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Specific functional connectivity alterations of the dorsal striatum in young people with depression

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ABSTRACT

Background: Altered basal ganglia function has been implicated in the pathophysiology of youth Major Depressive Disorder (MDD). Studies have generally focused on characterizing abnormalities in ventral "affective" corticostriatal loops supporting emotional processes. Recent evidence however, has implicated alterations in functional connectivity of dorsal "cognitive" corticostriatal loops in youth MDD. The contribution of dorsal versus ventral corticostriatal alterations to the pathophysiology of youth MDD remains unclear.
Methods: Twenty-one medication-free patients with moderate-to-severe MDD between the ages of 15 and 24 years old were matched with 21 healthy control participants. Using resting-state functional connectivity magnetic resonance imaging we systematically investigated connectivity of eight dorsal and ventral subdivisions of the striatum. Voxelwise statistical maps of each subregion's connectivity with other brain areas were compared between the depressed and control groups.
Results: Depressed youths showed alterations in functional connectivity that were confined to the dorsal corticostriatal circuit. Compared to controls, depressed patients showed increased connectivity between the dorsal caudate nucleus and ventrolateral prefrontal cortex bilaterally. Increased depression severity correlated with the magnitude of dorsal caudate connectivity with the right dorsolateral prefrontal cortex. There were no significant between-group differences in connectivity of ventral striatal regions.
Conclusions: The results provide evidence that alterations in corticostriatal connectivity are evident at the early stages of the illness and are not a result of antidepressant treatment. Increased connectivity between the dorsal caudate, which is usually associated with cognitive processes, and the more affectively related ventrolateral prefrontal cortex may reflect a compensatory mechanism for dysfunctional cognitive-emotional processing in youth depression.

1. Introduction

Molecular, structural and functional alterations of the basal ganglia are consistently described pathophysiological features of Major Depressive Disorder (MDD) and remain central to current neurobiological models (Price and Drevets, 2010, 2012). Neuroimaging studies have reported reduced caudate and putamen volumes in MDD patients (Bora et al., 2012; Krishnan et al., 1992; Matsuo et al., 2008) as well as reduced activation of basal ganglia regions during reward based learning and stimulus provocation (Pizzagalli et al., 2009; Smoski et al., 2009; Steele et al., 2007; Stoy et al., 2012). Regarding the latter, functional imaging studies primarily implicate alterations of ventral striatal–prefrontal circuitry as underlying core symptoms of the disorder including low mood, anhedonia and psychomotor retardation (Price and Drevets, 2010, 2012). These findings have been interpreted in line with the classical neuroanatomical schema of topologically organized ventral ("affective") versus dorsal ("cognitive") corticostriatal circuits (Alexander et al., 1986; Haber, 2003; Postuma and Dagher, 2006).

As highlighted in a recent review of functional magnetic resonance imaging (fMRI) studies (Kerestes et al., 2014), there is an emerging and specific research focus on the neurobiological correlates of adolescent and young adulthood-onset depression; the developmental period that

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coincides with the peak age of onset of the disorder (Blazer et al., 1994). Task-based fMRI studies of such populations suggest that there may be especially pronounced changes in ventral striatal function during the early stages of the disorder (Chantiluke et al., 2012; Forbes et al., 2006; Forbes et al., 2009; Shad et al., 2011). Specifically, young depressed patients have demonstrated blunted ventral caudate/nucleus accumbens and putamen activation in the context of reward-based learning together with predominantly increased activation of ventral medial prefrontal, anterior cingulate and orbitofrontal cortical regions — all major components of the so-called "ventral-affective" corticostriatal circuit. Pre-treatment ventral striatal and medial prefrontal cortex activation have been found to predict treatment response to psychotherapy and medication in this population (Forbes et al., 2010). Taken together these studies imply system-wide disturbances in the integrated function ("functional connectivity") of ventral corticostriatal regions in youth onset depression, although few studies to date have confirmed this notion directly.

