Subthalamic deep brain stimulation restores automatic response activation and increases susceptibility to impulsive behavior in patients with Parkinson’s disease

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ABSTRACT

Repeatedly reported deficits of patients with Parkinson’s disease (PD) in selecting an appropriate action in the face of competing response alternatives has led to the conclusion of a basal ganglia (BG) involvement in response selection and impulse control. Despite capacious research, it remains elusive how BG dysfunction affects processes subserving goal-directed behavior. Even more problematically, since PD pathology transcends a BG dysfunction due to dopamine depletion in the nigrostriatal DA system (by also comprising alterations in extrastriatal dopamine availability and other neurotransmitter systems), it is not yet clear which aspects of these deficits are actually caused by BG dysfunction. To address this question, the present study investigated 13 off-medication PD patients with bilateral therapeutic subthalamic deep brain stimulation (DBS) both with and without stimulation (DBS\textsubscript{ON} and DBS\textsubscript{OFF}, respectively) and 26 healthy controls. All participants performed a task that tests the relation between automatic response impulses and goal-directed action selection. Results show an improvement of automatic response activation under DBS\textsubscript{ON}, increasing the susceptibility to impulsive responses, and a reduced impact of automatic response activation under DBS\textsubscript{OFF}. We argue that the BG determine the efficiency of the regulation and transmission of stimulus-driven bottom-up response activation required for efficient response selection.

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1. Introduction

Impulse control refers to the ability to successfully refrain from responding to automatic stimulus-triggered response tendencies, when these tendencies interfere with intentional goal-directed actions. Therefore, the study of efficient action control requires an understanding of the interplay between automatic and habitual response impulses and inhibitory control to allow for goal-directed action selection (e.g., Goschke, 2000). Impulse control was found to primarily rely on a cortical network comprising the lateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), and parietal areas (e.g., Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002). In addition to that, recent approaches highlight the basal ganglia (BG; a complex of subcortical nuclei including striatum, globus pallidus, substantia nigra, and subthalamic nucleus (STN)) as significant contributors to goal-directed response selection processes by closely interacting with these cortical areas (Frank, 2011; Mink, 1996) based on the fronto-striato-thalamocortical circuits (Alexander, DeLong, & Strick, 1986; Jahfari et al., 2011).

Evidence for this assumption mainly comes from studies on Parkinson’s disease (PD), using PD as a model of BG dysfunction. PD is primarily characterized by motor symptoms (e.g., tremor, rigidity, akinesia/bradykinesia, postural instability). Additionally, PD patients, compared to age-matched healthy controls, show impairments in action selection in situations with competing response tendencies, for example, in the Stroop task (e.g., Henik, Singh, Beckley, & Rafal, 1993) or Eriksen–Flanker task (Praamstra, Stegeman, Cools, & Horstink, 1998; Wylie, Stout, & Bashore, 2005; Wylie et al., 2009). These results seem to speak in favor of an altered response selection in PD patients and thus, of a BG involvement in response selection processes.
However, typical PD patient-control group designs cannot be conclusive with respect to a causal BG involvement in response selection processes, as pathological changes in PD are not limited to BG dysfunction, for example, due to nigrostriatal dopamine (DA) depletion (e.g., altered extrastriatal DA levels, changes in the cholinergic and serotoninergic systems; Thobois, Jahanshahi, Pinto, Frackowiak, & Limousin-Dowsey, 2004). Moreover, cognitive impairments in PD are assumed to rise from changes in extrastriatal DA (most notably in the PFC) or pathological alterations of other neurotransmitter systems in addition to the observed striatal DA shortage and BG dysfunction (Broussolle et al., 1999; Cools, Stefanova, Barker, Robbins, & Owen, 2002). For PD-related response selection deficits, DA depletion within the lateral PFC and ACC (Cools et al., 2002; Kaasinen et al., 2000) seems to be critical considering the significance of those brain structures for response selection.

