptiline or olanzapine or Opipramol or Oxaflozane or Oxaprotiline).mp.
11. (Pargyline or Paroxetine or pharmacother* or Phenelzine or pheniprazine or Piribedil or Pirlindole or Pivagabine or Pizotyline or prazosin or procaine or propanolol or Prosulpride or Protriptyline or psychotropic*).mp.
12. (quetiapine or Quinupramine or quipazine or Reboxetine or risperidone or Ritanserin or Rolipram).mp.
13. (selegiline or seroto* or Sertraline or Setiptiline or SNRI* or SSRI* or sulphiride).mp.
14. (Teniloxine or Tetrindole or Thiazesim or Thozalinone or tiagapine or Tianeptine or Toloxatone or Tomoxetine or topiramate or Tranlycypromine or Trazodone or tricyclic* or Trimipramine or tryptophan).mp.
15. (Venlafaxine or Viloxazine or Viqualine or yohimbine or Zimeldine).mp.
16. or/1-15
17. posttraumatic stress disorder/
18. ((post-traumatic or post traumatic or posttraumatic) and disorder*).tw.
19. PTSD.tw.
20. or/17-19
21. major clinical study/
22. randomized controlled trial/
23. randomization/

24. placebo/
25. randomi#ed.ti,ab.
26. placebo\$.tw.
27. trial\$.ti,ab.
28. randomly.ab.
29. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$ or dummy)).mp.
30. (control\$ adj3 (trial\$ or study or studies\$)).tw.
31. ((animal or nonhuman) not (human and (animal or nonhuman))).de.
32. or/21-30
33. 32 not 31
34. 16 and 20 and 33
35. (2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$).yr.
36. (2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$).em.
37. or/35-36
38. 34 and 37
39. from 38 keep 1-773
40. ((serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj (uptake or reuptake or re-uptake)).mp.
41. (alprazolam or amitriptyline or brofaromine or citalopram or desipramine or fluoxetine or imipramine or inositol or lamotrigine or olanzapine or mirtazapine or nefazodone or paroxetine or phenelzine or risperidone or sertraline or venlafaxine or anticonvulsant* or antipsychotic* or benzodiazepine* or noradrenerg* or dopamin* or serotonin* or SNRI* or SSRI* or tricyclic* or anxiolytic* or pharmacother* or medicat*).mp.
42. 40 or 41
43. 20 and 33 and 37 and 42
44. from 43 keep 1-631
45. 39 not 44
46. from 45 keep 1-142

EMBASE:

Searched on 11 February, 2010

((serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj (uptake or reuptake or re-uptake)) or 5-hydroxytryptophan or Acetylcarnitine or Alaproclate or alprazolam or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or anticonvulsant* or Antidepress* or antipsychotic* or anxiolytic* or Befloxadone or Benactyzine or benzodiazepine* or Brofaromine or Bupropion or Butriptyline or Caroxazone or cck-4 or Chlorimipramine or Chlorphenamidine or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or clonidine or Clorgyline or Clovoxamine or cyproheptadine or d-cycloserine or Deanol or Demexiptiline or Deprenyl or Desipramine or Desvenlafaxine or Dibenzipin or Diclofensine or divalproex or dopamin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Escitalopram or Etoferidone or Femoxetine or Fenfluramine or flumazenil or Fluotracen or fluoxetine or Fluparoxan or fluphenazine or Fluvoxamine or Furazolidone or haloperidol or Harmaline or Harmine or hydrocortisone or Idazoxan or Imipramine or inositol or Iprindole or Iproniazid or Isocarboxazid or lamotrigine or Lithium carbonate or Lithium compounds or Litoxetine or Lofepamine or MAOI* or Maprotiline or medicat* or Medifoxamine or Melitracen or Metapramine or metyrapone or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monoamine Oxidase Inhibitor* or monocrotophos or naloxone or naltrexone or Nefazodone or Nialamide or Nomifensine or noradrenerg* or norfenfluramine or Nortriptyline or Noxiptiline or olanzapine or Opi Pramol or Oxaflozane or Oxaprotiline or Pargyline or Paroxetine or pharmacother* or Phenelzine or

pheniprazine or Piribedil or Pirlindole or Pivagabine or Pizotyline or prazosin or procaine or propanolol or Prosulpride or Protriptyline or psychotropic* or quetiapine or Quinupramine or quipazine or Reboxetine or risperidone or Ritanserin or Rolipram or selegiline or seroton* or Sertraline or Setiptiline or SNRI* or SSRI* or sulpiride or Teniloxine or Tetrindole or Thiazesim or Thozalinone or tiagapine or Tianeptine or Toloxatone or Tomoxetine or topiramate or Tranylcypramine or Trazodone or tricyclic* or Trimipramine or tryptophan or Venlafaxine or Viloxazine or Viqualine or yohimbine or Zimeldine

MEDLINE:

Searched on 2 February, 2010

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND (Stress Disorders, Post-Traumatic/drug therapy* OR "posttraumatic stress disorder" [tw] OR "post traumatic stress disorder" [tw] OR PTSD [tw]) AND (alprazolam [tw] OR amitriptyline [tw] OR brofaromine [tw] OR citalopram [tw] OR desipramine [tw] OR fluoxetine [tw] OR imipramine [tw] OR inositol [tw] OR lamotrigine [tw] OR olanzapine [tw] OR mirtazapine [tw] OR nefazodone [tw] OR paroxetine [tw] OR phenelzine [tw] OR risperidone [tw] OR sertraline [tw] OR venlafaxine [tw] OR anticonvulsant* [tw] OR antipsychotic* [tw] OR benzodiazepine* [tw] OR noradrenerg* [tw] OR dopamin* [tw] OR serotonin* [tw] OR SSRI* [tw] OR tricyclic* [tw] OR anxiolytic* [tw] OR Psychotropic Drugs [mh] OR Anticonvulsants [mh] OR Benzodiazepines [mh] OR Monoamine Oxidase Inhibitors [mh] OR Neurotransmitter Uptake Inhibitors [mh] OR Drug Therapy [mh] OR pharmacother* [tw] OR medicat* [tw])

PILOTS:

Searched on 2 February, 2010

Query: (control* OR random*) AND (PTSD OR "posttraumatic") AND (alprazolam OR amitriptyline OR brofaromine OR citalopram OR desipramine OR fluoxetine OR imipramine OR inositol OR lamotrigine OR olanzapine OR mirtazapine OR nefazodone OR paroxetine OR phenelzine OR risperidone OR sertraline OR venlafaxine OR anticonvulsant* OR antipsychotic* OR benzodiazepine* OR noradrenerg* OR dopamin* OR serotonin* OR SSRI* OR tricyclic* OR anxiolytic* OR Psychotropic Drugs OR Anticonvulsants OR Monoamine Oxidase Inhibitors OR Neurotransmitter Uptake Inhibitors OR pharmacotherapy OR medication)

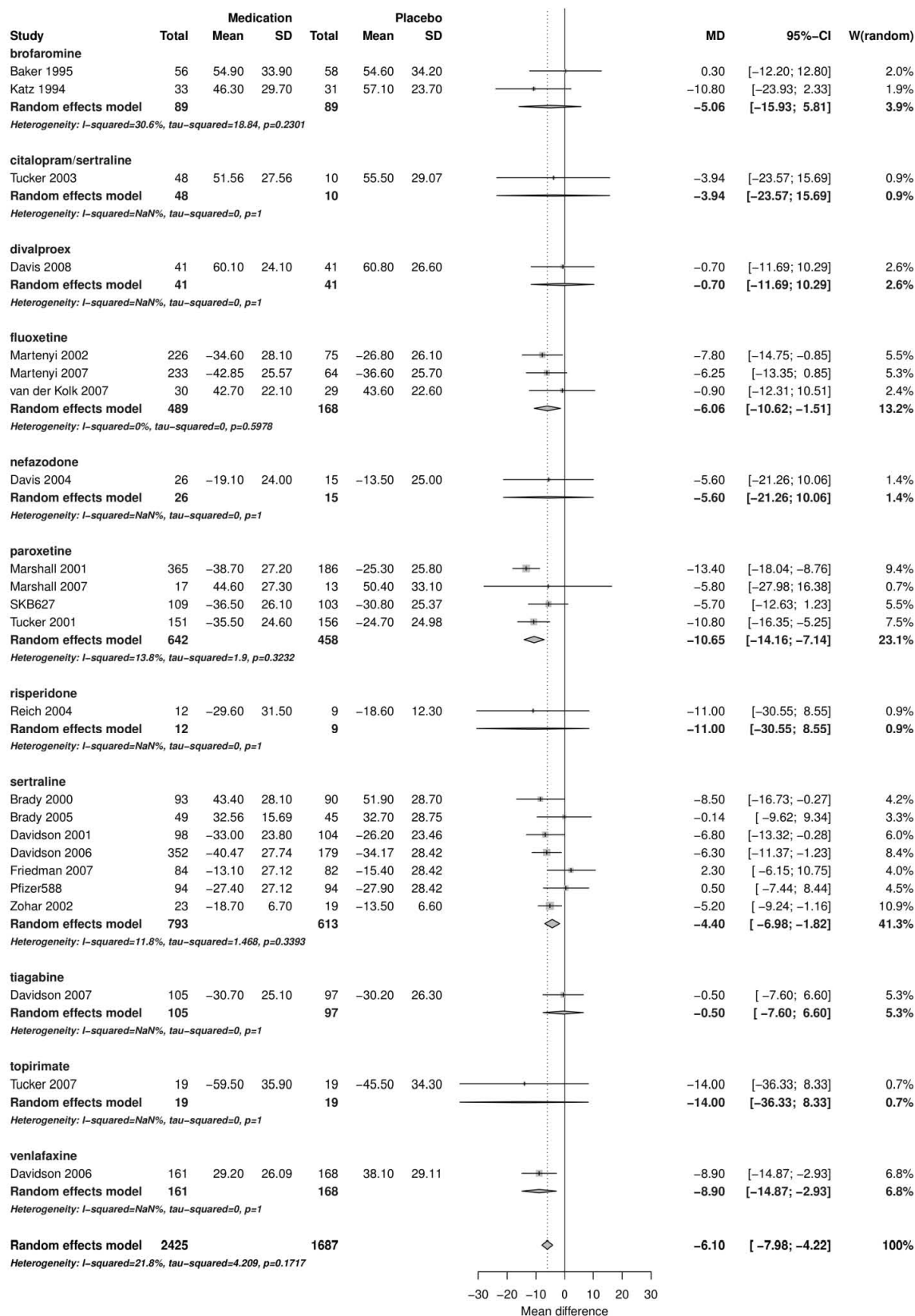


Figure 1. Results of meta-analysis, stratified by medication agent

4.9.3 Test of publication bias

Egger's regression test of funnel plot asymmetry was employed in order to determine whether there was evidence of possible publication bias (Egger 1997). The analysis was conducted using the metabias procedure in the meta package in the R statistical language. There was no evidence of publication bias ($t = 1.2859$, $df = 21$, $p > 0.05$), with the intercept of the linear regression model close to zero (see plot below).

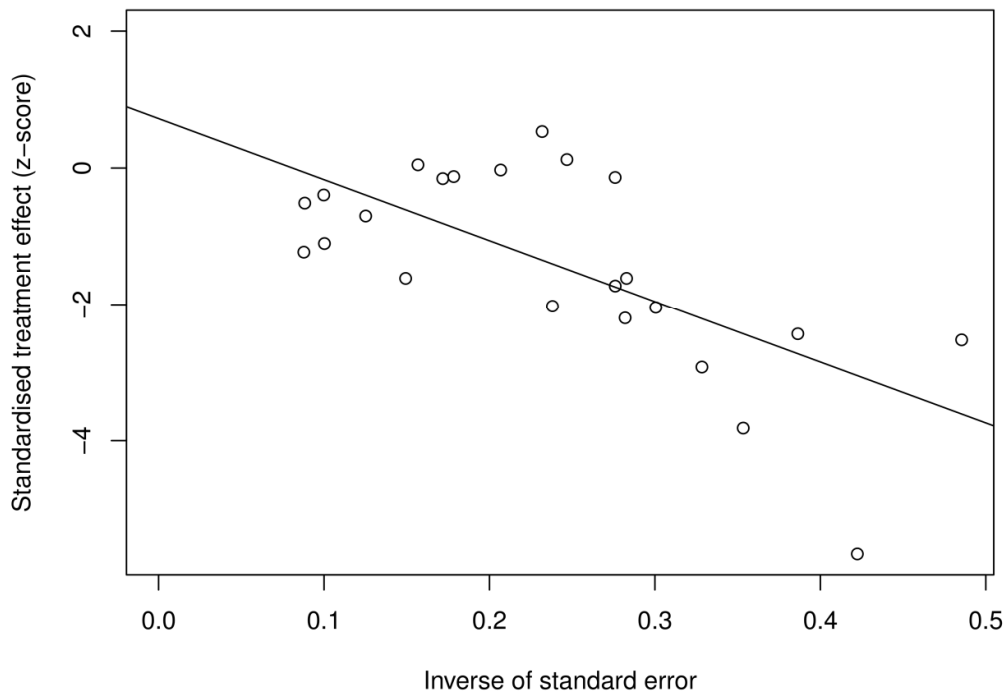


Figure 2. Egger plot of treatment effect regressed on precision of effect estimate

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University of Cape Town

5. IMAGING META-ANALYSIS OF RESPONSE INHIBITION AND THE GO/NOGO PARADIGM

5.1 Preface

Employing a laboratory measure of motor response inhibition as a proxy for impulsivity has numerous advantages over using self-rated impulsivity questionnaires, including the ability to identify neural correlates of inhibitory behaviour. In addition, comparing the standard version of the GNG paradigm with the affective version of this paradigm by means of a brain imaging meta-analysis would help identify commonalities of, and differences between, impulsivity and affect regulation in terms of their underlying neural circuitry. These findings can then be related to the neural systems known to be involved in PTSD.

Accordingly, we decided to conduct a meta-analysis comparing the effects of methodological differences between GNG tasks on brain activation, and to determine the extent to which additional brain regions are recruited for the inhibition of responses to affective stimuli.

5.2 Introduction

Adaptive social behaviour presupposes the ability to selectively inhibit inappropriate behaviour in a context-dependent fashion. The importance of this ability in everyday functioning, and evidence that it is impaired in a range of psychiatric conditions including ADHD and borderline personality disorder, has led to increasing interest in its neural underpinnings. A wide variety of behavioural paradigms are available to investigate psychological constructs thought to underlie inhibitory behaviour. These include tasks assessing interference suppression (Stroop task, Flanker), stimulus response associations (Stimulus – response contingency, Simon task), and inhibition of motor responses (Antisaccade, Go/NoGo (GNG) task, Stop-Signal task).

Technologies for the in-vivo imaging of brain activation, such as functional magnetic resonance imaging (fMRI) and positron emission tomograph (PET), offer great potential for elucidating those regions of the brain that are critical for behavioural inhibition. Studies comparing common regions of activation in the same participants across a range of tasks measuring inhibition have identified the right inferior frontal gyrus (rIFG) (Bunge, et al. 2002; McNab, et al. 2008; Rubia, et al. 2001), right dorsolateral prefrontal cortex (DLPFC) (Rubia, et al. 2001; Zheng, et al. 2008), anterior cingulate cortex (ACC) (Rubia, et al. 2001; Rubia, et al. 2006; Wager, et al. 2005), and the basal ganglia (Rubia, et al. 2006; Wager, et al. 2005) as forming part of an inhibitory network.

Activation of the frontal cortex and basal ganglia in these tasks is consistent with one of the most influential models of the neurocircuitry of motor inhibition (Casey, et al. 2002). This model proposes the involvement of a frontal-striatal loop in which representations of stimulus response are maintained in the frontal cortex, and guide the basal ganglia in inhibiting inappropriate behaviours through modulating motor output via the thalamus (Casey, et al. 2002). Although providing a useful theoretical framework in which to situate research

findings, the validity of this model has not been unanimously accepted. For instance, failure to detect consistent involvement of the striatum in a qualitative synthesis of results from 11 fMRI motor inhibition studies led Aron and Poldrack (2005) to question the involvement of the basal ganglia in response inhibition. Wager and colleagues (2005) in turn proposed an insular-prefrontal-cingulate inhibitory model, on the basis of common neural activation in healthy subjects on three inhibition tasks that are selectively dependent on different aspects of inhibition (Go/NoGo, Flanker, Stimulus Response Compatibility task).

One strategy to identify a characteristic pattern of brain activation associated with response inhibition would be to focus on the findings of studies employing the same paradigm. The GNG task is one potential candidate, given the frequency within which it is employed in both research and clinical settings. Adopting this strategy also has the advantage of not conflating brain activity that is responsive to systematic differences between inhibitory tasks. A recent ALE meta-analysis of 48 GNG and 21 stop-signal studies concluded that despite considerable overlap in the brain circuitry activated by these tasks, the neural activation they elicit is not identical (Swick et al. 2011). As stated by Swick and colleagues (2011), "While the functional significance of this difference is an important empirical question [...], it is clear that these two tasks are not equivalent, and caution is required when generalizing GNG or SST findings" (p1663). A similar conclusion can be reached on the basis of a comparison of the neural correlates of performance on the GNG and antisaccade task (Chikazoe, et al. 2007).

In the classic GNG task participants are presented with a series of distinct stimuli on a computer screen, one or more of which are designated as targets ('Go' trials). Subjects are instructed to press a response button as quickly as possible when presented with the 'Go' stimuli, and to withhold responding on presentation of other distractor stimuli ('NoGo' trials). The GNG is typically designed to reduce interference from ambiguous sensory stimuli, and responses to Go trials are considered to provide a relatively "pure" measure of response

inhibition. The GNG has also been cited as having reasonable temporal stability, relative to other behavioural inhibition tasks (Horn, et al. 2003). Finally, findings of a correlation between performance and neural activation on the GNG and self-rating measures of impulsivity in healthy subjects (Brown, et al. 2006; Chuah, et al. 2006; Horn, et al. 2003) underscore the validity of the GNG as a measure of impulse-control deficits.

