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Shared and disorder-specific task-positive and default mode network dysfunctions during sustained attention in paediatric Attention-Deficit/Hyperactivity Disorder and obsessive/compulsive disorder

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ABSTRACT

Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) and obsessive/compulsive disorder (OCD) share problems with sustained attention, and are proposed to share deficits in switching between default mode and task positive networks. The aim of this study was to investigate shared and disorder-specific brain activation abnormalities during sustained attention in the two disorders. Twenty boys with ADHD, 20 boys with OCD and 20 age-matched healthy controls aged between 12 and 18 years completed a functional magnetic resonance imaging (fMRI) version of a parametrically modulated sustained attention task with a progressively increasing sustained attention load. Performance and brain activation were compared between groups. Only ADHD patients were impaired in performance. Group by sustained attention load interaction effects showed that OCD patients had disorder-specific middle anterior cingulate underactivation relative to controls and ADHD patients, while ADHD patients showed disorder-specific underactivation in left dorsolateral prefrontal cortex/dorsal inferior frontal gyrus (IFG). ADHD and OCD patients shared left insula/ventral IFG underactivation and increased activation in posterior default mode network relative to controls, but had disorder-specific overactivation in anterior default mode regions, in dorsal anterior cingulate for ADHD and in anterior ventromedial prefrontal cortex for OCD. In sum, ADHD and OCD patients showed mostly disorder-specific patterns of brain abnormalities in both task positive salience/ventral attention networks with lateral frontal deficits in ADHD and middle ACC deficits in OCD, as well as in their deactivation patterns in medial frontal DMN regions. The findings suggest that attention performance in the two disorders is underpinned by disorder-specific activation patterns.

1. Introduction

1.1. Attention-Deficit/Hyperactivity Disorder and obsessive-compulsive disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) affects 3–8% of children worldwide and 4% of adults (Biederman et al., 2012), and is defined by age-inappropriate problems with inattention, impulsivity and hyperactivity (American Psychiatric Association, 2013).

Obsessive-compulsive disorder (OCD) has a lifetime risk of 2–3% (Ruscio et al., 2010). The key symptoms are obsessions, defined as recurrent and intrusive thoughts (e.g., on themes of contamination, checking, orderliness and symmetry), and compulsions, i.e. repetitive, ego-dystonic and time-consuming behavioural and mental rituals (e.g., repetitive washing or checking) (American Psychiatric Association, 2013). ADHD and OCD are frequently comorbid in young people and have been shown to share familial and genetic risk factors (Geller et al., 2007; Mathews and Grados, 2011), although the majority of the genetic

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risk is thought to be disorder-specific, rather than shared (Pinto et al., 2016).

1.2. Sustained attention and underlying brain networks

Sustained attention refers to the ability to voluntarily maintain the focus of attention for infrequently occurring critical events (Parasuraman et al., 1998; Warm, 1984). Neurofunctionally, it is dependent on the interplay of four canonical brain networks (Menon, 2011; Metin et al., 2015). First is the "task-positive" central executive network consisting of dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), lateral parietal, and dorsal striato-thalamic regions, which is engaged during tasks requiring the active maintenance of attention toward external stimuli, mediates goal-directed selection of stimuli and responses, and is associated with adaptive performance on sustained attention tasks (Dosenbach et al., 2007; Petersen and Posner, 2012). The task-positive ventral attention network, consisting of IFG and the temporo-parietal junction (TPJ), and the salience network, consisting of anterior insula and middle/dorsal anterior cingulate cortex (mACC/dACC), are involved in detecting behaviourally relevant cues, and engage the central executive network and disengage the default mode network according to perceived environmental demands (Cai et al., 2014; Menon, 2011; Seeley et al., 2007). The "task-negative" default mode network consists of anterior/ventromedial prefrontal cortex (A/VMPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus, and inferior temporal regions which are proposed to mediate internally generated cognition such as mind-wandering and rumination (Buckner et al., 2008). This network is usually deactivated during cognitive tasks (Raichle, 2015; Raichle et al., 2001). Activation in task-positive networks is typically anti-correlated with that in the default mode network, and a failure to adequately disengage default mode network activation is associated with poorer sustained attention performance, presumably due to an increase of self-referential thoughts at the expense of exteroceptive goal-directed attention (Christakou et al., 2013; Christoff et al., 2009; Rubia, in press).

1.3. Sustained attention in ADHD and OCD

Sustained attention has been found to be impaired in ADHD (Huang-Pollock et al., 2012; Losier et al., 1996; Malloy-Diniz et al., 2007; Mowinckel et al., 2015; Rubia et al., 2009b, 2007a; Willcutt et al., 2005) and OCD (Abramovitch et al., 2013; Baykal et al., 2014; Benzina et al., 2016; Bersani et al., 2013; Morein-Zamir et al., 2010; Rajender et al., 2011; Snyder et al., 2015; Trivedi et al., 2008). Both disorders have also been linked to increased spontaneous mind-wandering (Mowlem et al., 2016; Seli et al., 2016, 2015), which is proposed to reflect an imbalance between task-positive and default mode networks (Christakou et al., 2013; Metin et al., 2015), and to underlie poor performance on sustained attention tasks, as attention is focused on internal thoughts, thereby limiting attention resources available for task-relevant processing (Thomson et al., 2015). Moreover, both ADHD and OCD patients self-report impaired executive attention abilities (Armstrong et al., 2011; Benatti et al., 2014; Grassi et al., 2015; Malloy-Diniz et al., 2007; Nandagopal et al., 2011; Sohn et al., 2014).

