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Information processing speed in multiple sclerosis: Relevance of default mode network dynamics

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ABSTRACT

Objective: To explore the added value of dynamic functional connectivity (dFC) of the default mode network (DMN) during resting-state (RS), during an information processing speed (IPS) task, and the within-subject difference between these conditions, on top of conventional brain measures in explaining IPS in people with multiple sclerosis (pwMS).

Methods: In 29 pwMS and 18 healthy controls, IPS was assessed with the Letter Digit Substitution Test and Stroop Card I and combined into an IPS-composite score. White matter (WM), grey matter (GM) and lesion volume were measured using 3 T MRI. WM integrity was assessed with diffusion tensor imaging. During RS and task-state fMRI (i.e. symbol digit modalities task, IPS), stationary functional connectivity (sFC; average connectivity over the entire time series) and dFC (variation in connectivity using a sliding window approach) of the DMN was calculated, as well as the difference between both conditions (i.e. task-state *minus* RS; ΔsFC-DMN and ΔdFC-DMN). Regression analysis was performed to determine the most important predictors for IPS.

Results: Compared to controls, pwMS performed worse on IPS-composite ($p = 0.022$), had lower GM volume ($p < 0.05$) and WM integrity ($p < 0.001$), but no alterations in sFC and dFC at the group level. In pwMS, 52% of variance in IPS-composite could be predicted by cortical volume ($\beta = 0.49$, $p = 0.01$) and ΔdFC-DMN ($\beta = 0.52$, $p < 0.01$). After adding dFC of the DMN to the model, the explained variance in IPS increased with 26% ($p < 0.01$).

Conclusion: On top of conventional brain measures, dFC from RS to task-state explains additional variance in IPS. This highlights the potential importance of the DMN to adapt upon cognitive demands to maintain intact IPS in pwMS.

1. Introduction

Up to 50% of people with multiple sclerosis (pwMS) suffer from problems with information processing speed (IPS), also known as "cognitive slowing". Deficits in IPS are among the first cognitive symptoms in pwMS and related to reduced quality of life (Chiaravalloti and DeLuca, 2008; Benedict et al., 2006; Amato et al., 2010; Glanz et al., 2010). The search for neural correlates of IPS deficits resulted in several structural and functional brain measures. These include white and grey matter damage (e.g. lesions, atrophy and reduced tissue integrity) (Randolph et al., 2005; Mazerolle et al., 2013; Batista et al., 2012), but also changes in activation and functional connectivity (FC) during an IPS task or during resting-state (RS) (Genova et al., 2009; Dobryakova et al., 2016; Wojtowicz et al., 2014). Although these measures do explain IPS to a certain extent, there is still room to improve the relationship between brain measures and IPS. For example, intuitively IPS depends on the ability of the brain to rapidly transfer information within its functional network. As FC measures have previously been averaged over the entire scanning session (i.e. time series), from here on referred to as *stationary FC* (sFC), the *variability* in FC over time has not been taken into account. With this latter measure, the *changes* in connectivity strength *during* a time series are obtained, from here on referred to as *dynamic* FC (dFC). As dFC seems to be behaviorally relevant with respect to cognition in healthy subjects (Cohen,

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2017; Jia et al., 2014; Gonzalez-Castillo and Bandettini, 2017) or symptoms in neurological disorders (Zhang et al., 2016; Sambataro et al., 2017; Douw et al., 2015), we argue that dFC could also be of importance for maintained IPS in pwMS, as it could reflect the fast changing connectivity patterns within the brain that cannot be captured with sFC (Cohen, 2017).

1.1. Brain networks

The brain's functional network has an *intrinsic* organization, namely various (interconnected) RS networks that can be identified with RS functional magnetic resonance imaging (fMRI). This intrinsic organization of the brain has been linked to cognitive functioning, as it is thought enable the flow of activity (i.e. information) during task performance (Cole et al., 2016; Ito et al., 2017). An important brain network related to cognitive (dys)functioning is the default mode network (DMN) (Raichle, 2015). This network consists of several core regions, including the medial temporal lobe, medial prefrontal cortex, posterior cingulate cortex, and inferior parietal cortex (Raichle, 2015). Recent studies have shown task-related "responsivity" in sFC of the DMN, that is, the ability to change the connection strength upon task demands, to enable information integration throughout the brain (Elton and Gao, 2015; Vatansever et al., 2015a).

1.2. Dynamics of the DMN

Previous studies have linked DMN dynamics during RS or task-state to cognitive functioning, such as executive functioning, cognitive flexibility, concept formation, and (working) memory, in healthy subjects and individuals with neurological disorders (e.g. temporal lobe epilepsy and MS) (Douw et al., 2015; Liu et al., 2018; Douw et al., 2016; Simony et al., 2016; Vatansever et al., 2015b; Yang et al., 2014; Nomi et al., 2017; van Geest et al., 2018). Furthermore, one study in healthy subjects showed that a larger increase in dFC between the DMN and frontoparietal network during task-state relative to RS was related to better cognitive flexibility outside the scanner (i.e. Stroop task) (Douw et al., 2016). Together with studies showing differences in dFC between RS and task-state, the change in dFC of the DMN between RS and task-state might reflect the ability of the brain to adapt as task demands change, in order to optimally execute the task at hand (i.e. increased information processing throughout the brain) (Cohen, 2017; Braun et al., 2015; Lin et al., 2017; Xie et al., 2017).