Studies employing the GNG paradigm to delineate neural correlates of inhibitory behaviour have tended to detect diffuse patterns of brain activation in response to successful inhibitions. A search through the literature reveals reports of activation in a multitude of regions during successful inhibitions, including the right inferior frontal gyrus (rIFG, eg. Garavan 1999, Horn 2003), the dorsolateral prefrontal cortex (DLPFC, eg. Braver 2001, Fassbender 2004), the anterior cingulate cortex (ACC – eg. Borgwardt 2008, Brown 2006), the pre supplementary motor association areas (pre-SMA – eg. Kelly 2004, Rubia 2001), the orbitofrontal cortex (OFC – eg. Falconer 2008, Passamonti 2008), the inferior parietal cortex (eg. Chuah 2006, Hester & Murphy 2004), the basal ganglia (putamen – eg. Fassbender 2004, Wager 2005; caudate – eg. Menon 2001, Rubia 2006), the insula (eg. Garavan 1999, McNab 2008), the thalamus (eg. Passamonti 2008, Watanabe 2002), the occipital cortex (eg. Bonnet 2009, Langenecker 2007), and the cerebellum (eg. Laurens 2003, Zheng 2005).

This wide-spread pattern of activation is suggestive of activation that is idiosyncratic to particular implementations of the GNG paradigm, rather than core to the inhibition of the motor response itself. Attempts to identify task features that tap into the core construct of inhibition have unfortunately been hampered by the complexity of these tasks, lack of standardisation between different implementations of the same task, and failure to base task design on theoretical considerations. Accordingly, differences in task performance may reflect impairment in any one of multiple cognitive abilities, or, conversely, allow subjects the

opportunity to employ different strategies to achieve comparable performance (Chambers, et al. 2009).

Furthermore, given the complexity of the cognitive processes that are likely to be recruited by even the simplest behavioural tasks, one cannot simply adopt a “vote-counting” approach to identify an inhibitory network by tallying those regions that are most frequently activated across studies. The right inferior frontal gyrus is instructive in this regard. The rIFG is one of the most frequently identified brain regions in studies of motor inhibition. Its function as an “inhibition module” appears to receive support from lesion and transcranial magnetic stimulation studies that have mapped differences in performance on motor-inhibition tasks to disruption of the rIFG (Aron, et al. 2003; Chambers, et al. 2007). Nevertheless, a number of recent quantitative syntheses of coordinates from GNG studies have failed to observe consistent activation of the rIFG (Simmonds, et al. 2008; Swick, et al. 2011). In a meta-analysis of 10 GNG tasks, Simmonds et al. (2008) explained their negative finding with respect to the frontal operculum (Brodmann Area 47), a part of the rIFG that is regarded as particularly crucial to response inhibition, as possibly resulting from their decision to deliberately restrict their analysis to studies employing a baseline reference condition for the NoGo trials, as opposed to the more commonly employed Go trial reference condition.

The finding by Simmonds and colleagues (2008) highlights the sensitivity of study results to the procedures employed by individual teams of investigators. Differences in activation occur even with the introduction of relatively small differences in the jittering of trials for the same task (Goghari and MacDonald 2008). There are a number of potential sources of variability that might explain poor reliability in identifying activation of a particular region of interest in response to successful inhibitions. These include differences in subject characteristics, the way in which the task was implemented, pre-processing of this data, and the statistical

contrasts employed in the final analyses. Some of the more significant sources of heterogeneity in study findings will be described below.

The choice of the reference condition used for statistical contrasts has been highlighted as influential in determining the clusters of activation that are reported by imaging studies (Simmonds, et al. 2008). The majority of studies compare successful inhibitions on NoGo trials to correct responses to Go trials. Go and NoGo trials differ on a number of dimensions, however. Go trials are associated with the presence of motor activity and are frequently presented at a higher frequency than NoGo trials, in order to establish a prepotent response tendency. Differences in activation between Go and NoGo trials are therefore potentially confounded by attentional effects associated with the presentation of infrequent stimuli (the "oddball" effect). Indeed, overlap in many of the same brain regions involved in response inhibition, including the right IFG (see Laurens 2005), have been demonstrated in the past using the oddball paradigm. The fronto-striatal model of inhibition also identifies inhibitory processes as a precursor to the release of a motor response (Chambers, et al. 2009). The possible overlap in the neural substrate involved for both response inhibition and execution has therefore led to concerns regarding the validity of the subtraction paradigm when comparing activation coincident with Go and NoGo trials (Simmonds, et al. 2008).

Differences in the extent to which specific versions of the GNG task make demands on working memory can also influence where brain activity is observed. Variants of the GNG task in which the response required depends on the context in which it appears (complex GNG tasks) place a greater load on working memory than tasks in which the identity of the target trials remains constant (simple GNG tasks). Although studies employing complex Go/NoGo tasks frequently identify the right DLPFC and parietal lobe as critical to response inhibition, these same brain regions are implicated in working memory functioning (in the maintenance of the stimulus-response set and response selection, respectively). In reality

both working memory and response inhibition systems are likely to be involved in successful performance on the GNG task. This is suggested by the finding of an overlap between performance on this task and working memory capacity (Nyberg et al. 2009), as well as the observation, in a conjunction analysis of response inhibition and working memory tasks, of common signal in the rIFG, the right middle frontal gyrus and the right parietal lobe (McNab, et al. 2008).

The analytic strategy employed with regard to imaging data can have consequences for activation patterns that are observed. In fMRI studies employing the Go/NoGo paradigm as a blocked design, investigators typically attempt to isolate brain activity specific to motor inhibition by subtracting the blood oxygen level dependent (BOLD) signal in blocks of Go trials from blocks combining both trial types. In contrast, in event-related designs, the hemodynamic response function is convolved with specific inhibitory events. Authors have previously observed that left lateralisation of neural activity appears more frequently in blocked than event-related GNG designs (Fassbender, et al. 2004; Rubia, et al. 2001). The inclusion of errors in blocked designs might also be expected to result in activation of the ACC, given the postulated role of this region in conflict monitoring and error processing (Botvinick, et al. 2004).

Finally, inhibition-related brain activity has to be interpreted in light of the nature of the stimulus employed. A subset of GNG studies employ affective words or facial expressions as stimuli in order to test hypotheses regarding the influence of emotion on inhibitory function (Amin, et al. 2006; Berkman, et al. 2009; Elliott, et al. 2004; Elliott, et al. 2000; Elliott, et al. 2002; Goldstein, et al. 2007; Hare, et al. 2005; Hare, et al. 2008; Protopopescu, et al. 2005; Roiser, et al. 2009; Schulz, et al. 2008; Shafritz, et al. 2006; Wessa, et al. 2007). The indication from performance and brain imaging data that greater inhibitory demands are placed on subjects tested with the affective version of the Go/NoGo task might have

consequences in terms of the magnitude of the BOLD response, the recruitment of additional brain regions (or both)(Shafritz, et al. 2006). Employing linguistic stimuli also poses challenges in the interpretation of the hemispheric lateralization of brain activity in particular (Lutcke and Frahm 2008).

This paper shall attempt to isolate the neural circuitry underpinning motor response inhibition through applying meta-analytic techniques to whole-brain coordinate data from fMRI studies of the GNG task. By synthesising data from studies employing different versions of a specific task (or different analytic strategies), a meta-analysis allows one to identify neural activity that does not depend on particular idiosyncratic methodological characteristics of a specific study. Conversely, by comparing data from studies grouped by design feature, one can identify activity that is specific to that feature, and use this information to identify the function of the underlying brain regions. This should assist in selecting between different models of neural circuitry thought to underlie response inhibition.

We have utilized state-of-the-art meta-analytic methods in the service of these aims, and in recognition that the usefulness of a meta-analysis in answering a particular question depends to a large extent on the relevance and quality of the included studies. Therefore, in addition to conducting the most comprehensive search of the literature conducted thus far to identify all eligible GNG studies, we have attempted to optimize the validity of our results, both by controlling for variability in the precision of the data contributed by individual studies through using a random effects model (unlike Swick et al. 2011), and by restricting studies to those that employed GNG tasks (unlike Levy et al. 2011).

5.3 Method

A comprehensive search strategy was devised to identify eligible studies for inclusion in the review. The PubMed, psycINFO, Web of Science and BrainMap databases were searched

between June and October, 2009 using the following search terms: "functional magnetic resonance imaging", "response inhibition" and "nogo" (please contact the authors for more information). Additional studies were identified by searching the EMBASE database in January, 2009. In addition, the contact authors of the included studies were emailed for missing data, and queried regarding additional published and unpublished studies.

All fMRI studies of healthy subjects performing the GNG task were included, on the proviso that the study reported stereotactic coordinates from whole-brain analyses of activation associated with inhibitory responses. Studies from the clinical literature were included, provided they included a control group without psychopathology. Coordinates representing brain regions that were deactivated during successful inhibitions were not included in the meta-analytic component of the review (eg. Amin 2006). Studies were restricted to those that employed task features designed to establish a prepotent motor response, such as the presentation of a majority of target trials. Only studies employing versions of the GNG using visual stimuli were included. Given evidence of the maturation of the frontal cortex during adolescence (Hare, et al. 2008), and changes in brain systems underlying attentional functioning in later adulthood (Segalowitz and Dywan 2009), studies were limited to those which reported data for participants aged between 18 and 65 years of age, inclusive. Finally, studies that did not control for within-subject variance by means of random or mixed-effects analyses were excluded.

Two raters independently extracted data for each study on task design and sample characteristics, stereotactic (x, y, z) coordinates, and performance using a customised data-extraction form designed in accordance with the Brainmap database format (Fox and Lancaster 2002; Laird, et al. 2005b). An omnibus comparison of brain activation during successful inhibition was conducted across all of the studies included in this review. Where coordinates from multiple contrasts were provided in each study, preference was given to

those employing Go trials as baseline, as the majority of event-related studies provided data in this form. Data from block-designed tasks were restricted to analyses employing Go-only blocks as baseline or in which the BOLD signal was regressed on the proportion of Go trials across conditions.

Investigations of the impact of methodological differences on activation patterns were also conducted. Task design-related methodological criteria of interest included (1) the use of Go trials versus baseline as reference condition, (2) the use of blocked versus event-related designs, (3) the employment of simple versus complex GNG paradigms, and (4) the use of different types of stimuli. The latter comparison contrasted linguistic (including letters and words) versus other stimuli (including shapes, arrows and images of objects), as well as affective (including emotional facial images and words) versus non-affective stimuli.

In order to increase the likelihood of detecting differences resulting from working memory load, simple variants of the GNG task were defined as those in which each of the trial types was represented by a single invariant stimulus. Employing multiple letters as Go stimuli in the simple GNG task has been associated with differences in brain activation when compared to use of a single target stimulus, and represents a potential confound (Bonnet, et al. 2009; Laurens, et al. 2005). As all of the complex GNG tasks employed event-related or mixed designs (incorporating elements of both block and event-related designs), the comparison of blocked versus event-related designs was restricted to simple Go/NoGo tasks, to avoid confounding design with task complexity. The comparison of stimuli type (linguistic, affective) were restricted to studies employing the simple GNG task, for the same reason,.

Data from studies which reported stereotactic (x, y, z) coordinates were aggregated as part of an Activation Likelihood Estimation (ALE) meta-analysis. ALE involves the generation of a

statistical parametric map (SPM) of brain activity through the quantitative synthesis of whole-brain coordinate data across multiple studies. The likelihood that activation in particular voxels occurs by chance can subsequently be determined through reference to an empirically derived probabilistic map of brain activity (Laird, et al. 2005a; Turkeltaub, et al. 2002). ALE makes optimal use of the voxel-wise resolution of the study-level data, overcomes between-study heterogeneity in the positioning of activated voxels introduced through measurement error, and bypasses reliance on subjective and error-prone anatomical labeling (Laird, et al. 2005c). Moreover, ALE is fully automated and conclusions drawn from it can be statistically defended through reference to a null hypothesis distribution.

With the exception of subtraction analyses (detailed below) all ALE SPMs were generated by GingerALE 2.0 (Eickhoff, et al. 2009), part of the suite of software provided by the developers of the Brainmap database (<http://www.brainmap.org>). These SPMs were smoothed with study-specific Gaussian kernels, with the smoothing parameter (Full Width Half Maximum (FWHM)) weighed by the study sample size. The best-fitting icbm2tal algorithm (Lancaster, et al. 2007) was used to transform coordinates from MNI to Talairach space prior to data synthesis. Following recommendations in the GingerALE manual, coordinate data that was reported in Talairach coordinate space following conversion by the authors from MNI using the Brett transform was "unbretted" prior to this step (Laird 2009). The coordinates from separate studies with overlapping samples (eg. (Menon, et al. 2001; Mobbs, et al. 2007a), (Kaladjian, et al. 2007; Kaladjian, et al. 2009; Mazzola-Pomietto, et al. 2009) and (Passamonti, et al. 2008; Passamonti, et al. 2006)) were restricted to those from the study with the largest sample size in order to minimize dependency in the data (Menon et al. 2001, Kaladjian et al. 2007, Passamonti et al. 2008, respectively).

Inferential statistics were derived by comparing SPMs for the experimental contrast with null hypothesis distributions obtained using a method implemented in GingerALE 2 that

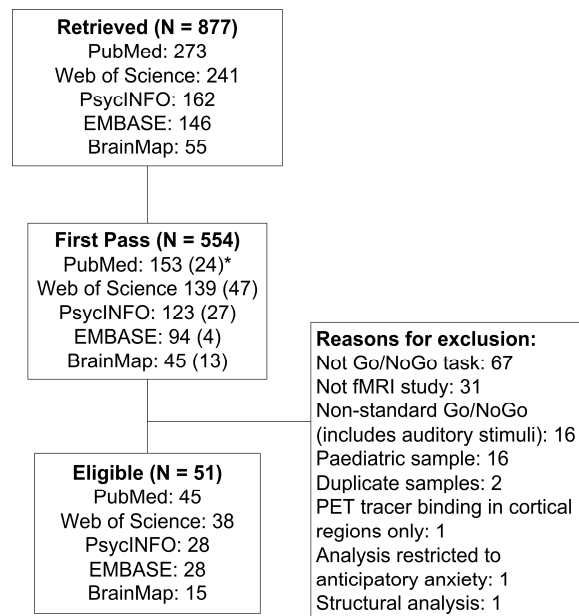
approximates non-parametric permutation analysis. The False Discovery Rate (FDR) method was applied as a correction for multiple comparisons, given its ability to maximise sensitivity while minimising false positive results (Laird, et al. 2005a). All random-effects ALE maps were thresholded at $p < 0.05$, with a smoothing parameter of 15 mm, and a minimum cluster size of 160mm^2 . Preliminary evidence indicates that a FWHM of 15mm is optimal in replicating image-based mega-analyses (Salimi-Khorshidi, et al. 2009). Of the coordinates provided by authors in response to requests for additional data, only those that passed a significance threshold of $p < 0.05$, corrected at the cluster level, were included in the meta-analysis.

Subtraction analyses between groups of studies were conducted using a fixed-effects method implemented in GingerAle 1.2, as random effects analyses of this kind are not currently supported. The interpretation of comparisons between groups of studies in subtraction analyses are confounded by (a) differences in the size of the dataset for each group, and (b) failure of the fixed-effects model used to account for between-study variability. Accordingly, the following procedure was implemented in order to obtain an estimate of the reliability of these findings with respect to particular clusters: 100 pairwise comparisons were conducted on coordinates from 6 randomly selected experiments in each of the groups being contrasted (eg. 6 experiments in each of the complex versus simple GNG groups). The number of times in which particular cluster labels were identified was subsequently tabulated across all 100 permutations, and correlated with the extent of the cluster (in mm^3) reported in the results from the analysis employing coordinates from all eligible studies. The pair-wise analyses were conducted using a batch file implementing the command-line interface to GingerALE version 1.2 (FWHM = 15mm, 1000 random permutations, minimum cluster volume = 100mm^2).

Basic descriptive and inferential statistics were computed for performance data. The mean reaction time on Go trials was calculated, as were the error rates for NoGo trials identified as targets (“commission errors”) and Go trials that were not identified as targets (“omission errors”). The increased precision afforded by larger sample sizes was factored into the between-group comparisons by weighing each study's error rates and reactions times by their sample sizes. Correlations between the ratio of Go to NoGo trials and errors of commission were also calculated, so as to determine the extent to which increasing the relative frequency of Go to NoGo trials increases the difficulty of inhibiting motor responses. This was in light of concerns that inhibitory brain circuits are not reliably activated when the number of go and no-go trials is equated (Braver, et al. 2001).

University of Cape Town

5.4 RESULTS



* Number in parentheses refers to the number of reports that were unique to that particular database

Figure 1. Flowchart of selection process for eligible studies

A total of 877 papers were initially retrieved through the search strategy (please refer to Figure 1 for a breakdown by source). Fifty one studies were considered eligible for inclusion in the review, with a combined sample size of 946 healthy subjects (46% female) (Table 1). The average age of the subjects was 29.2 years (SD = 6.3). Ten of the studies included in this review employed the affective version of the Go/NoGo task (N = 185), and included either facial images (N= 6) or emotive words as stimuli (Table 2).

With regards to the studies employing the non-affective Go/NoGo task (heretofore referred to as the “standard GNG”), the majority employed event-related designs (N = 25), with the remainder presenting the trials types in blocks (N=10), or combining blocked and event-related designs (N=6). The simple version of the Go/NoGo was used in 30 of these studies, while stimulus-response mappings changed depending on context in 12 (Mostofsky et al.

(2003) included both simple and complex versions of the task). Twenty six of these studies compared activation in response to NoGo versus Go trials, with 14 and 5 studies employing signal from baseline or oddball trials as comparators, respectively. Stimulus presentation times varied from 200 to 1400 ms, with the inter-stimulus interval ranging from 0 to 29 seconds. A tendency to respond was established in block-design studies by the inclusion of a block comprised exclusively of Go trials, with the majority of event-related trials (22/25) achieving a similar effect by including a high ratio of Go to NoGo trials (average ratio = 79%).

One potentially eligible supra-modal comparison of auditory and visual variants of the Go/NoGo task did not detect significant activation on the NoGo trials (relative to Go trials) for either modality, and was therefore not included in this review (Laurens, et al. 2005). Coordinates from a combined analysis of fMRI data for adults and adolescents in an affective Go/NoGo paradigm were included in the meta-analysis, as the influence of age was controlled for statistically (Hare, et al. 2008).

