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Changes in MEG resting-state networks are related to cognitive decline in type 1 diabetes mellitus patients

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ABSTRACT

Objective: Integrity of resting-state functional brain networks (RSNs) is important for proper cognitive functioning. In type 1 diabetes mellitus (T1DM) cognitive decrements are commonly observed, possibly due to alterations in RSNs, which may vary according to microvascular complication status. Thus, we tested the hypothesis that functional connectivity in RSNs differs according to clinical status and correlates with cognition in T1DM patients, using an unbiased approach with high spatio-temporal resolution functional network.

Methods: Resting-state magnetoencephalographic (MEG) data for T1DM patients with ($n = 42$) and without ($n = 41$) microvascular complications and 33 healthy participants were recorded. MEG time-series at source level were reconstructed using a recently developed atlas-based beamformer. Functional connectivity within classical frequency bands, estimated by the phase lag index (PLI), was calculated within eight commonly found RSNs. Neuropsychological tests were used to assess cognitive performance, and the relation with RSNs was evaluated.

Results: Significant differences in terms of RSN functional connectivity between the three groups were observed in the lower alpha band, in the default-mode (DMN), executive control (ECN) and sensorimotor (SMN) RSNs. T1DM patients with microvascular complications showed the weakest functional connectivity in these networks relative to the other groups. For DMN, functional connectivity was higher in patients without microangiopathy relative to controls (all $p < 0.05$). General cognitive performance for both patient groups was worse compared with healthy controls. Lower DMN alpha band functional connectivity correlated with poorer general cognitive ability in patients with microvascular complications.

Discussion: Altered RSN functional connectivity was found in T1DM patients depending on clinical status. Lower DMN functional connectivity was related to poorer cognitive functioning. These results indicate that functional connectivity may play a key role in T1DM-related cognitive dysfunction.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by failure of insulin secretion, caused by the destruction of pancreatic beta cells, requiring exogenous insulin administration. T1DM patients are exposed to high (hyperglycaemia) and low (hypoglycaemia) blood glucose levels and cumulative hyperglycaemic exposure can lead to microvascular end-organ damage, such as retinopathy and nephropathy (Brownlee, 2005).

Interest is growing into the potential effects dysglycaemia has on the central nervous system. Whereas cortical grey matter seems relatively spared in adult T1DM patients (Lyoo et al., 2012), alterations in white matter tract integrity, functional connectivity and functional networks have been found relative to non-diabetes controls (van Duinkerken et al., 2009, 2012a,b). Furthermore, mild to moderate speed-related cognitive decrements are consistently found (Brands et al., 2005; Jacobson et al., 2007; Wessels et al., 2008). Cumulative hyperglycaemia is hypothesised to be related to T1DM-related cerebral compromise (Jacobson et al., 2007; Wessels et al., 2008). As the retina shares

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developmental and physiological characteristics with the brain (Lyoo et al., 2012; Patton et al., 2005), proliferative retinopathy, a consequence of long-term hyperglycaemia, is hypothesised to be a marker of cumulative hyperglycaemia on the brain (Jacobson et al., 2010; van Duinkerken et al., 2009, 2012a,b).

In recent years, it has become clear that cognitive functioning strongly depends on the organization of functional brain networks (Bassett and Bullmore, 2009; Brands et al., 2005; Bullmore and Sporns, 2012; Stam and van Straaten, 2012). Neuronal dynamics within segregated functional systems, and their integration, underlie cognitive processing (Friston, 2002; Jacobson et al., 2007; Wessels et al., 2008). The oscillatory properties of these neuronal dynamics are considered a potential means for the implementation of functional communication (Engel et al., 2001). Phase relations between these oscillatory systems are thought to play a key role in such communications, providing the underling mechanism for both local and long-range synchronization (Fell and Axmacher, 2011; Fries, 2005; Sauseng and Klimesch, 2008; Varela et al., 2001). These functional connections between distinct neuronal populations can be measured using different modalities: electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) (Stam and van Straaten, 2012). This latter technique has established distinct neuronal circuits, so called resting-state networks (RSNs), that exhibit robust temporal correlations in spontaneous brain activity under resting condition (Damoiseaux et al., 2006; Rosazza and Minati, 2011; van den Heuvel and Hulshoff Pol, 2010). Changes in RSN connectivity patterns have been related to cognitive performance: either too much or too little RSN activity in various pathologies (Alzheimer, schizophrenia and epilepsy) has been correlated with cognitive deficits (Broyd et al., 2009), whereas increased RNS activity after resective surgery for glioma correlated with improved cognitive performance (van Dellen et al., 2013).

