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Striatal and thalamic GABA level concentrations play differential roles for the modulation of response selection processes by proprioceptive information

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ABSTRACT

The selection of appropriate responses is a complex endeavor requiring the integration of many different sources of information in fronto-striatal-thalamic circuits. An often neglected but relevant piece of information is provided by proprioceptive inputs about the current position of our limbs. This study examines the importance of striatal and thalamic GABA levels in these processes using GABA-edited magnetic resonance spectroscopy (GABA-MRS) and a Simon task featuring proprioception-induced interference in healthy subjects. As a possible model of deficits in the processing of proprioceptive information, we also included Parkinson's disease (PD) patients in this study.

The results show that proprioceptive information about unusual postures complicates response selection processes in controls, but not in PD patients. The well-known deficits of PD patients in processing proprioceptive information can turn into a benefit when altered proprioceptive information would normally complicate response selection processes. Striatal and thalamic GABA levels play dissociable roles in the modulation of response selection processes by proprioceptive information: Striatal GABA levels seem to be important for the general speed of responding, most likely because striatal GABA promotes response selection. In contrast, the modulation of response conflict by proprioceptive information is closely related to thalamic GABA concentrations with higher concentration being related to a smaller response conflict effect. The most likely explanation for this finding is that the thalamus is involved in the integration of sensorimotor, attentional, and cognitive information for the purpose of response formation. Yet, this effect in the thalamus vanishes when controls and PD patients were analyzed separately.

Introduction

Fronto-striatal-thalamic circuits are of tremendous importance for response selection and sensorimotor integration processes (Bolam et al., 2000; Middleton and Strick, 2000; Reig and Silberberg, 2014). One of the reasons why response selection processes are quite complex is that the representation of most of our actions and goals comprises several aspects that include different forms of information (Stock et al., 2013). In this context, proprioceptive information about the position/posture of our limbs is an often-neglected aspect that has nevertheless been demonstrated to be of importance (Stock and Beste, 2014; Stock et al., 2013). It has been shown that proprioceptive information on an unusual posture/limb position increases the difficulty to select an appropriate response, especially when there is a conflict to mapping a stimulus onto the appropriate response (Leuthold, 2011; Stock and Beste, 2014; Stock et al., 2013; Wascher et al., 2001). Such conflict effects can, for example, be induced in the Simon Task (e.g. Keye et al., 2013). There, responses are faster and less error-prone in case the task-irrelevant stimulus location corresponds to the location of the (correctly) responding effector, whereas responses are slowed down in case the locations of the stimulus and the responding effector mismatch, thus inducing a conflict (= Simon effect) (e.g. Keye et al., 2013). The size of the Simon effect reflects the extra demands and time required to suppress the interference caused by the incorrect response activation produced in non-corresponding trials that are absent in corresponding trials (Ridderinkhof, 2002; Wylie et al., 2010a). When proprioceptive information is altered (i.e., hand positions are varied) these correspondence effects are also varied (Stock et al., 2013):

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When an unusual hand position (i.e. crossed hands) is induced, correspondence effects are increased as compared to usual hand positions (i.e. parallel hands), suggesting that altered proprioceptive information complicates and hence slows down response selection processes (Stock et al., 2013).

For response selection processes, it has been suggested that the striatal GABAergic system plays an important role in the selection of appropriate responses. At the striatal level, the GABAergic neurotransmission is considered of importance, because it is assumed to constitute a winner-takes-all (WTA) network that is implemented via medium spiny neurons (MSN) (e.g. Bar-Gad et al., 2003; Bolam et al., 2000; Plenz, 2003). It has been shown that a high integrity of the WTA network leads to fast response selection and execution (e.g. Beste and Saft, 2015; Beste et al., 2012; Willemssen et al., 2011) and it has furthermore already been shown that high striatal GABA levels increase efficiency in response selection (Yildiz et al., 2014). Currently, it is however unknown if the fronto-striatal-thalamic GABAergic system also plays a role in modulatory effects of proprioceptive information on response selection processes. If so, it is likely that this is the case especially in response selection processes that are conflicting. In the current study, we use GABA-edited magnetic resonance spectroscopy (MRS) (Mullins et al., 2014) to investigate this question.

Aside from striatal structures, the thalamus has been suggested to play an important role in the processing of proprioceptive information (Lalonde and Strazielle, 2007; Müller et al., 2013). Moreover, thalamic structures are important for attentional orienting and feature-integration functions (e.g. Kim, 2014; Ruhl and Dicke, 2012; Salmi et al., 2007; Schneider, 2011; Yang and Mayer, 2014). These functions are of importance since congruency/correspondence effects in the Simon task (see above) not only depend on response selection. Instead, it also depends on attentional orienting processes because different stimuli signaling for distinct responses have to be integrated with information on the spatial position of these stimuli (for review: Hommel, 2011). Consequently, functional imaging evidence suggests that thalamic processing is important for performance in the Simon task (Rubia et al., 2011). We will therefore also investigate the role of the thalamic GABAergic system for the above-mentioned modulations of sensorimotor integration processes by proprioceptive information using GABA-MRS.

