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Cortical correlates of susceptibility to upper limb freezing in Parkinson's disease

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HIGHLIGHTS

- Dual tasking increased susceptibility to upper limb freezing.
- This was associated with increased cortico-cortical phase synchronization from 13 to 30 Hz over the left prefrontal area.
- This abnormal phase synchronization was predictive for freezing behavior.

ABSTRACT

Objective: Freezing behavior is an unmet symptom in Parkinson's disease (PD), which reflects its complex pathophysiology. Freezing behavior can emerge when attentional capacity is reduced, i.e. under dual task interference. In this study, we characterized the cortical network signatures underlying the susceptibility to freezing during continuous finger tapping.
Methods: Fourteen PD patients with STN-DBS and thirteen age- and gender-matched healthy controls performed continuous tapping with the index finger as single motor task and during dual tasking. Synchronized EEG and mechanogram of the finger tapping were recorded. Subsequently, we analyzed cortical activity and cortico-cortical phase synchronization. We correlated these spectral measures with the biomechanically confirmed numbers of freezing episodes during finger tapping.
Results: During dual tasking compared to the single motor task, PD patients showed an increase of cortico-cortical phase synchronization over the left prefrontal area from 13 to 30 Hz. This correlated with

Abbreviations: STN-DBS, Subthalamic nucleus deep brain stimulation; PD, Parkinson's disease; HC, healthy controls; EEG, Electroencephalography; FOG, Freezing of Gait; FOG-Q, Freezing of Gait Questionnaire; SI, synchronization index.

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increased occurrence of freezing episodes. Interestingly, PD patients lacked the increase of prefrontal cortico-cortical synchronization from 4 to 7 Hz during dual tasking as observed in healthy controls.
Conclusion: Dual task interference led to an increase of left prefrontal beta band synchronization (13–30 Hz) in PD and this increment predicted the number of freezing episodes. This increment may underscore the relevance of prefrontal executive dysfunction in freezing susceptibility.
Significance: These findings enhance our understanding of the pathological network mechanisms behind increased susceptibility to freezing behavior.

1. Introduction

Freezing behavior including freezing of upper limb movement and Freezing of Gait reflects an episodic phenomenon that occurs in the majority of advanced PD patients, leading to impairment in quality of life, falls, and morbidity (Bloem et al., 2004; Giladi et al., 2001; Rahman et al., 2008). Current standard treatments such as L-Dopa and deep brain stimulation of the subthalamic nucleus (STN-DBS) often fail to control freezing behavior in the advanced disease stage (Vercruysse et al., 2014; Weiss et al., 2013). This may mirror the incomplete understanding of the complex pathophysiology behind freezing behavior. As important pathophysiological background, maladaptive motor processing was demonstrated at widely distributed neuronal levels including the basal ganglia (Vercruysse et al., 2013; Weiss et al., 2012), brainstem (Peterson et al., 2014b; Shine et al., 2013b; Snijders et al., 2011), as well as distributed cortical processors (Bartels and Leenders, 2008; Scholten et al., 2016). At the cortical level, pronounced Lewy-body pathology (Virmani et al., 2015) and motor network abnormalities paralleled the increased vulnerability of cortical motor processing in freezers. In particular, motor network abnormalities were observed in the frontal and parietal areas. Altered function of these areas parallel executive dysfunctions (Kostic et al., 2012) relating to impaired motor program adjustments and loss of automaticity (Hallett, 2008; Vandenbossche et al., 2012) as observed in freezers. Congruently, interference of freezers with a second cognitive task was described as an effective procedure to provoke freezing events given the susceptibility of freezers to 'cortical processing conflicts' and 'capacity overloads' (Peterson et al., 2014a; Spildooren et al., 2010).

In keeping with this evidence, motor network abnormalities in freezers clearly exist outside the freezing episode itself (Snijders et al., 2011; Vercruysse et al., 2013), and finally the freezing episode might constitute an endpoint of motor network imbalance or even the beginning of compensatory attempts to reset an efficient motor program (Shine et al., 2014; Toledo et al., 2014). Therefore, if an adequate timeframe for therapeutic intervention exists to prevent freezing behavior, it should probably lie outside the freezing episode itself.

Here, we aim to identify pathological brain states with respect to freezing susceptibility by analyzing cortical activity and cortico-cortical synchronization signatures in advanced PD patients. Cortical activity is expressed as a measure of local neuronal activity along oscillatory amplitude characteristics, and cortico-cortical phase synchronization is determined as correlation of oscillatory phases between distributed brain regions (Engel et al., 2013; Fell and Axmacher, 2011). Both measures have a pivotal role in both motor and cognitive tasks including the pathological network states of PD (Silberstein et al., 2005; Uhlhaas and Singer, 2006; Weiss et al., 2015).

Therefore, we studied cortical spectral measures in PD patients under dual tasking conditions and compared them to the single motor task (outside freezing episodes and motor arrests, respectively). We explored whether these cortical activity and synchronization modulations were related to freezing susceptibility. Therefore, we correlated the spectral modulations induced by dual tasking with the biomechanically confirmed number of freezing events during finger tapping (referred to as 'upper limb freezing'). Finally, we explored whether the modulations observed in PD were disease-specific by additionally analyzing dual tasking effects in healthy controls (HC).

Table 1
Characteristics of PD patients.

	Gender (M/F)	Age (years)	PD duration (years)	Time since DBS implantation (months)	Segmental UPDRS III (items 20–26)	FOG-Q
PD01*	M	61	7	4	10	2
PD02*	M	53	10	35	35	5
PD03	M	59	15	41	12	2
PD04	M	75	8	2	10	7
PD05	M	67	25	77	16	10
PD06*	M	41	10	6	6	10
PD07	M	63	14	3	18	3
PD08*	F	65	24	35	20	15
PD09	F	65	12	47	25	15
PD10*	F	63	19	34	23	14
PD11*	M	32	2	7	26	6
PD12*	M	74	8	25	22	8
PD13*	M	66	8	11	20	4
PD14*	M	63	24	73	30	15

Abbreviations: M, male; F, female; UPDRS, Unified Parkinson Disease Rating Scale; items 20–26, item 22 included only rating of head and upper limbs (total score = 72), FOG-Q = Freezing of Gait Questionnaire (total score = 24).
* Patients with freezing of upper limb during dual tasking.