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Abnormally reduced frontal cortex activity during Trail-Making-Test in prodromal parkinson's disease–a fNIRS study

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder leading to typical motor as well as a range of non-motor symptoms, including cognitive decline mainly characterized by executive deficits. The latter are known to appear years before the typical motor signs, thus representing the prodromal phase of PD. However, appropriate methods for measuring executive dysfunction in this context are not well established yet. Traditionally, executive performance is associated with frontal structures. Here, we investigated prodromal, early PD patients and healthy controls regarding their executive functioning on the behavioral and neural level, measured by the Trail-Making-Test (TMT) combined with functional near-infrared spectroscopy. We observed significantly reduced neural activity in the right dorsolateral prefrontal cortex within PD patients compared to controls completing the TMT-A and -B in contrast to the TMT-C, but no differences on a behavioral level. These promising results need to be confirmed and checked for reliability in future studies to extend the spectrum of markers applied in prodromal PD.

1. Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder associated with pathological alpha-synuclein protein aggregates (the so-called Lewy bodies) accumulating in the nervous system (Dickson, 2018). Mainly the structural and functional impairment of dopaminergic neurons in the substantia nigra pars compacta (SNc) leads to severe alterations in basal ganglia circuits. Hence, it demonstrates the typical motor symptoms: rigidity, tremor, akinesia and postural instability (Reichmann, 2017). But particularly at later stages, PD becomes a multisystem disorder affecting various subcortical and cortical regions of the brain (Braak et al., 2004). Importantly, it is well known that different non-motor features, mainly olfactory dysfunction (Siderowf et al., 2012), depression (Ishihara and Brayne, 2006) and REM sleep behavior disorder (RBD) (Postuma et al., 2009) can precede the typical motor symptoms by years. Furthermore, several autonomic symptoms such as constipation, urinary and orthostatic dysfunction are not only apparent during the course of the disease, but may also be associated with an elevated risk of future PD (Abbott et al., 2001; Liepelt-Scarfone et al., 2015).

Cognitive impairment is a common symptom even in the early stages of PD (Muslimovic et al., 2005) and seems to occur during the prodromal phase of the disease as well (Heinzel et al., 2019). Regarding specific cognitive domains involved, Fengler et al. (2017) reported that executive dysfunction is observed most frequently in prodromal PD, whereas changes

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in memory or global cognition have been described less often. Executive dysfunction even has predictive value regarding the development of PD associated dementia that affects at least 30%–50% of all PD patients during the course of disease (Woods and Tröster, 2003) and impairs PD patients' quality of life (Kudlicka et al., 2014). Hence, Fengler et al. (2017) suggested to consider executive dysfunction as an additional non-motor feature of prodromal PD and emphasized the need for further studies in this field as well as the identification of appropriate methods for assessment. Several aspects of executive function have been described, including the ability of selection, inhibition and planning as well as abstract thinking, cognitive flexibility and regulation of behavior based on social rules (Leh et al., 2010). Traditionally, the frontal cortex has been considered as a major brain structure involved in this neuropsychological phenomenon (Leh et al., 2010). Brugger et al. (2015) correlated executive dysfunction in PD measured by the Frontal Assessment Battery on a morphological level with mainly frontal atrophy by voxel-based morphometry. In contrast, particularly at an early stage of the disease, other authors failed to identify any correlation between cognitive, especially attention and executive dysfunction and structural gray or white matter lesions (Dalaker et al., 2009; 2010). Using various techniques, more evidence is arising for neural changes on the functional imaging level associated with executive dysfunction even in incident PD. In their review article, Tahmasian et al. (2017) aimed at identifying consistent pathophysiological patterns focussing on resting-state fMRI. They identified functional aberrations of the parietal cortex as a convergent finding across studies, notably of the bilateral inferior parietal lobule and the supramarginal gyrus, and suggested these regions as a possible early imaging marker for PD. According to the authors' BrainMap database enquiry, the latter even shows a significant association with executive functions. Huang et al. (2007) described a metabolic pattern, characterized by reduced activity in frontal and parietal association areas in PET (Positron Emission Tomography), that correlated with cognitive, particularly memory and executive, deficits in PD. In prospective measurements it further predicted memory, visuospatial and perceptual motor speed performance. The authors therefore suggested this pattern as a reproducible imaging marker of cognitive function in PD. Furthermore, Diwadkar et al. (2000) emphasized the relevance of a fronto-parietal network for executive function in their fMRI study. In another fMRI study, Lewis et al. (2003) showed a significantly reduced activation – besides in regions of the basal ganglia – particularly in the ventrolateral as well as dorsolateral prefrontal cortex (DLPFC) during a working-memory task in PD patients with a selective executive impairment compared to PD patients without any cognitive impairment. Beside specific cortical and subcortical regions, furthermore a characteristic malfunctioning of the so-called default mode network (DMN) during executive tasks has been described in PD via fMRI, mainly characterized by a deficient deactivation of the corresponding brain areas (Eimeren et al., 2009).

Taken together, despite the above mentioned, there are promising studies concerning this field, whose results seem to be at least partly consistent although the neural substrates of cognitive symptoms in PD are yet poorly understood. In this context the prodromal phase of the disease has so far rarely been investigated. In line with this, a recent meta-analysis by Giehl et al. (2019) came to the conclusion that concerning the existing literature about whole brain imaging (fMRI or PET) of executive dysfunction in PD, there does not seem to be enough evidence for a common neural correlate yet, maybe due to the relatively small number of studies so far and their great methodological variability. Therefore, they emphasized the need for further research focusing on functional brain changes associated with executive dysfunction in this field. In the present study, we cross-sectionally investigated 21 prodromal and early PD patients and a matched healthy control group, which underwent the Trail-Making-Test (TMT), a widely used neuropsychological instrument to measure executive function. In order to understand the underlying functional neural alterations associated with neurodegeneration in general and subsequent executive dysfunction, we simultaneously measured cortical activity with fNIRS. This method has already shown to be suitable for the investigation of elderly subjects during TMT performance as well as the detection of aging-related differences in resulting cortical activation patterns (Hagen et al., 2014; Rosenbaum et al., 2016; 2018).

Due to the higher complexity of the task, we expected to detect increased cortical oxygenation during the performance of the TMT-B in comparison to the TMT-A in general. Considering preexisting findings, we further assumed to find different activation patterns, especially within the frontal cortical structures, between the (prodromal) PD patients and controls during performance of an executive task.

