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Network-specific resting-state connectivity changes in the premotor-parietal axis in writer's cramp

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ABSTRACT

Background: Writer's cramp is a task-specific dystonia impairing writing and sometimes other fine motor tasks. Neuroimaging studies using manifold designs have shown varying results regarding the nature of changes in the disease.

Objective: To clarify and extend the knowledge of underlying changes by investigating functional connectivity (FC) in intrinsic connectivity networks with putative sensorimotor function at rest in an increased number of study subjects.

Methods: Resting-state functional magnetic resonance imaging with independent component analysis was performed in 26/27 writer's cramp patients/healthy controls, and FC within and between resting state networks with putative sensorimotor function was compared. Additionally, voxel-based morphometry was carried out on the subjects' structural images.

Results: Patients displayed increased left- and reduced right-hemispheric primary sensorimotor FC in the premotor-parietal network. Mostly bilaterally altered dorsal/ventral premotor FC, as well as altered parietal FC were observed within multiple sensorimotor networks and showed differing network-dependent directionality. Beyond within-network FC changes and reduced right cerebellar grey matter volume in the structural analysis, the positive between-network FC of the cerebellar network and the basal ganglia network was reduced.

Conclusions: Abnormal resting-state FC in multiple networks with putative sensorimotor function may act as basis of preexisting observations made during task-related neuroimaging. Further, altered connectivity between the cerebellar and basal ganglia network underlines the important role of these structures in the disease.

1. Introduction

Writer's cramp (WC) is a task-specific focal hand dystonia (FHD) with a peak incidence between the 3rd and 5th decade causing abnormal and disabling postures through uncoordinated overflowing muscle activity solely during writing (simple WC) or also during fine motor tasks (dystonic WC) (Sheehy and Marsden, 1982). In the past, a number of neuroimaging studies have been conducted to further elucidate the yet not fully clear mechanisms of this disease, and both functional and structural changes in the primary sensorimotor and the premotor/supplementary motor cortex, the cerebellum and basal ganglia have been described (Hallett, 2006; Neychev et al., 2011). During the last years, the concept of resting state functional connectivity (FC) networks has gained much attention. It refers to the observation that networks of brain regions temporally correlate by low frequency fluctuations of the blood oxygen level dependent (BOLD) signal in the absence of experimental tasks (Biswal et al., 1997; Cordes et al., 2001; Fox and Raichle, 2007). Interestingly, those spatial

Abbreviations: ADDS, arm dystonia disability scale; BGN, basal ganglia network; BOLD, blood oxygen level-dependent; CN, cerebellar network; CONTR, healthy controls; FC, functional connectivity; FHD, focal hand dystonia; FWHM, full width at half maximum; FoV, field of view; GM, grey matter; IC, independent component; ICA, independent component analysis; ICN, intrinsic connectivity network; IPS, intraparietal sulcus; M1, primary motor cortex; PAT, writer's cramp patients; PCA, principal component analysis; PPN, premotor parietal network; PMd/v, dorsal/ventral premotor cortex; S1, primary somatosensory cortex; ROI, region of interest; rsfMRI, resting state functional magnetic resonance imaging; S2, secondary somatosensory cortex; SM1, primary sensorimotor cortex; SMA, supplementary motor area; SMG, supramarginal gyrus; v/dSMN, ventral/dorsal sensorimotor network; SPC, superior parietal cortex; TIV, total intracranial volume; WC, writer's cramp; WCRS, writer's cramp rating scale

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networks of temporally correlated brain areas have a distribution similar to what is observed in task activation studies, hinting at a common functionality. The correlation between the hubs in such networks has further been shown to increase in the presence of adequate tasks suggesting that task-related activity may constitute a superposition of spontaneous BOLD activity at rest (Fox and Raichle, 2007). In WC, task-based neuroimaging studies have promoted the identification of brain areas involved in this disease but, using various different experimental paradigms, yielded ambiguous results regarding the nature of changes. As an example, in FHD either reduced (Ibanez et al., 1999; Langbour et al., 2017; Nelson et al., 2009; Oga et al., 2002), increased (Lerner et al., 2004; Odergren et al., 1998) or opposed (Ceballos-Baumann et al., 1997) primary sensory (S1) and/or motor (M1) activity have been shown during sensory (Langbour et al., 2017; Nelson et al., 2009) or dystonic (Ceballos-Baumann et al., 1997; Lerner et al., 2004; Odergren et al., 1998) and asymptomatic (Ibanez et al., 1999; Oga et al., 2002) motor tasks. Studying the connectivity between brain regions in the absence of tasks might thus seem suitable to identify underlying changes in this disease. Still, earlier findings in resting state fMRI (rsfMRI) were not unequivocal. While one early rsfMRI study reported reduced left primary sensorimotor connectivity when investigating one sensorimotor network (Mohammadi et al., 2012), a seed-based approach reported increased connectivity between left S1 and M1 (Dresel et al., 2014) and had the constraint of a required prior spatial definition of regions of interest (ROIs). In this study, we aimed at further clarifying and possibly extending the knowledge of underlying changes in this disease by investigating cortical and subcortical intrinsic connectivity networks with attributed sensorimotor functionality applying an independent component based approach that avoids a possible bias induced by the choice of seed regions using an increased number of study subjects compared to previous trials. Additionally, a voxel-based morphometry analysis was performed to detect underlying grey matter changes as a possible cause of FC changes.