Table 1. Study characteristics for the standard GNG paradigm

Study ID	Year	N [†]	Imaging/analysis Specs [†]	Design	Type	Stimuli	Baseline	Go /NoGo Ratio
Asahi	2004	17	1.5T, GE EPI, T2*, TR=4s, TE=55ms, flip angle=90, fov=256, smoothing=8mm	Block	Simple	Letters	Go Block	50%
Bonnet	2009	16	1.5T Gyroscan Philips, T2*, TR=2s, TE=60ms, flip angle=90, fov=230mm, smoothing= 10x10x3.5mm	Block	Simple	Shapes	Go Block	70%
Booth	2003	12	1.5T General Electric, single shot EPI, TR=3s, TE=4ms, flip angle=90, fov=22cm, smoothing=7mm	Block	Simple	Shapes	Go Block	50%
Borgwardt	2008	15	1.5T Signa, T2*, TR=1.8s, TE=40ms, flip angle=90, smoothing=7.2mm	Event	Simple	Arrows	Oddball-Go	78%
Braver	2001	14	1.5T Siemens, TR=2.5s, TE=50ms, flip angle=90,	Event	Simple	Letters	Go	83%/50%

			whole-brain coverage, smoothing=6mm					
Brown	2006	58	3T Siemens Allegra, TR=2s, TE=25ms, fov = 20cm, smoothing=6mm	Block	Simple	Letters	Go	50%
Bunge	2002	19	3T Sigma, GE spiral sequence, TR=1s, TE=30ms, flip angle=60, fov=24cm, smoothing=6mm	Event	Simple	Shapes	Neutral	75%
Chikazoe	2009	25	1.5T, gradient EP, TR=4s, TE=50ms, flip angle=90, smoothing=8mm	Event	Simple	Coloured circles	Frequent Gos & Oddballs	75%
Chuah	2006	27	3T Allegra, Gradient EPI, TR=2s, fov=192, smoothing=8mm	Mixed	Complex	Letters	Fixation	90%
Cojan	2009	24	1.5T Intera, GRE EPI, TR=2.5s, TE=40ms, flip angle=80, fov=250mm, smoothing=8mm	Event	Simple	Shapes	Go	75%
deZubicaray	2000	8	1.5T GE, T2, TR=3s, TE=40ms, flip angle=90, smoothing=6mm	Block	Simple	Shapes	Go Block	60-78
Dibbets	2009	17	1.5T Philips, T2*, TR=1.75s, TE=27ms, flip angle=90, fov=224x120x225mm, smoothing=8mm	Event	Complex	Letters	Go	86%
Falconer	2008	23	1.5T Siemens Magnetom, T2*, TR=3s, TE=40ms, flip angle=90, fov=24cm, smoothing=8mm	Event	Simple	Coloured letters	Go	75%
Fassbender	2004	21	1.5T Siemens, EPI T2*, TR=2s, TE=50ms, flip angle=90, fov=256mm, smoothing=3mm	Mixed	Simple	Numbers	Baseline	89%
Fassbender	2006	17	1.5T Siemens, EPI T2*, TR=2s, flip angle=90, fov=240mm, smoothing=3mm	Event	Complex	Letters	Baseline	94
Garavan	1999	14	1.5T GE Signa, TR=2s, TE=40ms, fov=240mm, gaussian smoothing=4.2mm	Event	Complex	Letters	Tonic	76%
Garavan	2002	14	1.5T GE Signa, TR=2s, TE=40ms, fov=240mm, gaussian smoothing=4.2mm	Event	Complex	Letters	Tonic	94%
Garavan	2003	16	1.5T GE Signa, GE-EPI, TR=2s, TE=40ms, fov=240mm, smoothing=4.2mm	Mixed	Complex	Letters	Tonic	90%
Goghari	2009	12	3T Siemens, EPI, TR=2s, TE=28, flip angle=90, fov=224mm,	Event	Simple	Shapes	Go	80%

			smoothing=7mm					
Hester	2009	16	4T Bruker Medspec varian, TR=2s, TE=30ms, fov=384mm, flip angle=90, smoothing=3mm	Event	Complex	Letters	Tonic	92%
Hester	2004a	10	1.5T Siemens VISION, T2*, EPI, TR=2s, TE=50ms, fov=256mm, smoothing=3mm	Mixed	Complex	Letters	Tonic	93%
Hester	2004b	15	1.5T GE Signa, blipped gradient-echo EP, TR=2s, TE=40ms, fov=24cm, smoothing=3mm	Mixed?	Complex	Letters	Tonic	88%
Horn	2003	21	1.5T Philips Gyroscan, T2*, single-shot EPI, TR=3.1s, TE=50ms, flip angle=90, fov=230mm, smoothing=8mm	Block	Simple	Letters	Go Block	50%
Kaladjian	2007	30	3T MedSpec, T2*, FID EP, TR=3s, TE=35ms, flip angle=83, fov=19.2cm, smoothing=9mm	Event	Simple	Letters	Go	50%
Kaladjian	2009	10	3T Brucker, T2*, FID EP, TR=3s, TE=35ms, flip angle=83, fov=19.2cm, smoothing=9mm	Event	Simple	Letters	Go	50%
Kelly	2004	15	1.5T Siemens Vision, T2*, TR=2s, TE=50ms, fov=256mm, smoothing=3mm	Mixed	Complex	Letters	Tonic	92%
Langenecker	2007	17	3T GE Signa, TR=2s, fov=24cm	Event	Complex	Letters	Baseline	83%
Laurens	2003	16	1.5T GE, TR=3s, TE=40ms, flip angle=90, fov=24cm, gaussian smoothing=8mm	Event	Simple	Letters	Go	84%
Lawrence	2009	21	1.5T GE Signa, T2*, TR=1.8s, TE=40ms, flip angle=90, smoothing=7.2mm	Event	Simple	Shapes	Go/oddball	76%/88%
McNab	2008	14	1.5T GE Signa, T2*, spiral EP, TR=2.1s, TE=40, flip angle=76, fov=220mm, smoothing = 6mm	Event	Simple	Shapes	Go/oddball	75%
Menon	2001	14	1.5T GE Signa, TR=2s, TE=40ms, fov=240mm, flip angle = 89, smoothing=4mm	Block	Simple	Letters	Go/Rest	50%
Mostofsky	2003	48	1.5T ACS-NT (Phillips), single shot EPI, TR=2.5s, TE=40ms, flip angle=90, smoothing=7x7x9	Event	Both	spaceships	Fixation	82% (simple)
Passamonti	2008	35	1.5T GE, T2*, GE EP,	Block	Simple	Letters	Go Block	50%

			TR=3s, TE=50ms, flip angle=90, smoothing=6mm					
Roth	2007	14	1.5T GE Signa, TR=2.5s, TE=40ms, fov=24cm, flip angle=90, smoothing=10mm	Event	Simple	Shapes	Go	25/50/75%
Rubia	2001	12	1.5T GE Signa, T2*, TE=40ms, TR=3300ms, smoothing=3mm	Block	Simple	Objects	Go Block	50% & 70%
Rubia	2006	23	1.5T GE Signa, T2*, TR=1.8s, TE=40ms, flip angle=90, smoothing=7.2mm	Event	Simple	Arrows	Go	76%/88%
Schmitz	2006	12	1.5T GE Signa, T2*, TR=1.8s, TE=40ms, flip angle=90, fov=240mm, smoothing=10mm	Event	Simple	Arrows	Oddballs	76%/88%
Vollm	2004	8	1.5T GE Phillips, T2*, TR=5sec, TE=40ms, smoothing=10mm	Block	Simple	Letters	Go Block	50%
Wager	2005	14	3T GE Signa, spiral sequence, TR=1s, TE=30ms, flip angle=90, fov=24cm, smoothing=10mm	Event	Simple	Letters	Go	50% & 80%
Watanabe	2002	11	1.5T Siemens, GE-EPI, TR=2s, TE=60ms, flip angle=90, fov=256mm, smoothing = 12mm	Event	Simple	Shapes	Correl + Go	--
Zheng	2008	20	1.5T Siemens, TR=3s, TE=40ms, flip angle=90, fov=200mm, smoothing = 9mm	Event	Simple	Letters	Go	75%

* Number of participants in healthy subject groups only

† TR = repetition time, TE = echo time, fov = field of view

Table 2. Study characteristics for the affective GNG paradigm

Study ID	Year	N*	Imaging/analysis Specs [†]	Design	Stimuli	Source	Conditions
Amin	2006	20	3T Siemens Trio, SPGR, TR=1.5s, TE=30ms, flip angle=80, fov=220mm, smoothing=8mm	Block	Words	Affective Norms for English Words	happy, neutral, sad
Berkman	2009	14	3T Allegra Siemens, T2*, TR=2s, TE=25ms, flip angle=90, fov=20cm, smoothing=8mm	Event-related	Faces	NimStim face set	positive (fear, anger), negative (happy)
Elliott	2000	12	2T Siemens Vision, GE EP, TR=4s	Block	Words	Previously compiled database	happy, neutral, sad
Goldstein	2007	14	3T GE, T2* EPI, TR=1.2s, TE=30ms, flip angle=70, fov=240, smoothing=7.5mm	Block	Words	Words selected by panel	positive, negative, neutral
Hare	2005	10	3T, spiral in-and-out seq., TR=2.5s, TE=30ms, flip angle = 90, fov=200mm, smoothing=4mm	Block	Faces	NimStim face set	fearful, happy, neutral
Hare	2008	48	3T, spiral in-and-out seq., TR=2.5s, TE=30ms, flip angle = 90, fov=200mm, smoothing=6mm	Mixed	Faces	NimStim face set	calm, fearful, happy
Protopopescu	2005	12	3T GE Signa, GE EPI, TR=1.2s, TE=30ms, flip angle=70, fov=240mm, smoothing=7.5mm	Block	Words	Study-specific	negative, neutral, positive
Schulz	2008	23	3T Siemens Allegra, T2*, TR=3s, TE=27ms, flip angle=85, fov=21cm	Event-related	Faces	NimStim face set	happy, sad
Shafritz	2006	13	1.5T GE, T2*, TR=1.5s, TE=60ms, flip angle=60, fov=20cm, smoothing=6.3mm	Block	Faces & Letters	Ekman and Friesen (1976)	happy, sad faces, letters
Wessa	2007	19	1.5T GE, T2*, TR=2.4s, TE=35ms, flip angle=90	Block	Faces	Ekman and Friesen (1976)	fearful, happy, neutral

* Number of participants in healthy subject groups only

† TR = repetition time, TE = echo time, fov = field of view

Faces taken from the Ekman and Friesen (Ekman and Friesen 1976) and NimStim (Tottenham, et al. 2009) libraries

5.4.1 Performance data

The average speed of response to target trials in studies employing the standard GNG paradigm was 395.8 ms (SD = 74.3ms), with fewer omission than commission errors being

committed (1.7% (N = 20) versus 15.2% (N=32), respectively), supporting the effectiveness of these tasks in testing inhibitory ability (Wilcoxon signed-rank test $z = 3.8$, $p < 0.01$). Complex versions of the standard GNG were more difficult than simple versions of the task, as indicated by a greater proportion of commission errors (28.5% versus 12.1% respectively, Wilcoxon-Mann-Whitney $z = 2.3$, $p < 0.05$). The mean reaction time and percentage of omission errors did not differ significantly for simple (mean = 394.4ms and 1.5%, respectively) versus complex (mean = 402ms and 2.4%, respectively) versions of the task. There was no evidence that the proportion of trials that required a response in event-related trials had an influence on the number of incorrect responses on NoGo trials (Spearman rho = 0.12, $p > 0.05$, $n = 21$)⁴.

Subjects were slower on average in responding to target trials in GNG tasks that employed affective stimuli (mean = 567ms, SD=71.5ms, $n = 7$), than in the standard GNG tasks (mean = 395.8ms, SD = 74.3ms, $n=32$)(Wilcoxon-Mann-Whitney test $z = 3.7$, $p < 0.01$). No difference was observed between the commission and omission error rates on the 6 studies that provided this data for affective versions of the GNG task (9.8% versus 7.6%, respectively, Wilcoxon signed-rank test $z = 1.2$, $p > 0.05$). The comparison of performance metrics for happy and fearful target trials in the 3 studies that employed stimuli of both valences was insufficiently powered to detect differences on either reaction time (552.6ms, SD=99.7ms versus 591.6ms, SD=85.7ms, respectively) or commission error rate (8.7%, SD=1.2% versus 7.5%, SD=0.9%, respectively).

⁴ The results of this analysis were similar when the two studies that employed cueing methods to establish a prepotent response were excluded (Kaladjian, et al. (2007), Kaladjian, et al. (2009a))..

5.4.2 Omnibus comparison

As anticipated, synthesizing coordinate data across all 41 (484 foci) of the standard GNG tasks produced a diffuse pattern of activation, with the largest clusters observed in the right cerebral hemisphere. These included the frontal (BA 6, 9, 10) and parietal cortices, the ACC, and the insula/rIFG (see Table 3). Activation was specific to the right hemisphere for the cingulate cortex (posterior and anterior) and thalamus, with bilateral representation in the dorsal striatum (putamen & caudate), as well as in the cerebellum and temporal, parietal and frontal cortices.

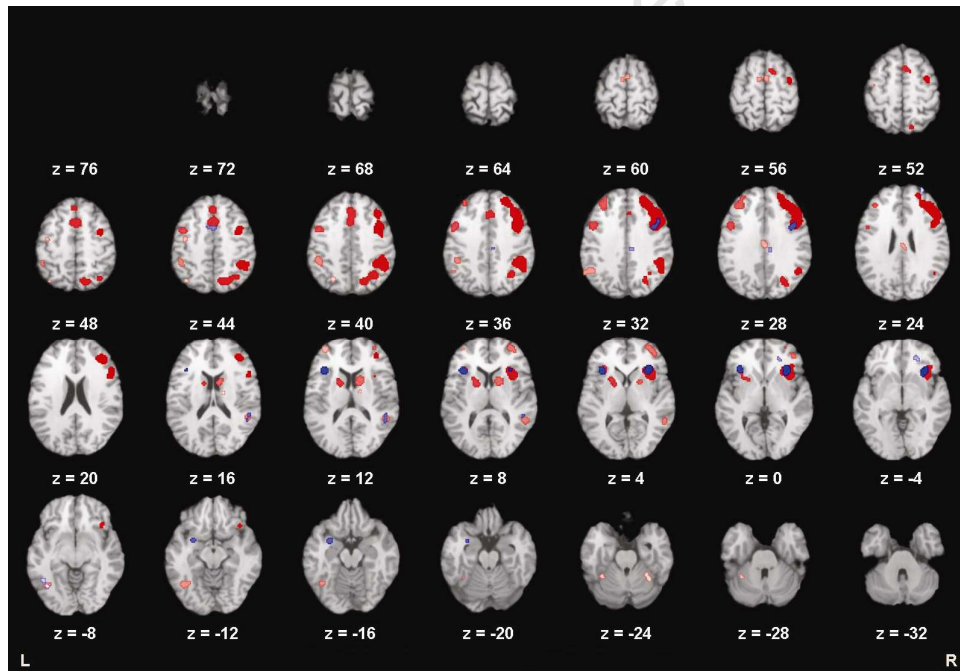


Figure 2. Activation map for correct inhibitions on the standard and affective versions of the GNG task (standard GNG = red, affective GNG = blue)

Table 3. Activation clusters for the inhibition condition on the standard Go/NoGo task

#	Label	Hemi	BA	Volume (mm ³)	Weighted Center (x,y,z)			Extrema Value (10 ³)	X	Y	Z
1	Frontal, Middle, inferior & precentral	R	6, 9, 10	14928	39	23	31	4.407	38	36	22
2	Parietal, supramarginal gyrus	R	40	4416	45	-47	37	4.024	46	-46	36
3	Insula/rIFG	R	47	4104	34	17	2	4.825	34	16	2
4	Parietal, superior, precuneus & angular	R	7, 31, 39	3848	24	-67	40	3.285	20	-70	42
5	Frontal, medial, superior (left); cingulate gyrus	R	6, 8, 32	3776	2	17	44	4.158	2	12	46
6	Insula and putamen	L	13	1960	-23	10	6	3.016	-32	22	4
7	Frontal, IFG and precentral)	L	6, 9	1864	-45	6	35	3.589	-46	8	32
8	Frontal, middle	L	9	1456	-33	38	30	2.795	-32	38	30
9	Caudate	R		1296	14	5	11	3.024	14	6	10
10	Frontal, middle, inferior & subgyral	R	10	1152	35	48	5	2.55	32	52	6
11	Temporal, superior	R	22	968	51	-47	10	2.871	50	-46	12
12	Parietal, inferior	L	40	928	-44	-42	41	2.768	-44	-40	38
13	Temporal, fusiform gyrus	L	37	800	-38	-61	-12	2.751	-38	-62	-12
14	Temporal, superior	L	39	536	-50	-56	32	2.378	-48	-56	32
15	Frontal, medial	R&L	6	496	0	-3	58	2.173	-6	-4	58
16	Cingulate gyrus	R	23	432	2	-20	27	2.182	2	-20	26
17	Frontal, middle	L	10	296	-35	50	12	2.409	-36	50	12
18	Frontal, precentral	L	6	248	-38	-12	46	2.095	-38	-12	46
19	Cerebellum, culmen	L		240	-33	-51	-25	2.026	-34	-50	-24
20	Cerebellum, culmen	R		224	31	-51	-25	1.967	32	-54	-24
21	Parietal, precuneus	L	7	152	-24	-67	40	2.106	-24	-68	40
22	Parietal, superior	L	7	128	-36	-70	46	2.104	-36	-70	46
23	Thalamus	R		112	14	-10	14	1.996	14	-10	14

* Coordinates for the weighted centre of mass for the cluster

† The most extreme t statistic for the voxels in the cluster

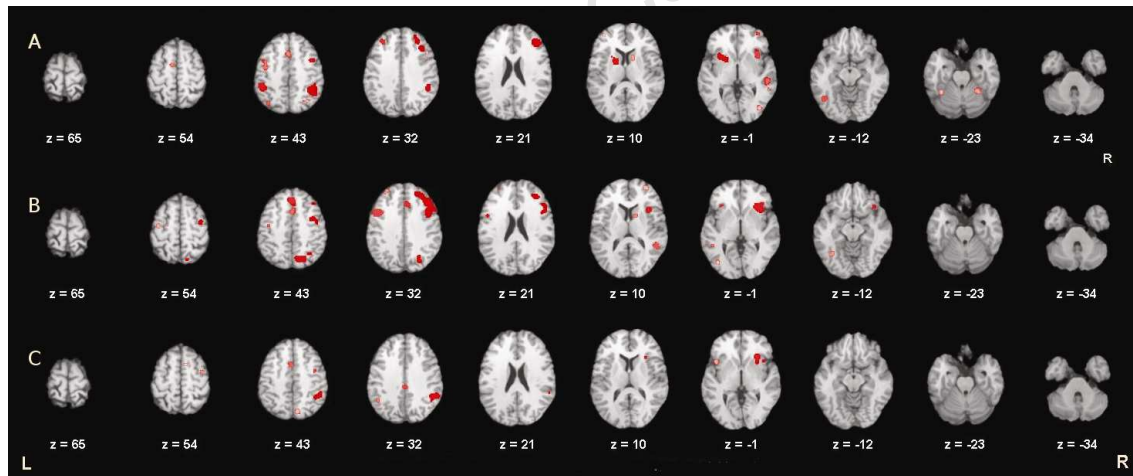
‡ The coordinates for the centre point of the cluster

Table 4. Number of experiments (foci) contributing to group comparisons

Comparison	1 st Group	2 nd Group
Baseline		
fixation	14 (172)	
go	26 (314)	
oddball	5 (86)	
Design		
block vs. event*	9 (100)	20 (204)
complex vs simple	12 (181)	14 (108)
linguistic vs. other*	13 (133)	16 (180)
affective vs standard	6 (57)	41 (484)

a. Foci that fell outside of talairach mask in GingerALE are not included in the table
 * Experiments were restricted to those from the simple Go/NoGo task paradigm, to simplify interpretation

5.4.3 Contribution of baseline condition to activation patterns



A = fixation baseline, B = Go trial baseline, C = Oddball trial baseline

Figure 3. Comparison of activation for NoGo trials using different baseline conditions

The extent of activation observed was inversely proportional to the specificity of the baseline condition employed, with the most widespread activation observed with the fixation baseline (24 clusters), followed contrasts with the Go (17 clusters) and Oddball (10 clusters) conditions. Regions activated for the fixation but not other baseline contrasts included the fusiform gyrus, the putamen and the culmen. Bilateral inferior parietal activation was also

more evident for this contrast, with no relative differences in recruitment of this region for inhibition relative to Go trials. Right frontal cortex activation was more prominent for the fixation and go baseline contrasts than the oddball contrast. Finally, activation of the frontal operculum portion of the right IFG (BA 47) was only observed for studies comparing NoGo with Go trials.