A method to test the BG involvement in response selection in a more straightforward way is deep brain stimulation (DBS) of the STN, which allows for a systematic and controlled within-subject variation of the BG functioning state. STN DBS represents a neurosurgical treatment method for advanced PD which leads to a normalization of the neural output activity of the BG on the neural level and an improvement of PD-related motor symptoms on the behavioral level (Benabid, Chabardes, Mitrofanis, & Pollak, 2009). By this means, STN DBS provides the unique possibility to switch between a pathological (DBSOff) and a more physiologically intact (DBSOn) state of BG function in a controlled way on a micro-time level (Jahanshahi et al., 2000; Witt et al., 2004). The efficacy of subthalamic DBS for treating motor dysfunction in PD patients has been well established and has led to its widespread use in clinical neurology. At the same time, however, the effects of this treatment on other functional domains are still to be fully understood, e.g., alterations of impulsive behavior have been reported and represent a major concern with rather contradictory results (Wylie et al., 2010).

Based on this, in the present study we aimed to advance our understanding of how BG dysfunction affects the interplay between automatic and habitual response impulses on one hand, and inhibitory control to allow for goal-directed action selection on the other, by applying DBS to the STN. To this end, we tested medication-free (withdrawn) PD patients that received bilateral stimulation of the STN exclusively. Patients and participants of a healthy control sample performed an interference paradigm (i.e., a spatial-compatibility task) that specifically targets the interplay between two mechanisms of response selection, namely, the processes of fast automatic response activation (i.e., response impulses) and goal-directed action selection (i.e., inhibitory control), respectively (Kornblum, Hasbroucq, & Osman, 1990; Riederinkhof, 2002b). In the present version of the task, participants responded with left and right key presses to the pointing direction of an arrow presented on the left or right of fixation. Although task-irrelevant, the stimulus location is assumed to automatically activate its spatially corresponding response, leading to automatic response tendencies that facilitate responding when the impulsive response tendency matches the required response (compatible condition), but interfere and need to be inhibited when it activates the competing response (incompatible condition). This typically results in longer response times and less response accuracy in the incompatible compared to the compatible condition denoting the spatial-compatibility effect (SCE). We specifically implemented a (Stroop-like) version of the spatial-compatibility task (Kornblum, Stevens, Whipple, & Requin, 1999). The current arrow stimuli involved by themselves a left-right dimension, which could or could not coincide with the left or right position of the stimulus on the display. The use of these stimuli should enhance the tendency for impulsivity in the first and the needs for inhibitory control in the latter case. In addition, Fischer, Plessow, and Kiesel (2010) have shown that this particular task situation provides reliable effects across different response time (RT) levels which is important, since (1) we expect generally slowed RTs under DBSOff compared to DBSOn and (2) a recent study found DBS interactions to be limited to certain RT bins (Wylie et al., 2010). Taken together, the present design ensured a maximum of the effects of automatic response activation and inhibitory control processes on participants’ performance in the current task; in addition, it ensured that potential effects of DBS manipulations on the balance between automatic response impulses and goal-directed action selection would be observable irrespective of overall response speed.

Regarding the effect of STN DBS-based manipulation of the BG functioning state on response selection processes, there are several possibilities. First, if especially inhibitory control processes are affected by pathological BG functioning (e.g., Praamstra et al., 1998; Wylie et al., 2005), impaired inhibitory control of competing response activation would be expected under DBSOff. These less efficient inhibitory control processes under DBSOff should result in increased susceptibility to impulsive and habitual response tendencies, which would be observable by increased response times/error rates when the automatically (by the stimulus location) activated response does not correspond to the required response (incompatible condition). This predicts a larger SCE under DBSOff (Hypothesis #1).

Alternatively, if especially automatic response activation processes are affected by pathological BG functioning, the efficiency of automatic response activation would be reduced under DBSOff, resulting in a smaller SCE. The weakened influence of automatic stimulus location-driven response activation would less interfere in the incompatible condition and would reduce the performance advantage in the compatible compared to the incompatible condition compared to a condition with physiologically intact BG functioning (Hypothesis #2). We would therefore predict that the DBSOn condition facilitates the efficiency of the transmission of automatic response activation; as a net effect this should result in an increased susceptibility to response capture by pre-potent action impulses and thus, to larger SCE effects for DBSOn (Wylie et al., 2010).