One possible means to deepen insights into the role of proprioceptive information for sensorimotor integration processes (as induced in the Simon task) and the relevance of the fronto-striatal-thalamic GABAergic system is to investigate the effects of Parkinson's disease (PD). The reason for this is that PD patients are well-known to have an increased threshold for the processing of proprioceptive information (Conte et al., 2013). PD seems particularly useful in this context since the cognitive deficits observed in this disease strongly depend on fronto-striatal-thalamic circuits (e.g. Kehagia et al., 2013). Moreover, response selection in the Simon task has been shown to be altered in PD (Fielding et al., 2005; Plessow et al., 2014; Praamstra and Plat, 2001; van Wouwe et al., 2014; Wylie et al., 2010b, 2012), but no study has yet examined the effects of proprioceptive information. In the current study, we therefore examine PD patients as a possible model of altered proprioceptive information processing thresholds. We hypothesize that because the threshold for proprioceptive information is increased, modulations of proprioceptive information should have smaller effects on sensorimotor integration processes in PD than in controls. This would imply that a deficit associated with PD can also be advantageous in some situations.

Materials and methods

Sample

Nineteen subjects with mild-to-moderate PD (mean age ± standard deviation: 63.68 ± 9.12 y, 10 males, no dementia, UPDRS-III score off medication: 33.34 ± 10.9) and eighteen healthy controls (mean age ± standard deviation: 59.63 ± 10.24 y, 11 males, UPDRS-III score: 5.43 ± 3.36) were recruited for the study. Three PD patients had never used any Parkinson's medication whereas the remaining patients were withheld from taking Parkinson's medication for at least 12 h before participating in the study. Subjects with a previous history of neurological disorder, dementia, severe rest tremor, claustrophobia, and those taking GABA-ergic drugs were excluded from the study. The range of disease duration of the PD subjects was between 0.75 and 11 years post-diagnosis. Written informed consent approved by the Indiana University Institutional Review Board was obtained from all subjects prior to participation.

Task

The experimental paradigm is a modified Simon Task, which is identical to a previous study by our group examining the role of proprioceptive information for sensorimotor integration processes (Stock et al., 2013). The experimental setup is shown in Fig. 1. For the presentation of stimuli as well as for the recording of the responses (reaction times (RTs) and correctness), Presentation (version 14.9. by Neurobehavioral Systems, Inc.) was used. Responses were collected using a standard computer keyboard. Response buttons were the left and right "Ctrl" keys.

A white fixation cross was continuously displayed in the center of the screen on dark blue background color. Two white frame boxes were laterally presented at the same vertical level as the fixation cross. The distance of the inner border of the two lateralized boxes (one right and one left) from the fixation cross was 1.1° visual angle. Like the fixation cross, the two boxes remained on the screen throughout the experiment. Each trial began with the presentation of a yellow capital letter (A or B) as a target stimulus within one of the two boxes. The opposing box always contained a noise stimulus (three horizontal white bars). Stimuli were approximately 0.5° wide and 0.6° high. These stimuli were presented simultaneously for 200 ms, after which the empty boxes remained on the screen. The study participants (patients and controls) were asked to respond as fast and accurately as possible with the index finger of their left hand, when the letter "A" was presented. When the letter "B" was presented they were required to respond with the index finger of their right hand. These responses were required to be carried out regardless of the target stimulus position on the screen (i.e. in the box left or right of the fixation cross). All trials in which the target stimulus and the correct response button

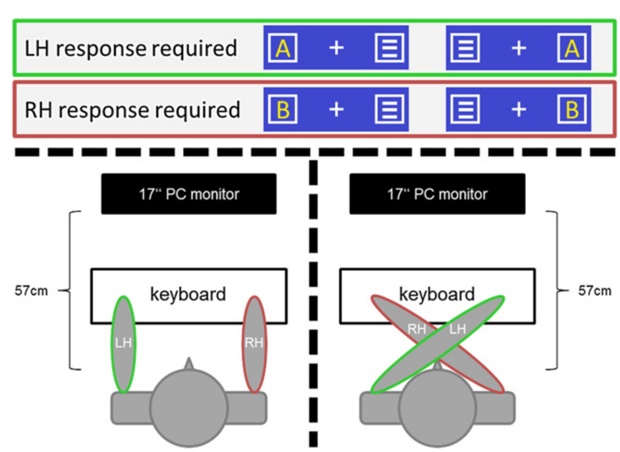

Fig. 1. Experimental setup of the Simon Task. The target stimuli (letters) could be located in either of the boxes as illustrated in the top rows. Letter A required a reaction of the left hand (respective box and limbs edged green) while letter B required a reaction of the right hand (respective box and limbs edged red). The parallel hand condition is shown in the bottom left part of the figure while the crossed hand condition is shown on the bottom right side.