5.4.4 Subtraction analyses

Substantial differences in agreement when comparing all of the coordinate data with those contrasts that were equated for sample size were observed for many of the group comparisons. The correlation between the number of times a particular region was activated in the 100 pairwise contrasts and cluster size for that region in the full-sample analyses was large for the simple versus complex GNG and the standard versus affective GNG contrasts ($\rho = 0.92$, $p < 0.01$; $\rho = 0.81$, $p < 0.05$, respectively), but less robust with regards to the comparison of tasks using linguistic versus other stimulus types, or those using event-related versus blocked-design analytic strategies ($\rho = 0.13$ and 0.09 , respectively). Indeed, for all 4 contrasts in the full-sample analyses, most of the regions where statistically significant between-group differences were observed favoured the group with the larger number of foci (event-related experiments, complex GNG tasks, linguistic stimuli, and standard GNG, respectively). With the exception of the comparison between experiments employing simple and complex GNG tasks, this pattern of results disappeared when groups were equated for sample size, suggesting that differences in the number of studies and/or coordinates within each group may be influencing the results of the full-sample analyses.

Accordingly, we decided to limit the presentation of the results of the full-sample analyses to the simple-complex GNG contrast. Discussion of the results of the other methodological comparisons will be restricted to brain regions that are reliably activated across the

permutation analyses. Reliable activation is defined within the context of particular comparisons as identification of regions through their Talairach labels in at least a third of all permutation analyses or in the top quartile with regards to frequency of “hits”, whichever led to the smaller number of activated regions. Clusters for which the average peak statistical threshold was below the critical t value for a two-tailed t-test ($t = 1.96$) were excluded, in order to eliminate regions that failed to consistently favour one group over the other across the pairwise contrasts.

Simple versus complex GNG tasks

The most marked changes in brain activation with the additional cognitive demands imposed by the complex version of the GNG task were in the inferior parietal lobes, bilaterally (Table 5). Other areas that were preferentially activated were primarily lateralised to the right hemisphere (with the exception of the putamen), and included the frontal cortex, caudate/clastrum, cingulate gyrus and occipital lobe.

Table 5. Areas that were more consistently activated for complex than simple GNG tasks

#	Label	Hemi	BA	Volume (mm ³)	Weighted Center (x,y,z)*			Extrema Value (10 ³) [†]	X	Y	Z [†]
1	Parietal, Inferior	R	40	6936	43	-46	40	9.24	42	-44	38
2	Putamen	L		5392	-21	6	5	7.46	-16	4	6
3	Frontal, Middle	R	46	4496	41	33	23	8.13	40	34	22
4	Parietal, Inferior	L	40	4144	-45	-42	43	7.97	-44	-42	42
5	Caudate and claustrum	R		4104	15	7	8	6.27	14	8	10
6	Temporal, Middle & Superior	R	21, 22	1528	50	-40	2	5.21	50	-48	8
7	Limbic, Cingulate	R	23	1488	2	-22	27	5.25	2	-22	26
8	Frontal, Medial	R	6	1088	16	0	61	4.57	16	0	60

9	Occipital, Superior	R	19	256	35	-76	30	4.51	34	-76	30
10	Temporal, Fusiform gyrus	L	20	160	-49	-32	-15	4.18	-48	-32	-16
11	Limbic, Cingulate	L	32	144	0	18	41	4.08	0	18	40

* Coordinates for the weighted centre of mass for the cluster † The most extreme t statistic for the voxels in the cluster

‡ The coordinates for the centre point of the cluster

Block versus event-related designs

Activations were more prominent for blocked than event-related designs, in keeping with the increased power attributed to blocked designs in detecting task-coupled changes in BOLD response. Greater activation in blocked-designs was most consistently observed bilaterally in the IFG and the precuneus, in the right middle frontal gyrus, temporal cortex, and cerebellum, and in the left occipital cortex (Table 6). Greater activation was observed for the left superior frontal gyrus (BA 9) and right superior temporal gyrus (BA 39) for event-related designs.

Table 6. Differential activation for block-design versus event-related GNG tasks

Region	Hemi	BA	Frequency*	Avg. Cluster size (mm ³) (SD) [†]	Avg. Peak Threshold (SD) [‡]	X	Y	Z [§]
Block > Event-related								
Frontal, Middle	R	9	80	3647 (2542)	3.558 (3.35)	44	22	30
Frontal, Inferior	R	47	80	727 (453)	2.388 (2.69)	40	20	-14
Occipital, Inferior	L	19	59	687 (326)	3.677 (0.29)	-38	-76	0
Frontal, Medial	L	8	59	1839 (997)	4.126 (0.65)	0	28	40
Frontal, Inferior	L	47	56	2475 (768)	3.675 (0.02)	-42	18	-8
Parietal, Precuneus	R	7	53	1711 (1541)	3.256 (1.8)	18	-70	46
Cerebellar Tonsil	R		45	423 (272)	3.048 (0.26)	30	-42	-36
Parietal. Precuneus	L	7	45	357 (146)	3.071 (0.88)	-14	-66	48
Temporal, Middle	R	37	44	1217 (957)	3.633 (0.67)	50	-62	6
Frontal, Inferior	L	45	40		3.624 (0.15)	-46	16	4
Event-related > Blocked								
Frontal, Superior	L	9	40	1562 (1173)	-4.03 (0.8)	-36	36	28
Temporal, Superior	R	39	37	1079 (887)	-3.47 (2.29)	48	-56	28

* Frequency refers to the number of times a particular cluster was identified across 100 permutations for 6 pseudo- randomly selected studies in each group being compared.

† Calculated across occurrences of the cluster identified in the permutation analysis

‡ Average and standard deviation of peak t statistic (10^3) for occurrences of cluster in the permutation analysis

§ Calculated as the mode of the coordinates for that cluster across the permutation analyses

Linguistic versus non-linguistic stimuli

In comparing data from all of the eligible studies in terms of the nature of the trial stimuli, greater activation for linguistic stimuli was observed in the amygdala (left), insula (bilaterally), and frontal operculum portion of the IFG (bilaterally). The only one of these regions that was reliably activated when sample size was controlled for was the right IFG (BA 47). Non-linguistic stimuli, on the other hand, activated the cerebellum (left), brain-stem (right), cingulate gyrus (right), and claustrum (right) exclusively. When sample size was equated, the right claustrum was still observed as being more active in response to non-linguistic than linguistic stimuli.

Table 7. Differential activation for GNG tasks that differ in linguistic content of stimuli*

Region	Hemi	BA	Frequency*	Avg. Cluster size (mm ³) [†]	Avg. peak threshold (SD) [‡]	X	Y	Z [§]
Linguistic > Non-linguistic								
Frontal, Superior gyrus	L	8	52	969 (799)	3.355 (0.61)	-6	32	46
Frontal, Inferior gyrus	R	47	49	1122 (811)	3.755 (1.11)	38	20	-14
Temporal, Middle gyrus	R	39	35	1329 (949)	3.912 (0.59)	50	-60	8
Non-linguistic > Linguistic								
Clastrum	R		51	1777 (1684)	-3.7 (2.08)	28	20	4
Medial Frontal Gyrus	L	6	38	2667 (1363)	-4.31 (0.9)	-4	-6	58
Inferior Frontal Gyrus	L	9	35	777 (581)	-3.47 (0.68)	-48	8	26

* Frequency refers to the number of times a particular cluster was identified across 100 permutations for 6 pseudo- randomly selected studies in each group being compared.

† Calculated across occurrences of the cluster identified in the permutation analysis

‡ Average and standard deviation of peak t statistic (10^3) for occurrences of cluster in the permutation analysis

§ Calculated as the mode of the coordinates for that cluster across the permutation analyses

Affective versus Standard versions of the Go/NoGo

Coordinate data could only be included for 6 experiments from 5 of the 10 included studies.

Reasons for excluding data from the Affective GNG studies included the lack of a Go-only comparison group for a blocked design study (Elliott, et al. 2000), the reporting of deactivated coordinates (Amin, et al. 2006) or between-group contrasts only (Protopopescu, et al. 2005; Silbersweig, et al. 2007; Wessa, et al. 2007), and failure to obtain coordinate data (Shafritz, et al. 2006).

Studies employing versions of the Go/NoGo task containing emotional stimuli were more likely to observe BOLD signal in the right cingulate, insula and the left amygdala. On the other hand, the parietal lobe (precuneus and inferior parietal) as well as the middle frontal gyrus (BA 9, 10) were more likely to be active in response to non-affective stimuli.

Table 8. Differential activation for comparison of standard and affective versions of the GNG task

Region	Hemi	BA	Frequency*	Avg. Cluster size (mm ³) [†]	Avg Peak threshold (SD) [‡]	X	Y	Z [§]
Affective > Standard								
Limbic, Cingulate gyrus	R	23	94	744 (377)	3.221 (2.13)	8	-24	32
Insula	L	13	93	2269 (943)	4.517 (0.6)	-34	20	8
Limbic, Amygdala	L		62	533 (210)	3.244 (0.1)	-28	0	-16
Temporal, Superior gyrus	R	13	59	2069 (1113)	3.754 (0.6)	48	-44	14
Insula	R		42	3627 (1013)	4.99 (0.7)	32	20	0
Frontal, Inferior gyrus	R	9	37	716 (637)	2.997 (1.07)	40	6	30
Temporal, Fusiform gyrus	R	37	35	425 (259)	2.809 (0.18)	-40	-60	-8
Frontal, Superior gyrus	R	10	33	234 (87)	2.738 (0.17)	28	58	24
Standard > Affective								
Frontal, Middle gyrus	R	9	42	1658 (1562)	-3.36 (2.33)	28	38	34
Parietal, Precuneus	R	7	36	1597 (1339)	-3.6 (1.43)	18	-70	42

* Frequency refers to the number of times a particular cluster was identified across 100 permutations for 6 pseudo- randomly selected studies in each group being compared.

† Calculated across occurrences of the cluster identified in the permutation analysis

‡ Average and standard deviation of peak t statistic (10^3) for occurrences of cluster in the permutation analysis

§ Calculated as the mode of the coordinates for that cluster across the permutation analyses

5.5 Discussion

This study represents the largest quantitative review of the neural correlates of successful motor inhibition using a single paradigm to date, collating coordinate-data from a total of 51 fMRI studies (946 subjects). The finding of a substantially higher commission than omission error rate on average for the standard GNG studies included in this review appears to support the adoption of this paradigm as a measure of motor inhibition for the MRI scanner.

Bilateral activation was observed across (standard) GNG studies in the frontal, temporal and parietal cortices, with the largest cluster in these meta-analyses detected in the right middle and inferior frontal cortex (extending to the precuneus). This prominence of right-hemispheric activation is consistent with findings in other imaging meta-analyses of the GNG task that employed similar parameters and inclusion criteria (Buchsbaum, et al. 2005;

Nee, et al. 2007; Simmonds, et al. 2008). Mirroring the findings from the most recent of these meta-analyses, we detected a largely right-lateralised pattern of concordance in fronto-parietal regions in response to successful inhibitions on the GNG, as well as bilaterally in the insula/putamen (Simmonds, et al. 2008). Greater activation was also observed in the thalamus, as well as the right insular cortex, extending to the pars opercularis of the rIFG (BA47). These findings concur with those reported for a mega-analysis of fMRI data from 5 studies (126 participants) utilizing the stop-signal paradigm, in which the only network out of 20 identified using independent components analysis that correlated significantly with inhibitory performance contained the bilateral IFC/frontal opercular/insular cortices, and the bilateral striatum, pallidum, and thalamus (Congdon, et al. 2010).

The findings of this review are largely in agreement with recent versions of the fronto-striatal model of motor inhibition, in which inhibitory behaviour is subserved by a neural network that includes the basal-ganglia, the rIFG, the supplementary motor area (SMA) and preSMA (Chambers, et al. 2009). This neural circuit is distinct from the inhibitory connections between the ventral ACC and nucleus accumbens that are conceptualized as crucial in predicting impulsive behavior associated with deficits in reward processing (Fineberg, et al. 2010). In the fronto-striatal model the inhibition of a motor response is achievable by means of two routes, both of which result in inhibition of excitatory projections from the thalamus to cortical motor areas. The first is a relatively slow indirect pathway in which activation of the striatum via cortical motor projections (dorsal motor cortex, preSMA, SMA, M1) results in the down-regulation of the globus pallidus pars externa (GPe) by means of inhibitory (GABAergic) connections, further reducing the inhibition of GPe afferents (globus pallidus pars interna (GPi)/reticular substantia nigra (SNr) and the subthalamic nucleus) that send inhibitory connections to the thalamus.

The second route by which motor inhibition might occur is through a so-called “hyperdirect pathway” in which the subthalamic nucleus is activated directly via excitatory connections from the rIFG, in turn resulting in stimulation of excitatory glutamatergic connections to the internal segment of the globus pallidus/reticular substantia nigra, and the activation of inhibitory projections to the thalamus. The differential delays associated with the indirect and hyperdirect pathways resonates with evidence that it may be easier to distinguish between correct inhibitions and commission errors on the temporal than the spatial plane (Garavan, et al. 2002).

The ventrolateral prefrontal cortex (VLPFC), and in particular the rIFG, has been identified as a core component of the fronto-striatal model of motor inhibition. The importance of this region for motor inhibition has recently been questioned however, with a number of scholars arguing that the preSMA may be more critical for inhibition (Simmonds, et al. 2008).

Activation of the insula/rIFG could potentially arise from incidental differences between trial types (eg. greater frequency of Go trials & greater difficulty of NoGo trials), rather than response inhibition per se. Indeed, activation of the pars opercularis, the region of the IFC encompassed by this cluster, was determined to be sensitive to reference condition, and was only detected in this review in comparisons with Go trials. This finding may partially explain discrepancies in the results reported in the two most recently published ALE meta-analyses of motor inhibition, in which Levy et al. (2011) discovered robust activation of both the right opercular and triangular regions of the rIFG, despite failure to detect rIFG involvement in a larger (N = 48) meta-analysis of the GNG (Swick et al. 2011). Levy and colleagues (2011) based their findings on an activation map produced by combining stop-signal and GNG tasks (N = 45), and, tellingly, restricted the latter to those using Go trials as a reference condition.

Although it may be tempting on the basis of the finding in our review to interpret the role of the IFG as primarily one of novelty detection, it should be noted that rIFG activation has

been observed in individual studies employing oddball comparators, in which frequency effects have been accounted for (Borgwardt, et al. 2008; McNab, et al. 2008). The possibility should also be considered that failure to detect activation of the rIFG when combining data from the 5 studies employing the oddball paradigm may be attributable to the limited power of this comparison. Finally, findings from other paradigms, such as the recent demonstration in a target-detection task that activation of the rIFG was not dependent on the frequency of targets (Hampshire, et al. 2009), also argues against describing the role of the rIFG as primarily one of novelty – detection.

The IFG is a large region of the brain, incorporating the pars opercularis, pars orbitalis, and pars triangularis. One possible explanation for the conflicting characterizations of the role of the IFG therefore is that it may incorporate multiple subregions, each with specialised functions. Indeed, task-specific activation patterns within the rIFG, visible on the millimetre scale, suggest caution in regarding this structure as monolithic in function (Goghari and MacDonald 2009; Hirose, et al. 2009). Treating the entire rIFG as a single region of interest carries with it the possibility that inhibitory effects might be diluted to below the level of the statistical threshold applied. The functional fractionation of the IFG is apparent in the distinction made by Chikazoe and colleagues (Chikazoe 2010; Chikazoe, et al. 2009) between the posterior IFG, inferior frontal junction (IFJ), and the insula/IFG. These authors argue that whereas the pIFG is specialised for inhibitory functioning, the IFJ is involved in processing infrequent stimuli. This is supported by the finding that the pIFG responds preferentially to infrequent NoGo trials, while the IFJ responds to both NoGo and infrequent Go or oddball trials, regardless of type (Chikazoe, et al. 2009) (however, see Braver 2001).

Levy et al. (2011) recently attempted to decompose the functional structure of the right VLPFC using meta-analytic methods, by comparing the results of tasks designed to measure reflexive reorienting (the posner task and the oddball task) with tasks designed to measure

response stopping (the GNG and stop-signal task). The authors concluded, on the basis of bilaterally-activated IFJ across all tasks that the function of this structure might better be interpreted with respect to the detection of task-relevant stimuli. Activation of the par opercularis and pars triangularis regions on the other hand was modulated by the inhibition but not the reorientation tasks, indicating that the function of these components of the IFG might be more closely tied to inhibition. The finding that the pars triangularis was activated by tasks where there was uncertainty regarding the identity of upcoming trials (GNG tasks with equiprobable trial types), and not where a dominant response was established by the task design (all stop-signal tasks and GNG tasks with a majority of Go trials) led the authors to conclude that one of the functions of this structure might be to resolve decision-level conflict in circumstances characterised by high levels of uncertainty.