2. Participants and methods

2.1. Study population

The *T*übingen evaluation of *R*isk factors for *E*arly detection of *N*euro*D*egeneration (TREND, Tübinger Erhebung von Risikofaktoren zur Erkennung von Neurodegeneration) is a prospective longitudinal study initiated in 2009 with biennial assessments. Inclusion and exclusion criteria are as follows: age between 50 and 80 years, no neurodegenerative disease at baseline and at least one of the following prodromal markers for neurodegeneration: depression, hyposmia and probable RBD. Individuals who did not experience any of these symptoms were recruited as controls. The assessment battery includes amongst others: medical history, neurological examination including motor assessment, autonomic testing, transcranial sonography, olfactory testing with Sniffin Sticks, cognitive testing with the CERADplus battery (Consortium to Establish a Registry for Alzheimer's Disease) (Morris et al., 1988) and MOCA (Montreal Cognitive Assessment) (Nasreddine et al., 2005) as well as self-report questionnaires assessing RBD, mood disturbances (Beck depression inventory version I), quality of life and health care (for more details visit: https://www.trend-studie.de/). All investigators are blinded to the results of all other examinations. Study data are collected and managed using REDCap electronic data capture tools hosted at the University of Tuebingen (Harris et al., 2009).

For the present analysis all PD-converters, diagnosed according to the official UK Brain Bank criteria (Hughes et al., 1992), up to and including the follow-up no. 4 (according to the years 2009–2017) from the TREND-study database were identified (n = 29). Five of these were not native German speakers and therefore excluded from the present analysis. Three of the remaining 24 subjects did not attend the follow-up no. 2 where the data of interest had been collected and therefore were excluded from the present analysis as well. A non-PD-diseased control sample was matched to the remaining 21 subjects via propensity score matching, controlling for the following variables: age, gender and years of education. We further tested for the influence of a subject's medication status on the results in an additional analysis.

Importantly, since the TMT/fNIRS dataset of interest was available only once (from follow-up no. 2), in the next step, the PD-converters were split into two groups of early (i.e. conversion before or very close to the measurement date relevant for the presented data, either at baseline n = 2, first follow-up n = 4, or second follow-up n = 3; total n = 9) and late (conversion after second

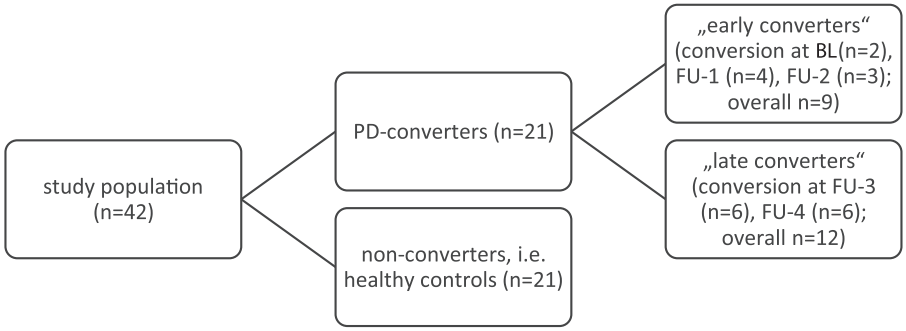

Fig. 1. Synopsis of the study subgroups. BL = baseline, FU = follow-up.

follow-up, i.e. at third follow-up n = 6, and fourth follow up n = 6; total n = 12) converters (Fig. 1). This means that part of the sample included in our analysis was already diagnosed with PD at the time of testing, whereas the other part was diagnosed at a later time following the reported data collection. Despite our leading interest in functional neural changes associated with the prodromal phase of PD, the experimental data of the former, of course, are even informative in order to complement the overall picture of the so far poorly understood neuroimaging alterations in early PD stages. Therefore, we first compared the whole group of PD-converters to their matched controls. In a second step, we analyzed the late converters (i.e. the prodromal PD patients) in comparison to the control group exclusively in order to investigate the clear prodromal pattern.

The study was approved by the ethical committee of the Medical Faculty of the University of Tuebingen (no.: 90/2009BO2). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

2.2. Trail-Making-Test

During the fNIRS data acquisition, subjects were asked to perform an adapted TMT. The TMT is a widely used paper-and-pencil neuropsychological instrument measuring executive function, e.g. in the CERADplus test battery (Morris et al., 1988). The adapted form used during the fNIRS experiment consisted of 3 subtests: TMT-A, TMT-B, and TMT-C. During the TMT-A, subjects were asked to connect encircled numbers in ascending order (1-2-3-4…) which were scattered randomly over a piece of paper. The TMT-B demanded task switching by connecting encircled numbers and letters in an alternating and ascending order (1-A-2-B-3-C…). Moreover, we used an additional control condition (TMT-C) in which lines between circles were already drawn and subjects were asked to retrace these lines. In every part of the TMT, 25 items were presented. Both, the TMT-A and TMT-B require visual search and motor speed abilities, whereas the TMT-B also stresses set-shifting and working memory functions. In contrast, the TMT-C only captures motor speed abilities. The TMT was assessed in an experimental block-design with the order A-B-C-A-B-C-A-B. All blocks were separated by 30-seconds rest periods. The first 2 blocks consisted of the presentation of the original TMT-A and TMT-B and their implementation as recommended in the CERADplus protocol. First, subjects attended the TMT-A following an instruction and a brief practice trial. After a 30-seconds pause, participants had a short practice trial for the TMT-B before performance of the actual trial. During the first assessment of the TMT-A and -B, subjects had no time limit for test completion (to allow for a standardized analysis of TMT behavioral data). In all following blocks, completion-time was restricted to 30 seconds (in line with typical block-design imaging protocols). After completion of the first 2 training blocks, 2 repetitions of the experimental 30-seconds blocks including the TMT-C, TMT-A and TMT-B were assessed. Including preparation time, the whole task took approximately 25 minutes. Analysis of the fNIRS data included averaging over the repetitions of the 3 condition blocks. For the conditions TMT-A and -B, averages excluded the practice trials.

2.3. Functional near-infrared spectroscopy and preprocessing of data

Data were assessed during the 5 minute resting state measurement and the subsequent TMT. We ensured proper time-locking between fNIRS acquisition and the TMT task by the investigator pressing a trigger button and simultaneously requesting the subject to start the task. The 30-s blocks for each condition were averaged with a 10-s baseline correction and a linear detrending. We used a continuous wave, multichannel near-infrared spectroscopy (NIRS) system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan) with a temporal resolution of 10 Hz to assess cortical blood oxygenation during the performance of the TMT. Data were recorded with a semiconductor laser and avalanche diodes at two wavelengths (695 ± 20 and 830 ± 20 nm) with 4.0 ± 0.2 mW for each wavelength at each optode. In this study, we used the same optode system as reported in Hagen et al. (2014), covering parts of the bilateral DLPFC (dorsolateral prefrontal cortex), SAC (sensory association cortex) and IFG (inferior frontal gyrus). 38 channels were divided into 2 frontal (3 × 3 optodes each: 5 emitters and 4 detectors) and 2 posterior probesets (2 × 3 optodes each: 3 emitters and 3 detectors). Optodes were placed on a plastic cap with reference points at F3/F4 and Fp1/Fp2 for the frontal probesets and C3/C4 for the posterior probesets, according to the international 10-20 system (Jasper, 1958; Homan et al., 1987). Channel positions for this probeset were described by Hagen et al. (2014) using a neuro-navigation system (LOCALITE GmbH, St. Augustin, Germany) on a volunteer's head. Corresponding brain areas of each channel were extrapolated from reference points as in the work by Singh et al. (2005) as well as Tsuzuki et al. (2007) and Tsuzuki and Dan, (2014) based on the Colin 27 template.

