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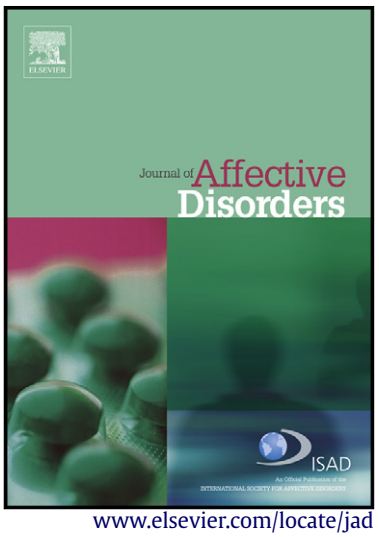

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Frontoparietal Function in Young People with Dysthymic Disorder (DSM-5: Persistent Depressive Disorder) during Spatial Working Memory

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Abstract

Background: Dysthymic disorder (DD) is a depressive disorder characterised by persistent low and/or irritable mood and has been identified as a major risk factor for developing major depressive disorder (MDD). MDD and DD have been associated with executive function difficulties of working memory and attention. Little is known about how executive function networks in the brain are affected in children and adolescents with MDD and even less in DD. This study used fMRI and two spatial working memory paradigms to investigate associated brain function in young people with DD and an age-, gender- and IQ- matched typically developing group.

Methods: Nineteen male patients with DD (mean age 11.2 +/- 1.5 years) diagnosed according to DSM-IV criteria and sixteen typically developing boys (mean age 10.5

+/- 1.1 years) performed a mental rotation and a delay-match to sample (DMTS) task while undergoing fMRI. All participants were medication-naïve at the time of testing

Results: Compared to typically developing young people, the DD group showed less activation in left frontal regions including left ventro- and dorsolateral prefrontal cortices (PFC) during mental rotation. Medial frontal regions including dorsomedial PFC, anterior cingulate cortex and frontal pole also showed relatively reduced activation. During the DMTS task patients showed significantly more activation in the right precuneus and posterior cingulate cortex.

Limitations: This was a cross-sectional study with a small sample limiting the generalizability of the results.

Conclusions: The results complement previous findings in adults with MDD that have shown differential activation of left PFC regions during working memory tasks. Additionally, altered function of cortical midline structures in young patients with DD was identified. This supports findings in children, adolescents and adults with MDD suggesting that the pathophysiology of depressive disorders extends to DD as a risk factor for MDD and exhibits continuity over the lifespan.

Keywords

Working Memory; fMRI; Dysthymic Disorder; Persistent Depressive Disorder; Children; Pediatric

1. Introduction

Dysthymic disorder (DD) in children and adolescents is characterised by persistent sad and/or irritable mood for a period lasting one year or longer (American

Psychiatric Association, 2000). Because DD is associated with mild to moderate depressive symptoms the condition often goes unrecognised and untreated until a major depressive episode occurs. In a ten-year follow-up study of early onset DD (i.e. before the age of 21), 94.2% of participants experienced a major depressive episode at some point in their life (Klein et al., 2000). This suggests that the majority of DD patients are at risk for developing major depressive disorder (MDD) later in life. It also means that a better understanding of the psychosocial and biological factors that put children and adolescents at risk of developing MDD will help create prevention and early intervention strategies and help reduce the burden of MDD later in life.

Depressive disorders in adults have often been linked to cognitive impairments in attention, memory and psychomotor speed (Castaneda et al., 2008; Hammar and Ardal, 2009). In particular, deficits in executive functions, such as response inhibition, working memory, planning and set shifting have been reported (Hammar and Ardal, 2009; Wagner et al., 2011) and are linked to frontal lobe dysfunction (Rogers et al., 2004). Compared to the extensive literature on adult MDD, relatively little research has been conducted into depressive disorders in children and adolescents. Executive function deficits in paediatric depressive disorders are less established and results have been mixed (Cataldo et al., 2005; Emerson et al., 2005; Klimkeit et al., 2011; Korhonen et al., 2002; Kyte et al., 2005; Maalouf et al., 2011; Matthews et al., 2008). Inconsistencies across studies may be explained by differences in medication status, comorbidity patterns and the presence or absence of a major depressive episode at the time of testing. Often studies of children and adolescents with depressive disorders include different diagnoses such as MDD, remitted MDD, or familial risk for developing MDD and DD.

DD may best be considered at the lower end of a depressive spectrum with less severe but more persistent symptoms. The change of label from DD to Persistent

Depressive Disorder in the new DSM-5 (APA, 2013) nosology reflects this dimensional approach. While children with DD manifest fewer symptoms of anhedonia, more oppositional, defiant and disobedient behaviour was also noted compared to those with MDD (Kovacs, 1994). In addition, this study reported lower levels of concentration difficulties. Yet, one study that has looked exclusively at paediatric DD demonstrated a spatial working memory deficit (Franklin et al., 2010) and another study with a predominantly DD sample found deficits in complex attention (Günther et al., 2011) compared to typically developing children. Together this may suggest that attention difficulties in children with DD are only detectable in more complex tasks including working memory tasks.