Levy et al. (2011) interpreted the role of the right pars opercular activation as one of updating action plans, despite evident specificity of this region for the inhibition as opposed to orienting tasks, partly on the basis of evidence of its invariance with respect to the difficulty of inhibitions. This concurs with the suggestion that the rIFG constitutes a general purpose relevance-detection mechanism that signals the dorsal frontal cortex for task-set maintenance (Hampshire, et al. 2010). Indeed, evidence in support of this hypothesis is particularly strong for the frontal operculum, as the cluster of activation incorporating the insula and frontal operculum has been related to a diverse range of cognitive functions that have been subsumed under the category of awareness (Craig 2009). Its involvement across a variety of tasks has led to the suggestion that the insula/rIFG forms part of a core task-set system along with the dorsal ACC/medial superior frontal cortex (Dosenbach, et al. 2006), and that it may form part of a network including the VMPFC and ACC in assigning salience to stimuli (Sridharan, et al. 2008). Although the insula has been implicated in many studies as central to inhibition (Garavan, et al. 1999; Swick, et al. 2011; Wager, et al. 2005), and was the only region (after correction for multiple comparisons) to correlate significantly with performance across 3 different inhibitory tasks (Wager, et al. 2005), its involvement in

inhibition may therefore be part of its broader function in flagging stimuli as relevant to the requirements of a particular task. This is consistent with the hypothesis that the insula forms part of a frontal-striatal attentional network that is integral to inhibitory performance via its connections with the prefrontal cortex and anterior cingulate gyrus (Schmitz, et al. 2006).

The findings of this review provide support for the involvement of the preSMA in inhibition (Fassbender, et al. 2004). This agrees with the meta-analytic observation that the SMA/preSMA was activated in both GNG and the stop-signal task paradigms (Swick, et al. 2011). Using a novel triangularisation technique, Aron et al. (2007) demonstrated a structural network linking the preSMA, sub-thalamic nucleus (STN) and the right IFC that corresponded closely with functional activation patterns in a subsequent modified stop-signal task. The same pathways were activated for delayed responses and correct inhibitions. The finding of effective connectivity between the preSMA and the rIFG was confirmed recently in the analysis of BOLD data from a stop-signal paradigm using Granger Causality Analysis (Duann, et al. 2009). In this study activation in preSMA and PMC directly predicted activation of the caudate and STN, respectively, whereas the rIFC exerted influence on the basal ganglia indirectly via its connectivity with the preSMA. These connectivity patterns were stronger for correct than failed inhibitions. Duann et al. (2009) go on to suggest that their findings necessitate the revision of the fronto-striatal model of motor inhibition, as they are not consistent with the existence of the hyperdirect pathway between the IFC and the subthalamic nuclei.

The issue of the specificity of the rIFG and preSMA to inhibitory control has generated much debate. A recent study employing the stop-signal paradigm detected great activation of the pre-SMA during better inhibitory performance (Chao, et al. 2009), with failure to find parallel activation of the rIFG interpreted by the authors as reflecting its role in the orientation of attention. The authors noted, however, that it is difficult to separate the contribution of the preSMA to inhibitory functioning from its traditional association with motor response

preparation (Zubicaray 2000, p1288). This latter interpretation of the role of the preSMA is consistent with the finding that this region responds to both target and inhibition trials (Hampshire, et al. 2010). Although the ACC/preSMA has been identified as a component of a core cognitive control network, the exact role of the preSMA vis-a-vie response inhibition still needs to be determined (Cole and Schneider 2007; Dosenbach, et al. 2006).

Concurrent activation of the dorsal ACC was also observed for successful inhibitions in this review. Increasing reliance on the ACC has been observed with maturation from adolescence to adulthood (Rubia, et al. 2006), and it has been posited to be crucial to conflict monitoring and error detection (Braver, et al. 2001). The dorsal portion of the ACC has reciprocal connections to the frontal cortex as well as afferent connections to the associative premotor and primary motor regions, and is therefore particularly well situated to coordinate cognitive-motor interactions (Mohanty, et al. 2007; Paus 2001). It is conjectured, based on evidence of functional connectivity, that the dACC may recruit the DLPFC and parietal cortex to exert greater attentional control in response to conflicts between task requirements and behavioural tendencies (Carter, et al. 2000; Mohanty, et al. 2007). For instance, Mohanty and colleagues (2007) demonstrated that over 70% of the variance in DLPFC activation during the incongruent word-colour condition of a Stroop task was explained by activation of the dACC.

Finally, there was a small cluster of activation in the right thalamus on correct inhibitions. The thalamus plays a pivotal role in models of motor response inhibition. Afferent connections to the thalamus from the prefrontal cortex and ACC, regions of the brain putatively involved in task-set maintenance, conflict resolution and response selection, implicate the role of the thalamus as gatekeeper for motor control on the level of response execution. The GNG task is considered to be a relatively selective measure of response execution compared to other tasks used as behavioural measures of inhibition. This could account for the finding reported

by Wager et al (2005) of a correlation between activation of the thalamus and performance on the GNG but not other measures of interference resolution, such as the Flanker and Stimulus Response Compatibility task (Wager, et al. 2005).

5.5.1 Effect of differences in task design on inhibition-related brain activation

There was no evidence in this study that manipulating the ratio of Go to NoGo trials in event-related studies resulted in differences in task performance. The absence of fronto-parietal activation in studies in which the number of trial types has been kept equivalent could be interpreted as evidence that inhibitory function is not being tested in these studies (Braver, et al. 2001; Konishi, et al. 1998) This rests on the assumption that the fronto-parietal network identified in this and other studies is a core component of inhibition. However, Simmonds et al. (2008) phrase the involvement of the fronto-parietal circuitry in terms of its function in the maintenance and manipulation of stimulus-response associations rather than inhibitory function per se. Indeed, we were able to confirm that the fronto-parietal circuit was activated to a greater extent in complex versions of the GNG, where dynamic stimulus-response associations place a greater burden on these regions in updating working memory.

The choice of the reference condition used for assessing the neural correlates of inhibition appears to have substantial effects on patterns of brain activity. A more diffuse pattern of activation was observed when NoGo trials were compared to baseline rather than Go trials. Specifically, regions that have been implicated in motor control, including the bilateral inferior parietal cortex and the putamen were evident only when baseline was used as a reference condition. This is in line with accounts that describe inhibition as involving the triggering of a “kill switch” for a motor response that has been initiated (Chambers, et al. 2009). In this scenario, use of Go trials as a reference condition would mask this motor-related activity. Activation of the putamen and culmen for the baseline contrast were located in the left

hemisphere, consistent with a contralateral response to the use of a right button-box in the majority of studies.

There was substantial overlap between areas that were preferentially activated for complex GNG tasks and for studies that compared inhibition to a baseline reference (left putamen, bilateral inferior parietal lobe, left fusiform gyrus). Although discrepancies in the size of the clusters were observed, there was almost complete correspondence in the location of the peak coordinates. This can be attributed to a confound between reference condition and working memory load, with the vast majority of the studies conducting NoGo > Go comparisons employing simple GNGs (25/26), and over 70% of the studies using baseline comparisons employed complex GNGs (10/14). Nevertheless, the inferior parietal cortex has been consistently identified with working memory performance (Berryhill and Olson 2008; Muller and Knight 2006), suggesting that it would be recruited to a greater extent for conditions requiring updating of a stimulus-response set.

Brain regions that were uniquely activated for the complex - simple GNG contrast included the ACC, as well as the right medial posterior cingulate cortex (BA 23), an area that has been linked to self-monitoring processes (Blakemore, et al. 1998). Previous studies have detected a shift of activation from the right DLPFC to the ACC with increasing task difficulty (de Zubicaray, et al. 2000; Garavan, et al. 2002), a phenomenon that is interpreted as reflecting a transition from a more deliberative to a more 'urgent' response style (Garavan, et al. 2002). Activation of the ACC in this review is consistent with this interpretation, with a greater number of commission errors being detected for complex than simple GNG tasks.

Blocked study designs and analytic procedures are frequently employed, as they are regarded as more sensitive than event-related designs to differences in BOLD signal between conditions. Event-related designs, on the other hand, allow the investigator to (a)

isolate trial-specific activation, (b) remove error responses, and (c) characterize the shape of the hemodynamic response. In comparing blocked versus event-related GNG tasks in this review, more activation was detected in blocked-design studies in the right parietal and temporal hemispheres, as well as bilaterally in the frontal cortex (BA 9, 47). Interestingly, a relatively large cluster (average extent: 2475 mm³) was observed in the left lobe for the inferior frontal gyrus (BA 47). Though the function of the left IFG has been discussed in terms of the inhibition of conflicting verbal information (McNab, et al. 2008) and interference resistance (Nelson, et al. 2009), a neurophysiological study recently demonstrated impairments in motor inhibition in patients with lesions in the left IFG (Swick, et al. 2008). One possibility is that the right-lateralised network identified in event-related designs is an artifact of the lower sensitivity of these designs to detect signal changes.

5.5.2 Effect of differences in stimulus type on inhibition-related brain activation

Relative to the standard GNG, we observed a high error rate on the affective GNG (average of 8.7% over both trials types), as well as a slower reaction time for the Go trials. This concurs with evidence from the literature that it is more difficult to inhibit responses to emotional than non-emotional stimuli in healthy individuals (Schulz, et al. 2007; Verbruggen and Houser 2007). This may also underlie the finding that the ACC was the most consistently activated region in response inhibition in studies employing this paradigm, given the central role it is posited to play in monitoring conflict (Botvinick, et al. 2004). Hare et al. (2005) have postulated that one source of conflict that occurs in the affective GNG is between task instructions and the approach or withdrawal orientation associated with positive and negative emotions, respectively. Although we had insufficient power to replicate Hare et al.'s (2005) finding of a higher commission error rate for happy faces and a slower reaction time for fearful targets in this review, the differences that were observed were in the expected direction.

Clusters that were most consistently activated in the affective relative to the standard GNG included the right cingulate gyrus, the insula (bilaterally), the left amygdala, and the right temporal and frontal lobes. The amygdala has frequently been associated in the literature with emotional processing, and fear conditioning in particular. Its association with exposure to negative affect has led to an initial emphasis on its involvement in fear processing. For instance, previous meta-analyses of imaging studies employing emotional stimuli have generally detected greater activation for fearful than happy stimuli (Murphy, et al. 2003; Phan, et al. 2002). The characterization of the amygdala as a threat-detection module is consistent with the finding that this structure is frequently activated amongst anxiety disordered patients in stimulus exposure paradigms (Freitas-Ferrari, et al. 2010; Shin, et al. 2006). The inverse association between prefrontal and amygdala activation typically observed in these paradigms supports a model in which the prefrontal cortex moderates amygdala activation, and finds its anatomical basis in the bidirectional neural pathways between the OFC/ventromedial prefrontal cortex (vmPFC) and the amygdala.

The role of the amygdala is likely to be more complex than suggested by the naïve frontal-limbic model, however. For instance, Mobbs et al. (2007b) were able to demonstrate specificity of subdivisions within the amygdala to the physical and psychological proximity of a virtual predator. The exclusivity of the amygdala's role in relation to fear/threat has also been questioned, with a region-of-interest meta-analysis observing greater activation of the amygdala for happy than fearful faces (Sergerie, et al. 2008). The finding of the sensitivity of the amygdala to the task-relevance of emotional faces, rather than their emotional valence per se (Santos, et al. 2011), and its activation in response to non-affective stimuli in GNG paradigms and other measures of executive functioning (Pourtois, et al. 2010), suggests that the amygdala may possess a more general function in detecting the behavioural significance or salience of environmental stimuli.

Finally, it should be noted that although previous studies have detected associations between behavioural performance and amygdala activation using the affective GNG paradigm (eg. Hare et al. 2005), this paradigm is not necessarily optimized for detection of activity in the amygdala. In fact, there is evidence that the executive component of affective inhibitory control, mediated by the frontal cortex, may inhibit activation of the amygdala (Berkman, et al. 2009). Nevertheless, the possibility that deficits in the frontally-mediated regulation of the limbic lobe (including the amygdala) could serve as an endophenotype for affective disorders suggests that the affective GNG might have application in clinical populations. Even more tantalizing are indications that this task could serve to discriminate between competing diagnoses, as suggested by a series of studies conducted by Rebecca Elliott on patients with unipolar and bipolar depression (Elliott, et al. 2004; Elliott, et al. 2002). In these studies, ventral regions of the ACC were selectively responsive to sad as opposed to happy target words in depressed patients, with the converse finding observed in normal controls (Elliott, et al. 2002). Although patterns of activation were similar in manic patients, they were observed in response to both happy and sad words, suggesting a general deficit in emotion regulation in this clinical population (Elliott, et al. 2004).

The finding in this review that the use of affective stimuli was associated with bilateral insula activation concurs with evidence that this structure might be involved in the explicit discrimination of stimuli based on their emotional content (Gorno-Tempini, et al. 2001; Iaria, et al. 2008). Shafritz et al (2006) argue that the insula may be important in the integration of emotions in decision-making processes. It therefore follows that the processing of information conveyed by these emotions may fall within the more general function proposed for the insula of achieving homeostasis through monitoring a person's internal physiological states (via interoception – see Craig 2002). This is reminiscent of the central role postulated by proponents of the somatic marker hypothesis for affective feedback in explaining complex decision-making (Damasio 1996), and could also explain the dysregulation of the anterior

insula reported for anxiety prone individuals (Stein, et al. 2007) as well as individuals who experience unusually strong emotions in response to affective stimuli (Iaria, et al. 2008).

Finally, this review provides some evidence that the nature of the stimuli that are employed in the standard GNG paradigm may impact on the brain regions that are activated. Tasks employing shapes or objects as stimuli as opposed to letters were more likely to detect activation in the right claustrum, a thin layer of cells lying subcortically between the putamen and the insula. Although the exact function of this structure is not known, it is speculated that it might be important in the cross-modal integration of features of an object (Crick and Koch 2005). Its activation in this instance is therefore arguably incidental to the properties of the stimuli employed.

5.5.3 Limitations

Conducting subgroup analyses of groups separated on a single factor does not control for confounding effects of other factors that might be differentially represented in the two groups. In this review, there was substantial overlap between reference condition, working memory load and experimental design (blocked versus event-related). This made teasing apart the effects of these different design factors on brain function challenging. Although the development of brain imaging meta-analysis approaches that allow one to regress the effects of a continuous covariate on brain activation may go some way towards addressing this concern (e.g. Signed Differential Mapping (Radua and Mataix-Cols 2009)), possible confounding variables should ideally be considered at the design stage. This is particularly the case when one considers the subtlety of some of the proposed interactions, such as that between specific stimulus types and the brain areas involved in mediating the relationship between working memory and inhibition (McNab, et al. 2008).

We decided to restrict the analysis to correct inhibitions rather than errors of commission as

there was a far greater amount of data for correct responses, affording us the opportunity to interrogate the effects of methodological features on variance in brain activation. This decision also receives partial justification from evidence that activation patterns elicited by correct and incorrect inhibitions may be more distinguishable in the temporal than the spatial domain (Garavan, et al. 2002). However, even with the adoption of this strategy, conclusions drawn from comparisons in this review still need to be considered in light of quite severe sample-size constraints (particularly with respect to the affective GNG comparison).

This review examined brain activation associated with motor inhibition in healthy participants, and did not address the literature employing the GNG paradigm in clinical samples. Nevertheless, collating data from fMRI studies in healthy populations can be seen as a first step in providing a frame of reference for the identification of clinically-relevant brain activity patterns in patient samples. Diffuse non-task-specific activity in clinical populations is frequently interpreted as a compensatory response to hypoactivation of regions, such as the rIFG, that have been regarded as more pertinent to the task at hand in normally functioning individuals, particularly in the context of equivalent behavioural performance (Schmitz, et al. 2006). The finding in Kana et al. (2007) that differences between schizophrenia patients and healthy controls only manifested in a version of the GNG containing a substantial working memory component highlights the importance of matching the design features of the task employed to the particular patient sample .

It was unfortunately not possible to distinguish on a neural level between the effects of different emotions, due both to heterogeneity in the stimulus sets that were employed and the contrasts that were performed. The relationship between emotional valence and activation of the amygdala in the context of inhibition might have been particularly informative, given controversy over the generality of activation in this region. The specificity in the context of motor inhibition of the reported involvement of the pregenual ACC on

exposure to sad emotions (Shafritz, et al. 2006), and the caudate in connection with positive emotions (Hare, et al. 2005) awaits confirmation from future research.

Despite the limitations of this review, we were able to address a number of the shortcomings of previous quantitative syntheses of imaging data for motor inhibition tasks, as described by Simmonds et al. (2008). With the exception of Levy et al. (2011), previous meta-analyses assigned the same weighting to coordinate data contributed by different studies, despite substantial inter-study differences in the sample size and statistical thresholds employed. By way of illustration, 2 of the 48 GNG studies included in Swick et al. (2011) (Konishi, et al. 1999; Konishi, et al. 1998) contained an average of 6 participants, but from an analytic point of view were considered equivalent to a study contributing data from 48 participants (Mostofsky, et al. 2003). In addition, we took pains to exclude studies reporting on the same sample, in an attempt to minimize dependency in the data. Notably, recent meta-analyses have included data from as many as 5 studies containing overlapping sample, partially undermining the strength of the conclusions drawn (Levy and Wagner 2011; Swick, et al. 2011).

This review employed a version of the ALE algorithm that adjusted the extent of smoothing applied to coordinate foci on a study-by-study basis, using a Gaussian full-half-width-maximum (FWHM) kernel proportional to the sample size (Eickhoff, et al. 2009). In this way bias introduced through small under-powered studies with overly lenient statistical thresholds was minimized. Activation was also restricted to biologically plausible regions through the use of a grey matter mask. Finally, the effects of variation in the number and clustering of foci between studies was explicitly controlled for through the use of a random-effects model. This allows us to extrapolate our findings beyond the particular studies included in this review. The generalisability of our findings was further strengthened by restricting inclusion to studies that employed random or mixed-effects analytic strategies.

5.6 Conclusion

Inhibitory behaviour can be decomposed into a tightly integrated set of interacting cognitive components, including stimulus detection, response selection and response execution. Moreover, differential study-specific demands will be made on neural substrates involved in task-set maintenance, attention and conflict resolution, depending on the characteristics of the task and population tested. A potential consequence of the inclusion of extraneous cognitive components in tasks such as the GNG are reduced correlations between performance and brain activation. Individuals may also compensate for inefficient response inhibition by monopolising memory or selective attention demands, in line with their strengths (Wager, et al. 2005).