Raw data were exported as TBL directory from the NIRS machine and reconstructed with self-written MATLAB code. The changes in absorbed NIR-light were transformed into relative O_2Hb and HHb levels by means of a modified Beer–Lambert law. fNIRS preprocessing was performed with MATLAB R2017a (MathWorks Inc., Natick) and included the following steps: bandpass filtering (0.001 to 0.1 Hz) based on discrete cosine transform-II and inverse discrete cosine transform-II filters, correlation-based signal improvement according to Cui et al. (2010) for motion correction procedures, interpolation of single high artifact-loaded channels by visual inspection, independent component analysis (ICA)-based re-

duction of clenching artifacts, and a further low cutoff filtering at 0.01 Hz. Note that the TMT in some cases induces high arousal artifacts that cannot be corrected by the ICA procedure due to too frequent high-amplitude signals. In this dataset, six subjects showed such artifacts. In these cases, the signal was corrected by a principal component analysis reduction of the first component (Brigadoi et al., 2014). Finally, we applied a principal component analysis-based Gaussian kernel filtering for removement of the global signal (Zhang et al., 2016) and z-standardized each subject's fNIRS data (within-subject centering). Brain maps were computed with self-written MATLAB routines, plotting measured cortical oxygenation of corresponding brain areas onto a brain-template. With respect to the brain maps, differences in Cohens d were mapped on a template brain at the respective channel coordinates. The brain surface voxels between the channels were interpolated using Gaussian radial basis functions (Haeussinger et al., 2014). The MATLAB code of the analysis is available on request.

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics Version 24. For behavioral (performance) and fNIRS data, repeated measurement analyses of variance (ANOVAs) were performed. For fNIRS data the within-subject factors ROI (Region of Interest) (DLPFC versus SAC, both bilateral) and testing condition (TMT-C versus -A versus -B) and between subject factor group (PD-converters vs. controls) were used. It is important to note that we included the factor ROI in the linear models even though the interpretation of the main effect of ROI is difficult due to differences in optical path lengths. We chose to include the factor ROI as the main effect over all regions of interest is interpretable despite different optical path lengths. The IFG was excluded because of frequent artefacts in the dataset. For effect sizes, partial η^2 is reported. fNIRS data were analyzed separately for each of the four ROI's, with correction for multiple testing of post-hoc analysis with Helmert contrasts. Behavioral data was analyzed in the same manner, however without the factor ROI.

For analysis and comparison of medication status between the two groups, a Chi-square-test was performed. For level of significance, Fisher's value is reported.

In order to illustrate the variance between subjects and allow to interpret the outliers, we added boxplots of all bargraphs in the supplemental material.

3. Results

3.1. Population characteristics and prevalence of PD risk factors

We recruited a total of 21 healthy controls (non-converters) and 21 PD-converters. PD-converters were further separated into early (n = 9) and late converters (n = 12) according to the time of conversion. Both groups were comparable regarding their gender distribution and their mean years of education (descriptive statistics are to find in Table 1).

Furthermore, we compared the occurrence of the three most relevant PD risk factors (RBD, hyposmia and depression) between the different subgroups. Within the group of the converters, 9 individuals (43%; n = 5 early and n = 4 late converters) showed REM sleep behavior disorder (RBD), 12 reported hyposmia (57%; each n = 6 early and late converters) and 2 were diagnosed with depression (10%; each n = 1 early and late converter). Within the group of the healthy controls, 5 (24%) individuals showed RBD, 4 hyposmia (19%) and 1 (5%) was diagnosed with depression. All data refer to the time of testing (Table 1).

3.2. Behavioral data

In order to investigate whether non-converters and converters differed in their performance in the TMT, we analyzed the mean number of completed items (correct and incorrect), the number of errors made as well as the mean number of correctly solved items as a performance index. We analyzed these behavioral outcome measures using a repeated measures ANOVA dependent on task (TMT-A VS: TMT-B vs. TMT-C) and group (converters vs. non-converters). For descriptive statistics see Table 2.

3.2.1. Mean number of completed items

With respect to the number of completed items, we observed a significant main effect of the factor TMT task (TMT-C vs. TMT-A vs. TMT-B), $F(2, 80) = 295.895$, $p < 0.001$, $\eta^2 = 0.88$). Post-hoc comparisons with Helmert contrasts revealed significant differences between TMT-C and TMT-A/B, $F(1, 40) = 313.178$, $p < 0.001$, $\eta^2 = 0.89$, and between TMT-A and TMT-B, $F(1, 40) = 279.163$, $p < 0.001$, $\eta^2 = 0.88$. Subjects completed more items during the TMT-C than during both, TMT-A/B, and more items during the TMT-A than during the TMT-B.

3.2.2. Mean error rates

Analyzing the mean number of errors, we used a Wilcoxon-Test as error rates were non-normally distributed. We found no significant differences between converters and non-converters in error rates during the TMT task conditions, however, all subjects made more errors during TMT-A ($Z = -2.333$, $p < 0.05$, $r = -0.37$) and during TMT-B ($Z = -2.165$, $p < 0.05$, $r = -0.34$) than during TMT-C.

3.2.3. Performance

In terms of correctly solved items (performed items – errors), again we observed a significant main effect of TMT task, $F(2, 80) = 299.171$, $p < 0.001$, $\eta^2 = 0.88$. As for the number of completed items, post-hoc comparisons revealed significant differences between TMT-C and TMT-A/B, $F(1, 40) = 329.742$, $p < 0.001$, $\eta^2 = 0.89$, and between TMT-A and TMT-B, $F(1, 40) = 271.247$, $p < 0.001$, $\eta^2 = 0.87$. Subjects performed better during TMT-C than during TMT-A/B as well as during TMT-A as compared to the TMT-B.

In summary, no significant differences were observed between converters and non-converters on a behavioral level (Fig. 2).

