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Abnormal premotor–motor interaction in heterozygous *Parkin*- and *Pink1* mutation carriers

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HIGHLIGHTS

- Asymptomatic heterozygous Parkin/PINK1 mutation carriers show altered premotor–motor inhibition.
- A single L-dopa administration could partly reverse this alteration.
- These mutation carriers can serve as *in vivo* models to study pre-symptomatic stages of Parkinsonism.

ABSTRACT

Objectives: Mutations in the *Parkin* and *PINK1* gene account for the majority of autosomal recessive early-onset Parkinson cases. There is increasing evidence that clinically asymptomatic subjects with single heterozygous mutations have a latent nigrostriatal dopaminergic deficit and could be taken as *in vivo* model of pre-symptomatic phase of Parkinsonism.
Methods: We charted premotor–motor excitability changes as compensatory mechanisms for subcortical dopamine depletions using transcranial magnetic stimulation by applying magnetic resonance-navigated premotor–motor cortex conditioning in 15 asymptomatic, heterozygous *Parkin* and *PINK1* mutation carriers (2 female; mean age 53 ± 8 years) and 16 age- and sex-matched controls (5 female; mean age 57 ± 9 years). Participants were examined at baseline and after acute L-dopa challenge.
Results: There were L-dopa and group specific effects during premotor–motor conditioning at an interstimulus interval of 6 ms indicating a normalisation of premotor–motor interactions in heterozygous *Parkin* and *PINK1* mutation carriers after L-dopa intake. Non-physiologically high conditioned MEP amplitudes at this interval in mutation carriers decreased after L-dopa intake but increased in controls.
Conclusion: Premotor–motor excitability changes are part of the cortical reorganization in asymptomatic heterozygous *Parkin*- and *PINK1* mutation carriers.
Significance: These subjects offer opportunities to delineate motor network adaptation in pre-symptomatic Parkinsonism.

1. Introduction

Parkin and PINK1-associated Parkinsonism is the most common cause of autosomal-recessive early-onset Parkinsonism (Klein and Schlossmacher, 2006) and is phenotypically almost indistinguishable from genetically undefined, i.e. iPD (Albanese et al., 2005; Klein and Schlossmacher, 2006) although in some cases the clinical presentation can be atypical (Hedrich et al., 2006). Genetic studies

Abbreviations: AMC, asymptomatic, heterozygous *Parkin* and *PINK1* mutation carriers; AMT, active motor thresholds; DRD, dopa-responsive dystonia; EMG, electromyography; FDI, first dorsal interosseus muscles; fMRI, functional magnetic resonance imaging; iPD, idiopathic Parkinsonism; M1, primary motor cortex; MEP, motor-evoked potential; PMd, dorsal premotor cortex; RMT, resting motor thresholds; SMA, supplementary motor area; TMS, transcranial magnetic stimulation.

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confirmed that *Parkin* and *PINK1* interact with each other in the same mitochondrial metabolic pathway and share a similar pathology (Rakovic et al., 2013). Moreover, the related consequences of the mutations (Clark et al., 2006; Park et al., 2006) seem to cause a similar functional and structural phenotype at a brain network level (Binkofski et al., 2007; van Nuenen et al., 2009).

Clinical (Hedrich et al., 2006) and histopathological (Pramstaller et al., 2005) studies in AMC, who per definition are not aware of symptoms themselves, but can have signs of Parkinsonism when examined by a movement disorders specialist, have fuelled the discussion about possible pathologic effects of single mutant alleles in these recessive disorders. Furthermore it has been shown that around 8% of all Parkinson patients carry a heterozygous *Parkin* mutation, whereas it was only present in 2% of healthy controls (Klein et al., 2007). Additionally, functional (Buhmann et al., 2005; van Nuenen et al., 2009; Anders et al., 2012), metabolic (Hilker et al., 2001; Khan et al., 2002; Eggers et al., 2010) and structural imaging studies (Binkofski et al., 2007; Hagenah et al., 2007, 2008) in *Parkin* and *PINK1* AMC have supported the notion of a latent nigrostriatal dysfunction. Such a subcortical deficit could probably lead to compensatory mechanisms at a cortical level in these subjects. This adaptive reorganisation of neuronal activity can be examined non-invasively *in vivo* by TMS. TMS studies in genetically determined Parkinsonism that could serve as model diseases for idiopathic forms are scarce. In particular, AMC are a unique chance to study subclinical effects of dopaminergic cell loss. A previous TMS study in *Parkin* AMC demonstrated reduced sensorimotor inhibition possibly representing a cortical compensatory effect due to latent nigrostriatal dysfunction (Baumer et al., 2007). Moreover, changes in neuronal activity in the pre-supplementary motor area (pre-SMA) and the PMd were found in carriers of a single mutant *Parkin* allele (Buhmann et al., 2005; van Nuenen et al., 2009). In particular, AMC revealed overactivity in PMd in a fMRI study when performing an internally cued motor task equally well compared to the control group, which was interpreted as a possible compensation for nigrostriatal dopamine deficiency (Buhmann et al., 2005). These regional cortical activity changes may be crucial to maintain an unaffected motor phenotype with normal movement capacity. Moreover, pointing in the same direction, fMRI studies in iPD have repeatedly shown an altered connectivity pattern characterized by a reduced activity within basal ganglia-mesiofrontal cortical loops including the SMA and probably compensatory overactive basal ganglia-PMd connections in the OFF state, whereas the reversed activity pattern was present after L-dopa administration (Samuel et al., 1997; Rowe et al., 2010; Michely et al., 2015). To further explore PMd–M1 connectivity changes in Parkinsonism we applied a neuronavigated dual-pulse TMS paradigm in 15 subjects with heterozygous *Parkin* and *PINK1* mutations and compared results to a group of healthy controls. We hypothesized that there are excitability changes in PMd–M1 pathways in these patients possibly as an adaptation to compensate for latent nigrostriatal dopamine deficiency.

