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Research report

Fronto-striatal correlates of impaired implicit sequence learning in major depression: An fMRI study

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ABSTRACT

Background: Neural network models of major depression (MD) suggest that the striatum is involved in the pathophysiology and is linked to key cognitive and clinical features. However, functional imaging studies have largely assessed the prefrontal cortex and have utilised emotional paradigms. This study sought to probe the integrity of fronto-striatal circuits using functional magnetic resonance imaging (fMRI) in conjunction with a theoretically-driven motor sequencing implicit learning (IL) task.
Methods: Nineteen patients with MD (mean age = 56.1 years, sd = 9.8) and 20 control participants (mean age = 50.6 years, sd = 11.9) participated. A blocked fMRI paradigm was used in association with a motor sequencing task which included an IL and random sequence (baseline) condition. Although the study was hypothesis driven, within and between groups whole-brain analysis was used to examine fMRI patterns in the IL compared to BL condition.
Results: While both groups activated the striatum, there was no significant difference between patients and controls in striatal activation. Instead, control subjects showed significantly greater activity in the middle frontal gyrus whereas the patients exhibited greater activity in the superior temporal gyrus and cerebellum.
Limitations: Most patients were receiving antidepressant medication when assessed. An event-related fMRI design would have enabled more fine-grained temporal analysis of IL related activation.
Conclusions: IL deficits in MD are not due primarily to striatal dysfunction. IL performance may depend on more specific sub-components of the striatum or a more distributed neural network involving frontal, temporal and cerebellar regions.

1. Introduction

Aetiological theories of major depression (MD) increasingly emphasise dysregulation of both discrete, as well as functionally integrated neural networks. Indeed, models highlight the critical role of structural, functional and neurotransmitter abnormalities in fronto-subcortical pathways and are beginning to incorporate the dynamic interplay of stress, neurotrophins, genetic vulnerabilities, medical and immunological risks factors and glial cells (Belmaker and Agam, 2008; Drevets et al., 2008; Hickie et al., 2001; Hickie et al., 1999; Hickie et al., 2007b; Mayberg, 2003). While limbic circuitry dysregulation appears to be prominent (Hickie et al., 2005; Mayberg, 2003), subcortical regions have also been of interest, particularly the striatum. Using structural magnetic resonance imaging (MRI), studies have reported

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reductions in the size of the striatum and (Lorenzetti et al., 2009; Steffens and Krishnan, 1998) of significance, have demonstrated links with cognitive functioning (Naismith et al., 2002); a key determinant of treatment response (Hickie et al., 1996), longitudinal decline (Steffens et al., 2009) and disability (Naismith et al., 2007). However, while structural neuroimaging studies have been informative for determining the critical role of the striatum in MD and its associated features, they are unable to probe broader network abnormalities. In this regard, functional neuroimaging methods allow for a more holistic and concurrent examination of the cortical, subcortical and limbic circuitry (Mayberg, 2003).

Functional neuroimaging studies focusing on regional cerebral blood flow changes and metabolism have generally corroborated fronto-subcortical models of MD. Using single photon emission tomography, we have previously demonstrated that striatal blood flow abnormalities are related to psychomotor change in MD (Hickie et al., 1999; Hickie et al., 2007a). Consideration of the role of the striatum is important not only because of literature demonstrating its relationship with key clinical and cognitive features (Hickie et al., 2005; Naismith et al., 2002), but also since human and animal research highlights the critical role of the dorsal striatum in cognitive functions previously thought to depend solely on regions of the prefrontal cortex (PFC) including motivational behaviour, decision-making and choice [see review by (Balleine and O'Doherty, 2010)]. Indeed, these are prominent clinical features of MD, suggesting the need to consider the fronto-striatal circuitry more broadly. Unfortunately, to-date, studies utilising functional MRI (fMRI; eliciting patterns of blood oxygen level dependent (BOLD) activation) have largely focused on the PFC (Ebmeier et al., 2006) and have not attempted to specifically probe the striatum using theoretically-driven cognitive tasks.