Attention and spatial working memory share common neural substrates in a frontoparietal network that may be affected in children with DD (Awh and Jonides, 2001). Neuroimaging investigations into adult MDD have revealed dysfunction in frontal regions including medial, orbital, dorsolateral (dlPFC) and ventrolateral prefrontal cortex (vlPFC) as well as the anterior cingulate cortex (ACC) (Koenigs and Grafman, 2009; Mayberg, 1997; Mayberg, 2003; Price and Drevets, 2012). Some of these regions play distinctive roles in working memory with vlPFC thought to reflect maintenance and dlPFC monitoring and manipulation of information (Curtis and D'Esposito, 2003; Wood and Grafman, 2003). The ACC supports a more general function of conflict monitoring (Botvinick et al., 2004) and response selection (Turken and Swick, 1999) that is shared by many tasks of executive function including working memory (Lenartowicz and McIntosh, 2005). Key regions in the working memory network such as the inferior and dorsal frontal regions including dorsal ACC have also been implicated to play an important role in emotion regulation a major deficit of patients with depressive disorders (Ochsner et al., 2002; Ochsner and Gross, 2008; Phan et al., 2005; Wager et al., 2008; Johnstone et al., 2007; Beauregard et al., 2006).

Functional imaging studies of working memory tasks in adults with MDD have reported abnormal frontal activity primarily on the left (Harvey et al., 2005; Matsuo et al., 2007). However, the direction of the activation has been contradictory, with both hypo- and hyperactivation being reported (Walter et al., 2007b). One explanation has been that patients show increased activation in less demanding tasks but reduced activation in more complex tasks (Walter et al., 2007a). It has been suggested that working memory capacity is already reached in the simple task and breaks down in the more complex tasks (Matsuo et al., 2007). Additionally, coupling between dlPFC and medial PFC has been found to function abnormally in patients with MDD (Koenigs and Grafman, 2009). Specifically, hyperactivity of medial PFC at rest has been linked to MDD (Drevets et al., 2008). It is less clear however whether this pattern also plays a key role in paediatric depressive disorders.

Few studies have examined the function of these brain regions in children or adolescents with depressive disorders during tasks of executive function. Halari and colleagues (2009) observed diminished activation of right dlPFC, inferior frontal cortex and ACC in adolescents with MDD during tasks of attention, set-shifting and inhibitory control. To date no fMRI study has examined working memory function in paediatric depressive disorders. Only one study with an at-risk sample has been reported (Mannie et al., 2010). Adolescents aged 16 to 20 years with a familial history of MDD were scanned while performing a verbal n-back task. Hyperactivity in lateral occipital, superior parietal and superior temporal cortices were found. Participants in this sample had no personal history of depressive disorders; hence the results may not be comparable to those with current symptoms and may explain the absence of activation differences in PFC regions.

Typically developing adolescents recruit similar regions during working memory processing to adults but activation patterns appear more diffuse suggesting specialization continues until adulthood (Tau & Peterson, 2010). Also, during

adolescence greater activation of the dlPFC has been observed possibly reflecting greater effort to accomplish successful task performance (Luna, Padmanabhan, & O'Hearn, 2010). Children recruit subcortical areas such as the hippocampus, caudate nucleus and insula to a greater extent during working memory tasks than the frontal cortex (Tau & Peterson, 2010; Finn et al., 2010). Yet, recruitment of frontal brain regions during working memory has been observed as young as eight years of age (Casey et al., 1995).

Given the shared neural basis of attention and spatial working memory as well as evidence for a spatial working memory and complex attention deficit in children with DD this study employed a delay-match to sample (DMTS) and a mental rotation task in order to examine functional neural differences between young people with DD and typically developing children. Both tasks tap into working memory processes. However, they differ in that the DMTS task only requires simple recognition of visual patterns while the rotation task requires manipulation of information during working memory. If cognitive deficits in young people with DD are only apparent at more demanding tasks the mental rotation task may be more sensitive in picking up any differences in underlying brain function. In addition, the tasks may be able to highlight differences in the engagement of different prefrontal regions. The two spatial tasks were also chosen to avoid a potential confound of verbal processing proficiency which has previously been found impaired in children with depressive disorders (Kovacs & Goldston, 1991).

Given the lack of previous fMRI studies investigating working memory in paediatric depressive disorders the study was explorative in nature. However, because of the consistent implication of left dlPFC in adult MDD during working memory, it was hypothesised that patients with DD would show abnormal recruitment of left dlPFC compared to typically developing control participants. No predictions were made with regard to the direction of activation.