3.3. fNIRS

Further, we investigated cortical oxygenation in our regions of interest (right DLPFC, left DLPFC, right SAC, left SAC) dependent on TMT task (TMT-C vs. TMT-A vs. TMT-B) using a mixed ANOVA dependent on group (converters vs. non-converters). Correcting violated sphericity assumptions using Huynh-Feldt in case of ROI ($\varepsilon = 0.817$) and the interaction of TMT task and ROI ($\varepsilon = 0.714$), we found a significant main effect of ROI ($F(2.688, 107.50) = p < 0.01$, $\eta^2 = 0.11$), a significant interaction of ROI and TMT task ($F(4.981, 199.229) = 3.384$, $p < 0.01$, $\eta^2 = 0.08$) and a significant interaction of group, ROI and TMT task ($F(4.981, 199.229) = 2.741$, $p < 0.05$, $\eta^2 = 0.06$). As comparisons between ROI's are limited in fNIRS due to different optical path lengths, we performed post-hoc comparisons for each ROI separately.

With respect to the interaction of TMT task and ROI, post-hoc comparisons revealed significant increases in cortical oxygenation from TMT-C to TMT-A/B in the left DLPFC ($F(1, 40) = 5.965$, $p < 0.05$, $\eta^2 = 0.13$) but for none of the other ROI's.

With respect to the interaction of conversion by TMT task by ROI, we observed significant differences between converters vs. non-converters in the contrast of TMT-C and TMT-A/B in the

Table 1
Population characteristics including the prevalence of PD risk factors within all subgroups analyzed.

Subgroup Attribute	Converters (total; n = 21)	Early converters (n = 9)	Late converters (n = 12)	Healthy controls (n = 21)	Test statistic CON vs. HC
Mean age	71.9 (4.6)	73 (3.2)	71 (5.3)	72 (4.7)	$t(40) < 1$ $p > 0.1$
Gender	m: n = 16 f: n = 5 (24%)	m: n = 7 f: n = 2 (22%)	m: n = 9 f: n = 3 (25%)	m: n = 18 f: n = 3 (14%)	$\chi^2 = 0.618$ $p > 0.1$
Mean y of education	14.1 (2.2)	14.3 (3.5)	13.5 (1.5)	13.9 (2.5)	$t(40) < 1$ $p > 0.1$
RBD	n = 9 (43%)	n = 5 (55%)	n = 4 (33%)	n = 5 (24%)	$\chi^2 = 1.714$ $p > 0.1$
Hyposmia	n = 12 (57%)	n = 6 (66%)	n = 6 (50%)	n = 4 (19%)	$\chi^2 = 6.462$ $p < 0.05$
Depression	n = 2 (10%)	n = 2 (22%)	n = 0 (0%)	n = 1 (5%)	$\chi^2 = 0.359$ $p > 0.1$

The test statistic refers to the *t*-tests/ χ2-tests comparing converters and healthy controls.
CON = converter; f = female; HC = healthy control; m = male, RBD = REM sleep behavior disorder.

Table 2
Means and standard deviations of performance measures dependent on TMT task (TMT-C, TMT-B and TMT-A) and group (converters and non-converters).

	Converters (total; n = 21) mean ± SD	Non-converters (n = 21) mean ± SD
Mean number of completed items TMT-C	23.17 ± 2.71	23.95 ± 0.22
Mean number of completed items TMT-A	19.26 ± 4.71	19.64 ± 4.33
Mean number of completed items TMT-B	8.81 ± 3.70	9.69 ± 3.39
Mean number of correctly solved items TMT-C	23.17 ± 2.71	23.95 ± 0.22
Mean number of correctly solved items TMT-A	19.12 ± 4.67	19.57 ± 4.26
Mean number of correctly solved items TMT-B	8.67 ± 3.84	9.60 ± 3.48
Mean number of errors TMT-C	0.00 ± 0.00	0.02 ± 0.11
Mean number of errors TMT-A	0.14 ± 0.36	0.07 ± 0.18
Mean number of errors TMT-B	0.14 ± 0.32	0.10 ± 0.26

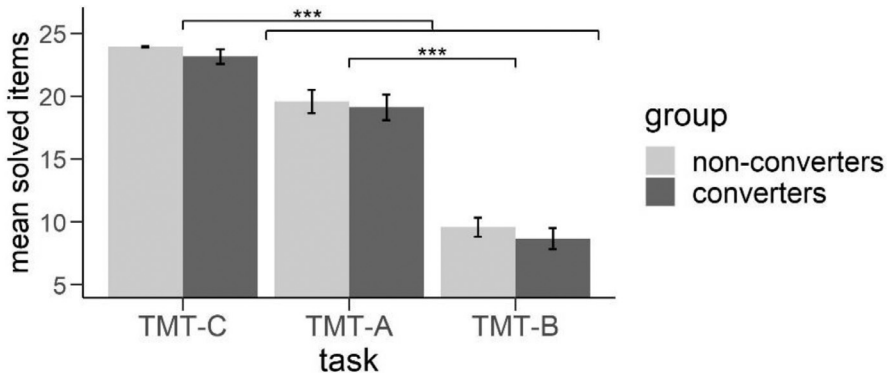

Fig. 2. Mean number of correctly solved items dependent on TMT task (TMT-A, TMT-B, TMT-C) for the PD-converters vs. non-converters. No significant differences between the two groups are observed ($p = 0.963$). Significance lines represent the contrasts. Error bars indicate standard errors. $^{***}p < 0.001$.

right DLPFC ($F(1, 40) = 12.553$, $p < 0.001$, $\eta^2 = 0.24$) but not in the bilateral SAC or left DLPFC. However, when analyzing the right SAC separately, a main effect of conversion was significant ($F(1, 40) = 5.727$, $p < 0.05$, $\eta^2 = 0.13$). The significant post-hoc test in the right DLPFC reflected a significant increase in activity from TMT-C to TMT-A/B in the non-converters ($t(20) = 2.81$, $p < 0.05$, $d = 0.61$), but a decrease in the converters ($t(20) = 2.16$, $p < 0.05$, $d = 0.47$). In the same way, converters showed a generally reduced pattern of cortical oxygenation in the right SAC (Fig. 3).

4. Controlling for confounding factors

4.1. Time of diagnosis

As our sample consisted of subjects with a conversion to PD before or very close to the date of TMT task measurement (n = 9) and subjects with a conversion in the years following the TMT task measurement, we checked our results by comparing only these late converters (i.e. the prodromal PD patients; n = 12) with the control group (i.e. the non-converters) and performed, equivalent to our previous analyses, a repeated measures ANOVA dependent on task (TMT-A VS: TMT-B vs. TMT-C) and group (late converters vs. non-converters). For descriptive statistics see Table 3.

4.1.1. Mean number of completed items

Concerning the mean number of completed items, we observed a significant main effect of TMT task ($F(2, 38) = 137.794$, $p < 0.001$, $\eta^2 = 0.88$). More specifically, we observed a significant decrease from TMT-C to TMT-A/B ($F(1, 19) = 140.133$, $p < 0.001$, $\eta^2 = 0.88$) and from TMT-A to TMT-B ($F(1, 19) = 135.597$, $p < 0.001$, $\eta^2 = 0.89$).