Finally, in line with studies that did not reveal SCE difference between PD patients and matched healthy controls (e.g., Praamstra & Plat, 2001; Wylie et al., 2009), it is also conceivable that DBS manipulation does not specifically affect the response selection mechanism or any specific part of it, yielding to a similar SCE in both DBSOn and DBSOff (Hypothesis #3).

2. Methods

2.1. Participants

Thirteen patients with advanced idiopathic Parkinson’s disease and treatment with bilateral STN DBS (Medtronic 3389, Minneapolis, USA) and 26 age-matched healthy controls took part in this study (see Table 1 for details). All participants gave their written informed consent prior to their inclusion in the study in accordance with the Declaration of Helsinki and the guidelines of the local ethics committee. None of the patients reported any other neurological or psychiatric conditions. All participants had normal or corrected-to-normal vision and were studied exclusively without antiparkinsonian medication (in case of regular treatment with antiparkinsonian drugs after an overnight withdrawal).

2.2. Procedure and design

Stimuli were presented white against black on a 17-inch monitor using Experimental Run Time System (www.berisoft.com, BeriSoft Corporation). Viewing distance was approximately 60 cm.
Each trial started with a central fixation cross (0.81° × 0.81°) for 1000 ms, followed by a blank screen for 600 ms. Subsequently, the target display consisting of two geometrical figures (a square of 1.91° × 1.91° and a triangle-shaped arrow head of 1.43° × 2.77°, pointing to either the left or right; line width 0.29°; total display size: 6.56° × 2.77°) was displayed for 200 ms. One figure appeared 2.8 cm left, the other one 2.8 cm right of the screen centre. Participants responded with their index fingers by pressing external response keys (1.0 cm × 1.0 cm) fixed to the table surface. They were instructed to press the left key if a left-pointing arrow appeared and vice versa. When the response location (e.g., left key for left-pointing arrow) matches the stimulus location (e.g., arrow presented on the left), this denotes a compatible condition. Conversely, when response location (e.g., left key for left-pointing arrow) mismatches the stimulus location (e.g., arrow presented on the right), this denotes an incompatible condition. The SCE was computed by incompatible conditions minus compatible condition. Participants were informed that both the other geometrical form and the arrow location were completely task-irrelevant. A correct response was followed by a blank screen for 300 ms. A trial was counted as erroneous, when, for example, a right key was pressed to a left-pointing arrow or vice versa. In this case, the word “falsch” (wrong) was provided as feedback instead of the blank screen for 300 ms. In case of no response within 2000 ms, the feedback “zu langsam” (too slow) appeared. After 500 ms the next trial started.

The experiment consisted of four blocks with 48 trials each. Each participant conducted half of the trials under DBSON, the other half under DBSoff. Order of the two experimental conditions was counterbalanced across patients. After a change in DBS state, a comparable break of at least 30 min ensured stable clinical conditions. Additionally, a neurologist validated the clinical stability. Participants in the control group also performed two experimental conditions counterbalanced across patients. After a change in DBS state, a comparable break of at least 30 min ensured stable clinical conditions. For half of the control group, the first part of the experiment was declared as DBSON and the second part as DBSoff. For the other half this assignment was reversed. Error bars represent standard errors of the mean.

