Peculiarities of tremor-related brain activation in Parkinson’s disease during motion: fMRI study

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Purpose

Parkinson's disease (PD) typically manifests with unilateral motor signs and subsequently evolves a number of motor and non-motor symptoms [Hoehn and Yahnr, 2001]. Resting tremor is one of the main Parkinson's disease (PD) symptoms. Tremor asymmetry is considered a crucial criterion for PD and may influence hemisphere-associated cognitive functions [Erro et al. 2012]. It is still debated whether the lateralization of PD symptoms influences the way of future disease progression, especially concerning non-motor symptoms development and the role of DMN in this process [Erro et al. 2012, Riederer and Sian-Huelsmann, 2012]. PD is associated with abnormal hypersynchronicity in basal ganglia-thalamocortical loops [Baudrexel, 2011]. Subthalamic nucleus (STN) gained increased attention in PD due to its role in deep brain stimulation for PD symptoms treatment. STN was shown to be activated during the movement execution [Rodrigues-Oroz, 2001]. Also, bilateral activation and synchronization of left and right STN upon or prior to the hand movement onset and until the end of movement was shown for left and right unilateral hand movement [Darvas, 2014]. STN was shown to participate in movement error detection [Tan, 2014] and to function as a central component of an arbitrary system of the basal ganglia [Servestani, 2011]. Different effects of DBS of left/right/bilateral STN in PD was shown, comprising speech worsening in left STN DBS, while no such effect in right or bilateral STN DBS, supposing laterality dependent STN functioning [Schulz, 2012]. Nevertheless altered pattern of brain activation in tremor/no-tremor PD patients was shown, no tremor laterality and severity patients’ subdivision was previously done. We propose the analysis of brain activation in PD patients with different tremor laterality and severity for evaluation of PD-subtype specific fMRI response.
Methods and materials

Group of 30 right-handed PD patients (12F, 46-74 y.o.) was studied by fMRI with 1.5T SIGNA (GE, USA). According to the UPDRS tremor severity and sidedness, it was divided into four subgroups. Left side tremor: G\textsubscript{L} light (7 patients, 2F, tremor 0-1), G\textsubscript{L} severe (11 patients, 5F, tremor 2-4). Right side tremor: G\textsubscript{R} light (6 patients, 3F, tremor 0-1), G\textsubscript{R} severe (6 patients, 1F, tremor 2-4). Total brain activation was analysed for G\textsubscript{L} light, G\textsubscript{L} severe, G\textsubscript{R} light, G\textsubscript{R} severe. Right-hand finger tapping task was used for fMRI activation. Also, brain activation during the audio-motor transformation phase (AMT, onset of voice command of movement start/stop) and movement execution phase (solely) was analyzed for age-matched healthy volunteers (Gr1), left (Gr2) and right (Gr3) lateralized tremor PD patients (taken and combined from the previously described groups with medium tremor severity). Gr1 consisted of 7 healthy subjects (4F, 51-83 y.o.). Gr2 consisted of 6 non-demented (MoCA 25-27, tremor 1-3) PD patients with left-side (non-primary hand) tremor (2F, 53-74 y.o.). Gr3 consisted of 5 non-demented (MoCA 25-30, tremor 1-3) PD patients with right-side (primary hand) tremor (2F, 56-74 y.o.). Simple reaction time in Gr1/Gr2/Gr3=302/352/328 ms.

Single shot GE-EPI sequence was used for BOLD imaging (TR/TE=3000/71 ms, voxel size=4x4x5 mm). Anatomical images were acquired with FSPGR sequence (TR/TE=11.6/5.2 ms, TI=450 ms, voxel size=1x1x1.5 mm). FMRI data processing was carried out using GLM (FEAT) and ICA (MELODIC) based software from FSL (Oxford, GB). Pre-processing, including motion correction, slice timing correction, spatial smoothing (FWHM=8 mm) was done. Single subject and group GLM and ICA analyses were done.
Results

fMRI data showed the common pattern of brain activation for all studied subjects: bilateral primary (M1S1), premotor, supplementary motor cortex, thalamus and cerebellum Fig. 1 on page 5. Increase of activation volume (voxels) / #BOLD (%) amplitude was shown in (Gr_light > Gr_severe > Gl_severe > Gl_light): (3736/2.22, 3281/1.96, 1664/1.36, 1274/1.33) respectively Fig. 2 on page 5. Activation of the subthalamic region was shown in Gr_light, Gr_severe during the movement execution. Decrease of M1S1 activation was shown in Gr_severe Fig. 1 on page 5. Bilateral cortex activation in PD patients under unilateral motor task execution is explained by plasticity changes in brain motor network. Activation of the subthalamic region in severe tremor patients might have the compensative physiological background. Decreased activation of M1S1 in Gr_severe reveals the decrease of excitatory background. Decreased activation of M1S1 in Gr_severe reveals the decrease of excitatory input in M1S1.

Also, the brain activation during AMT was analyzed. We hypothesized that AMT plays the important role in voice-guided movements' initiation and STN involvement, especially in lateralized PD. GLM and ICA-based analyses of AMT for Gr1, Gr2, Gr3 revealed activation of neural network consisted of the bilateral posterior temporal lobe, precuneus, supplementary motor area and cingulate motor region Fig. 3 on page 6. Left STN activation during AMT was shown for Gr1, Gr2, Gr3 Fig. 4 on page 7. Bilateral activation of STN for G2 during AMT was shown. Specifically, bilateral activation of STN during the movement phase (additional to the left STN activation during the AMT) was shown for G3 Fig. 5 on page 8. Increased total volume of activation was shown for G3 in comparison to G2 Fig. 6 on page 9.

The process of voice-guided movement execution and AMT in PD patients and age-matched subjects evokes activation of several neural networks. Auditory cortex, SMN and pC participate in AMT, which was previously shown [Warren et al. 2005]. PD symptoms laterality have no impact onto the AMT neural network activation while it has an important impact onto the STN functioning. Left STN was shown to have more importance for AMT. Bilateral STN activation in left sided PD symptoms suppose the idea that specifically left STN play important role in PD symptoms, while right STN activates only in case of left PD symptoms prevalence. While STN was shown to correlate with tremor laterality and occurrence [Helmich, 2012], it was shown that STN participate in movement error correction [Servestani, 2011]. Specific activation of bilateral STN during the movement execution in primary side affected PD patients, together with increased total volume of activation and quite shorter simple reaction time suppose STN compensative and corrective role in movement.
Fig. 1: Common pattern of brain activation for all studied subjects. Green - GLlight, Blue - GLsevere, Red - GRlight, Yellow - GRsevere.

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**Fig. 2:** Activation volume and #BOLD amplitude change in studied PD patients (GRlight, GRsevere, GLsevere, GLlight).

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Fig. 3: Regions of brain activation during the AMT for G1 (green), G2 (blue) and G3 (red).

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Fig. 4: STN activation during the AMT for G1 (green), G2 (blue) and G3 (red).

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**Fig. 5:** STN activation during the movement execution phase in G3 (pink).

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**Fig. 6:** Volume of total brain activation in G1 (green), G2 (blue) and G3 (red).

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Conclusion

Tremor severity and sidedness influences brain activation pattern and BOLD response in PD patients. We identified PD symptoms laterality dependent STN activation peculiarities. Obligatory left STN activation in AMT suppose it's role in motor command switching. Bilateral STN activation during the movement execution supports it's proposed role as a motor error correction node.
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