In ADHD, poor concentration is a symptom of the disorder (American Psychiatric Association, 2013) associated in particular with poor educational and workplace performance (Todd et al., 2002). In OCD, difficulty in sustaining attention toward external goal-relevant stimuli is a plausible neurocognitive mechanism which may underlie difficulties in disengaging from internally generated obsessional thoughts, which are hypothesised to be mediated by the default mode network (Seli et al., 2016; Stern et al., in press). However, the extent to which sustained attention performance is associated with shared and disorder-specific neural dysfunctions in ADHD and OCD is unknown. Shared neural dysfunction during sustained attention would suggest that alterations in sustained attention networks are a transdiagnostic mechanism in ADHD and OCD, while largely distinct neural abnormalities would suggest that disorder-specific neural mechanisms are associated with difficulties in maintaining attentional focus in the two disorders.

1.4. Neuroimaging evidence in ADHD and OCD

ADHD patients show reduced recruitment in task-positive (insula/IFG/DLPFC/striatum/cerebellum) regions and increased default mode (ACC/PCC/precuneus) activation during attention tasks (Christakou et al., 2013; Cubillo et al., 2012; Hart et al., 2013; Metin et al., 2015; Rubia et al., 2009a, 2009d). The IFG, in particular, is a key region in ADHD, which has been shown to be reliably underactive across multiple tasks of cognitive and attention control (Cortese et al., 2012; Hart et al., 2012, 2013; Lei et al., 2015; Rubia, in press). It has been found to be disorder-specific relative to OCD (Rubia et al., 2010a), as confirmed in a meta-analytic comparison of 541 ADHD and 287 OCD patients during inhibitory control tasks (Norman et al., 2016) as well as relative to bipolar disorder (Passarotti et al., 2010a, 2010b) and conduct disorder (Rubia, 2011; Rubia et al., 2010b, 2009c, 2009d) during cognitive control and attention tasks.

Patients with OCD demonstrate abnormalities in task-positive and default mode connectivity at rest (Posner et al., 2017; Stern et al., 2012; Zhu et al., 2016), and deficits in switching between default mode and task-positive networks during cognitive tasks (Cocchi et al., 2012; Stern et al., in press). In particular, increased A/VMPFC activation has been reported in OCD at rest (Menzies et al., 2008; Zhu et al., 2016), during symptom provocation (Brennan et al., 2015; Rotge et al., 2009) and during cognitive tasks (Agam et al., 2014; Brennan et al., 2015; Page et al., 2009; Stern et al., 2011, 2013) suggesting that OCD symptoms may be associated with a failure to adequately regulate activity in this default mode region (Agam et al., 2014; Stern et al., 2012, in press, 2011, 2013). Abnormalities have also been reported in the salience network, which is hyperactive to errors (Stern et al., 2011), emotional stimuli (Berlin et al., 2015), and during symptom provocation (Brennan et al., 2015), but shows decreased negative connectivity with the default mode network at rest (Posner et al., 2017; Stern et al., 2012). Furthermore, functional alterations in central executive network regions such as DLPFC, dorsal striatum and cerebellum have been reported previously in OCD during cognitive tasks (Gu et al., 2008; Kang et al., 2013; Page et al., 2009; Woolley et al., 2008), and structural abnormalities in these regions are found reliably in OCD (Carlisi et al., in press-b; de Wit et al., 2014; Norman et al., 2016). Finally, in our recent comparison of adolescents with autism, adolescents with OCD and age matched healthy controls during sustained attention, patients with OCD showed a disorder-specific pattern of progressively decreasing activation in salience/ventral attention regions including left insula/IFG, as well as progressively increasing activation in default mode region the A/VMPFC with increasing attention load, relative to autism and healthy control groups (Carlisi et al., in press-a).

1.5. Aims and hypotheses of the present study

In this study, we aimed to conduct the very first direct comparison of neurofunctional task-positive and default mode network abnormalities in paediatric ADHD and OCD during sustained attention. For this purpose, we used a parametrically modified sustained attention task with three levels of sustained attention load (Christakou et al., 2013; Murphy et al., 2014; Lim et al., 2016; Carlisi et al., in press-a). We purposely chose a relatively simple sustained attention task that is modelled on a sensorimotor vigilance task in order to probe attention networks in the context of relatively intact or minimally impaired task performance (Christakou et al., 2013; Lim et al., 2016; Murphy et al., 2014; Carlisi et al., in press-a). We hypothesised that both disorders would show reduced activation in task-positive regions, as well as