2. Method

2.1 Participants

A total of 35 participants took part in the study (age range 8.0 - 13.5 years). Nineteen boys (mean age 11.2 +/- 1.5 years) meeting DSM-IV criteria for DD were recruited through an outpatient assessment clinic at a large metropolitan child psychiatry unit. The main reasons for referral were oppositional defiant behaviour and irritable, sad and/or miserable mood. Diagnosis was defined categorically using parent and child ratings on the Anxiety Disorders Interview Schedule for Children (ADIS-C) (Silverman and Nelles, 1988) and dimensionally using parent ratings on the Child Behavior Checklist (CBCL) (Achenbach, 1978) and child ratings on the Children's Depression Inventory (CDI) (Kovacs, 1992). A fully trained research assistant conducted the interview and diagnosis was corroborated by an experienced child psychiatrist (A.V.). All children were medication-naïve at the time of testing and had a full-scale IQ of above 70 as measured by the Wechsler Intelligence Scale for Children (4th Edition). Fourteen of the DD patients also met diagnostic criteria for Generalised Anxiety Disorder, nine for Separation Anxiety Disorder and six for Social Phobia as assessed with the ADIS-C. In addition, thirteen patients were also rated in the clinical range for Oppositional Defiant Disorder by their parent(s). None of the patients met diagnostic criteria for a current major depressive disorder. Sixteen healthy typically developing boys (mean age 10.5 +/- 1.1 years) were recruited through local schools and matched to the patients on age and IQ. These control participants also completed ratings on all clinical measures to ascertain normal behavioural functioning. None of the children had known other medical, neurological or psychiatric disorders and all were right-handed. All children were from a white Australian background and attended either grade four, five or six of local primary

schools. Socio-economic status was assessed using the Social Adversity Status (SAS) from the demographic screen instrument section from the Parental Account of Childhood Symptoms (PACS) (Taylor et al., 1986). Informed consent was obtained from both a parent and the child, and all procedures were approved by the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne, Australia.

2.2. Procedure

Mental Rotation: Participants performed a mental rotation task slightly modified from an earlier version of the task (Silk et al., 2005; Vance et al., 2007). Mental rotation stimuli consisted of Shepard–Metzler three dimensional cube objects, with target and test stimuli differing by between 45° and 180° rotation. The baseline condition required a simple visual match judgement in which target and one test stimuli were an identical match. Stimuli were presented for 10 s with 1 s inter-stimulus interval grouped into blocks of three trials forming 33 s blocks. Six baseline blocks were alternated with six rotation blocks over a total scan duration of 6 min 36 s. Each trial involved the simultaneous presentation of a single target stimulus above fixation and two-test stimuli below. Participants were required to indicate by button-press which test stimulus matched the target.

Delayed Match to Sample (DMTS): The DMTS paradigm of the Cambridge Neuropsychological Test Automated Battery (CANTAB) was adapted for functional imaging. Stimuli consisted of rectangular shapes divided into four quadrants of differing colour and shape. A target stimulus appeared on screen for two seconds, followed by the presentation of two choice patterns beneath presented for 6s. One choice pattern was identical to the target stimulus. The other differed by colour and shape in three quadrants. A randomly chosen fourth quadrant was held constant in

each trial to discourage memory strategies based on a single quadrant. Subjects were instructed to select the stimulus matching the target. Choice stimuli were presented below either simultaneously with the target (simultaneous condition), immediately after (0s delay condition) or 4s (4s delay condition) after the onset of the target. Conditions were presented in blocks of three, and blocks alternated pseudo-randomly over a total of 6 min and 16 s. The simultaneous and zero-second delay conditions were presented in 24s blocks and four-second delay conditions were presented in 36 s blocks to allow equal response time across conditions. The simultaneous condition served as baseline for data analysis.

2.3. Data acquisition

Data were acquired on a 3T Siemens TIM Trio scanner (Siemens, Erlangen, Germany) at the Royal Children's Hospital, Melbourne. Participants lay supine with their head supported in twelve-channel volume coil. T2*-weighted functional images were acquired using a gradient-echo, echo-planar imaging (EPI) pulse sequence with the following parameters: TR (repetition time) = 2000 ms, TE (echo time) = 30 ms, FA (flip angle) = 90 ^{o}, matrix = 128 x 128, FOV (field of view) = 25 cm. Twenty-eight 3.0 mm transverse slices were taken (in-plane resolution 2.0 x 2.0 mm). The field of view was aligned parallel with the commissural line and included the dorsal-most aspect of the brain. A total of 174 whole-brain volumes were acquired during each task. High resolution T1-weighted structural MRI images were also acquired for each participant (TR = 1900 ms, matrix = 256 x 256, slice thickness = 1.0 mm, in-plane resolution 0.5 x 0.5 mm). Stimuli were displayed using Presentation 10.1 (Neurobehavioral Systems, Albany CA, USA) software, projected onto a 1.6 x 1.2 m screen at the foot of the MRI scanner bed, and viewed by participants via a mirror mounted on the head coil within the MRI scanner.