It is therefore striking that, this variability in task design notwithstanding, we were able to detect consistent involvement of brain regions regarded by many as critical for motor inhibition, such as the rIFG, preSMA, ACC, insula and basal ganglia. Furthermore, by using novel meta-analytic strategies to collate data across multiple studies that employ different GNG paradigms, we were also able to observe a substantial impact of differences in task design and analytic strategy on the reported distribution of fMRI coordinates. Most striking was the observation that the rIFG, a region that has frequently been identified with motor response inhibition, was reliably activated only when inhibitory trials were compared to Go trials. Differences in task demands may also explain the preferential recruitment of the inferior parietal (implicated in working memory) in the complex variant of the GNG paradigm.

The nature of the stimuli associated with the instruction to withhold or execute a motor response was also determined to have a substantial and systematic impact on patterns of brain activity. This was the case both for aspects of task design that can be regarded as incidental to the main aims of the studies included in this review (use of linguistic versus non-linguistic trial stimuli), as well as those that were more central to the comparisons of

interest (affective versus non-affective stimuli). Relatively greater activation of the amygdala when affective stimuli were employed highlights the importance of preliminary attempts to disentangle the contribution of inhibitory process and affect regulation to limbic activation (Shafritz, et al. 2006), especially in light of the increasing recognition of a strong relationship between emotion regulation and impulse control (Cyders and Smith 2008).

Evidence of task-specific differences in brain response within the same paradigm emphasizes the importance of an explicit and systematic consideration of the impact of task design during the planning stages of an fMRI study. This is underscored by consideration of the functional overlap of different brain regions as described in the research literature, in combination with the conceptual challenges in separating behavioural domains (eg. emotion regulation and impulse control). Although the emergence of structural and functional connectivity studies that adopt a systems approach to understanding communication between different brain regions should help to impose constraints on the role of particular regions vis-a-vie one another, investigators are encouraged to seek guidance in the design of these tasks and the interpretation of the resulting data by consulting mechanistic accounts of motor inhibition, such as provided by the fronto-striatal model. The full potential of brain imaging studies as sensitive indicators of differences in inhibitory control will only be realized if investigators are cognizant of how task features may affect brain activation, and design their tasks accordingly.

5.7 References (those marked with * were included in the meta-analysis)

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6. EARLY PSYCHOLOGICAL TRAUMA INFLUENCES LATER EMOTION RECOGNITION: UNDERSTANDING THE ROLE OF THE OPIOID SYSTEM

6.1 Preface

This study assessed the effects of the partial mu-opioid agonist buprenorphine on the emotional behaviour of University students with a history of early life adversity. Exogenous opioid agents are routinely employed as analgesics, and the opioid system has been implicated in animal and clinical research in the modulation of the affective component of physical pain, as well its emotional and social analogues (Panksepp, 2003; Zubieta et al., 2003). Accordingly, one of the central hypotheses of this study was that the administration of buprenorphine would result in improved social interaction and a reduction of fearful responses, as evidenced in a series of affective tasks, and that this would be particularly apparent in a traumatised sample that was likely to demonstrate enhanced reactivity to, and reduced control of, aversive emotions.

6.2 Introduction

There is substantial evidence that early psychological trauma is associated with later deficits in affect regulation and the processing of aversive emotions. A number of studies indicate that childhood adversity is associated with altered recognition of anger and fear faces (Masten et al., 2008; S. D. Pollak, Cicchetti, Hornung, & Reed, 2000; Seth D Pollak & Kistler, 2002; Seth D Pollak & Tolley-Schell, 2003; Scrimin, Moscardino, Capello, Altoè, & Axia, 2009). Using a facial morphing paradigm to assess adult responsiveness to angry, happy and sad faces, Gibb et al (2009) found that a history of childhood trauma increased both attention to angry faces and the accuracy with which anger was recognized (Gibb, Schofield, & Coles, 2009).

An immediate question is the nature of the neural circuitry and molecular systems which mediate such changes. Several converging lines of evidence point to involvement of the opioid system in affect regulation, as well as in mediating response to psychological trauma. Animal research has demonstrated that mu-opioids are secreted during formation of social attachments such as the infant-mother bond, and that they have a role in regulating separation distress or “social pain” (Panksepp, 2003). Furthermore, there is evidence that the opioid system plays an important role in mediating affective components of physical pain (Bruehl, Burns, Chung, & Chont, 2009; Stein, van Honk, Ipser, Solms, & Panksepp, 2007). Finally, empirical research indicates that the opioid system may play a compensatory role in response to psychological trauma, and that this may be compromised in posttraumatic stress disorder (Kraus et al., 2009; Liberzon et al., 2007).

Despite this growing body of evidence on the role of the opioid system in emotional regulation and trauma, there is little data on whether administration of an opioid agent is able to normalize dysregulated systems in those exposed to early adversity. Given the putative role of the opioid system in inhibiting regions of the brain (such as the amygdala), that are

responsive to threat via up-regulation of localized mu-opioid receptors (Liberzon et al., 2007), one hypothesis is that exogenous administration of opioids would lower the threshold at which emotions such as fear and anger are detected. Tests of this hypothesis would be useful in strengthening our understanding of the role of the opioid system in stress and emotional regulation, and may also provide proof of principle evidence for the use of opioid agents in related clinical settings.

The emotion recognition paradigm is frequently used in approaches that employ pharmacological challenges to investigate the involvement of specific neural systems in affective behaviour. For instance, findings of impaired performance in recognising angry faces after acute treatment with 15mg of diazepam have been interpreted as implicating activation of benzodiazepine receptors in orbitofrontal cortex (Blair & Curran, 1999; Blair, 2003). Similarly, the reduction of accuracy in recognising fear and anger after acute treatment with citalopram and reboxetine was discussed in terms of their specific effects on serotonin and noradrenergic neurotransmitters, respectively (Harmer, Shelley, Cowen, & Goodwin, 2004). These studies provide a useful paradigm for investigating the effects of the opioid system on emotion processing.

We hypothesized that administration of an opioid agonist would normalize responses to fear and anger in an emotion recognition paradigm, in subjects with a history of early adversity. Data on whether responses to these emotions is facilitated or disrupted is sparse and somewhat contradictory, however. Although Gibb et al. (2009) reported increased accuracy in recognising angry faces following childhood trauma exposure, an unpublished study that stratified 162 adults by childhood physical trauma history did not reveal any differences in error rates for the recognition of angry faces (Gapen, 2009). Moreover, a number of studies using the dot-probe attention task have reported findings that are perhaps more consistent with avoidance of threatening emotions in adults who were abused as children (Fani, Bradley-Davino, Ressler, & McClure-Tone, 2011; Johnson, Gibb, & McGeary, 2010).

Therefore, one of the aims of this study is to provide greater clarity on the direction of the effect that early trauma history has on the processing of negative emotions.

6.3 Method

The study was approved by the Ethics Committee of the Faculty of Health Sciences at the University of Cape Town, and complied with ethical guidelines established by the Declaration of Helsinki (World Medication Association, 2000). Subjects were required to sign an informed consent form prior to participation. Subjects completed a range of measures to assess eligibility (see below). Those who qualified were provided with 0.2mg of buprenorphine or placebo on separate testing occasions, during which the emotion recognition task was conducted. Subjects were asked to eat a light meal two hours prior to testing, and then to fast until testing was complete.

6.3.1 Subjects

878 students from the University of Cape Town were recruited using study flyers. Students were eligible for inclusion in this study if they were free of psychopathology (as assessed on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and depressive symptoms (as defined by a score of 13 or less on the Beck's Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)).

A smaller group (n=47) of traumatised and non-traumatised participants were identified from scores on the short form of the Child Trauma Questionnaire (CTQ). This is a validated self-rating scale consisting of 28 items scored using a 5-point response format (ranging from never true to very often true)(Bernstein et al., 2003). The CTQ contains 5 items each representing domains of physical, sexual and emotional abuse, as well as physical and

emotional neglect, and 3 items included to assess validity. Participants who obtained a rating of at least "moderate to severe" on one or more of the CTQ subscales were rated as traumatised. The control group consisted of participants with at most a single low to moderate severity rating on any of the CTQ subscales. In order to be included in the study, subjects had to be classified in the same trauma group across two administrations of the instrument. Invalid response patterns, defined as obtaining a rating of "questionable validity" on either administration of the CTQ, or "some denial/minimization" on both administrations, were grounds for exclusion.

6.3.2 Medication Administration

The administration of medication was blinded, with the order of placebo/medication administration determined in a randomised and counterbalanced fashion. The dose of buprenorphine used was 0.2mg, in order to minimize nausea. Behavioural tasks were given 120 minutes after medication administration.

6.3.3 Emotion recognition task

A modified version of the emotion recognition task developed by Montagne et al. (Barbara Montagne, Kessels, Haan, & Perrett, 2007) was used. In this task subjects are presented with sequences of faces that dynamically morph from neutral to one of a series of prototype emotions (see Figure 1). The participant is subsequently asked to identify the emotion displayed. Dynamic facial displays of emotion are more readily recognised than the static images that have traditionally been employed in studies of emotion recognition, with this advantage particularly apparent at low emotional intensities (Ambadar, Schooler, & Cohn, 2005).

Participants were presented with the image of a face with a neutral expression on a 17 inch colour computer monitor. On pressing the Enter key the faces morphed into one of 4 emotions (angry, fearful, happy, sad) in increments of 2 percent intensity. The intensity of the final image in the sequence ranged from 20 to 100% of a prototype image, across 9 intensity levels presented in consecutive order (20%, 30%, 40%, 50%, 60%, 70%, 80% and 100%). Each intensity level contained 4 randomly presented trials per emotion, for a total of 144 trials. After the image was presented, the subject was instructed to press a key between 1 and 4 that corresponded to the order of the emotion labels displayed under each face. Depending on the intensity of the emotion, the presentation time varied between approximately 1 and 3 seconds, with no time-limit imposed on the response time. Each participant was given 4 practise trials at the beginning of the task.

The stimuli used consisted of grayscale images of faces of two male and two female actors. One of the actors was selected from the Eckman library (Ekman & Friesen, 1976) and 3 were selected from the Karolinska Directed Emotional Faces libraries (Lundqvist, Flykt, & Ohman, 1998(Oosterhof & Todorov, 2008)). The images were selected on basis of the highest mean ratings provided by 12 subjects on a 9 point scale for each emotion. The morphed images were created with the WinMorph software (<http://www.debugmode.com/winmorph/>), and presented using Eprime 1.2 (Psychology Software Tools Inc., 2002).

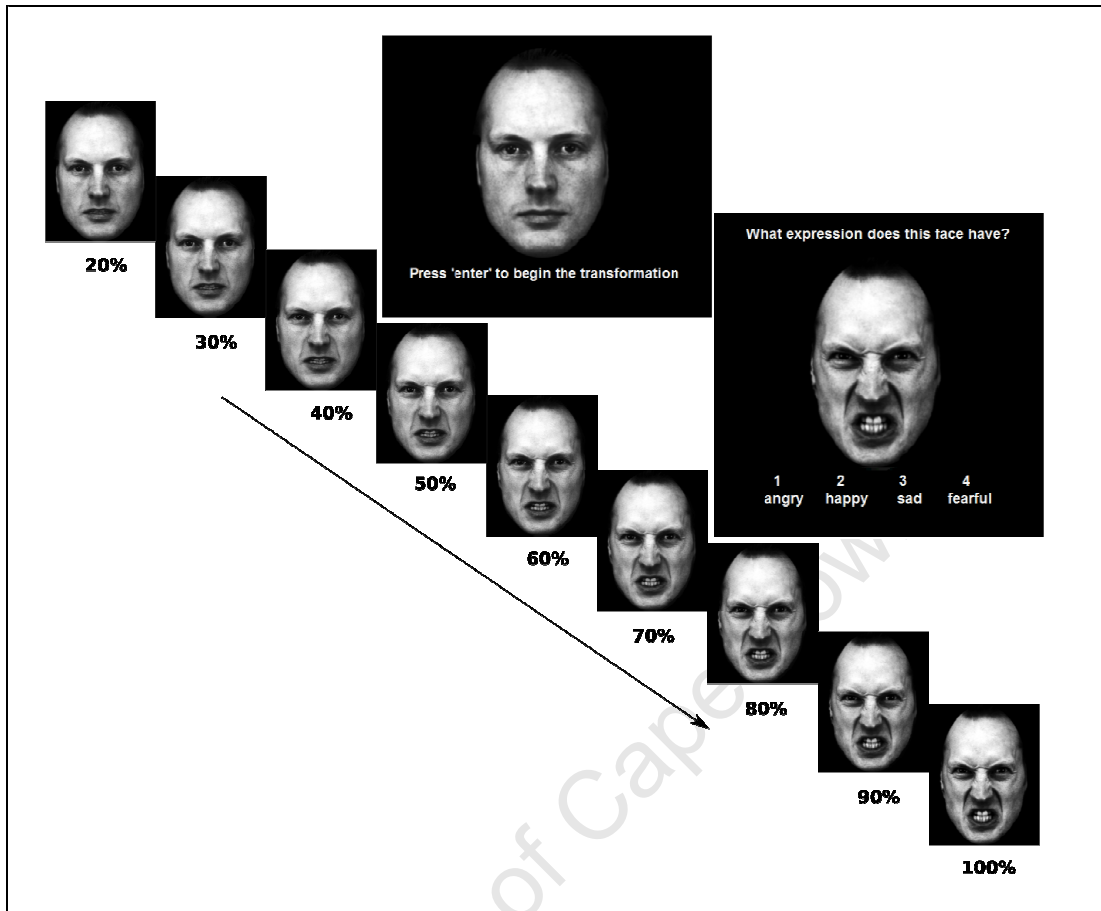


Figure 1. Example of dynamic display of angry emotions during the facial morphing task

6.3.4 Additional Measures

Differences between the trauma groups in accurately identifying emotions on the facial morphing task might partially be accounted for by group differences in (a) the threshold for discriminating between emotions or for responding in favour of particular emotions, (b) symptoms of anxiety or depression, (c) subjective mood states, and (d) forms of impulsivity that are sensitive to affect. Therefore, in addition to a self-rating measure of emotional awareness and clarity, we also analysed data from measures of these factors to aid in the interpretation of the results of the emotion recognition task.

Self-rating measures of clarity in identifying emotions and emotional awareness were obtained from the respective subscales of the Deficits in Emotion Regulation Scale (DERS)

(Gratz & Roemer, 2004). The DERS has demonstrated adequate test-retest reliability and convergent validity with other measures of affect regulation (Gratz & Roemer, 2004), and has been effective in identifying differences in a diverse range of healthy and clinical populations (Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007; Fox, Hong, & Sinha, 2008; Glenn & Klonsky, 2009; Orgeta, 2009).

The potential contribution to task performance of impulsive traits that are influenced by an individual's emotional state were assessed using the self-rated UPPS-P Impulsive Behaviour Scale (Lynam, Smith, Cyders, Fischer, & Whiteside, 2007). The 12-item urgency subscale provides a measure of the "tendency to act rashly in response to distress" (Cyders & Smith, 2008) (p808), and has consistently predicted impulsive behaviour in substance abusing and gambling populations (Anestis, Selby, & Joiner, 2007; Billieux, der Linden, & Ceschi, 2007; Fischer, Anderson, & Smith, 2004).

Differences between the trauma groups on anxiety and depression symptoms were assessed using the Beck Depression Inventory (Beck et al., 1961) and the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), respectively. Both of these are well validated instruments that are frequently employed in research settings. The effects of medication on subjective experiences of mood were assessed both at the beginning of the testing session and the end using visual analogue mood scales (VAMS) (Stern, Arruda, Hooper, & Wolfner, 1997). Although originally designed for testing aphasia patients, the VAMS has demonstrated reliability in normal populations. Changes in task-relevant mood were assessed using subscales for fear, anger, happiness and sadness. In addition, VAMS scales measuring how tired and energetic the subjects were provided some indication of the sedative effects of the medication.

6.3.5 Data Analysis

The effect of medication and trauma status on accuracy in identifying fearful and angry faces was tested using generalized estimating equation models (GEEs). GEEs allow testing for the effects of predictor variables on emotion identification accuracy, while controlling for common variance introduced through repeated measurements. Between-group differences in the time taken to correctly recognise angry and fearful faces was tested using multivariate regression, employing restricted Maximum Likelihood Estimation (REML). Both random effects GEE and REML procedures were implemented in Statistica (version 10) (www.statsoft.com).

Separate GEE models were fitted for accuracy in recognising angry and fearful faces. The models included the following dependent variables (coding between parentheses): the order in which medication or placebo was administered for that subject (placebo first vs. placebo second), whether a particular trial came from a medication or placebo session (medication vs. placebo), the intensity of the emotion displayed (levels 1 to 9), trauma status of the subject (traumatised vs. non-traumatised), and gender (male vs. female). Interaction terms for these variables were also included in the models, with the highest order term testing for 4-way interactions between intensity level, medication status, trauma status and gender.

Non-parametric signal-detection measures of perceptual discriminability (d') and response bias were calculated separately for anger and fear (Donaldson, 1992). In this context perceptual discriminability refers to an individual's ability to distinguish between particular emotions, whereas response bias refers to the internal threshold at which a person indicates that they detected an emotion. The computation formulae for discriminability (A') and response bias ($B''D$), as implemented in the R statistical language (version 2.10; R Development Core Team 2011) (Pallier, 2002), are provided below:

$$A' = 1/2 + [(H - FA)(1 + H - FA)]/[4H(1 - FA)].$$

$$B'D = [(1 - H)(1 - FA) - HFA]/[(1 - H)(1 - FA) + HFA].$$

, where H = hit rate or number of correct responses, and FA = false alarms, or number of incorrect responses. Response bias scores are constrained to fall between -1 and 1, with a score of 0 indicating no bias, negative scores indicating more liberal tendencies to respond, and positive scores reflecting tendencies to withhold responses. A discriminability score of 0.5 indicates chance performance, with near perfect performance reflected by scores approaching 1. Differences between trauma groups on these metrics were compared using Wilcoxon Rank Sum tests.

Differences between the trauma groups on the scores from the respective subscales of the DERS and UPPS-P questionnaires were assessed using independent t-tests, or the Wilcoxon Mann-Whitney test where assumptions of normality were violated. Relationships between scores on these questionnaires and differences in accuracy or reaction time as a function of medication were assessed using Pearson's correlations, or non-parametric equivalents, where indicated. Between-group differences in changes in the VAMS mood scores from the beginning to the end of the testing session were determined using repeated-measures analysis of variance, with medication as a within-group factor. These analyses were conducted in R, with statistical significance set at alpha = 0.05 (R Development Core Team 2011).