4.1.2. Mean error rates

Regarding the number of errors, we could not find any differences regarding group or TMT task.

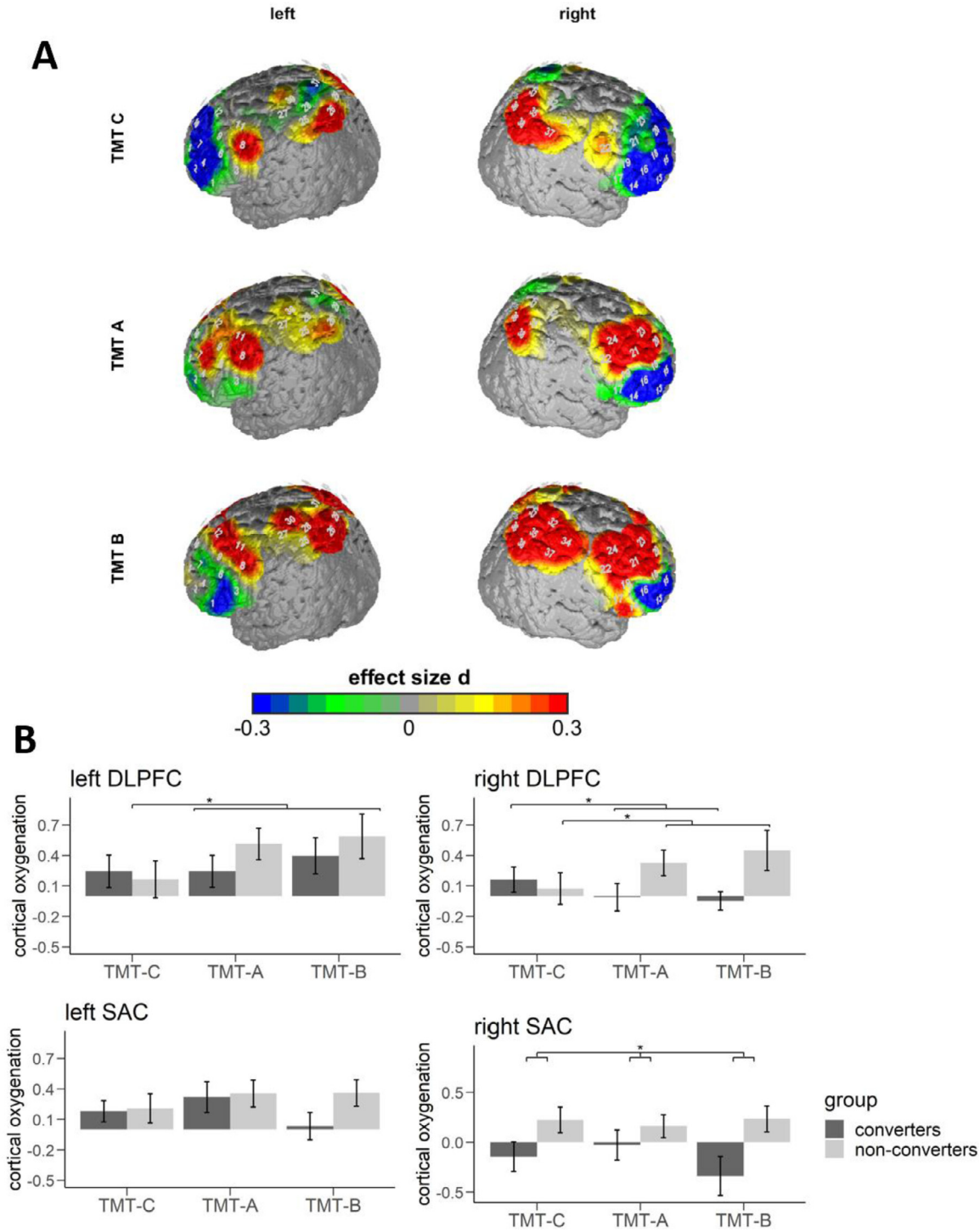

Fig. 3. Displaying the interaction of group by ROI by TMT task. (A) Brain maps of the contrast non-converters vs. converters. Differences are depicted in effect size *d*. Warm colors indicate higher activity in the non-converters than the converters. (B) Bar plots of the depicted effect in the brain maps for the four regions of interest. DLPFC = dorsolateral prefrontal cortex, SAC = somatosensory association cortex. Significance lines represent the contrasts. Error bars indicate standard errors. $^{*}p < 0.05$.

4.1.3. Performance

When we set the number of solved items and number of errors in relation, and only considered the number of correctly solved items as an index of performance, we observed a significant main effect of TMT task ($F(2, 38) = 138.062$, $p < 0.001$, $\eta^2 = 0.88$). Planned Helmert-contrasts revealed significant decreases from TMT-C to TMT-A/B ($F(1, 19) = 155.763$, $p < 0.001$, $\eta^2 = 0.89$) and from TMT-A to TMT-B ($F(1, 19) = 123.973$, $p < 0.001$, $\eta^2 = 0.87$ (Fig. 4)).

4.1.4. fNIRS

We performed a three-way repeated measures ANOVA dependent on group (late converters vs. non-converters), task (TMT-A vs. TMT-B vs. TMT-C) and region of interest (lDLPFC vs. rDLPFC vs.

Table 3
Means and Standard deviations of performance measures dependent on TMT task (TMT-C, TMT-B and TMT-A) and group (non-converters and late converters).

	Late converters (total; n = 12) mean ± SD	Non-converters (n = 21) mean ± SD
Mean number of completed items TMT-C	22.17 ± 4.04	23.95 ± 0.22
Mean number of completed items TMT-A	19.50 ± 5.57	19.64 ± 4.33
Mean number of completed items TMT-B	7.78 ± 3.30	9.69 ± 3.39
Mean number of correctly solved items TMT-C	22.17± 4.04	23.95 ± 0.22
Mean number of correctly solved items TMT-A	19.39 ± 5.62	19.57 ± 4.26
Mean number of correctly solved items TMT-B	7.56 ± 3.58	9.60 ± 3.48
Mean number of errors TMT-C	0.00 ± 0.00	0.02 ± 0.11
Mean number of errors TMT-A	0.11 ± 0.22	0.07 ± 0.18
Mean number of errors TMT-B	0.22 ± 0.36	0.10 ± 0.26

