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Motor phenotype and magnetic resonance measures of basal ganglia iron levels in Parkinson's disease☆

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ABSTRACT

Background: In Parkinson's disease the degree of motor impairment can be classified with respect to tremor dominant and akinetic rigid features. While tremor dominance and akinetic rigidity might represent two ends of a continuum rather than discrete entities, it would be important to have non-invasive markers of any biological differences between them *in vivo*, to assess disease trajectories and response to treatment, as well as providing insights into the underlying mechanisms contributing to heterogeneity within the Parkinson's disease population.
Methods: Here, we used magnetic resonance imaging to examine whether Parkinson's disease patients exhibit structural changes within the basal ganglia that might relate to motor phenotype. Specifically, we examined volumes of basal ganglia regions, as well as transverse relaxation rate (a putative marker of iron load) and magnetization transfer saturation (considered to index structural integrity) within these regions in 40 individuals.
Results: We found decreased volume and reduced magnetization transfer within the substantia nigra in Parkinson's disease patients compared to healthy controls. Importantly, there was a positive correlation between tremulous motor phenotype and transverse relaxation rate (reflecting iron load) within the putamen, caudate and thalamus.
Conclusions: Our findings suggest that akinetic rigid and tremor dominant symptoms of Parkinson's disease might be differentiated on the basis of the transverse relaxation rate within specific basal ganglia structures. Moreover, they suggest that iron load within the basal ganglia makes an important contribution to motor phenotype, a key prognostic indicator of disease progression in Parkinson's disease.

1. Introduction

Recent evidence suggests that motor-impairments in Parkinson's disease (PD) can be classified on a continuum with tremor dominant (TD) and akinetic rigid (AR) symptoms as extreme ends [1]. However, the precise underlying differences in neural pathology remain to be established. Physiologically, patients with predominantly AR phenotype have higher levels of neuronal loss, gliosis, extra-neuronal melanin deposits and neuro-axonal dystrophy in the SN compared to individuals with predominantly TD phenotype [2]. Furthermore, AR symptoms are associated with greater reductions in dopamine levels within the globus pallidus [3], and higher levels of cortical Lewy bodies [4]. Nigro-striatal degeneration in PD closely correlates with bradykinesia and rigidity but, importantly, *not* with tremor [5].

Another pathological hallmark of PD is alteration of brain iron level [6]. In particular, iron levels of the basal ganglia (BG), including substantia nigra (SN), are increased in PD pointing

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toward a dopamine-related dysfunction of the brain's iron homeostasis [6]. Moreover, work in animals [7] raises the possibility of a direct link between AR/TD motor symptoms and changes in iron levels within the BG.

In vivo, structural changes can be quantified on the basis of MRI measures such as R2* and magnetization transfer (MT) [8]. R2* is sensitive to iron levels [9] and in the midbrain it correlates with impaired motor performance [10]. MT, on the other hand, relates to the exchange of magnetization between mobile water protons and protons that are immobilized by macromolecules [11]. Although MT changes can have several region-specific physiological causes, within the SN of PD patients [12] and healthy older controls [13] MT changes likely relate to neuronal loss and/or degradation of the neuromelanin macromolecule scaffolding [14].

Here, we investigated the pathophysiology of PD and their relationship with motor symptoms using MRI. We predicted higher structural integrity (MT and/or size) of the BG in healthy controls compared to PD patients, and a direct relationship between iron content (R2*) and AR/TD motor symptoms. Finally, we investigated the relationship between MT and R2* within these structures [6].

2. Methods

2.1. MRI acquisition

Whole-head quantitative MRI was performed on a 3-tesla whole body magnetic resonance imaging scanner (Magnetom TIM Trio, Siemens). It comprised multi-parameter mapping, which was based on multi-echo 3D FLASH (fast low angle shot) acquisitions at a spatial resolution of 1 mm^3 [8]. Briefly, whole brain images were acquired with predominant T1-, proton density, and MT-weighting imposed by the choice of repetition time (TR) and flip angle (T1-w: 18.7 ms/20°; PD-w and MT-w: 23.7 ms/6°) and by applying an off-resonance Gaussian-shaped RF pulse (4 ms duration, 220° nominal flip angle, 2 kHz frequency offset) prior to non-selective excitation for the MT-w acquisition, respectively. Alternating gradient echoes were acquired at six equidistant echo times (TE) between 2.2 ms and 14.7 ms for the T1- and MT-weighted acquisitions with two additional echoes at TE = 17.2 ms and 19.7 ms for the proton density-weighted acquisition. These multiple TE images were later averaged into one image for each weighting (e.g., T1-w, MT-w, PD-w) to increase signal to noise ratio.