### 3. Results

#### 3.1. RT

As expected, DBS interacted with group, \( F(1, 37) = 12.66, p = .001, \eta^2 = .26 \). That is, DBS affected general performance for patients (DBS\textsubscript{ON}: 577 ms, DBS\textsubscript{OFF}: 717 ms), \( F(1, 12) = 6.75, p = .023, \eta^2 = .36, \) but not for controls, \( F(1, 25) = 1.00, p = .326, \eta^2 = .04 \). Most importantly, we found a significant interaction between spatial compatibility, DBS, and group, \( F(1, 37) = 6.61, p = .014, \eta^2 = .15 \). For patients only, DBS significantly affected the size of the SCE, \( F(1, 12) = 6.41, p = .026, \eta^2 = .35 \). Consistent with Hypothesis #2, Post Hoc t-tests revealed a large SCE under DBSON (100 ms), \( t(12) = 5.04, p < .001, 95\% \text{ CI} [57, 143] \), which was reduced under DBSoff (42 ms) where it did not reach statistical significance, \( t(12) = 1.49, p = .16, 95\% \text{ CI} [–20, 105] \) (see Fig. 1 left panel). Controls showed a medium size SCE (68 ms), \( F(1, 25) = 69.92, p < .001, \eta^2 = .74 \), that did not differ between DBS conditions, \( F < 1 \), and was numerically in between that of patients in the DBSON (100 ms) and DBSoff (42 ms) conditions (see Fig. 1 right panel). Yet, the difference of the SCE between patients and control approached significance in the DBSON condition, \( F(1, 37) = 2.86, p = .099, \eta^2 = .07 \), but not under DBSoff, \( F(1, 37) = 0.99, p = .325, \eta^2 = .03 \). Overall, patients responded slower than controls, \( F(1, 37) = 4.72, p = .036, \eta^2 = .11 \), due to increased RTs for patients specifically in the DBSoff condition (patients: 717 ms, controls: 548 ms), \( F(1, 37) = 11.23, p = .002, \eta^2 = .23 \). In the DBSON condition, no RT difference was found between patients (577 ms) and controls [564 ms], \( F < 1 \).

To further investigate whether the SCE difference between DBSON and DBSoff in patients depends on the observed change in mean RT level between the two conditions (due to bradykinesia in DBSoff), we analyzed the vincentized cumulative RTs (Ratcliff, 1979; Schubert, 1999). For that purpose, we computed the quartile values for each participant based on the whole RT distribution and calculated the mean values per condition and group (Fischer et al., 2010; Fischer, Plessow, & Kiesel, 2013).

#### A mixed-model analysis of variance (ANOVA) with the within-subject factors spatial compatibility (incompatible vs. compatible) and DBS (DBSON vs. DBSoff) as well as the between-subject factor group (PD patient vs. healthy control) was conducted on median RTs and percent error, respectively.

### 2.3. Data analysis

A mixed-model analysis of variance (ANOVA) with the within-subject factors spatial compatibility (incompatible vs. compatible) and DBS (DBSON vs. DBSoff) as well as the between-subject factor group (PD patient vs. healthy control) was conducted on median RTs and percent error, respectively.

#### Table 1

Demographics for all subjects and clinical characteristics for patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients with Parkinson’s disease (n = 13)</th>
<th>Healthy controls (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64.31 (6.59)</td>
<td>65.08 (8.14)</td>
</tr>
<tr>
<td><strong>Males (n)</strong></td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td><strong>Highest education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vocational training (n)</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>University (n)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease onset (years)*</td>
<td>17.00 (6.03)</td>
<td></td>
</tr>
<tr>
<td>Surgery (months)</td>
<td>20.31 (14.23)</td>
<td></td>
</tr>
<tr>
<td>UPDRS-3 motor score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBSON</td>
<td>16.31 (8.38)</td>
<td></td>
</tr>
<tr>
<td>DBSoff</td>
<td>38.15 (17.88)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Means (standard deviation). Abbreviations: UPDRS = Unified Parkinson’s Disease Rating Scale (Fahn, Elton, & Committee, 1987), DBS = Deep brain stimulation.

* n = 12.

b Scores are provided for off medication.
Separate repeated-measures ANOVAs with the within-subject factors spatial compatibility, DBS, and quartile showed that the effects of DBS on the SCE were not modulated by differences in RT levels neither in the patient, $F < 1$, nor in the control group, $F(3, 75) = 1.11, \eta^2 = .04$. Furthermore, in a combined mixed-model ANOVA the factors spatial compatibility, DBS, quartile, and group did not interact, $F(3, 111) = 1.28, p = .267, \eta^2 = .03$ (see Fig. 2).