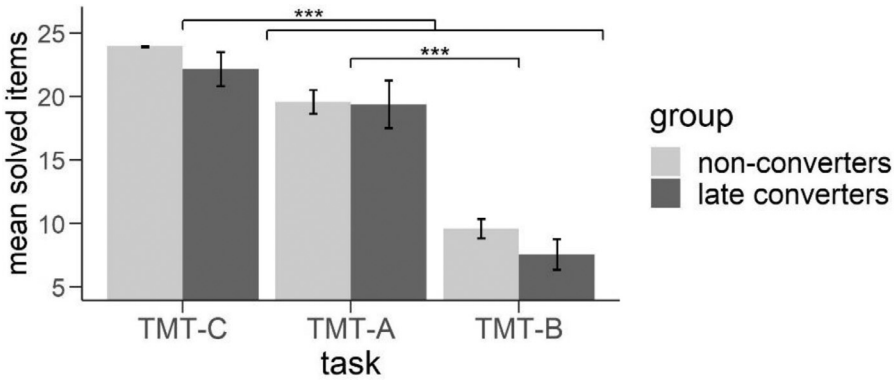

Fig. 4. Mean number of correctly solved items dependent on TMT task (TMT-A, TMT-B, TMT-C) for the late PD-converters vs. non-converters. No significant differences between the two groups were observed ($p = 0.752$). Significance lines represent the contrasts. Error bars indicate standard errors. $^{***}p < 0.001$.

lSAC vs. rSAC). Correcting for violated sphericity assumptions using Huynh-Feldt in case of the main effect of ROI ($\varepsilon = 0.911$) and the interaction of TMT task with ROI ($\varepsilon = 0.911$), we observed a significant main effect of ROI ($F(2.732, 84.685) = 3.622$, $p < 0.05$, $\eta^2 = 0.11$), as well as a significant interaction of TMT task and ROI ($F(5.466, 169.439) = 6.235$, $p < 0.001$, $\eta^2 = 0.17$) and a three-way interaction of task, ROI and group ($F(5.466, 169.439) = 4.218$, $p < 0.001$, $\eta^2 = 0.12$). Further, we found a significant main effect of group, indicating overall attenuated cortical oxygenation in late converters vs. non-converters ($F(1, 31) = 4.196$, $p < 0.05$, $\eta^2 = 0.12$ (Fig. 4)). Our planned contrasts for each ROI revealed significant differences in cortical oxygenation from TMT-C to TMT-A/B in the left DLPFC ($F(1, 31) = 4.173$, $p < 0.05$, $\eta^2 = 0.12$) and significant differences from TMT-A to TMT-B in the right SAC ($F(1, 31) = 4.315$, $p < 0.05$, $\eta^2 = 0.12$) but none of the other ROI's. With respect to the interaction of conversion by TMT task by ROI, we observed significant differences between late converters vs. non-converters in the contrast of TMT-C and TMT-A/B in the right DLPFC ($F(1, 31) = 8.102$, $p < 0.01$, $\eta^2 = 0.21$) and as well as in the contrast of the TMT-A to the TMT-B in case of the right SAC ($F(1, 31) = 6.657$, $p < 0.05$, $\eta^2 = 0.18$) (Fig. 5)

4.2. Motor-affected body side in PD-converters

Within the group of the PD-converters (total; n = 21), we further analyzed the body side affected by motor symptoms. There was n = 8 (38%; n = 2 early and n = 6 late converters) of the converters predominantly affected on the right and n = 11 (48%; n = 6 early and n = 5 late converters) on the left body side. Unfortunately, there were no data available regarding the motor-affected body side for n = 2 of the converters.

4.3. Medication status

We further reanalyzed our data with respect to the individual's medication status as another covariate. Converters showed a higher usage of blood pressure medication, which was marginally significant ($p = 0.058$). However, the intake of any kind of assessed medication was not related to O_2Hb levels during the TMT in this sample (all $p > 0.1$). Further, adding the covariate of blood pressure medication into the model somehow rendered the levels of significance, but results stayed mostly stable (Interaction conversion group*TMT task*ROI: $F(6,234) = 2.199$, $p < 0.05$, $\eta^2 = 0.053$) as expected from the lack of a significant effect of blood pressure medication on O_2Hb levels.

For further details of the subjects' medication status, see the supplemental material.

5. Discussion

The aim of the current study was to investigate the neural correlates of subjects with prodromal or early PD compared to a control group during the acquisition of the TMT by means of functional near-infrared spectroscopy.

We observed a well-known behavioral effect of the TMT versions with more completed items during TMT-C and TMT-A than during TMT-B. Interestingly, on behavioral measures, PD-converters did not differ from the control group. On a functional neural level, we observed higher O_2Hb levels during the completion of the TMT-A and TMT-B in comparison to TMT-C. Further and most interestingly, we found significant differences between the prodromal as well as early PD-converters and controls in their O_2Hb increases between TMT-C and TMT-A/B in the right DLPFC. Here, the PD converters in comparison to the control group did not show the expected pattern of a linear increase in cortical oxygenation due to

