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Cognitive flexibility depends on white matter microstructure of the basal ganglia

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ABSTRACT

Ample evidence shows that the basal ganglia play an important role in cognitive flexibility. However, traditionally, cognitive processes have most commonly been associated with the prefrontal cortex. Indeed, current theoretical models of basal ganglia function suggest the basal ganglia interact with the prefrontal cortex and thalamus, via anatomical fronto-striato-thalamic circuits, to implement cognitive flexibility. Here we aimed to assess this hypothesis in humans by associating individual differences in cognitive flexibility with white matter microstructure of the basal ganglia. To this end we employed an attention switching paradigm in adults with ADHD and controls, leading to a broad range in task performance. Attention switching performance could be predicted based on individual differences in white matter microstructure in/around the basal ganglia. Crucially, local white matter showing this association projected to regions in the prefrontal cortex and thalamus. Our findings highlight the crucial role of the basal ganglia and the fronto-striato-thalamic circuit for cognitive flexibility.

1. Introduction

Our constantly changing environment demands cognitive flexibility, i.e. the ability to switch attention away from previously relevant representations and towards newly relevant representations. Accumulating evidence suggests that such cognitive flexibility is supported by the basal ganglia. Thus, selective lesions of the basal ganglia in experimental animals impair set shifting and reversal learning (Crofts et al., 2001; Oberg & Divac, 1975; Taghzouti, Louilot, Herman, Le Moal, & Simon, 1985). In humans, functional magnetic resonance imaging (fMRI) studies have demonstrated BOLD signal increases in the basal ganglia during the performance of paradigms that require cognitive flexibility, such as task switching, reversal learning and set-shifting paradigms (Cools, Clark, Owen, & Robbins, 2002; Cools, Clark, & Robbins, 2004; Leber, Turk-Browne, & Chun, 2008; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Evidence that the basal ganglia are not just activated, but in fact *necessary* for cognitive flexibility in humans comes from studies with Parkinson's disease and stroke patients with focal basal ganglia lesions, who exhibit significant set switching deficits (Cools, Van den Bercken, Horstink, Van Spaendonck, & Berger, 1984; Cools, Barker, Sahakian, & Robbins, 2001; Cools, Ivry, & D'Esposito, 2006; Downes et al., 1989; Owen et al., 1992).

The above described studies convincingly show a role for the basal ganglia in cognitive flexibility. This might seem surprising in the context of classic models of cognitive control that emphasize a particularly important role for the prefrontal cortex (Miller & Cohen, 2001; Milner, 1963; Owen, Roberts, Hodges, & Robbins, 1993; Rogers, 1998). In fact there is a long history of research on the similarities between the functional consequences of frontal and basal ganglia lesions (Divac, 1972). Based on this classic work, the functions of the basal ganglia have been hypothesized to be determined by its cortical and possibly by its thalamic input (Divac, 1972). Anatomical evidence for the existence of strong white matter connections between these regions in fronto-striato-thalamic circuits (Alexander, DeLong, & Strick, 1986; Draganski

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et al., 2008) strengthened this hypothesis, which is also in line with more recent theoretical work, suggesting more explicitly that cognitive flexibility depends on interactions between the basal ganglia, the prefrontal cortex and the thalamus (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2007). However, despite this strong anatomical and theoretical basis, there is no direct evidence for the importance of structural connectivity of the basal ganglia for cognitive flexibility. Here we establish this link between cognitive flexibility and individual differences in white matter microstructure of the human basal ganglia by employing diffusion tensor imaging (DTI).

An attention switching paradigm was used to assess cognitive flexibility. This paradigm was previously shown to reliably recruit the basal ganglia during a switch of attention (van Schouwenburg, den Ouden, & Cools, 2010; van Schouwenburg et al., 2013). White matter microstructure of the basal ganglia was indexed by fractional anisotropy (FA), measured with DTI. We and others have used this approach previously to link cognitive measures to white matter microstructure (Boorman, O'Shea, Sebastian, Rushworth, & Johansen-Berg, 2007; Forstmann et al., 2008; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Tuch et al., 2005). For example, we have shown, using the same attention switching paradigm, that BOLD signal in the basal ganglia depends on individual differences in FA values in the basal ganglia (van Schouwenburg et al., 2013). We now aim to extend this prior work to individual differences in performance on the task.

In our previous study, which included only healthy subjects, the narrow distribution of task performance prevented us from assessing this relationship between white matter microstructure and performance. Here, we anticipated that the inclusion of subjects diagnosed with attention deficit hyperactivity disorder (ADHD) would lead to a broader range of task performance. ADHD has previously been associated with performance deficits on set-shifting (Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005) and task switching paradigms (King, Colla, Brass, Heuser, & Von Cramon, 2007; McLean et al., 2004), suggesting that ADHD is accompanied by cognitive inflexibility.

2. Methods

2.1. Subjects

Nineteen healthy volunteers and 19 volunteers diagnosed with ADHD were recruited from an existing database (Dutch cohort of the International Multicenter persistent ADHD CollaboraTion (IMpACT) (Hoogman et al., 2011)). All participants were assessed using the Diagnostic Interview for Adult ADHD at the time of inclusion in the IMpACT study (Kooij & Francken, 2007). This interview focuses on the 18 DSM-IV symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether a symptom is currently present or was present in childhood. The Structured Clinical Interview for DSM-IV (SCID-I) was used for comorbidity assessment. Assessments were carried out by trained professionals (psychiatrists or psychologists).

