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Cerebral compensation during motor imagery in Parkinson's disease

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Abstract

In neurodegenerative disorders, neural damage can trigger compensatory mechanisms that minimize behavioural impairments. Here, we aimed at characterizing cerebral compensation during motor imagery in Parkinson's disease (PD), while controlling for altered motor execution and sensory feedback. We used a within-patient design to compare the most and least affected hand in 19 right-handed PD patients with markedly right-lateralized symptoms. We used a motor imagery (MI) task in which the patients were required to judge the laterality of hand images, rotated either in a lateral or in a medial orientation with respect to the body sagittal plane. This design allowed us to compare cerebral activity (using fMRI) evoked by MI of each hand separately, while objectively monitoring task performance. Reaction times and parieto-premotor activity increased in a similar manner as a function of stimulus rotation during motor imagery of left and right hands. However, patients were markedly slower when judging images of the affected hand in lateral orientations, and there was a corresponding increase in activity in the right extrastriate body area (EBA) and occipito-parietal cortex during mental rotation of the affected hand. Furthermore, these regions increased their connectivity towards the left PMd for right (affected) hands in a lateral orientation. We infer that, in strongly lateralized PD patients, motor imagery of the most-affected hand exploits additional resources in extrastriate visual areas. These findings characterize the cerebral bases of the increased dependence on visual information processing during the generation of motor plans in PD, pointing to its compensatory role.

Keywords: Functional magnetic resonance imaging; Extrastriate body area; Visual cortex; Mental rotation; Biomechanical constraints; Body schema

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by deficits in motor control, which are clinically apparent as bradykinesia, hypokinesia and akinesia (Berardelli, Rothwell, Thompson, & Hallett, 2001). At the neuronal level, the disease is characterized by progressive cell death in the substantia nigra pars compacta, which leads to dopamine depletion in the striatum and indirectly to cortical dysfunction (Marsden, 1982; Braak et al., 2003). The clinical signs are an expression of altered neural processing at one or more stages of movement generation, including motor planning, motor execution and sensory feedback (Marsden, 1982). The motor deficits can be improved when PD patients are provided with external sensory cues (Bloem, Hausdorff, Visser, & Giladi, 2004). This suggests that impaired motor-related cerebral function can be compensated for by additional processing (e.g. enhanced attention or increased reliance on visual features), which implies that cerebral compensatory mechanisms occur in chronically progressive neurodegenerative disorders (Palop, Chin, & Mucke, 2006). These mechanisms may rely on local changes in neuronal properties, like synaptic plasticity (Bezard & Gross, 1998), but they may also arise from system-level changes in cerebral circuits supporting a given cognitive process. In computational terms, compensation within a cerebral circuit is known as degeneracy, namely 'the ability of elements that are structurally different to perform the same function or yield the same output' (Edelman & Gally, 2001). Degeneracy implies that structurally different cerebral circuits are able to contribute to one particular function. If one node or circuit fails, other circuits may take over and prevent deficits in overt behaviour. In PD, degeneracy may explain why so many neurons in the substantia nigra can die before they are missed

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at the clinical level, and why the disease progresses so slowly. Specifically, degeneracy might involve the engagement of additional (compensatory) brain regions in a cerebral circuit, thereby preserving its functional output in behavioural terms. Also, the chronicity of neurodegenerative disorders *allows* the brain to deploy compensatory mechanisms—for example, by increasing neuronal activity in relatively unaffected regions. Thus, within the boundaries set by neuronal loss, the nervous system has a notable capacity to maintain neurological functions (Palop et al., 2006; Price & Friston, 2002). This may have important implications, since it shifts the focus of therapeutic intervention from neurons that are lost to those that survive.

Several neuroimaging studies have been performed to investigate changes in functional networks in PD, finding decreased activity in mesial frontal regions and increased activity in cerebellum, lateral premotor and parietal regions (Haslinger et al., 2001; Sabatini et al., 2000; Samuel et al., 1997). A similar pattern of increased activity in the right rostral cingulate motor area and left dorsal premotor cortex (PMd) was found in presymptomatic gene-carriers at risk for developing PD (Buhmann et al., 2005), confirming that compensatory changes at the network level are very early adaptations of the brain to maintain behavioural functions, even before a neurodegenerative disease becomes visible to the clinical eye.