We further analyzed the effect of DBS on trial-to-trial sequential modulations of the SCE. Prior studies have shown that automatic information transmission from stimulus to motor response is strongest in an actual trial $n$ if it follows a compatible trial in $n-1$ but is usually reduced when following incompatible trials in $n-1$ (e.g., Fischer, Dreisbach, & Goschke, 2008; Soutschek, Müller, & Schubert, 2012; Stürmer, Leuthold, Soetens, Schröter, & Sommer, 2002; Wühr & Ansorge, 2005). For this, we calculated the SCE in trial $n$ depending on previous trial history (i.e., compatible versus incompatible in trial $n-1$). Post-hoc RT analyses confirmed that the sequential modulation of the SCE differed between groups according to DBS condition as reflected in the significant interaction between spatial compatibility, DBS, and quartile, $F(1, 37) = 4.83, p = .034, \eta^2 = .12$. More specifically, whereas for controls, the sequential modulation of the SCE, $F(1, 25) = 10.89, p = .003, \eta^2 = .30$, was evident irrespective of experimental condition, $F(1, 25) = 1.30, p = .265, \eta^2 = .05$, for patients the sequential modulation of the SCE was found only for DBSON (following compatible: 123 ms, following incompatible: 32 ms), $F(1, 12) = 9.64, p < .01, \eta^2 = .45$, but not for DBSOFF (following compatible: 19 ms, following incompatible: 33 ms), $F < 1$. The latter observation suggests an impaired transmission regulation of response activation under DBSOFF, which is consistent with findings of recent studies (e.g., Praamstra & Plat, 2001; Rustamov et al., 2013).

### 3.2. Error rates

Patients committed significantly more errors (17.43%) than healthy controls (5.83%), $F(1, 37) = 6.68, p = .014, \eta^2 = .15$, and displayed a larger SCE (incompatible condition: 23.08%, compatible condition: 11.78%) than healthy controls (incompatible condition: 7.81%, compatible condition: 3.85%), $F(1, 37) = 6.85, p = .013, \eta^2 = .16$. Mirroring the RT data, there was a significant interaction between DBS, spatial compatibility, and group, $F(1, 37) = 5.23, p = .028, \eta^2 = .12$, suggesting that the SCE was differentially affected by the DBS condition between patients and controls. Indeed, for patients the SCE in the error data was numerically larger for DBSON (15.06%) compared to DBSOFF (7.53%). Although this result closely mirrors the RT data, in the patient group the interaction between spatial compatibility and DBS only approached statistical significance, $F(1, 12) = 3.32, p = .09, \eta^2 = .22$ (see also Fig. 1 left panel). Importantly, no main effect of DBS was found, $F(1, 12) = 1.53, p = .240, \eta^2 = .11$, ruling out assumptions of a speed accuracy trade-off. For controls, as expected, the SCE did not differ between DBS conditions, $F < 1$ (see Fig. 1 right panel). Finally, in the DBSON condition patients produced more errors by tendency, $F(1, 37) = 4.03, p = .052, \eta^2 = .10$, and showed a larger SCE than controls, $F(1, 37) = 12.04, p = .001, \eta^2 = .25$. In the DBSOFF condition, patients produced more errors than controls, $F(1, 37) = 7.80, p = .008, \eta^2 = .17$. At the same time, no differences in the SCE in error rates were found under DBSOFF, $F(1, 37) = 1.26, p = .269, \eta^2 = .03$.

### 4. Discussion

The present study aimed at directly addressing whether and how the basal ganglia (BG) are involved in the interplay between automatic and habitual response impulses and inhibitory control. Healthy controls and medication-free (withdrawn) patients with advanced idiopathic PD and treatment with bilateral DBS of the subthalamic nucleus conducted a spatial-compatibility task under DBSON and DBSOFF. This manipulation of the BG functioning revealed a main effect of DBS on response times (RTs) which reflects the therapeutic effect of DBS on the motor system and parallels earlier findings of our group with DBS of the globus pallidus internus (Schubert et al., 2002). More importantly, DBS modulated the size of the spatial-compatibility effect (SCE). For patients, a clear SCE was found only under DBSON that was reduced under DBSOFF which clearly rules out Hypothesis #3 (no effect of DBS on the SCE). This result is also not in accordance with Hypothesis #1 predicting stronger interference and therefore a larger SCE effect under DBSOFF due to impaired cognitive response inhibition. We refrain from interpreting the reduced SCE under DBSOFF as evidence for improved inhibitory control, as it seems highly unlikely that the more pathological BG functioning state is associated with more efficient response selection.