Resting-state fMRI has emerged over the past decade as a powerful tool for examining the large-scale organization and functional connectivity of brain networks in healthy and clinical populations (Fornito and Bullmore, 2010). It has been successfully used to map brain corticostriatal circuits in vivo, providing clear and compelling evidence for the existence of functionally organized dorsal and ventral circuits as well as specific alterations across diverse neuropsychiatric disorders including obsessive–compulsive disorder (Harrison et al., 2009; Harrison et al., 2013), psychosis (Dandash et al., 2014), autism (Di Martino et al., 2011) and depression (Furman et al., 2011). Perhaps surprisingly, evidence has emerged in support of primary functional connectivity alterations involving dorsal as opposed to ventral corticostriatal circuits in adults (Furman et al., 2011) and young (Gabbay et al., 2013) depressed populations. Specifically, Furman and colleagues (2011) reported decreased functional connectivity between the ventral striatum and subgenual anterior cingulate cortex in adult depressed patients, but increased connectivity between the dorsal caudate and dorsolateral prefrontal cortex. By contrast, Gabbay and colleagues (2013) reported increased connectivity between dorsal and ventral striatal regions and the dorsomedial prefrontal cortex in medication-free adolescents (12–19 years) with depression. Collectively, these findings challenge the notion of ventral regions being the primary site of basal ganglia alterations in MDD (Cullen et al., 2009; Davey et al., 2012a; Jiao et al., 2011; Shad et al., 2011; Zhu et al., 2012). However, considering the non-overlap of findings between these two existing studies, and the inconsistent evidence for the nature of striatal connectivity abnormalities in young depressed patients, further examination appears warranted.

The aim of the current study was therefore to systematically examine corticostriatal network alterations in a well characterized sample of young people with moderate-to-severe MDD. Clinically milder cases were excluded from this analysis as we suspect that the broader range of illness severity represented in past studies may have contributed to the inconsistency of results. To achieve a more homogenous sample, all patients were medication-free at the time of the imaging assessment similar to Gabbay et al. (2013), but distinct to Furman et al. (2011) who examined medicated patients. As indicated above, our primary intention was to address the nature of dorsal versus ventral corticostriatal alterations and the prevailing hypothesis that depression is primarily associated with changes in ventral-affective corticostriatal circuits.

2. Methods and materials

2.1. Participants

Twenty-one depressed patients (mean age 19.3, S.D. ±2.5) and 21 age, gender, education and estimated IQ-matched healthy subjects (mean age 19.2, S.D. ±2.3) were recruited from an ongoing larger study (Table 1). Each participant's MRI data included here satisfied our imaging quality control criteria (see below). Patients were recruited from three specialized youth mental health clinics in Melbourne, Australia. All patients were between the age of 15 and 24 years old, in accordance with the youth focus of these mental health services. Patients had a primary diagnosis of Major Depressive Disorder determined by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Exclusion criteria included current or past diagnosis of a psychotic disorder, bipolar disorder, substance dependence disorder, pervasive developmental disorder or intellectual disability. Depression severity was assessed with the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), where a score ≥20 was required for study inclusion (see Supplementary Table 1 for further information). Healthy subjects were recruited through primarily online advertisements and were confirmed to be without current or past diagnosis of an Axis I psychiatric or neurological disorder. Participants were excluded if they were being treated with psychoactive medication or were pregnant, which was confirmed with a urine pregnancy test. All participants (and their parents if <18 years of age) provided written informed consent to complete this study after a complete description of its protocol, which was approved by the Melbourne Health Human Research Ethics Committee.

2.2. Image acquisition

A 3T Signa Excite system (General Electric) equipped with an 8-channel phased-array head coil was used in combination with ASSET parallel imaging (Sunshine Hospital, Western Health, Melbourne). The functional sequence consisted of a Single shot gradient recalled EPI sequence with a parallel imaging ("ASSET") in the steady state (repetition time, 2000 ms; echo time, 35 ms; and pulse angle, 90°) in a 23-cm field of view, with a 64 × 64-pixel matrix and a slice thickness of 3.5 mm (no gap). 36 interleaved slices were acquired parallel to the anterior–posterior commissure line with a 20° anterior tilt to achieve more optimal coverage of ventral brain regions. The total sequence time was 8 min, corresponding to 240 whole brain echo-planar imaging volumes. For this sequence, participants were instructed to simply relax, stay awake and to lie still without moving, while keeping their eyes closed throughout. A high-resolution T1-weighted anatomical image was also acquired for each subject to assist with functional time-series

Table 1
Participant demographics and clinical variables.

	MDD (n = 21)	HC (n = 21)	Statistics	p value (two-tailed)
Age (years) (S.D.)	19.3 (2.5)	19.2 (2.3)	$t(40) = 0.1$	0.9
Female, % (n)	52 (11)	52 (11)	$\chi^2(1) = 1.0$	1
Education, mean years (S.D.)	12.1 (1.9)	13 (1.6)	$t(40) = 1.5$	0.4
WTAR, mean (S.D.)	104.7 (8.2)	107.8 (7.5)	$t(40) = 1.2$	0.6
MADRS score, mean (S.D.)	33.7	–		
First episode of depression, % (n)	33 (7)	–		
Median length of episode (weeks)	20	–		
Co-morbid anxiety disorder, % (n)	71 (15)	–		

MDD, Major Depressive Disorder; HC, healthy controls; WTAR, Wechsler Test of Adult Reading; MADRS, Montgomery–Åsberg Depression Rating Scale; S.D., standard deviation.