2.4. fMRI Data Analysis

Whole-brain image preprocessing and statistical analysis were conducted using FEAT-FMRI Expert Analysis Tool part of FSL Software 4.1.4 (fMRIB, Oxford, UK). Preprocessing involved motion correction for each subject using rigid body transformation to remove the effect of subjects' head movements in the x, y, and z axis, and the rotation around these axes during the experiment. Criteria for head motion exclusion was a mean volume-to-volume (relative) displacement greater the acquired voxel size (2mm). Spatial smoothing was conducted using a 5mm full width half maximum (FWHM) isotopic smoothing kernel. Each participant's functional EPI was registered to their own structural T1 image before being spatially normalized to the MNI152 standard template brain (Montreal Neuropsychological Institute, Montreal, Canada). For first level analysis, a general linear model (GLM) was defined for each subject in a block design. In the higher-level analysis, independent sample t-tests are applied to analyse differences between the groups. The threshold of the z statistic was estimated by clusters determined by $z > 2.3$, with family-wise error rate corrected cluster significance of $p < 0.05$.

3. Results

3.1. Behavioural results

Groups did not differ significantly in age, full-scale IQ or SAS but did differ significantly on parent- and self-ratings of depression (see Table 1). For both mental rotation and DMTS tasks, mean response times were recorded (see Table 2). Group differences were assessed using an independent sample t-test. No significant differences between the groups were detected with the exception of accuracy on the

DMTS 4s delay condition in which the DD group were significantly less accurate than typically developing children.

Approximate position of Table 1

Approximate position of Table 2

3.2. *fMRI Results*

Head Motion

During the Rotation task the DD group had a mean absolute displacement of 0.20 ± 0.08mm and relative displacement of 0.22 ± 0.14mm, compared to controls 0.21 ± 0.11mm and 0.18 ± 0.14mm respectively. Similarly during the DMTS task the DD group had mean absolute displacement of 0.30 ± 0.20mm and relative displacement of 0.30 ± 0.20mm, compared to controls 0.41 ± 0.87mm and 0.26 ± 0.28mm respectively. For both Rotation and DMTS tasks, independent-sample t-tests revealed no significant between-group differences in either the absolute or relative mean displacement.

Rotation

Within Group Contrast (see supplementary material for global and local maxima of within group contrasts) presents task-related activation for each group separately:

When contrasting the rotation with the simple match condition controls showed significant activation in bilateral ACC (BA 32), dlPFC (BA 9/46), insula and right caudate. Further activation peaks were found in precuneus (BA 7), right inferior parietal (BA 40) and left superior parietal regions (BA 7). In addition, primary and

secondary visual cortex (BA 17/18/19) and premotor cortex (BA 6) were more active during rotation than simple matching. For the same contrast patients only showed significant activation in right fusiform gyrus (BA 19/ 37), precuneus (BA 7) and the supplementary motor area (SMA) (BA 6).

Between Group Analysis:

Compared to typically developing children, young people with DD showed less activation in left frontal regions including left ventrolateral (BA 45/47) and dlPFC (BA 46) during mental rotation. Medial frontal regions including left rostral anterior cingulate cortex (BA32) and frontal pole (BA10) as well as dorsomedial PFC (BA 8/ 9) including a cluster of dorsal ACC (BA32) also showed relatively less activation. No regions showed significantly greater activation in patients compared to controls. Table 3 lists global and local maxima for the between group contrast (also see Figure 1).

DMTS

Within group contrast (see supplementary material for global and local maxima of within group contrasts):

When contrasting the 0s delay with the simultaneous condition only patients showed significant activation in visual processing areas (BA 18/19). No regions of significant activation were found for controls.

For the 4s delay minus simultaneous condition controls showed significant activation in left claustrum/insula and inferior frontal gyrus (BA 45/46). Patients showed

significant activation in medial frontal clusters including ACC (BA 32) and SMA (BA 6).

Finally, contrasting 4s with 0s delay conditions revealed activations in left insula, inferior frontal gyrus (BA 45) as well as SMA (BA 6) in controls and right precuneus (BA 7) as well as left inferior parietal (BA 40) in patients.

Between group contrast:

No significant group differences were found for 0s (0s > sim) and 4s (4s > sim) delay conditions. However, a significant group difference emerged for the 4s > 0s contrast with patients showing significantly greater activation in right posterior cingulate (PCC) (BA 31) and precuneus (BA 7) extending into superior parietal lobe. (see Table 3 for global and local maxima for this comparison; Figure 1).