6.4 Results

6.4.1 Subjects

A total of 47 participants completed at least one behavioural testing session, with data from 40 subjects included in the analysis. Approximately equal numbers of subjects were classified as traumatised ($n = 18$) or non-traumatised ($n = 22$).

There was little overlap in the CTQ total scores for the subject groups (range: non-trauma - 36.5, 45; trauma - 44.5, 68) (Table 1). Fifteen of the trauma group experienced some form of abuse, with only 3 participants in this group exclusively exposed to neglect. The trauma group obtained substantially higher scores on the awareness subscale of the DERS ($W = 73.5$, $p < 0.05$). The groups were comparable in terms of age and gender, as well as on depression and anxiety symptomatology. No between-group differences were observed on the urgency subscale of the UPPS-P. Similarly, trauma status had no apparent effect on the scores for any of the visual analogue moods scales, including those for tiredness and energy levels, both prior to and after the testing session.

Table 1. Characteristics of participants

	Trauma	Non-Trauma	Z score
Sample	18	22	-
Age	21.2 (3.8)	21.2 (3.8)	-0.40
Male	9	11	-
CTQ total score	53.8 (6.9)	40.9 (2.3)	$t = -7.61^{**}$
BDI	6.4 (4.6)	5.2 (4.8)	$W = 85$
STAI	39 (6.1)	38.1 (8.7)	$W = 129$
DERS Awareness	14.85 (3.31)	12.3 (3.53)	$W = 73.5^*$
DERS Clarity	17.08 (1.44)	17.1 (1.65)	$W = 134$
UPPS-P urgency	29 (5.97)	25.35 (5.76)	$W = 90.5$

Statistical comparisons conducted using non-parametric Wilcoxon-Mann-Whitney test Sample on BDI (Non-trauma = 18, Trauma = 11), STAI (Non-trauma = 21, Trauma = 14), CSI avoidance (Non-trauma = 13, Trauma = 9), DERS and UPPS subscales (Non-trauma = 20, Trauma = 13)

*significant at $p < 0.05$ **significant at $p < 0.01$

6.4.2 Emotion recognition performance

Participants with a history of trauma were less accurate in recognising angry faces than those without such a history (Wald $\chi^2 = 4.43$, $df = 1$, $p < 0.05$) (Figure 2). These differences in accuracy were associated with an overall bias against identifying faces as angry ($B_D = 0.688$ versus 0.412 , Wilcox Rank Sum = 265.5, p -value < 0.02), with no between-group differences observed in the ability to discriminate between anger and the other emotions. A main effect of intensity level for angry faces (Wald $\chi^2 = 178.71$, $df = 8$, $p < 0.01$) was observed, with accuracy strongly predicted by emotional intensity (Pearson $r = 0.934$). Finally, there was a significant correlation between emotional awareness (as assessed by the relevant subscale of the DERS), and accuracy in recognising anger ($r = 0.42$, p -value < 0.05). No evidence was detected of an association between impulsivity scores and accuracy for either anger or fear faces.

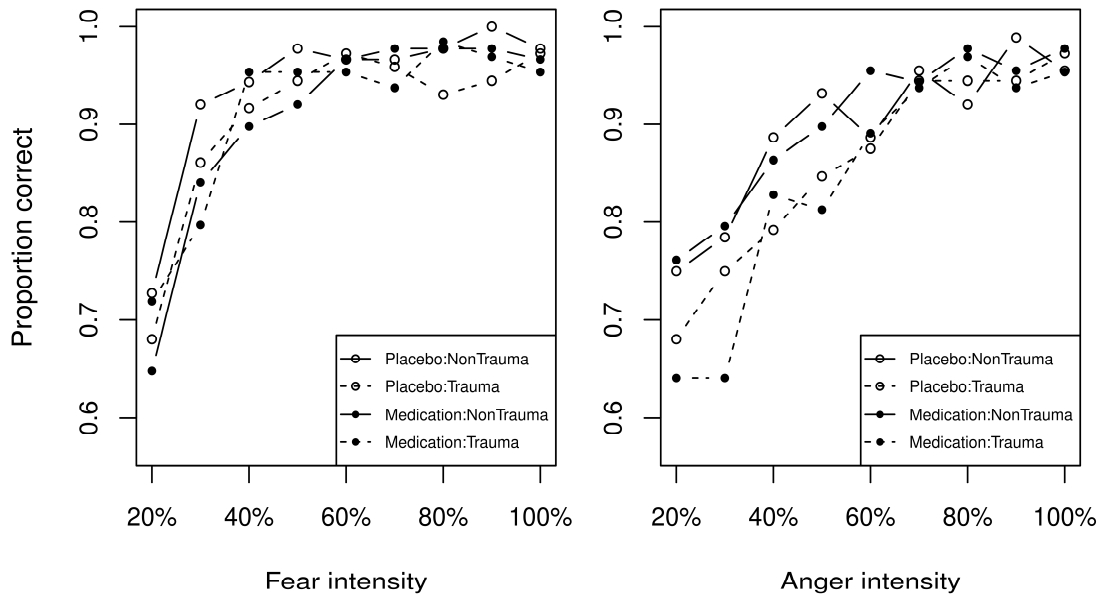


Figure 2. Comparison of accuracy in identifying aversive emotions between trauma groups and medication conditions

Main effects on accuracy in recognising fearful faces were observed for session, intensity and gender. As for anger, increases in the intensity of fearful expressions was strongly associated with performance improvements (Wald $\chi^2 = 99.57$, $df=8$, $p < 0.01$). Similarly, subjects' performance improved significantly in the 2nd session relative to the 1st (Wald $\chi^2 = 34.27$, $df = 1$, $p < 0.01$). Males were less accurate overall in recognising fear than females (Wald $\chi^2 = 3.86$, $df=1$, $p = 0.05$). An interaction was observed between trauma status and medication condition, with the trauma group experiencing an increase in accuracy following administration of buprenorphine, relative to placebo, and the converse pattern observed in the non-trauma participants ($F=4.36$, $df=1$, $p>0.05$) (Figure 3).

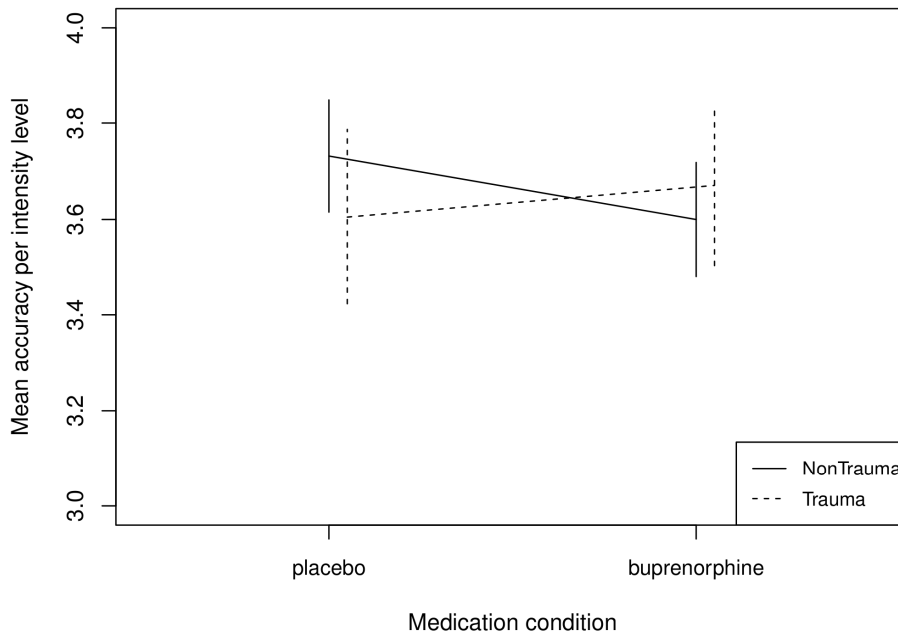


Figure 3. Interaction of childhood trauma and medication on accuracy for fear faces

Similar patterns in the reaction time data were observed for both fear and anger. Increasing intensity of the angry and fearful emotions were associated with a reduction in response time ($F_{8,542} = 46.383, p < 0.01$ and $F_{8,542} = 59.519, p < 0.01$, respectively). Reaction time in recognising fear ($F_{1,542} = 71.47, df = 8, p < 0.01$) and anger ($F_{1,542} = 62.42, p < 0.01$) was significantly reduced in the second session compared to the first. Subjects were slower in responding to the angry and fearful faces in the medication than placebo sessions ($F_{1,542} = 16.378, p < 0.01$ and $F_{1,542} = 10.201, p < 0.01$, respectively). This finding appears to be due to faster responses in the trauma than the control group when on placebo, with the relative reaction time advantage for the trauma group disappearing once buprenorphine was administered ($F_{1,542} = 12.065, p < 0.01$ for anger and $F_{1,542} = 14.119, p < 0.01$ for fear, respectively). Although no effect of gender was detected overall, females were faster than males in correctly identifying anger ($F_{1,542} = 3.921, p < 0.05$) in the buprenorphine condition, with a similar trend observed for fear ($F_{1,542} = 3.069, p = 0.08$).

6.5 Discussion

This is the first study to compare the effects of exogenous opioids on emotion recognition in healthy adults with a history of childhood adversity. The main findings of this study are (1) that adults with a history of childhood adversity are less accurate in identifying anger and display deficits in emotional awareness, and (2), that administration of a single dose of buprenorphine reduced trauma-associated differences both in the accuracy with which fear was identified, as well as the speed with which participants with a history of trauma were able to identify fear and anger.

Adults with a history of trauma were less accurate in recognising angry faces than control participants, reflecting a general tendency in this group to avoid identifying faces as angry. One interpretation of this finding is that early adversity may disrupt the processing of socially antagonistic emotions. A similar interpretation was made of the finding of reduced sensitivity to angry faces in 13 patients with depersonalization personality disorder, a disorder that has been associated with severe psychological trauma, using a similar facial morphing paradigm (Montagne et al., 2007). Interpreting impairment in the ability to identify anger as resulting from avoidance is also consistent with the association we found between performance on the awareness subscale of the DERS and accuracy at identifying anger. The DERS awareness subscale can be conceived of as a measure of the acknowledgement of primarily adverse emotions, as illustrated by the wording of its items (eg. "When I'm upset, I acknowledge my emotions") (Gratz & Roemer, 2004).

Additional support for interpreting poor accuracy in identifying angry faces in terms of avoidance mechanisms is provided by a study of 129 adults with a history of child abuse (as assessed on the CTQ) recruited from general medical clinics (Fani et al., 2011).

Performance on the affective dot-probe task in this sample failed to discriminate between the trauma groups for either fearful or angry faces. Instead, a significant positive bias ($r = 0.25$,

$p < 0.01$) towards happy faces was observed in the trauma group. This finding, in combination with the positive association between the happiness bias and symptoms of avoidance/numbing on the Modified PTSD Symptom Scale (Falsetti, Resnick, Resick, & Kilpatrick, 1993) led the researchers to suggest that their sample may have demonstrated avoidance of aversive stimuli in favor of positive stimuli.

Our findings differ from the only published study of the long-term effects of childhood trauma on emotion recognition in healthy adults, which found that trauma exposure was linked to improvements in the accuracy with which angry faces were identified (Gibb et al., 2009). The authors suggested that increased accuracy in identifying anger may be due to an attentional bias in adults with childhood trauma, as detected on a dot-probe task included in the study. However, a recent publication using an identical dot-probe task to that employed in Gibb et al. (2009) found evidence of avoidance with respect to angry faces (Johnson et al., 2010). Methodological differences that may have contributed towards the discrepant findings reported between this study and that of Gibb et al. (2009), include differences in the task employed (dynamic versus static display), the fact that our study employed a placebo-controlled pharmacological challenge design, and the facial stimuli employed.

As hypothesized, administration of a single dose of buprenorphine partially normalised responses of participants with a history of trauma to both fear and anger. This finding appears to contradict observations reported in a recent publication (Carroll et al., 2011), in which the acute administration of opioids produced no discernable effect on the recognition of anger or fear amongst 20 patients in a pain-management setting. However, this study did not contain a control group nor did it assess childhood adversity. Furthermore, the authors also noted that the failure to detect an effect of opioid medication may have been attributable to habituation effects, as all of the patients were receiving sustained opioid interventions.

Instead, the observation that the effect of a partial mu-opioid agonist on responses to threatening emotions can be predicted by an adult's early life history suggests that a dysregulated opioid system may be mediating these effects. In a PET study, Liberzon et al. (2007) found that the OFC was one of the few regions that differentiated trauma exposed individuals with PTSD from those without PTSD in terms of opioid receptor occupancy levels, indicating possible compensatory failure in the clinical population. The observation that PTSD is frequently associated with the poor control of aggressive impulses is consistent with the characterisation of the OFC as one of the primary sites involved in regulating anger (Blair, 2003). These observations support a putative role for the opioid system in dampening responses to both physical pain and "social pain", and provide proof of principle support for future research on the therapeutic use of opioid agents in patients with emotion dysregulation.

Our data emphasize that gender differences are important in understanding the influence of trauma history on processing aversive emotions. Across conditions, women were significantly more accurate in recognising fear than men. Moreover, women with a history of childhood trauma were significantly faster in recognising fear across placebo and medication sessions compared to women without a history of trauma (no effect was observed for anger). These findings are consistent with evidence from the literature for greater sensitivity amongst females to negative emotional expressions (Montagne, Kessels, Frigerio, de Haan, & Perrett, 2005; Thayer & Johnsen, 2000), particularly at low emotional intensities.

Scores on self-rating scales of urgency, a form of impulsivity that is conceptualized as being moderated by negative affect (Whiteside & Lynam, 2001), did not differentiate between trauma and non-trauma groups, or correlate with the effects of medication on accuracy for either angry or fearful faces. This was despite recent findings that scores on the impulsivity and deliberation facets of the self-rated NEO PI-R personality scale predicted endogenous mu-opioid levels amongst healthy men in regions associated with emotion regulation,

including the right anterior cingulate, ventral basal ganglia and basolateral amygdala, both at baseline and in response to a physical pain stressor (Love, Stohler, & Zubieta, 2009).

Nevertheless, other individual differences may contribute to variance in the effect of opioids on the association between child trauma exposure and responses to negative emotions. There is evidence, for example, that the amygdala, a core component of brain circuitry involved in emotion regulation, is differentially active in individuals with the short variant of the serotonin transporter gene on exposure to emotional faces (Hariri et al., 2002; Hariri et al., 2005). Indeed, preferential avoidance of angry faces in the dot-probe task amongst women who had been physically abused as children was only observed for subjects with this genetic variant (Johnson et al., 2010). Ethnicity has also been identified as a possible determinant of responses to emotional faces. A meta-analysis reported that emotion recognition was more accurate in individuals from the same ethnic group as the actors whose faces are displayed (Elfenbein & Ambady, 2002). Responses to the ethnic composition of faces was also cited by Fani et al. (2011) in explaining the bias towards positive emotions that they observed in their mainly African American sample. This was interpreted by the investigators as possibly reflecting avoidance of neutral and angry Caucasian faces that were perceived as particularly threatening.

A number of additional alternative explanations for this study's findings should be considered. There was evidence of improvements in task performance across testing sessions for both fear and anger faces. Although this may be indicative of possible learning effects, it is unlikely to explain trauma-specific increases in accuracy and reaction across sessions. The observation that trauma was associated with faster responses and worse accuracy might also suggest that these trauma-effects could be explained in terms of speed-accuracy trade-offs. Specifically, it has been suggested that the selective effects of medication on the recognition of negative emotions in previous studies could represent an interaction between the agent's sedative properties and the greater difficulty associated with

identifying negative emotions (Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009). However, we failed to detect differences between trauma groups on the tiredness and energy visual analogue mood scales, indicating that this cannot account for the differences observed between the trauma groups.

Overall, these data support our hypothesis of an association between the opioid system, early adversity, and modulation of facial processing. In particular, early adversity may lead to neurochemical alterations that facilitate recognition of threatening emotions, and administration of opioid agonist may act to normalize such emotional processing. Future research on emotion recognition should assess subjects for history of early adversity. The findings here provide support for additional research on the opioid system and emotional dysregulation in clinical populations, including the use of opioid agents to ameliorate deficits in affect regulation.

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7. DISCUSSION

The primary aim of the review of pharmacotherapy for disruptive behavioural disorders in children and adolescents was to attempt to identify the involvement of serotonin in these disorders, and relate serotonergic abnormalities to the impulsivity and deficits in affect regulation that frequently characterise these disorders. Unfortunately, none of the randomised controlled trials included in our review, or in a recent review of psychopharmacology for aggression in children and adolescents with a primary psychiatric disorder (Nevels, Dehon, Alexander, & Gontkovsky, 2010) specifically tested the efficacy of agents that selectively target serotonergic systems.

Instead, psychostimulants emerged as the class of agents most frequently tested in treating child and adolescent disruptive behavioural disorders, with evidence of efficacy for methylphenidate (Ritalin) being particularly apparent. The mechanism of action of the psychostimulants has typically been described in terms of their molecular effects on the dopamine neurotransmitter system (Del Campo, Chamberlain, Sahakian, & Robbins, 2011; Heal, Cheetham, & Smith, 2009). The majority of the evidence-base implicates dopamine with regards to impulsive acts that are reward-related, such as assessed using delayed discounting tasks, however, rather than motor inhibition, per se (Fineberg et al., 2010; Pine, Shiner, Seymour, & Dolan, 2010). For instance, in a recent review of the neuropsychopharmacology of action inhibition, Eagle and colleagues (2008) found little evidence for an association of either D1 or D2 genotypes with performance on the stop-signal or GNG tasks. Moreover, the reviewers drew attention to the fact that those few studies that find an effect of non-stimulant dopaminergic challenges on nogo performance only do so when correct inhibitions are rewarded.

Although there is little evidence that abnormal levels of dopamine have direct bearing on differences in the effect of psychostimulants on aggressive impulsivity, there is evidence

implicating the downstream involvement of serotonergic pathways in the effects of the methylphenidate on symptoms of impulsivity and aggression.

