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Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in Parkinson's disease

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ABSTRACT

The basal ganglia play an important role in beat perception and patients with Parkinson's disease (PD) are impaired in perception of beat-based rhythms. Rhythmic cues are nonetheless beneficial in gait rehabilitation, raising the question how rhythm improves movement in PD. We addressed this question with magnetoencephalography recordings during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation. Analyses focused on (i) entrainment of slow oscillations, (ii) the depth of beta power modulation, and (iii) whether a gain in modulation depth of beta power, due to rhythmicity, is of predictive or reactive nature. The results show weaker phase synchronisation of slow oscillations and a relative shift from predictive to reactive movement-related beta suppression in PD. Nonetheless, rhythmic stimulus presentation increased beta modulation depth to the same extent in patients and controls. Critically, this gain selectively increased the predictive and not reactive movement-related beta power suppression. Operation of a predictive mechanism, induced by rhythmic stimulation, was corroborated by a sensory gating effect in the sensorimotor cortex. The predictive mode of cue utilisation points to facilitation of basal ganglia-premotor interactions, contrasting with the popular view that rhythmic stimulation confers a special advantage in PD, based on recruitment of alternative pathways.

1. Introduction

There is evidence that rhythmic cues can improve gait in patients with Parkinson's disease (PD) (for review see Keus et al., 2007; Nombela et al., 2013; Spaulding et al., 2013). Recent studies, however, have shown that PD patients are impaired in rhythm perception, especially of beat-based rhythms with strong temporal regularity (Grahn and Brett, 2009). This deficit might have its basis in the involvement of the basal ganglia in rhythm perception and production, as suggested by neuroimaging studies (Grahn and Rowe, 2009, 2013) and by neural recordings in monkey basal ganglia (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2015). The impairment in rhythm perception and its presumed basis in basal ganglia dysfunction raise the question how rhythm can improve movement in PD patients (Chen et al., 2009; Nombela et al., 2013; Te Woerd et al., 2014).

An important element of the recent evidence for basal ganglia involvement in rhythm perception is that putaminal activity and associated putamen-premotor interaction during rhythm perception are engaged in a predictive fashion (Grahn and Rowe, 2009, 2013; Merchant et al., 2015). Notably, relevant putamen-premotor interactions include interactions with the supplementary motor area but also with the lateral premotor cortex. The predictive engagement of putamen-lateral premotor cortex circuits by rhythm processing underscores the significance of the question how rhythm improves movement in PD. This is because this predictive engagement contradicts the popular view that the lateral premotor cortex supports compensation in PD due to a mode of processing that is more externally driven than requiring internal generation and prediction (Cunnington et al., 1995, 2001; Jahanshahi et al., 1995; Samuel et al., 1997; Sabatini et al., 2000; Debaere et al., 2003; Vercruysse et al., 2012).

To investigate the physiological basis of rhythmic stimulation benefits in PD, we recorded movement-related brain activity during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation, using magnetoencephalography (MEG) in 15 PD patients and 15 control subjects. There is increasing recognition that brain oscillations tend to entrain to environmental regularities and that this physiological mechanism may underlie behavioural advantages conferred by such regularities (Schroeder and Lakatos, 2009). Hence we analysed slow brain oscillations in the frequency range of the stimulus presentation rate. Of key interest was, furthermore, the response of the sensorimotor beta rhythm, which is a known pathophysiological marker of PD (e.g. Gatev et al., 2006; Hammond et al., 2007; Pollok et al., 2012; Brittain and Brown, 2014), and which is hypothesised to represent an internal likelihood index for pending voluntary action (Engel and Fries, 2010; Jenkinson and Brown, 2011). The magnitude of the

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movement-related beta amplitude modulation, commonly attenuated in PD (e.g. Devos et al., 2003; Doyle et al., 2005; Heinrichs-Graham et al., 2014), was expected to demonstrate a gain with rhythmic stimulus presentation. Crucially, to evaluate whether such a gain is due to the adoption of a more predictive mode of control, as opposed to reactive responding, movement-related beta suppression was separated into a predictive and a reactive phase, occurring before and after a reaction stimulus, respectively (Praamstra and Pope, 2007; Te Woerd et al., 2014). Fig. 1 outlines the different outcome scenarios based on this distinction.

2. Methods

2.1. Participants

Participants were 15 PD patients (10 men; aged 61 ±5 years) and 15 healthy subjects (9 men; aged 61 ±5 years). Control subjects were without history of neurological or psychiatric disease. PD patients were of mild to moderate disease severity (see Table 1). Participation was based on informed consent according to the Declaration of Helsinki and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication and had a mean score of 28 (±7) on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (see Table 1). The investigation and UPDRS rating were performed in the morning, after overnight withdrawal of medication (>12 h).