Approximate position of Table 3

Approximate position of Figure 1

Correlations with symptom severity

To assess a potential relationship between the clinical measures and observed brain activation changes we used individual parent ratings of the anxious/depressed and attention problems scales of the CBCL and the self-ratings of the CDI and correlated those with each individual's z-score of the four peak clusters observed during the rotation task and the one cluster during the DMTS task using Pearson product-moment correlation coefficient. Ratings on the attention problems and anxious/depressed scales of the CBCL correlated negatively with individual z-scores in dlPFC (attention: $r = -.409$; $p < .05$) (anx/dep: $r = -.408$, $p < .05$) and vlPFC

(attention: r = -.342; p < .05) (anx/dep: r=-.496, p < .01) during rotation; higher parent ratings of anxious/depressed and inattention symptoms were associated with lower activation in dlPFC and vlPFC. In addition, scores on the attention problems scale correlated positively with individual z-scores in PCC/precuneus during DMTS (r = .502, p < .01) indicating that greater parent-rated symptoms of inattention are related to greater activation in this region. The correlations were significant for the whole sample but failed to reach significance when examining the clinical group only. No significant correlation was found between self-ratings of depression and individual z-scores in any of the clusters.

4. Discussion

This study employed two different types of working memory paradigms relying on spatial rather than verbal processing to investigate underlying function in a frontoparietal network in young people with a diagnosis of DD. It was hypothesised that young people with DD would show abnormal recruitment of the left dlPFC during working memory. The hypothesis was supported by the results of the mental rotation task but not the DMTS task. This is likely due to the task demands, as the rotation task requires manipulation of information to a greater extent than the DMTS task. In addition, patients showed less activation in regions of left vlPFC but also in dmPFC regions (BA 9) including dorsal ACC (BA 32) and the rostral ACC/frontal pole (BA 32/10) compared to typically developing participants. These regions all form part of a working memory network (Braver et al., 1997; Bunge and Wright, 2007; Ciesielski et al., 2006; O'Hare et al., 2008; Rottschy et al., 2012) that has previously been identified in patients with MDD to function abnormally (Bench et al., 1993; Harvey et al., 2005; Matsuo et al., 2007; Vasic et al., 2009; Walter et al., 2007b). In contrast,

during the DMTS task patients showed increased activation of right posterior medial regions including the precuneus (BA7) and the PCC (BA31).

The results of the mental rotation task are concordant with several studies in adults with MDD that have reported altered activation of primarily left dlPFC (Walter et al., 2007b). While the present study found reduced activation of left PFC, others have reported hyperactivation during working memory (Harvey et al., 2005; Matsuo et al., 2007; Walter et al., 2007b). Hyperactivation of dlPFC in adult patients with MDD has been suggested to reflect a compensatory mechanism to maintain task performance (Harvey et al., 2005; Walsh et al., 2007; Walter et al., 2007b). This is evident particularly when analysing correct trials in an event-related design only (Walter et al., 2007b). In the current study patients did not differ from typically developing participants in task performance except for their accuracy on the 4s delay in the DMTS task in which patients were less accurate. However, here, a block design was employed in which it is difficult to separate the blood oxygenation level dependent signal to correct and incorrect responses. Yet, the present results are consistent with a study in adolescents with MDD that found reduced activation of dlPFC in the absence of task performance differences using an event-related design (Halari et al., 2009). Absence of group differences in task performance also reflects the mixed results of neuropsychological investigations of working memory in children with depressive disorders (Franklin et al., 2010; Klimkeit et al., 2011; Korhonen et al., 2002; Matthews et al. 2008).

This was a paediatric sample and thus predictions made about hyper- and hypoactivations in adults may not hold true for younger populations. Another possibility is that hypofunction in children and adolescents with DD may reflect a developmental difference similar to observations in children with attention-deficit/hyperactivity disorder that have linked PFC hypofunction to a delay in structural maturation (Rubia et al., 1999; Shaw et al., 2006). For childhood DD to be

diagnosed, symptoms must be present for a period of at least twelve months. Persistent sad and/or irritable mood may delay PFC maturation, or, conversely negative mood may be a result of delayed PFC development. Longitudinal studies would be necessary to test either hypothesis.

The present results are compatible with other studies in children and adolescents with depressive symptoms. Halari et al. (2009) also observed reduced activation in ventrolateral, dorsolateral and anterior cingulate frontal regions in adolescents with MDD albeit employing tasks of attention, response inhibition and set-shifting. However, they reported right lateralised dysfunction in these regions. This may be related to task demands as they employed paradigms that are subserved by more right lateralised networks (Halari et al., 2009; Rubia et al., 2007). Yet, working memory tasks have more frequently been associated with altered activation of left PFC regions in MDD (Walter et al., 2007b). Left dlPFC activation is related to improvement in depressive symptoms after repetitive transcranical magnetic stimulation (Pascual-Leone et al., 1996); it has been linked to support emotion regulation (Johnstone et al., 2007) and during working memory it has been shown to correlate with depressed mood (Bench et al., 1993) in adults. Although it has been suggested that left-sided functional abnormalities may be considered a trait marker of MDD (Kerestes et al., 2012) it is possible that laterality differences (as observed during fMRI tasks) simply reflect task differences (Halari et al., 2009). For example, during a Stroop interference task depressive symptoms were positively correlated with activation in left dlPFC and negatively with activation in right dlPFC in adolescents (Killgore et al., 2007) suggesting that both hemispheres may contribute to cognitive deficits in people with depressive symptomatology.