2. Methods

2.1. Participants

We investigated 26 WC patients (PAT; age 46.8 ± 13.7 years, m/f 15/11) and 27 healthy subjects (CONTR; age 49.3 ± 13.9 years, m/f 14/13) < 70 years of age with no neuro(psychiatric)/major internal disease, no neuroleptic or anticholinergic medication and a normal structural MRI, whose functional scans fulfilled the criteria of a composite (translation and rotation (Power et al., 2014)) head displacement of less than the voxel size in maximum and half the voxel size on average. No patient had received botulinum toxin therapy within the last three months prior to the study. The functional motor impairment of the hand was assessed with the arm dystonia disability scale (ADDS) for fine motor tasks, and specifically for writing using the writer's cramp rating scale (WCRS). The university ethics board approved the study. All participants gave their written informed consent according to the Declaration of Helsinki.

2.2. Data acquisition and preprocessing

For rsfMRI, 303 T2* echo-planar whole-brain functional MR images were acquired for each participant on a Philips Achieva 3.0 T scanner with an 8-channel head coil (TR/TE 2200/30 ms, field of view (FoV) 216 × 216 mm^2, 36 slices, voxel size 3 × 3 × 3 mm^3, scan time 11 min). The participants were instructed to keep their eyes closed during the whole experiment. To minimize the risk of motion artifacts, the head was fixed with foam pads. After rsfMRI, a high-resolution 3D T1-weighted structural image was acquired for anatomical reference (TR/TE/TI 59/4/780 ms, FoV 240 × 240 mm^2, 170 slices, voxel size 1 × 1 × 1 mm^3, scan time 6 min).

Preprocessing of functional data was performed in SPM12 (http://www.fil.ion.ucl.uk/spm) and Matlab2013a (The MathWorks, Natick, Massachusetts), and involved realignment for head motion correction, slice timing correction, coregistration with the anatomical reference image and normalization to the Montreal Neurological Institute (MNI) space with resampling to 2 × 2 × 2 mm^3 voxels. The data were spatially smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM). The first five scans of the rsfMRI run were discarded to ensure longitudinal magnetization equilibrium. The average framewise displacement (Power et al., 2014) (translation and rotation) was 0.10 ± 0.03 mm in PAT and 0.10 ± 0.03 mm in CONTR ($F_{1,51}$ = 0, p = 1.0), the composite maximum head displacement 1.32 ± 0.71 mm in PAT and 1.15 ± 0.53 mm in CONTR ($F_{1,51}$ = 0.90, p = 0.35) and the total intracranial volume (TIV) 1612.1 ± 191.4 mm^3 in PAT and 1544.1 ± 164.9 mm^3 in CONTR ($F_{1,51}$ = 1.96, p = 0.17).

2.3. Group independent component analysis

Group spatial independent component analysis (ICA) on the rsfMRI data of each patients and healthy controls was performed as implemented in the GIFT v3.0 software (http://mialab.mrn.org). ICA estimates spatially maximally independent sources from the linearly mixed signals contained in a spatiotemporal fMRI dataset, providing spatial maps of temporally coherent brain regions (functional spatial networks) (Calhoun et al., 2001). This approach has been shown to effectively identify and remove various sources of motion and non-motion-related noise in fMRI data (Griffanti et al., 2014). Further, its suggested property of being sensitive to the detection of subtle changes (Koch et al., 2012) is desirable when investigating task-specific dystonia. The calculated spatially independent components (ICs) represent either meaningful (i.e. intrinsic connectivity networks (ICNs)) or spurious (e.g. noise) information.

In a first step, the number of components in the whole dataset was determined by a dimensionality estimation using the minimum description length algorithm resulting in an estimate of a maximum of 52 and a mean number of 33 ICs. Based on these estimates, a stepwise dimensionality reduction was performed in each group using principal component analysis (PCA) (Celone et al., 2006; Wu et al., 2011), retaining 52 components at the subject- and 33 components at the group-level. This was followed by IC separation using the InfoMax algorithm (Bell and Sejnowski, 1995). Reliability testing was performed using the ICASSO toolbox (Himberg et al., 2004): ICA was repeated 40 times, the components were clustered, and their quality quantified using the index I_q (range 0 to 1) which mirrors the difference between intra- and extra-cluster similarity. Back-reconstruction of subject-specific spatial maps was performed from the aggregate spatiotemporal data set using a method based on PCA compression and projection robust for low model orders (GICA I) (Calhoun et al., 2001). To identify components of likely functional relevance in WC for further analysis, the spatial IC maps were correlated with publicly available maps of ICNs identified in a meta-analysis of task fMRI studies performed by Laird and colleagues (Laird et al., 2011) using multiple regression. The non-noise IC with the best fit (highest coefficient of determination) was selected. ICs representing noise were identified by standardized visual inspection of their spatial (activation pattern and tissue overlap with grey matter (GM)) and temporal characteristics (e.g. presence of saw tooth and high frequency patterns or spikes) as previously described (Kelly et al., 2010). Those identified components with attributed sensorimotor function in the meta-analysis (Laird et al., 2011) were then selected for further analysis (see Fig. A.1): a basal ganglia-thalamus network (BGN, ~Laird's ICN3), a cerebellar network (CN, ~Laird's ICN14), a premotor-parietal network (PPN, ~Laird's ICN7), a dorsal sensorimotor network (dSMN, ~Laird's ICN8/9) and a ventral sensorimotor network (vSMN, ~Laird's ICN17). The primary visual network (VN, ~Laird's ICN12) was chosen as a control. All investigated components were highly stable ($I_q \geq 0.95$). All selected networks have been previously