All subjects gave written informed consent and were compensated for participation. The study was approved by the local ethics committee (committee for the protection of human subjects of the Arnhem/Nijmegen region; CMO protocol number 2009/260).

All 38 subjects performed the attention switching paradigm as described below. None of the subjects participated in any of our previous studies using the same paradigm (van Schouwenburg et al., 2010, 2013). Subjects were asked to complete the ADHD DSM-IV-TR Rating Scale (ADRS) at home and to bring it with them on the day of testing (Kooij et al., 2005). This self-report questionnaire was used to assess inattentive symptoms and hyperactivity symptoms in the last six months. ADRS data were missing from two subjects (one control subject and one ADHD patient). Structural MRI and diffusion tensor images were missing for five additional subjects (three control subjects and two ADHD patients). Accordingly, results are reported from 31 subjects. These 31 subjects included 15 control subjects (9 men), and 16 ADHD patients (7 men). None of the volunteers had (co-morbid) psychiatric or neurological disorders at the time of testing. There were no significant differences between the ADHD and control group with respect to gender ($X^2=1.57$, $p=0.21$), age ($t_{29}=-0.40$, $p=0.69$), or IQ ($t_{29}=-0.03$, $p=0.97$) (Table 1). Four of the ADHD patients were medication-naive and three had taken medication in the past, but were off medication at the time of the experiment. The remaining nine ADHD patients took regular medication, but withdrew from medication approximately 24 h prior to the experiment.

Table 1
Demographics of ADHD patients and healthy controls.

	ADHD ($n=16$)		Control ($n=15$)	
	Mean	SEM	Mean	SEM
Age	32.5	1.7	31.6	1.4
IQ[a]	11.6	0.6	11.5	0.7
Inattentive symptoms	5.7	0.7	0.8	0.4
Hyperactivity/Impulsivity symptoms	3.9	0.6	0.9	0.2

[a] Scores represent the average of the standard scores for the block design and vocabulary assessments of the Wechsler Adult Intelligence Scale-III.

2.2. Paradigm

An attention switching paradigm was employed in which subjects switched attention when they detected a change in the stimulus exemplars of a non-selected category of face/scene stimuli (van Schouwenburg et al., 2010). Subjects were presented with a series of stimulus-pairs, each consisting of a superimposed face exemplar and scene exemplar (Fig. 1A). Subjects were instructed to select one of four exemplars by making a left (left index finger) or right (right index finger) response, depending on the location of the exemplar of their choice. This self-chosen exemplar was then set as the correct stimulus and subjects were instructed to continue selecting that stimulus on subsequent trials. Stimulus-pairs were presented twice within each trial and subjects were instructed to select the same stimulus on both presentations within a trial. The specific pairing of the superimposed face and scene exemplars was opposite on the second presentation relative to the first presentation (e.g. if face 1 overlapped scene 1 on the first presentation, then face 1 overlapped scene 2 on the second presentation), enabling us to identify which stimulus exemplar was selected by the subject (Fig. 1). Feedback was presented after each trial, and was positive only if the subject selected the correct stimulus twice within the trial. If subjects selected the pattern that did not contain the correct exemplar or did not respond within a personalized cut-off time, then negative feedback was presented.

After a variable number of correct trials, exemplars of the *ignored* category were replaced with novel exemplars. Subjects were instructed prior to the experiment to switch attention to this other category, and to choose one of the two novel exemplars, as soon as they detected a change. Trials on which novel exemplars were introduced, and on which subjects detected the change and switched to one of the novel exemplars where classified as novel switch trials (Fig. 1C). On some trials subjects failed to detect the novel exemplars and continued to respond to the previously correct exemplar (novel non-switch trials) (Fig. 1D). In this case negative feedback was presented, usually leading subjects to switch on the subsequent trial. Trials on which no novel stimuli were introduced were defined as repeat trials (Fig. 1B). For more details about the paradigm we refer to our previous study (van Schouwenburg et al., 2010).

Subjects performed a practice block before the start of the main experiment, consisting of on average 140.2 trials ($\pm$4.5 [SEM]). During the main experiment, subjects were presented with an average of 405.0 repeat trials ($\pm$11.5) (control: 401.0 $\pm$ 14.6, ADHD: 408.7 $\pm$ 18.0), and novel exemplars were introduced on 82 trials. The sequence of the faces and scenes presented was randomized across subjects but were matched between groups. The timing of the paradigm was slightly adjusted compared to our previous study. Time between presentation of the first and second stimulus was reduced to 500 ms (previously 1000 ms) and feedback was given immediately after the second response (previously jittered between 0 and 4500 ms to allow for desynchronization of trials necessary for fMRI analyses). These adjustments reduced the duration of the experiment by approximately 15 min (total current duration: 25–30 min).

The paradigm was programmed using Presentation software (Neurobehavioural systems, Albany, USA).

2.3. MRI data acquisition

Whole-brain imaging was performed with a 1.5 T MR scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) at the time of inclusion in the IMpACT study (0–3.5 years prior to the current experiment) (Hoogman et al., 2011). A high-resolution T1-weighted MP-RAGE anatomical scan was obtained from each subject (176 sagittal slices, repetition time=2730 ms, echo time=2.95 ms, voxel size=1.0 × 1.0 × 1.0 mm, field of view=256 mm). In addition, diffusion tensor

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