Hypoactivity of rostral ACC in depression has been linked to difficulties in controlling working memory contents as well as disengaging from irrelevant information (Foland-Ross and Gotlib, 2012). This cluster also extended into the frontal pole (BA10), which

has previously been implicated in the maintenance and rehearsal of spatial information (Braver et al., 2001; Owen et al., 1996). Furthermore, it has been proposed that rostral PFC plays a key role in the selection between incoming perceptual information, as compared to self-generated information (Burgess et al., 2007). This is concordant with the task demands of the mental rotation in which attention is required to shift from the stimulus oriented visual input to the self-generated, stimulus independent mental rotation. Thus, greater activation in controls as observed in the current study, may reflect more efficient cognitive processing. Decreased regional cerebral blood flow in rostral medial regions has previously been associated with more general cognitive deficits (Bench et al., 1993) and reduced functional connectivity of these regions in patients with MDD has also been reported (Vasic et al., 2009) during working memory.

Those regions exhibiting less activation in young people with DD including vlPFC, dlPFC, dmPFC and dorsal ACC support emotion regulation in healthy adults using a reappraisal strategy (Ochsner et al., 2002; Ochsner and Gross, 2008; Phan et al., 2005; Wager et al., 2008). Although to date no fMRI study has employed a reappraisal strategy in children or adolescents with depressive disorders, a recent fMRI study in children with a history of preschool onset depression showed reduced activation in frontal, and increased activation in limbic areas during negative mood induction compared to typically developing children (Pagliaccio et al., 2012). Altered activation of frontal regions including those identified in the current study, may account for both working memory and emotion regulation deficits in patients with depressive symptoms. This is also reflected in the negative correlation between activation in vlPFC and dlPFC and parent ratings of both, anxious/depressed symptoms as well as symptoms of inattention observed here, highlighting the possible role of these regions in supporting both functions.

Greater activation of right PCC and precuneus during the 4s delay in the DMTS task was observed in the DD compared to the typically developing group. A similar region was also identified to be less active in adolescents with MDD during a Simon task (Halari et al., 2009). The precuneus is involved in a variety of processes including visuo-spatial imagery, episodic memory retrieval, self-processing and consciousness (Cavanna and Trimble, 2006). In addition, activation in this region has been found to depend on working memory load (Jahn et al., 2012; O'Hare et al., 2008; Stollstorff et al., 2010).

Precuneus and PCC belong to cortical midline structures that together with medial PFC have been implicated in the pathophysiology of MDD (Grimm et al., 2009; Lemogne et al., 2009). These structures are also associated with the default mode network (DMN), a network made up of functionally connected regions that are more active during periods of rest and cease activation during periods of increased cognitive demands (Raichle et al., 2001). In adult patients with MDD these medial portions have been reported overactive at rest and associated with self-reflection and negative affect (Johnson et al., 2009; Lemogne et al., 2011; Lemogne et al., 2009). In the current study greater activation in this posterior region correlated with higher parent ratings of symptoms of inattention for the whole sample. Greater self-directed thought may hinder the deactivation of this region during cognitively demanding tasks and thus contribute to greater attention difficulties (Johnson et al., 2006). The group difference became apparent when contrasting the lower load with the higher load condition but not with baseline. Increased activation in patients in this region during the higher load together with a difference in accuracy for the high load condition may reflect a difficulty in suppressing activity in this region and switching to an executive network. This may not be necessary for lower load conditions that are cognitively less demanding.

There are some limitations of the present study: First, the sample was rather small. However, compared to other studies the age range was kept comparably narrow and all the DD patients were medication-naive. This was an all-male sample and although the prevalence of DD in children is similar for boys and girls (Rutter, 1986), throughout adolescence girls are more likely to be diagnosed with a depressive disorder consistent with the greater prevalence of MDD in adult women (Weissman, 1977). The results, therefore, may have restricted external validity. We found significant correlations between clinical measures and activation changes in the clusters identified in the between group contrasts for the whole sample but these failed to reach significance when examining the clinical group only. Therefore, these observed correlations should be interpreted cautiously. This was a cross sectional study; as many patients with DD go on to develop MDD, longitudinal studies are needed to determine whether structural and functional brain changes in DD can predict the onset of MDD. It should also be noted that DD in children and adolescents may be diagnosed on the basis of chronic irritability and/or sadness. There may be considerable difference between those that exhibit primarily irritable mood and those that present with sadness. In light of the recent inclusion of Disruptive Mood Dysregulation Disorder (DMDD) in DSM5 (APA, 2013) it may be possible that some children and adolescents who have received a diagnosis of DD in the past may be better accounted for by DMDD. Further research is needed to clarify whether chronic irritability and/or chronic sadness equally predispose individuals to develop MDD and which factors mediate this relationship.