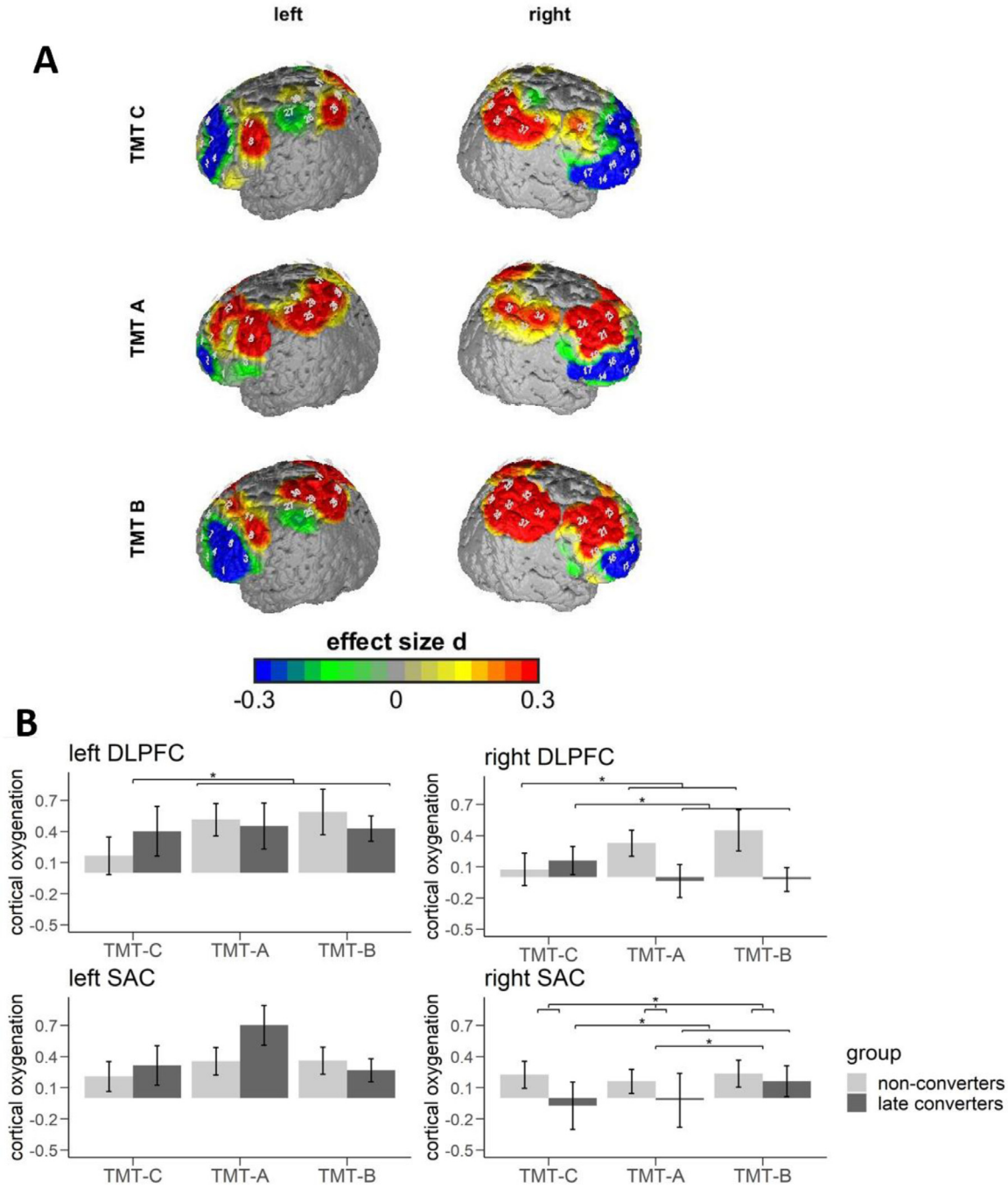

Fig. 5. Displaying the interaction of group by ROI by TMT task. (A) Brain maps of the contrast non-converters vs. late converters. Differences are depicted in effect size *d*. Warm colors indicate higher activity in the non-converters than the late converters. (B) Bar plots of the depicted effect in the brain maps for the four regions of interest. DLPFC = dorsolateral prefrontal cortex, SAC = somatosensory association cortex. Significance lines represent the contrasts. Error bars indicate standard errors. $^{*}p < 0.05$.

increased task difficulty. This effect was observed within the whole group of PD-converters and the subgroup of patients being prodromal at the time of fNIRS measurement (the 'late converters'), likewise. On the one hand, this tells us that this really seems to be a very early and presumably PD-specific pattern, on the other hand we were thereby able to exclude that the differences between converters and non-converters on the neural level were solely evoked by a common analysis of the prodromal with the early but manifest PD patients.

We selected the ROI's for our fNIRS measurement of neural activity (the DLPFC and IFG as another part of the frontal gyrus, that had to be excluded from analysis afterwards, as well as the SAC representing the parietal lobule) according to preexisting research findings. On a neuroanatomical level, conventionally the frontal cortex, mainly the prefrontal cortical areas such as the DLPFC, have been considered the major structures determining executive performance. Predominantly fMRI studies have additionally shown the importance of many other brain regions, e.g. the parietal, temporal and hippocampal cortex as well as the basal ganglia (Leh et al., 2010). In their fNIRS study of the TMT in elderly subjects, and thus from a methodological point of view quite comparable to our investigation, Hagen et al. (2014) found task-related activation

of the dorsolateral prefrontal cortex, the frontopolar area and Broca's area as well as the left motor, somatosensory cortices and somatosensory association cortices. Further, fMRI (Zakzanis et al., 2005; Jacobson et al., 2011) and fNIRS (Shibuya-Tayoshi et al., 2007; Kubo et al., 2008) studies investigating executive function using different versions of the TMT have been pointing towards predominantly frontal (e.g. the prefrontal, inferior and medial frontal cortex and the precentral gyrus) as well as temporal (the angular, middle and superior temporal gyrus) ROI's, too.

The significant increase of cortical oxygenation in the left DLPFC in our investigation when switching from the TMT-C to the TMT-A/B presumably reflects a higher cortical activity due to the more complex task that is preserved even within the group of the PD-converters. This result is in line with the insights of Ko et al. (2008) who induced a transient functional disruption of the bilateral DLPFC by continuous theta burst stimulation and subsequently measured the subjects' Montreal-card-sorting-task performance as well as the striatal dopamine release in PET. They observed a significant hemispheric asymmetry in the sense that both of these parameters were impaired only after stimulation of the left DLPFC, but not the right DLPFC, which underlines the relevance of the former for executive functioning. Zakzanis et al. (2005) also confirmed left-sided frontal activity in their fMRI study of the TMT. In their fNIRS study, Hagen et al. (2014) basically explained the more pronounced activation in the left hemisphere, amongst others in the somatosensory association cortex, by the fact that most of the participants were right-handed and accordingly used their right hand to perform the paper-and-pencil version of the TMT. In contrast, in their fMRI study with a computer adapted version of the TMT (pcTMT), Jacobson et al. (2011) showed a significantly greater activation during the TMT-B compared to the TMT-A especially in right frontal cortical areas and concluded that these might be candidate regions underlying set-shifting abilities. Consistent with this finding, we have shown within the group of the non-converters compared to – each the prodromal and early – PD-converters an increase of cortical activity in the right DLPFC when switching from the TMT-C to the TMT-A/B. When switching from the TMT-A to the TMT-B, we could even show much lower O_2Hb levels in the right hemisphere within the late converters compared to the controls, this time in the SAC. This result seems interesting, as there appeared a certain tendency in the sense that more individuals were motor-affected on the left body side. But due to the very small sample size and partly missing clinical data, one should be very cautious to prematurely draw conclusions here. Nevertheless, this would be a very interesting question to address within further studies. However, Kubo et al. (2008) and Shibuya-Tayoshi et al. (2007) described a bilateral prefrontal activation in fNIRS analyses of the TMT, more pronounced in the TMT-B compared to the TMT-A, possibly reflecting a stronger involvement of executive functions and increased difficulty during the TMT-B.