To investigate whether dFC of the DMN is indeed a neural correlate of IPS in MS, and relevant next to previously identified correlates, we explored its incremental value when explaining IPS variance on top of conventional measures of brain abnormalities (defined as: brain atrophy, lesions, white matter integrity, and sFC of the DMN). We hypothesized that dFC of the DMN, and especially the *difference* in dFC between RS and task-state, that is, the ability of the brain to adapt upon task demands, would explain unique variance in IPS.

2. Materials and methods

2.1. Subjects and study design

In this prospective observational study, all pwMS ($N = 33$) and healthy controls (HCs; $N = 19$) met the following inclusion criteria: 1) aged 18–65 years; 2) no contra-indications for MRI; 3) no psychiatric or neurological disease (for pwMS: other than MS). For pwMS, additional inclusion criteria were: 4) a diagnosis of relapsing-remitting MS, and; 5) without relapse or steroid treatment for at least four weeks prior to study measurements. Subjects performing below chance level (< 50% correct, $n = 3$ pwMS) on the fMRI paradigm were excluded from the entire study, as well as subjects with many frame-to-frame head displacements (> 0.5 mm for > 20% of frames, $n = 1$ pwMS and $n = 1$ HC) during fMRI to minimize motion effects on dFC measures (Shine et al., 2016). The study was approved by the local institutional ethics review board and conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. All subjects gave written informed consent.

This study is part of a study investigating the effect of fingolimod on the brain and cognitive functions over a period of 1.5 years. Here, the baseline data are presented (no prior publications on this dataset). The final MS group consisted of pwMS switching from first-line treatment ($n = 7$) or natalizumab ($n = 6$) to fingolimod treatment (from here on referred to as *switchers*), and pwMS continuing first-line therapy ($n = 16$; from here on referred to as *non-switchers*). The MS group and HCs were matched for age, sex, educational level, and disease duration for pwMS only.

2.2. Clinical measures

All subjects underwent neuropsychological testing, including, among others, the Letter Digit Substitution Task (LDST; oral version, 90 s), which is an equivalent of the Symbol Digit Modalities Test (SDMT) (Jolles et al., 1995), and the Stroop Test (for all tests see Appendix) (De, 1973). Scores on all neuropsychological tests were converted into a *Z*-score relative to HCs. Scores on the LDST and Stroop Card 1 were averaged into one IPS composite *Z*-score. Anxiety and depression levels were assessed with the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). Fatigue was measured using the Checklist of Individual Strength (Vercoulen et al., 1994). Additionally, physical disability was assessed by a trained physician using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

2.3. MRI acquisition

All subjects were examined using a 3 T whole-body MRI scanner (GE Signa-HDxt, Milwaukee, WI, USA) with a 32-channel head coil. The protocol included the following sequences: three-dimensional (3D) T1-weighted fast spoiled gradient echo for volume measurements (repetition time (TR): 8.22 ms; echo time (TE): 3.22 ms; inversion time (TI): 450 ms; flip angle 12°; 1.0 mm sagittal slices; 0.94 × 0.94 mm^2 in-plane resolution); 3D fluid-attenuated inversion recovery (FLAIR; TR: 8000 ms; TE: 128 ms; TI: 2343 ms; 1.2 mm sagittal slices; 0.98 × 0.98 mm^2 in-plane resolution) for white matter (WM) lesion detection; and diffusion tensor imaging (DTI; TR: 7200 ms; TE: 83 ms; flip angle 90°; 57 axial slices with an isotropic 2.0 mm resolution) with 5 volumes without directional weighting and 30 volumes with non-collinear diffusion gradients (b-value: 1000 s/mm^2) to assess WM integrity. To correct for echo planar imaging (EPI) induced artifacts, two scans with reversed phase-encode blips were acquired for DTI. Furthermore, RS fMRI (eyes closed; EPI, 202 volumes, TR: 2200 ms; TE: 35 ms; flip angle 80 degrees; 3 mm contiguous axial slices; 3.3 × 3.3 mm^2 in-plane resolution) and task-related (i.e. task-state) fMRI (IPS paradigm; EPI, 460 volumes, TR: 2000 ms; TE: 30 ms; flip angle 80 degrees; 4 mm contiguous axial slices; 3.3 × 3.3 mm^2 in-plane resolution) were performed to measure sFC and dFC.

2.4. Structural MRI measures

2.4.1. Whole-brain and lesion volume

Lesions were automatically segmented on FLAIR images and filled on the 3DT1 images using LEAP (Steenwijk et al., 2013; Chard et al., 2010). WM and grey matter (GM) volumes were measured using SIENAX (Smith et al., 2002). Volumes of deep GM structures were measured using FIRST (FSL v5.0.9, fmrib.ox.ac.uk/fsl). Cortical GM volume was measured by subtracting the FIRST segmentation from SIENAX's GM segmentation. All volumes were normalized for head size using the v-scaling factor obtained by SIENAX, resulting in normalized WM volume (NWMV), normalized cortical GM volume (NCGMV), normalized deep GM volume (NDGMV), and normalized lesion volume (NLV).