Earlier EEG/MEG functional connectivity (Cooray et al., 2011; van Duinkerken et al., 2009) and fMRI RSN analyses (van Duinkerken et al., 2012b) have revealed a reduction in functional connectivity measures in T1DM patients with proliferative retinopathy, whereas increased functional connectivity has been found in patients without proliferative retinopathy. This reduction correlated with cognitive performance suggesting that functional connectivity is involved in cognitive functioning (van Duinkerken et al., 2009, 2012b). However, the results of these studies could have been affected by biases in the analysis approach (effects of volume conduction and the use of sensor-level analysis in EEG/MEG; poor temporal resolution of fMRI). Here, we therefore analysed MEG data from a previously described patient cohort (van Duinkerken et al., 2009, 2012b) using an unbiased approach with better spatio-temporal resolution to estimate RSN functional connectivity. In particular: i) A larger cohort is used than in the original MEG study (van Duinkerken et al., 2009) to enhance statistical power; ii) Analyses are performed in source-space instead of sensor-space, in order to enhance the interpretability of the results; iii) A functional connectivity estimator, the phase lag index (PLI), that is insensitive to spurious interactions (Stam et al., 2007) is used, instead of the synchronization likelihood (Montez et al., 2006; Stam and Van Dijk, 2002); iv) Although fMRI allows for the spatially accurate reconstruction of RSNs (van Duinkerken et al., 2012b), it does not capture the rich temporal dynamics of the neuronal activity that underlies the Blood Oxygenation Level Dependent (BOLD) signal. Here, using fMRI literature to define meaningful RSNs (Rosazza and Minati, 2011) in combination with the beamforming technique (Hillebrand et al., 2012), we are able to reconstruct frequency-specific functional connectivity within these RSNs.

Our aim was to test whether functional connectivity in RSNs differs according to clinical status and correlates with cognition in T1DM patients with and without proliferative retinopathy, using an unbiased approach with high spatio-temporal resolution functional network.

2. Methods

2.1. Participants

Forty-two type 1 diabetes mellitus patients with proliferative retinopathy ($T1DM^+$), 41 diabetes mellitus patients without microvascular complications ($T1DM^-$) and 33 healthy control subjects, matched for sex, BMI, and education were recruited in this study. Age range criteria were 18–56 years and participants were excluded if they had a BMI above 35 kg/m^2, use of drugs affecting cerebral functioning, current or history of alcohol (men >21 and women >14 units a week) or current drug use, psychiatric disorders, anaemia, thyroid dysfunction, use of glucocorticoids, hepatitis, stroke, severe head trauma, epilepsy, pregnancy, or poor visual acuity. For T1DM patients a disease duration of at least 10 years was required.

To control for confounding effects of depression on cognitive performance and functional connectivity, depressive symptoms were assessed using the Centre for Epidemiological Studies scale for Depression (CES-D). To prevent confounding due to current blood glucose level differences, these were measured in T1DM patients before the MEG recording. Blood glucose levels between 4 and 15 mmol/l (72–270 mg/dl) were regarded as appropriate. A detailed description of the inclusion/exclusion criteria for patients and control subjects is provided in our previous work (van Duinkerken et al., 2009), where the MEG data from a sub-set of these participants ($n = 15$, 29, and 26 for $T1DM^+$, $T1DM^-$, and healthy controls, respectively) were analysed at sensor-level. The original dataset consisted of 148 subjects, but 32 subjects were discarded either because of bad MEG recordings ($n = 24$) or problems with MRI co-registration ($n = 8$).

2.2. Structural assessment

Structural MRI scans were performed in order to assess differences in white matter hyperintensities and in whole brain and total grey matter volume.

Magnetic resonance imaging was performed on a 1.5 T whole body MR-scanner (Siemens Sonata, Erlangen, Germany) using an 8-channel phased-array head coil.

SIENAX, which is part of FMRIB's Software Library (FSL, version 5.0.4; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was used to calculate whole brain volume as well as total grey matter volume. For this analysis a high resolution T1-MPRAGE (repetition time 2.700 ms, echo time 5.17 ms, inversion time 95 ms, flip angle 8°, 248×330 mm^2 field of view, $1.0 \times 1.0 \times 1.5$ mm voxel size) was used. To increase the reliability of the analyses all scans were first corrected for scanner induced geometric distortion and then excessive neck tissue was removed by registering the Montreal Neurological Institute 152 (MNI152) standard brain to each participant's T1-MPRAGE.

White matter hyperintensities were visually rated by a neuropsychologist trained to assess structural abnormalities on MRI (EvD) according to the Fazekas score (Fazekas et al., 2002). For this rating a 3D-FLAIR sequence (repetition time 6500 ms; echo time 385 ms; variable flip angle (Mugler et al., 2000)) was used.

2.3. Neuropsychological assessment

As described in detail in van Duinkerken et al. (2009) all participants were assessed using a battery of neuropsychological tests to evaluate cognitive performance in six cognitive domains: memory, information processing speed, executive functioning, attention, motor speed and psychomotor speed. For each neuropsychological test z-values were created based on the mean and standard deviation of the controls. These were then grouped to form the cognitive domains (see Appendix A). When necessary, z-values were transformed so that higher z-scores represent better performance. In this study we considered 'general cognitive