Still, the following limitations of our study have to be taken into account. The missing evidence of behavioral differences between the PD-converters and non-converters in our experiment on the one hand may be what one is hoping for in search of an early marker within the field of neurodegenerative diseases (in this case corresponding to the simultaneously dissimilar functional neuroimaging patterns). On the other hand, this is indeed a surprising result, as the full picture of executive dysfunction in PD is characterized by deficits in internal control of attention, set shifting, planning, inhibitory control, dual task performance, and on a range of decision-making and social cognition tasks (Dirnberger and Jahanshahi, 2013). Hence, one might argue that the TMT is not the most suitable test to examine executive (dys-)function in this patient population. Actually, we used an adapted version of the standard TMT according to the CERAD protocol (Morris et al., 1988). This represents a conventional procedure in the context of imaging studies for the purpose of optimized compatibility (Hagen et al., 2014) and is performed under relatively narrow time restriction. However, due to this fact, our testing method was not primarily designed to generate best possible behavioral data. One could speculate that a decreasing concentration and thus test performance, that might have appeared over time within the group of the PD-converters, has not been detected due to this methodical challenge. Moreover, a well-known psychological phenomenon, the so-called 'Yerkes-Dodson-Law', implies that there exists an inverse U-shaped relationship between mental arousal and general performance (Yerkes and Dodson, 1908). One could assume that the healthy controls may have not been challenged enough due to the comparatively simple test design, i.e. within our experiment they were located within the first third of a corresponding curve, which in turn could mask a performance difference between the two groups. However, we are on principle not the first group making such an observation of functional imaging without behavioral differences in the context of PD. For instance, Dagher et al. (2001) reported that PD patients performed the Tower of London task as well as a control group, although however, such as in our analysis, they showed a different pattern of neural activation in PET. A possible explanation may be compensatory mechanisms in the already neurodegenerating brain. In this regard, Dagher et al. (2001) described an enhanced right hippocampal activity within the PD patients compared to the controls and supposed this to represent a shift to the declarative memory, possibly due to an insufficient working memory capacity within the frontostriatal system. Moreover, Metzger et al. (2016) demonstrated that such compensatory mechanisms can differ between different neurodegenerative diseases. In their fNIRS analysis during a verbal fluency task, the healthy controls showed an activation of frontoparietal cortical areas, such as the DLPFC. The activation pattern of Alzheimer's disease patients was similar but weaker. In contrast, patients with frontotemporal dementia showed a qualitatively different pattern, rather involving frontopolar regions. However, we were not able to detect such a compensation effect, but all the converters in our investigation generally showed reduced cortical activity. This may be justified within the limits of our selection of ROI's, i.e. while on the one hand fNIRS is a method well-suited to obtain physiological data of the cerebral cortex, its depth resolution – on the other hand – is even restricted to this anatomical structure (Rosenbaum et al., 2016). This constitutes a technical disadvantage compared to other functional imaging methods and is especially challenging within the field of PD where subcortical areas are substantially involved in pathophysiology. Hence, although the abovementioned TMT target areas were displayed quite well in our analysis, it was unfortunately not possible to completely analyze, for instance, the frontostriatal network or the DMN. Though, regarding the relevance of the different, underlying dopaminergic pathways in the brain, Sawamoto et al. (2008) showed in their PET study that executive deficits attributable to frontal lobe dysfunction in patients with early PD are rather a consequence of impaired nigrostriatal dopaminergic function, indirectly resulting in abnormal processing in the cortico-basal ganglia circuit. In contrast, the direct mesocortical dopaminergic transmission appears to be surprisingly well preserved. In their SPECT (Single-Photon Emission Computed Tomography) study, Nobili et al. (2010) likewise used a biomarker of nigrostriatal function to demonstrate that especially a nigral-caudate impairment is associated with an executive dysfunction in PD. Thus, it is indeed meanwhile recognized that executive functions both in healthy individuals and PD patients not only depend on cortical areas but also on several other brain structures that are closely linked with the frontal cortex to form a functional neural network (Leh et al., 2010).

Another technical limitation has to be mentioned in the context of fNIRS. Like fMRI, it is based on neurovascular coupling and consequently does not directly reflect neural activation. Mediating factors of this effect can be age or diseases affecting the vascular system such as hypertension, but even blood pressure medication (Hagen et al., 2014). The significantly higher use of these substances in the group of the converters compared to the non-converters was therefore of critical importance. However, statistically there was no difference in the cortical activation patterns when comparing fNIRS results for the medicated versus the unmedicated group. Moreover, four out of 21 (19%) PD-converters already received a dopamine (DA) replacement therapy, which did not cause a statistically significant effect either. With respect to the preexisting literature it furthermore seems that dopamine (DA) replacement therapy can in general have either oppositional (Cools et al., 2001; Aarts et al., 2014) or maybe no effects at all on cognitive and especially executive performance (Huang et al., 2007). Despite the methodological disadvantages mentioned above, in case of the TMT, fNIRS was especially useful because – due to its flexible applicability – it enables the test situation to be as natural as possible since the subjects can sit at a table and work on the original paper-and-pencil version of the TMT (Hagen et al., 2014).

A further limitation of our study consists in the quite small sample sizes examined. Therefore, the results should be considered carefully and need to be studied further in larger sample sizes. This becomes especially important in the investigation of biomarkers. We did not investigate a separate sample to check for reliability due to the limitation of the sample. Moreover, as the TREND study on principle is investigating a collective at risk concerning the development of a neurodegenerative disease like PD, we cannot exclude that some of the current controls will convert within the next few years as well, which in turn might have biased our results. This difficulty is thoroughly visible within the presented population characteristics (Table 1). Here, not only the late compared to the early converters show a barely surprising tendency towards lower burden of PD risk factors (slightly younger and higher portion of women, less individuals with RBD, hyposmia or depression), but even within the healthy controls the prevalence of PD risk factors is not infrequent (especially for RBD and hyposmia). Finally, during the last years, huge progress has been made in the field of PD research regarding its underlying genetic causes and risk factors. Some of these (e.g. the GBA mutation) are known to be associated with a higher risk of cognitive decline (Winder-Rhodes et al., 2013; Kim and Alcalay, 2017). Hence, it might be a fruitful approach to even incorporate such findings into future research, for example by means of stratifying for different genetic patient subgroups.

To conclude, we have confirmed the major role of the prefrontal cortex separately in prodromal as well as early PD, which is in line with all other fNIRS studies using the TMT (Shibuya-Tayoshi et al., 2007; Kubo et al., 2008; Hagen et al., 2014). Namely, we observed reduced cortical activity in the prodromal PD patients compared to controls even before expectable differences could be detected on a behavioral level. Therefore, it should be seriously sought to confirm these promising results preferably in larger samples sizes with the goal to continuously extend our picture of the prodromal PD syndrome. A relevant question in this context will be the relation of executive dysfunction and conversion speed as well as other non-motor symptoms of PD as that way a characteristic temporal sequence in the development of prodromal symptoms could be unraveled. In this regard, our research group is currently performing a longitudinal follow-up study within a large corresponding PD-at-risk collective. This approach is of special interest as by identifying individuals at risk it would allow a diagnosis and potential treatment at a very early stage of the disease.

Disclosure statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.04.014.

CRediT authorship contribution statement

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