2. Material And methods

2.1. Subjects and study design

We investigated 6 *Parkin*, 9 *PINK1* AMCs (2 female; mean age 53 ± 8 years; all right handed), and 16 healthy control subjects who did not differ from AMC with respect to age and gender (5 female; mean age 57 ± 9 years; all right handed). All AMC underwent a standardised neurological examination using the Unified Parkinson Disease Rating Scale part three (UPDRS III) (Martinez-Martin et al., 1994) and the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (Burke et al., 1985).

We determined RMT and AMT and applied a conditioning paradigm from left PMd to left M1. TMS measurements were carried out on the first day before (baseline) and on the second day 30 min. after the administration of 200 mg/50 mg L-dopa/benserazide (On LD state). To avoid common side effects of L-dopa like nausea all subjects received 3 × 10 mg of Domperidone one day before the L-dopa intake and 30 mg 30–45 min prior to L-dopa on the actual day of the L-dopa administration. There was no randomization with respect to the dopaminergic stage and subjects and investigators were not blinded to the treatment condition.

All subjects gave written informed consent to the study that was approved by the local ethics committee of the University of Lübeck.

2.2. Experimental setup

We used an experimental setup similar to that in previous studies (Baumer et al., 2009; Weissbach et al., 2015). To bring subjects in a relaxing position during the experiment, they were seated individually in a comfortable position with their head resting on a holder. To avoid muscle tension arms were positioned on a pillow and subjects were instructed to relax but stay alert with eyes open.

The EMG was measured using Ag/Ag-Cl disc surface electrodes that were positioned over the right FDI in a belly tendon montage. The earth electrode was placed over the wrist. A D360 amplifier (Digitimer Limited, Welwyn Garden City, Hertfordshire, UK) was used to filter (20 Hz and 2 kHz) and amplify EMG signals. With the help of a laboratory interface (Micro 1401; Cambridge Electronics Design (CED), Cambridge, UK) the EMG signal, that was sampled at 5 kHz, was digitized and recorded. Data was stored on a personal computer using the SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).

2.3. MR-navigated left PMd–M1 conditioning paradigm

TMS measures were done using two Magstim 200 magnetic stimulators (Magstim Company, Whitland, Dyfed, UK). For stimulating the M1 a 70 mm figure-of-eight coil was used. The M1 coil was rotated in a 45° angle to the midline and induced a posterior to anterior directed current. To produce the maximal muscle activation within the FDI the TMS coil was moved in small steps of about 0.5 cm within the assumed motor area of the right hand. The area in which a TMS pulse of supra-threshold intensity produced continuously the largest mean MEP was determined as the 'motor hot spot'. To achieve a consistent local stimulation this coil position was marked on the head skin with a pen indicating the anterior bifurcation of the coil as well as the orientation of the coil.

A custom made 25 mm, branding iron style figure-of-eight-shaped coil was used to produce the conditioning stimulus over the PMd ("baby coil"; Magstim Company, Whitland, Dyfed, UK). The PMd coil was held in the same angle as the M1 coil approximately 45° towards the midline, inducing an anterior to posterior current in the PMd, which has been shown to be most effective in previous studies (Baumer et al., 2009). To perform a simultaneous targeting of both coils we used a similar approach as described previously (Weissbach et al., 2015). The M1 coil was slightly lifted at its anterior bifurcation allowing for an alignment of both coils in a minimal distance, as shown in Fig. 1. The PMd target region was identified individually for each subject anatomically by using the Brainsight neuronavigation system (Rogue Research, Montreal, Canada) and the individual T1-weighted MRI of each subject, resulting in peak Talairach coordinates of $x = -30$; $y = -4$, $z = 58$ in analogy to a previous meta analysis (Mayka et al., 2006). Prior to TMS measurements subjects were investigated on a 3 T MR