These studies have used motor execution tasks, and their results indicate that degeneracy may occur at the level of motor planning, motor execution, or even be related to abnormal sensory feedback (Boecker et al., 1999; Seiss, Praamstra, Hesse, & Rickards, 2003). To resolve this ambiguity, other studies have used motor imagery (MI) paradigms in PD patients (Cunnington et al., 2001; Samuel, Ceballos-Baumann, Boecker, & Brooks, 2001; Thobois et al., 2000), where patients were asked to *imagine* performing movements while brain activity was recorded. These studies excluded that the altered cerebral activity during MI in PD could be due to altered motor output or sensory feedback, but it remains unclear to what extent these results reflect the inability of PD patients to solve a task, i.e. to select appropriate motor circuits and inhibit inappropriate ones. It has been argued that to reliably attribute cerebral activation patterns to compensatory mechanisms, it is necessary to use tasks that the patient can perform (Price & Friston, 2002), while allowing for objective measures of patients' performance and strategies.

Here, we have quantified performance of PD patients during a motor imagery task, while measuring cerebral activity with event-related fMRI. When asked to judge the laterality of a rotated image of a hand, human subjects solve the task by mentally moving their own hand from its current position into the stimulus orientation for comparison (Parsons, 1987). A direct comparison between mental rotation of hands (motor imagery) and mental rotation of letters (visual imagery) has revealed that MI is supported by a specific parieto-premotor network (de Lange, Hagoort, & Toni, 2005) that closely resembles the cerebral network activated during motor preparation (Thoenissen, Zilles, & Toni, 2002) and partially overlaps with structures involved during movement execution (Decety, 1996; Hanakawa et al., 2003), showing the same somatotopical distribution (Michelon, Vettel, & Zacks, 2006). Psychophysical studies in healthy controls have documented that making hand laterality judgements and executing a movement to match the hand position depicted on the screen follow the same temporal profile and the same hand-specific joint-constraints (Parsons, 1987, 1994; Sekiyama, 1982). Furthermore, the position of the subjects' own hand has been found to affect both behavioural performance (Shenton, Schwoebel, & Coslett, 2004) and cerebral activity (de Lange, Helmich, & Toni, 2006) during the hand laterality judgement task in a hand-specific manner. This underlines that the hand laterality judgment task implies first-person motor imagery. Using a different task involving third-person motor imagery, no such effect of body posture was found (Fischer, 2005). Accordingly, the hand laterality judgement task allows one to assess behavioural and neural correlates of motor imagery separately for the left and right hand. We have exploited this task feature and tested PD patients with *lateralized* symptoms during performance of hand laterality judgements, comparing behavioural and neural performance between the most and least affected hand in a within-patient design. By quantifying motor imagery performance and its supporting cerebral activity, it becomes possible to distinguish whether differences in cerebral activity during motor imagery of the two hands were related to altered task performance or to compensatory mechanisms.

2. Methods

2.1. Patients and controls

2.1.1. Main experiment

Nineteen right-handed idiopathic Parkinson's disease patients (13 men, 53.2 ± 9.1 years, mean $\pm$ S.D.) participated after giving written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands). Before scanning, the patients' disease severity was assessed by one examiner (RCH) using the Hoehn and Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS; see Table 1). Patients were included when they had idiopathic Parkinson's disease, diagnosed according to the UK Brain Bank criteria by an experienced movement disorders specialist (BRB), with clearly right-lateralized symptoms. Exclusion criteria were: moderate-severe tremor, cognitive dysfunction (i.e. mini mental state examination <24), other neurological diseases (such as severe head trauma or stroke), and general exclusion criteria for MRI scanning (such as claustrophobia, pace-maker, and implanted metal parts). Six patients did not yet use any anti-Parkinson medication; the others used dopaminergic medication (levodopa or dopamine-agonists). The experiments were carried out in the morning, and the patients were asked not to take their medication the evening before the experiment. Thus, they were all off-medication for at least 12 h during the experiment (i.e. in a practically defined off-condition; Langston et al., 1992).

2.1.2. Control experiment

In a second behavioural (control) experiment, we compared 12 of the PD patients mentioned above (8 men, 56.4 ± 10.0 years, mean $\pm$ S.D.) with two groups of right-handed, healthy control subjects: 10 age- and sex-matched elderly volunteers (6 men, 57.0 ± 6.2 years, mean $\pm$ S.D.) and 15 young volunteers (7 men, age 26.7 ± 3.3, mean $\pm$ S.D.).

2.2. Stimuli, time course and procedures

2.2.1. Main experiment

We used line drawings of left and right hands, with either the back or the palm of the hand in view. The left and right hands drawings were identical