Hints that the effects of methylphenidate on impulsivity may be mediated through non-dopaminergic neurotransmission was provided by the finding in one study that methylphenidate reduced motor activity in a dopaminergic-knockout ADHD mouse model, despite high extra-cellular levels of dopamine in the brains of these animals (Giros, Jaber, Jones, Wightman, & Caron, 1996). Thakur and colleagues (2010) subsequently probed the implications of this and other findings from the animal literature for human subjects, by investigating the possibility that serotonergic function might explain the response of ADHD symptoms to methylphenidate in 157 children between the ages of 6 and 12. Using a randomised placebo-controlled design, they demonstrated that those subjects who were homozygous for the long variant of the 5-HTTLPR polymorphism of the SLC6A4 gene serotonin transporter gene responded to 1 week treatment with 0.5mg/kg/day of methylphenidate but not placebo on the Connors Global Index for Parents (a scale composed of the factors of “emotional lability” and “restless-impulsive behaviour” - (Connors, 1999)). The converse pattern was observed in individuals with a genotype (s/s) that is less efficient in the transcription of serotonin. The implication that serotonergic mechanisms might be mediating the effects of methylphenidate is further strengthened by parallel findings from a study of the treatment of borderline personality disorder with the SSRI fluoxetine, in which reduction of scores on the anger subscale of the OAM were only observed in carriers of the more efficient l/l 5-HTT polymorphism (Silva et al., 2010).

The mood stabiliser lithium is frequently prescribed for the treatment of aggressive behaviour in youth, and our review indicated that it may be efficacious in this regard (see also Masi et al. 2009). There is evidence that lithium treatment over the long term may be associated with the synthesis of 5-HTT, and that this may be at least partially responsible for its anti-aggression properties (Eichelman, 1987; Muller-Oerlinghausen, 1985). This is particularly

likely given evidence from the animal and human literature reviewed by Krakowski and colleagues (2003) that low levels of CNS serotonin are associated with aggressive behaviour.

These observations in combination indicate that future investigations of the effects of serotonin in affecting anger regulation and impulsivity in ODD populations may be warranted. This is likely to be particularly important given the evidence that ODD may be a potential precursor to conduct disorders, which in turn is associated with antisocial personality disorder in adulthood (Biederman et al., 1996; Copeland, Shanahan, Costello, & Angold, 2009; Whittinger, Langley, Fowler, Thomas, & Thapar, 2007).

A review of pharmacotherapy for PTSD in adults was subsequently conducted to determine whether the responsiveness of overall PTSD symptoms, as well as individual PTSD clusters to serotonergic agents could provide information on the interaction between serotonin and long-term dysregulations of affect following trauma exposure. Indeed, we detected significant treatment effects for medication overall on the total CAPS scores, with the majority of evidence for the SSRIs. Medication effects were also observed for the individual intrusion/re-experiencing, avoidance/numbing and hyperarousal symptom clusters. In addition, effects of medication on mood were detected, with a reduction in symptoms of depression but not anxiety following pharmacotherapy.

At the level of individual medication classes, however, no differences were observed between the SSRIs and the other medications on any of the symptom clusters. This is consistent with the finding of no differences across symptom clusters in a direct comparison of 12 weeks of treatment with the SSRI fluoxetine, the serotonin reuptake enhancer tianeptine, and the reversible monoamine oxidase inhibitor (RIMA), MAO-I moclobemide (Onder, Tural, & Aker, 2006). This was despite predictions by the authors that the effects of fluoxetine would be selective for numbing and avoidance symptoms, tianeptine for

hyperarousal symptoms, and moclobemide for re-experiencing and avoidance symptoms.

A closer look at the agent-specific effects for SSRIs across the different symptom clusters (data extracted from PTSD pharmacotherapy meta-analysis) also reveals a substantial amount of consistency in the ranking of the effects of the particular agents, with paroxetine demonstrating the largest effect across all symptom clusters (Table 1).

Table 1. Agent-specific effects of serotonergic medications on PTSD symptom clusters

	Intrusion		Avoidance		Hyperarousal	
	Sample	Effect	Sample	Effect	Sample	Effect
Paroxetine	3; 888	-3.26 [-4.73, -1.78]	3,728	-5.04 [-6.87, -3.20]	3,728	-3.64 [-4.95, -2.33]
Fluoxetine	2; 599	-2.38 [-4.12, -0.64]	2; 598	-2.42 [-4.57, -0.27]	2; 599	-2.32 [-3.95, -0.69]
Sertraline	5; 864	-0.99 [-2.08, 0.09]	5; 864	-3.32 [-4.99, -1.65]	5; 864	-2.07 [-3.32, -0.82]
Citaloram	1; 35	1.66 [-6.31, 9.63]	1; 35	2.08 [-7.76, 11.92]	1; 35	1.04 [-5.44, 7.52]

Sample: No. of studies; participants

Effect: Random effect estimates of Weighted mean difference between medication and placebo groups on the CAPS (point estimate, 95% confidence interval)

One possible explanation for these null findings is that the temporal resolution of these trials may not be sufficient to distinguish between primary effects of medication, and secondary knock-on effects on other symptoms. This is suggested by separate pooled analyses of the SSRI sertraline and the serotonin – noradrenergic reuptake inhibitor (SNRI) venlafaxine in treating PTSD (Davidson, Landerman, Farfel, & Clary, 2002; D. J. Stein et al., 2009). Both of these studies observed a reduction in angry outbursts or irritability as early as 2 weeks after initiation of treatment across two RCTs, with improvements in other symptoms only observed later. Reductions following venlafaxine treatment in numbing symptoms measured using the clinician administered PTSD scale, 1 week symptom status version (CAPS-SX17), were only

observed after 6 to 8 weeks of treatment. This effect was explained as a possible serotonergic response that mediated subsequent reductions in other symptoms (D. J. Stein et al., 2009).

The suggestion that medication effects in reducing overall PTSD symptom severity are mediated by serotonergic dampening of anger/irritability is consistent with evidence from longitudinal studies that reductions in symptoms of hyperarousal, of which anger and irritability is one component, may drive subsequent changes in avoidance/numbing and intrusion symptoms (Schell, Marshall, & Jaycox, 2004; Z. Solomon, Horesh, & Ein-Dor, 2009). A similar temporal precedence has been observed for hyperarousal symptoms with respect to numbing symptoms in traumatised children (Weems, Saltzman, Reiss, & Carrion, 2003). Conversely, studies have typically found that the association between anger and PTSD becomes stronger as the duration with which individuals have lived with PTSD increases (Ehlers, Mayou, & Bryant, 1998; Feeny, Zoellner, & Foa, 2000), suggesting that poorly regulated anger may be a crucial component in the maintenance of pathological responses to trauma.

Assessing the direct effect of medication on affect might therefore provide further insight into the possible neurocircuitry involved in pathological responses to psychological trauma. Unfortunately, few of the clinical trials of PTSD included in the review reported on treatment-associated changes in affect. Investigation of the association between impulsivity and affect regulation are rendered even more problematic, given the multidimensional nature of both constructs and the use by different research teams of a variety of (frequently non-validated) measures of these constructs. Investigations of the association of trauma-exposure and aggressive impulsivity are further complicated by the tendency of anger researchers to use implicit definitions of “aggression” versus “impulsivity”, or indeed, to use these terms interchangeably (see Garcia-Forero et al. 2009 for a recent review).

In an attempt to introduce some conceptual clarity regarding the relationship between aggression and impulsivity, Garcia-Forero and colleagues (2009) recently compared scores on self-reported measures of trait impulsivity and trait aggression in 768 healthy participants (ages ranging between 12 and 72 years), using Spanish adaptations of the Barrat Impulsivity Scale (Mathias, Stanford, Marsh, Frick, & Moeller, 1991), and the Aggression Questionnaire - Refined (AQ-R; (Gallardo-Pujol & Andres-Pueyo, 2006)), respectively. They detected a maximum canonical correlation between the scales of 0.42, leading them to conclude that impulsivity and aggression are largely independent constructs. Nevertheless, correlations between individual subscales of the AQ-R and the total BIS score revealed the largest association between anger and impulsivity ($R = 0.37$), providing some support for the concept of affect-driven impulsivity.

One potential useful strategy in investigating the relationship between affect regulation and impulsivity that would bypass the paucity of information on affect regulation in clinical trials of pharmacotherapy for PTSD, as well as the conceptual confusion regarding the definition of these constructs, is to operationalise affect regulation and impulsivity in terms of performance on laboratory tasks. Performance on these tasks is likely to be a more reliable measure than scores on self-report questionnaires, thereby reducing the contribution of random error to contradictory findings in the literature. Moreover, fMRI allows one to use blood oxygenation (fMRI) as a relatively high (spatial) resolution proxy for brain activation that coincides with task execution. Reviewing studies that employ fMRI within the context of behavioural testing may therefore help to elucidate those regions of the brain that form the functional substrate of the particular behavioural construct under investigation.

The ALE review of fMRI studies employing the standard GNG paradigm identified motor inhibition as being served by a largely right-lateralised fronto-parietal circuit that included the striatum and thalamus. This is consistent with the findings of previous meta-analyses of this

paradigm (Buchsbaum et al., 2005; Nee et al., 2007; Swick et al., 2011). In addition, differences between the affective and standard versions of the task were evident in regions of the brain typically considered to be part of the “emotional brain”, and included the amygdala, cingulate and anterior insula.

The GNG imaging meta-analysis was based on the largest number of studies to date, using methods that accommodate between study variability in sample size and precision. The results of this meta-analysis may therefore form a useful reference against which to compare activation patterns in the brains of individuals with a history of trauma or who have been diagnosed with impulsive disorders.

Evidence that trauma-associated psychopathology may interfere with normal inhibitory processes was provided by Falconer et. al. (2008), who not only detected a higher commission error rate in 23 PTSD patients versus controls, but also reported a negative correlation between the severity of PTSD symptoms and activation of the rIFG, DLPFC, medial PFC and cerebellum, regions identified by the ALE meta-analysis as involved in motor inhibition in healthy individuals. Moreover, controlling for differences in performance, Falconer et al. (2008) observed greater activation of the right inferior frontal/VLPFC cortex in control subjects (including healthy controls and trauma-exposed non-PTSD subjects), with the PTSD patients recruiting the cuneus, cerebellum, putamen, parahippocampus and postcentral cortex to a greater extent than healthy controls. The finding that somatosensory and striatal regions of the brain were recruited to a greater extent during inhibitory performance in the PTSD group was interpreted by the authors as suggesting a state of hyperarousal in these participants, with concomitant increases in the processing of sensory stimuli. This would conceivably have placed greater demands on inhibitory control centres in the brain (hence the increased striatal activation), impairing the capacity of the cortex to inhibit motor activity (Falconer et al., 2008).

Another fMRI study compared 14 healthy control children to 16 children with exposure to at least one criterion A interpersonal stressor, and with posttraumatic stress symptoms (PTSS), as assessed using the Clinician Administered PTSD scale for Children (Carrion, Garrett, Menon, Weems, & Reiss, 2008). The investigators hypothesised that increased activation would be observed in brain regions associated with hyperarousal states, such as the insula, with corresponding reductions in frontal regions associated with inhibition. Although no differences between groups in performance were observed, these hypotheses were largely upheld, with decreased activation observed in the middle frontal cortex in children with PTSS relative to healthy controls, as well as greater left inferior temporal and occipital activation (once depression was controlled for). Activation in the insula correlated with severity of PTSD symptoms, and particularly with hyperarousal and avoidance/numbing symptoms (Carrion et al., 2008).

Although the literature on the effects of trauma exposure on motor inhibition, as assessed by the GNG paradigm, is sparse, the findings are largely in agreement with the argument that hyperarousal symptoms may account for inhibitory deficits following trauma exposure. Nevertheless, there are a number of caveats that need to be made with reference to this line of reasoning. Firstly, the extent to which inhibitory deficits and their functional correlates are related to trauma exposure versus a clinical diagnosis of PTSD merits further investigation. For instance, Falconer and colleagues (2008) discovered that the findings they observed with respect to abnormal patterns of brain activation in PTSD patients were not evident in trauma exposed non-PTSD subjects, who did not differ in any of the regions of interest from healthy controls. Secondly, greater attention should be paid to the possible influence of comorbid psychiatric conditions on inhibitory performance in patients with post-traumatic symptoms, particularly when the comorbidities are associated with increased impulsivity. This is indicated by the finding in Carrion et al. (2008) that a history of self-injurious behaviours in their PTSS sample predicted activation of many of the core regions associated

with correct inhibitions in our ALE meta-analysis, including the insula, putamen, and inferior frontal cortex/operculum, all in the right hemisphere.

Nevertheless, despite these caveats, in general these findings indicate that the GNG might be usefully employed to examine trauma-specific deficits. Moreover, the association of serotonin deficiencies with hyperarousal (including anger) are grounds for arguing that this paradigm might be particularly sensitive to the effects of serotonin in individuals who have been exposed to trauma. This argument is supported by our finding that SSRIs are effective in treating PTSD, as well as by the conclusion reached by Eagle and colleagues (2008), in a review of human and animal psychopharmacology research on motor inhibition, that performance on the GNG, as opposed to the stop-signal task, is specifically influenced by levels of serotonin.

In the final component of this dissertation, we argued that the opioid system holds particular promise in explaining the relationship between trauma exposure and affective dysregulation. The possibility that the analgesic effects of endogenous opioids may be involved in down-regulating responses to negative emotions is suggested by the observation that neural circuitry common to both pain and affect regulation, including the anterior insula, rostral ACC, amygdala, ventral striatum (such as the nucleus accumbens), OFC and periaqueductal gray (PAG), are rich in mu-opioid receptors (Bruehl et al., 2009). The consistent observation across studies of a correlation between pain and the expression of anger (anger-out), as reviewed by Bruehl et al. (2009), has implications for the affective sequelae of psychological trauma, given the association of PTSD with poor anger control and lower pain thresholds (Kraus et al., 2009). The observation in our study that opioid administration improved the accuracy of recognising fearful faces in adults with a history of childhood trauma provides indirect evidence that the poor recognition of fear may be due to altered opioid neurotransmission following childhood trauma exposure.

Our finding of a relationship between a person's accuracy in recognising anger and their preparedness to acknowledge negative emotions suggests that non-acceptance of emotional responses might be crucial to the phenomenology of impaired emotional responses in those with a history of childhood abuse and/or neglect. Indeed, the intensity of negative emotions predicted posttraumatic symptoms in victims of childhood interpersonal abuse, but only via mediation through non-acceptance or fear of those emotions (Tull, Jakupcak, McFadden, & Roemer, 2007). Further evidence that the acceptance of negative emotions might be a crucial component of deficits in emotion regulation associated with trauma exposure is provided by the finding of a relationship between PTSD symptoms and anxiety sensitivity, defined as the fear of experiencing anxiety-related physical sensations (Federoff, Taylor, Asmundson, & Koch, 2000; Zahradnik, Stewart, Marshall, Schell, & Jaycox, 2009).

It might have been predicted that trauma history would have increased attentiveness towards threatening stimuli, rather than what appears to be avoidance responses. Indeed, this is what Gibb and colleagues (2009) observed in their study employing a similar paradigm to the one we employed (Gibb, Schofield, & Coles, 2009). Moreover, studies have typically found PTSD in adults to be associated with increased attention to threat (eg. see Weber et al. (2008) for a recent review).

However, it should be noted that the findings of an attentional bias towards threatening stimuli in adults has most consistently been observed with respect to the allocation of attentional resources to trauma-specific sources of threat (Weber, 2008). Additionally, it seems reasonable to speculate that trauma exposure during childhood and adulthood might differ with regards to their consequences for emotion regulation strategies. For instance, there is evidence that physical abuse can result in chronic hypoarousal of the autonomic nervous system in children, with behavioural correlates of emotional numbing and dissociation (Ford, Fraleigh, Albert, & Connor, 2010; Pollak, Vardi, Putzer Bechner, & Curtin,

2005). This would be consistent with the speculative notion that emotional numbing and avoidance behaviour might be an adaptive response in children to abuse by caregivers who are in a relative position of power.

8. CONCLUSION

This dissertation attempted to employ a range of methods to determine the extent to which there is evidence for a relationship between behavioural impulsivity and poor regulation of affect amongst individuals with a history of psychological adversity. We were able to ascertain, via a meta-analysis of randomised controlled pharmacotherapy trials, that there has been very little rigorous testing of the efficacy of serotonergic agents in treating disruptive behavioural disorders in children and adolescents. This, despite indications from the research literature that (a) the poor regulation of anger is a prominent feature of DBDs, (b) that anger may be mediated by insufficient levels of serotonin, and (c) by evidence that other commonly employed agents in treating these disorders, such as lithium and the stimulant, methylphenidate, may achieve their efficacy with respect to the affective aspects of these disorders by means of interactions with the serotonergic system.

In contrast to the treatment literature for paediatric oppositional defiant disorder and conduct disorder, the selective serotonin reuptake inhibitors are regarded as first-line agents in the treatment of PTSD. However, a quantitative synthesis of treatment data from pharmacotherapy trials for PTSD revealed that despite predictions that the SSRIs should be particularly efficacious for hyperarousal and avoidance symptoms, there was little evidence from the RCT evidence base that this is actually the case. This may be a consequence of insufficient temporal resolution of the effects of SSRIs to discriminate between the primary and secondary effects of these agents. Indeed, there is some evidence that an early response of hyperarousal symptoms in general, and anger in particular, to agents that act via serotonergic pathways might predict subsequent improvement on re-experiencing and avoidance/numbing symptoms. Further medication studies in trauma-exposed individuals using direct behavioural measures of affect are required to test this hypothesis.

The GNG paradigm represents one potential method of discerning the effects of changes in affect on impulsive behaviour. The validity of this paradigm in isolating neural circuits regarded as crucial for the inhibition of motor responses was confirmed by means of an ALE meta-analysis of 51 studies employing different versions of the GNG task. This meta-analysis demonstrated that variants of the GNG task that employ affective stimuli are able to elicit responses from limbic regions of the brain that have been implicated as hyperactive in patients with PTSD. Other studies using this paradigm in trauma-exposed populations have observed brain activation patterns consistent with an interpretation of the disruption of inhibitory circuits through sensory hyperarousal. These observations, in combination with preliminary evidence for the selectivity of SSRIs for hyperarousal symptoms, suggests that the affective GNG paradigm might be a suitable candidate for the reliable measurement of the effects of serotonergic agents on emotionally-driven impulsive behaviour in trauma-exposed populations.

Finally, the strategy of identifying neurotransmitter systems that may play a role in the aetiology of trauma-related disturbances in impulse control and affect regulation by studying the effects of pharmacotherapy was implemented in the final component of this dissertation. A placebo-controlled test of the hypothesis that mu-opioids would remediate any hypersensitivity in adults with a history childhood adversity to aversive emotions revealed that acute treatment with buprenorphine normalised deficits in the recognition of fearful faces in the trauma group. In addition, we found evidence that poorer accuracy in identifying angry faces in the trauma group relative to the controls may be partly explained by the tendency not to acknowledge aversive emotions in the traumatised group.

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University of Cape Town