A potentially suitable cognitive paradigm for probing these circuits is the motor sequencing implicit learning (IL) task. IL refers to a type of learning that occurs independently of attention and conscious control, and is thus less sensitive to the confounds of poor effort, postulated to be a confounding factor in many cognitive paradigms used in MD (Elliott, 1998; Naismith et al., 2006). IL is assessed through improvements in performance without conscious awareness of learned patterns (Elliott, 1998). Thus, for motor sequencing tasks, IL is demonstrated by an improvement in reaction time while completing fixed sequences compared to random sequences. The neural correlates of IL have been investigated by several fMRI studies, and the striatum appears to be activated during this form of learning (Rauch et al., 1997c; Reiss et al., 2005). Given that the striatum is linked to cognition and motor speed in MD (Naismith et al., 2002), IL tasks would be ideally suited as neurobehavioural probes of striatal functioning (Naismith et al., 2006).

Few investigators have specifically sought to probe concurrently the fronto-striatal circuitry in MD. One study conducted by Aizenstein et al. (2005) did utilise an IL task in eleven elderly patients with depression and twelve control subjects. This study reported that there was no difference between groups in striatal activation. However, the groups did differ in BOLD activation during an explicit learning task, where increased striatal activation and decreased PFC activation was evident. In contrast, we have previously reported that patients with MD learn implicitly at only half the rate of control subjects (Naismith et al., 2006) and performance was associated with poorer performance on neuropsychological tests that commonly recruit frontal–subcortical circuitry. In this study, we therefore aimed to examine the neural correlates of IL in patients with MD using fMRI. We hypothesised that patients with MD would demonstrate altered levels of BOLD activation in functionally relevant striatal and frontal regions in comparison with age-matched control subjects.

2. Methods

2.1. Participants

Nineteen patients with a lifetime history of unipolar depression and meeting DSM-IV criteria for current MD were recruited from outpatient services of South Eastern Sydney (mean age = 56.1 years, sd = 9.8; 74% female). Twenty healthy control participants (mean age = 50.6 years, sd = 11.9; 70% female) were recruited via media advert and were screened by a psychologist for any history of psychiatric and neurological disorders. Participants were excluded from the study if they had a history of alcohol dependence or abuse or any major medical or neurological illness including prior stroke, head injury which resulted in a loss of consciousness, electroconvulsive therapy within the last three months (for patients) or suspected dementia.

2.2. Clinical assessments

As described previously (Naismith et al., 2006), a psychologist administered the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the National Adult Reading Test (NART) (Nelson and Willison, 1991) to all participants as part of a broader neuropsychological test battery. Additionally, patients were assessed by a psychiatrist who confirmed DSM-IV MD diagnosis, rated depression severity on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960) and recorded medication details.

2.3. Experimental paradigm

All participants were scanned whilst performing a block-designed IL task (Rauch et al., 1997b). The paradigm comprised a four-choice reaction time task where participants were required to respond to a stimulus (circle) on the screen by pressing the corresponding button on a four-button response box. Fig. 1 demonstrates the blocked design. During the baseline (B) condition, 24 stimuli (circles) were presented at pseudo-random locations in one of four locations with the constraint that no two consecutive stimuli occurred at the same location. In the IL condition, stimuli were presented in a fixed 12-item sequence (e.g., location 1–2–1–4–2–3–4–1–3–2–4–3) that was repeated six times (72 stimuli in total). IL blocks were alternated with the B condition. Each run included a total of 312 trials and lasted approximately 6.25 min [see (Naismith et al., 2006)]. Participants were tested on two runs using different stimulus sequences that were counter-balanced across subjects. Visual stimuli and behavioural responses were delivered and recorded using *Neuroscan STIM* software. The experimental paradigm was back-projected onto a frosted screen that the subjects viewed via a mirror fitted onto the head coil of the MRI