Instead, our findings are in line with Hypothesis #2 which predicted a DBS-induced regulation of the efficiency of automatic information transmission with reduced versus increased efficiency in DBSOFF versus DBSON, respectively. Reduced efficiency of automatic information transmission in DBSOFF consequently decreases the impact of automatic location-based response activation on response selection. Less automatic response activation slows responses in compatible conditions but benefits the identification of the correct response in incompatible conditions reducing the SCE under DBSOFF. It is important to note that the smaller SCE under DBSOFF cannot be explained by the generally slower RT level or to specific blurring due to bradykinesia, since differences between the BG states were not tied to specific tails of the RT distribution.
Although we did not find evidence of a statistically reliable SCE under DBS_OFF, it should also be noted that at least some numerical value of the SCE seemed to remain. One possibility might be that automatic information transmission under conditions of DBS_OFF is only impaired to some extent but not completely blocked.

Hypothesis #2 further predicted that DBS_ON might improve information transmission and may thus re-establish the impact of automatic response activation in the response selection mechanism. Intact automatic response activation facilitates compatible responses but results in increased interference in response incompatible trials. Consequently and in line with this prediction, we found a reliable SCE for patients in DBS_ON that was larger than in DBS_OFF.

Moreover, the SCE for patients in DBS_ON not only exceeded the one in DBS_OFF but also appeared to be more pronounced (in error rates and at least by tendency in RTs) than the SCE revealed by healthy controls. This finding fits well with recent observations that PD patients with DBS reveal a higher susceptibility to impulsive response tendencies to habitual and automatized conflicting response alternatives (e.g., Wylie et al., 2010). It can therefore also perfectly account for findings of increased interference susceptibility in a Stroop task under DBS_ON compared to DBS_OFF that have previously been discussed as evidence for impaired response inhibition under DBS (cf. Jahanshahi et al., 2000; Schroeder et al., 2002; Witt et al., 2004). The assumption of an increased efficiency of transmission of automatic response activation for patients in DBS_ON is also compatible with recent observations of increased impulsivity under DBS_ON compared to DBS_OFF (e.g., Ballanger et al., 2009; Frank, Samanta, Moustafa, & Sherman, 2007; Wylie et al., 2010). At the same time, however, the error data closely mirrored RT data, ruling out the possibility of an unspecified shift in the speed accuracy trade-off.

Our results extend previous findings, by providing further novel support of the argumentation of restored automatic information transmission under DBS. As a window into the adaptive regulation of pre-potent response tendencies, we analyzed trial-to-trial sequential modulations of SCE. It has been argued that automatic information transmission and thus, the influence of pre-potent response tendencies towards the stimulus location is typically strongest following compatible trials in n–1 (Stürmer et al., 2002). This pattern has clearly been demonstrated for the healthy controls. For patients, however, sequential modulations of the SCE were exclusively obtained in conditions of DBS_ON but not DBS_OFF. For the latter, we did not find an effect of automatic information transmission following compatible trials in n–1, thus, providing further empirical support for the notion of impaired information transmission in PD patients that can be restored by means of subthalamic DBS.

The present demonstration of restored automatic information transmission and increased impulse behavior by DBS is in line with and extends findings of previous studies (e.g., Wylie et al., 2010). Wylie and colleagues found increased susceptibility to pre-potent responses under DBS stimulation for the faster parts of the RT distribution, although no overall effect of DBS on the SCE was found. It should be noted though, that the authors implemented a standard spatial-compatibility task that is generally sensitive to response activation due to BG dysfunctioning also reduces the need for subsequent inhibitory control primarily revealed by frontal cortical areas. Finally, our results are also in line with current anatomical and functional BG models that postulate a close link between the BG and frontal cortical areas via multiple BG-thalamocortical circuits and, based on that, BG contribution to motor-program selection (Alexander et al., 1986; Mink, 1996).

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References