To the best of our knowledge this is the first fMRI study that has looked at brain function associated with working memory processes in a group of boys with dysthymia. We found differential recruitment of brain regions in a frontoparietal network when comparing typically developing children and those with a diagnosis of DD. Largely in accord with results in adult patients with MDD, the current study found

reduced activation across lateral frontal regions. Despite using working memory task to assess executive function, aberrant function in cortical midline structures, often identified during resting-state studies, were also found here. Chronic negative mood may impact this network over time so that a major depressive episode develops. Taken together the results of the current study suggest that the pathophysiology of DD in children resembles that of adult patients with MDD suggesting continuity across the lifespan. It remains to be determined which functional changes are associated with the onset of a major depressive episode.

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Contributors

RC, TS and AV designed the study and wrote the protocol. TS carried out the recruitment of participants and collected the data. JC conducted the statistical analysis. VV conducted a literature review and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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Tables

Table 1: Demographic and clinical information

	DD		TDC			
	M.	**S.D.**	**M.**	**S.D.**	**t (df)**	**p < .05**
Age	11.2	1.5	10.5	1.1	1.536 (33)	n.s.
Full Scale IQ[†]	95.6	13.3	103.5	10.9	-1.807 (32)	n.s.
Social Adversity Status (SAS) [††]	7.4	1.7	7.0	1.2	1.69 (31)	n.s.
CBCL – Anxious/ Depressed Scale Parent Rating[†]	68.3	9.6	53.7	5.3	5.626 (29.1)[*]	< .001
CDI self report[†]	53.6	12.8	42.7	4.6	3.549 (23.6)[*]	< .002

[*]*Equal variance not assumed*

[†] Data from one TDC was not available

[††] Data from two TDC was not available

Table 2: fMRI task performance of DD patients and controls

	DD		TDC			
	M.	**S.D.**	**M.**	**S.D.**	**t (df)**	**p < .05**
Rotation Task †						
Accuracy						
Simple Matching	92.7	11.2	92.1	13.2	.145 (28)	n.s.
Rotation	75.3	10.9	77.8	15.1	-.510 (28)	n.s.
Reaction Time						
Simple Matching	1707	547	1637	458	.380 (28)	n.s.
Rotation	2306	507	2186	560	.615 (28)	n.s.
DMTS††						
Accuracy						
Simultaneous	92.2	10.0	97.1	5.0	.105 (30)	n.s.
0s delay	87.0	14.6	95.2	8.5	-1.808 (26.2)*	n.s.
4s delay	77.8	18.5	88.1	9.1	-2.066 (25.9)*	.049
Reaction Time						
Simultaneous	1309	311	1298	366	.095 (30)	n.s.
0s delay	1326	336	1228	294	.869 (30)	n.s.
4s delay	1552	416	1530	254	.190 (28.6)*	n.s.

Reaction times are given in ms, accuracy in percent correct.

**Equal variance not assumed*

† Data from 16 patients and 14 controls

†† Data from 18 patients and 14 controls

Table 3: Regions of significant difference between patients (n = 19) and controls (n = 16). Z > 2.3 (corrected) cluster threshold p < 0.05

Region	Left/Right	BA	Coordinates			Number of Voxels	Z Score
			x	y	z		
Rotation > Simple Matching							
Control > DD							
Inferior Frontal Gyrus	**L**	**47**	**-40**	**18**	**-8**	**510**	**4.01**
Inferior Frontal Gyrus	L	47	-36	32	-10		3.37
Inferior Frontal Gyrus	L	47	-34	20	-14		3.36
Inferior Frontal Gyrus	L	47	-36	28	-8		3.33
Middle Frontal Gyrus	L	47	-42	40	-12		3.14
Inferior Frontal Gyrus	L	47	-52	30	-6		3.05
Middle Frontal Gyrus	**L**	**46**	**-52**	**30**	**20**	**475**	**4.14**
Middle Frontal Gyrus	L	46	-48	30	20		3.73
Middle Frontal Gyrus	L	46	-48	26	8		3.54
Middle Frontal Gyrus	L	45	-48	34	10		3.26
Middle Frontal Gyrus	L	45	-52	20	14		3.19
Middle Frontal Gyrus	L	45	-48	20	14		3.18
Anterior Cingulate	**L**	**32**	**-20**	**48**	**2**	**428**	**3.29**
Anterior Cingulate	L	32	-22	44	0		3.27
Superior Frontal Gyrus	L	10	-30	64	10		3.22
Superior Frontal Gyrus	L	10	-24	38	-8		3.22
Superior Frontal Gyrus	L	10	-26	58	-10		3.17
Anterior Cingulate	L	32	-22	40	-4		3.11
Medial Frontal Gyrus	**L**	**32**	**-6**	**38**	**28**	**420**	**3.65**
Superior Frontal Gyrus	L	9	-4	60	22		3.42
Medial Frontal Gyrus	L	9	-2	42	28		3.26
Medial Frontal Gyrus	R	9	2	52	28		3.16
Superior Frontal Gyrus	L	8	-16	54	36		3.12
Medial Frontal Gyrus	L	9	-4	60	30		3.12
DMTS 4s delay > 0s delay							
DD > Control							
Posterior Cingulate	**R**	**31**	**10**	**-56**	**26**	**1256**	**3.79**
Precuneus	R	7	22	-58	54		3.64
Cuneus	R	7	8	-70	36		3.63
Precuneus	R	7	10	-62	34		3.59
Precuneus	R	31	16	-58	22		3.50
Superior Parietal Lobe	R	7	8	-66	60		3.41