2.2. Task and procedure

The experiment consisted of a serial choice response task to arrow stimuli presented on a screen, with the response being an index or middle finger button press, depending on the direction of the arrow. The ordering of left and rightward arrows was always random. The critical experimental manipulation concerned the temporal predictability of successive stimuli, which was manipulated by using two types of blocks. In one version (the "rhythmic" condition), the SOA (stimulus onset asynchrony) between successive stimuli was always 1.5 s. In the other version (the "non-rhythmic" condition), the SOA between successive stimuli varied between 1 and 2 s (in 0.1 s steps, with the majority being 1.5 s (~40%)). Subjects used one hand during each block, starting the first block with their dominant hand and switching to the other hand for the next block. Half the subjects started with the rhythmic, the other half with the non-rhythmic condition. Rhythmicity was alternated every two blocks, such that all subjects first performed one condition with both hands before switching to the other condition.

The experiment was divided in eight blocks of ~5 min each, containing 160 stimuli per block. Each block was preceded by a 20 s resting period during which ongoing brain activity was recorded. In order to make an unbiased comparison between conditions, only the 1.5 s intervals from the non-rhythmic condition were used for analyses and an equal number of stimuli from the rhythmic condition. The experiment was preceded by a short practice block and participants were instructed to press the correct button as swift as possible, and were not made aware of the rhythmicity manipulation. Stimuli were presented with Presentation 14.9 software (Neurobehavioral Systems), using a liquid crystal display video projector, and back-projected onto a translucent screen in the magnetically shielded room. Participants were seated in the MEG-chair with their eyes 75 cm from the screen, and response pads attached to the armrests of the chair. Stimuli were presented in white on a grey background for 300 ms. The fixation area was permanently indicated by white brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of 7.2° × 6.1° of visual angle; the arrows measured 1.2° × 1.2° of visual angle.

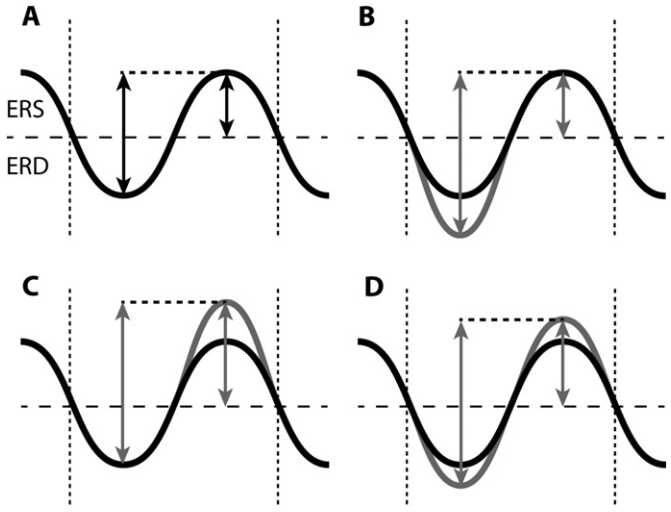

Fig. 1. Possible outcome scenarios of changes in beta power modulation as a result of rhythmic vs. non-rhythmic stimulus presentation. (A) Typical time course of beta power in a serial reaction task with stimuli presented at time points indicated by vertical lines. A decrease of beta power relative to baseline is called event-related desynchronisation (ERD). An increase of power is called event-related synchronisation (ERS). Movement preparation and execution is accompanied by a beta ERD (movement-related beta suppression). This suppression can be divided in a predictive and a reactive part. Predictive beta suppression is calculated as the power change from pre-stimulus ERS-peak to stimulus-onset (shown by the right arrow in A) relative to the modulation depth (from pre-stimulus ERS-peak to subsequent ERD-trough; left arrow in A). Rhythmic stimulus presentation is expected to increase the beta modulation depth. (B) This increase might be mediated by a stronger desynchronisation, producing higher amplitude reactive beta suppression. (C) Alternatively, it might be mediated by a stronger synchronisation, indicating a predictive mode of cue utilisation and yielding higher predictive beta suppression. (D) An increase in beta modulation may also consist of increased synchronisation and desynchronisation phases.

2.3. MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localisation coils that were placed at the nasion and in the left and right ear canals. Vertical electro-oculogram (EOG) was recorded from the supra- and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

2.4. Behavioural analyses

Reaction time analyses were performed on the responses to the visual cues. We excluded trials with erroneous responses and discarded trials in which the response was too slow (>900 ms). Mean response times were determined for each condition separately. Differences in reaction time variability, at the individual subject level, were determined by using the coefficient of variation (ratio of standard deviation to the mean response time). As musical training could influence the experimental outcomes (Grahn and Rowe, 2009), all subjects filled out the subpart 'musical training' of the Goldsmiths Musical Sophistication Index (v1.0) (Müllensiefen et al., 2014). All correlations between reaction time and other behavioural or neurophysiological markers are calculated by means of a (parametric) Pearson correlation, and are listed with uncorrected p-values. However, if a correlation does not survive a Bonferroni correction for multiple comparisons, this is explicitly mentioned.

2.5. MEG data preprocessing

MEG data were analysed with MATLAB (2011b) (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analyses, epochs of 5000 ms (3000 ms