Each scanning sequence (MTw, T1w, and proton density-weighted) was relatively short (only ~7 min) which reduces possible within-scan motion. Between scan motion was accounted for by co-registration of the acquired images. To keep motion artifacts to a minimum, care was taken that each subject could rest on the scanner bed in a comfortable position and cushion padding was used for head fixation. Therefore, motion artifacts were minimized, which was further corroborated by visual inspection of the images.

2.2. Data processing and region of interest analysis

Data were reconstructed using SPM8 routines (www.fil.ion.ucl.ac.uk/spm) and Matlab tools (The Math-Works Inc.; Natick, MA, USA). For each subject, we calculated parameter maps of the MT saturation and the effective transverse relaxation rate R2* [8]; the images for different modalities were co-registered using rigid-body transformation. MT saturation can be regarded as a semi-quantitative measure, which corresponds to the percentage loss of magnetization imposed by a single MT pulse (in percent units – p.u). MT is implicitly corrected for differences in relaxation times and excitation flip angle, thus differing from the more commonly used MT ratio, the percentage reduction of the steady state signal. We did not use MT-ratio (MTR) since it is sensitive to non MT-specific effects such as changes in T1 or the RF transmit field inhomogeneities.

For each subject the following 'Regions Of Interest' (ROIs) were defined from native space (T1-image) using *FreeSurfer* (http://surfer.nmr.mgh.harvard.edu/): pallidum, putamen, caudate, nucleus accumbens and (entire) thalamus. Further subdivision of these structures was beyond the scope of this study. The thalamus was included since it constitutes a major input/output region of the BG and thus is of interest in the pathophysiology of PD. For each ROI we computed its volume, and mean R2* and MT value (Table S1).

FreeSurfer does not support routines to automatically segment the SN. Therefore, it was defined manually for each subject on the basis of their MT-image (see Fig. 1) by a rater who was blind with respect to the subject's identity (C.E.). For a subset of 14 images this procedure was performed twice. An Intraclass Correlation Coefficient agreement (ICC agreement) of 0.90 for the right and 0.91 for the left hemisphere indicated high intra-rater reliability.

The SN was segmented on the basis of MT images for three reasons. First, on MT-images the SN can be distinguished from surrounding structures as a bright stripe while the adjacent red nucleus and cerebral peduncle appear dark (Fig. 1); second,

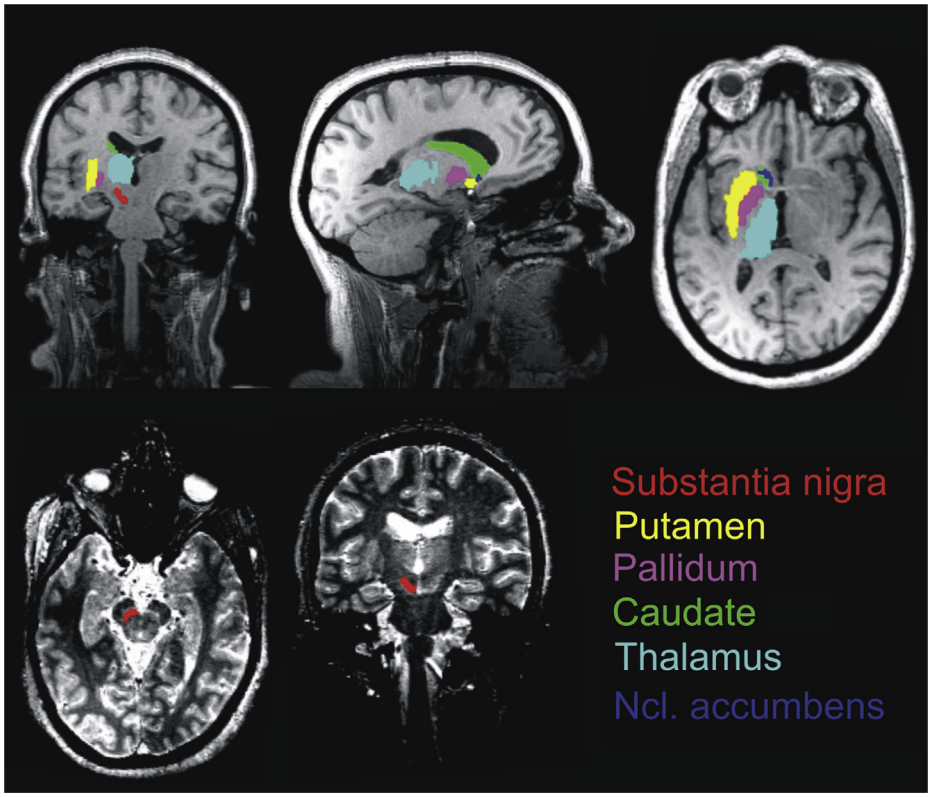

Fig. 1. Regions of interest (ROI). The SN was defined manually for each subject. All other ROIs were segmented automatically (see Methods). Upper row shows left hemisphere ROIs overlaid on an individual T1-weighted image and lower row shows the subject's MT-image.