L = left, R = right; BA= Brodmann Area; Coordinates are in MNI space.

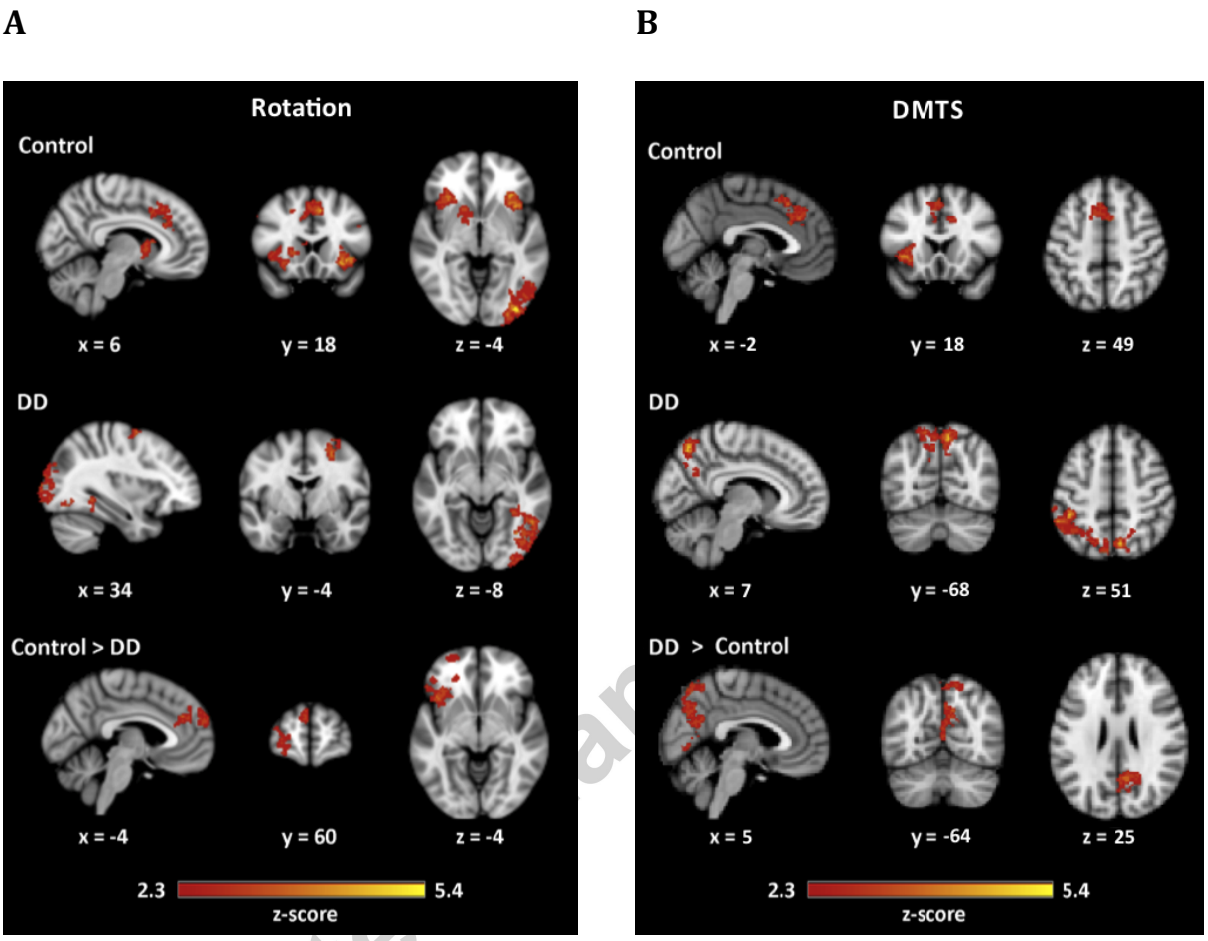

Figure 1: Within and between-group differences in BOLD response during rotation (A) and DMTS (B). Sagittal, coronal and axial images depicting statistical activation maps showing regions of significant activation in control and DD groups separately; and regions showing significantly greater activation in the control group compared with the DD group during mental rotation (A) as well as regions showing significantly greater activation in the DD group compared with the control group during the DMTS task (B). (Coordinates are in MNI space)