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Dynamic causal modeling revealed dysfunctional effective connectivity in both, the cortico-basal-ganglia and the cerebello-cortical motor network in writers' cramp

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ABSTRACT

Writer's cramp (WC) is a focal task-specific dystonia characterized by sustained or intermittent muscle contractions while writing, particularly with the dominant hand. Since structural lesions rarely cause WC, it has been assumed that the disease might be caused by a functional maladaptation within the sensory-motor system. Therefore, our objective was to examine the differences between patients suffering from WC and a healthy control (HC) group with regard to the effective connectivity that describes causal influences one brain region exerts over another within the motor network. The effective connectivity within a network including contralateral motor cortex (M1), supplementary motor area (SMA), globus pallidus (GP), putamen (PU) and ipsilateral cerebellum (CB) was investigated using dynamic causal modeling (DCM) for fMRI. Eight connectivity models of functional motor systems were compared. Fifteen WC patients and 18 age-matched HC performed a sequential, five-element finger-tapping task with the non-dominant and non-affected left hand within a 3 T MRI-scanner as quickly and accurately as possible. The task was conducted in a fixed block design repeated 15 times and included 30 s of tapping followed by 30 s of rest. DCM identified the same model in WC and HC as superior for reflecting basal ganglia and cerebellar motor circuits of healthy subjects. The M1-PU, as well as M1-CB connectivity, was more strongly influenced by tapping in WC, but the intracortical M1-SMA connection was more facilitating in controls. Inhibiting influences originating from GP to M1 were stronger in controls compared to WC patients whereby facilitating influences the PU exerts over CB and CB exerts over M1 were not as strong. Although the same model structure explains the given data best, DCM confirms previous research demonstrating a malfunction in effective connectivity intracortically (M1-SMA) and in the cortico-basal ganglia circuitry in WC. In addition, DCM analysis demonstrates abnormal reciprocal excitatory connectivity in the cortico-cerebellar circuitry. These results highlight the dysfunctional cerebello-cortical as well as basalganglio-cortical interaction in WC.

1. Introduction

Dystonia is a clinical syndrome characterized by sustained muscle contractions, producing twisting, repetitive, and patterned movements, or abnormal postures. The dystonic syndromes include a large group of diseases that have been classified into various etiological categories, such as primary, dystonia-plus, heredodegenerative, and secondary (Albanese et al., 2013). In addition to the investigation of differences in isolated brain regions between patients and healthy controls, a series of studies indicated abnormalities in brain circuits as the underlying mechanism of focal dystonia with focus on the primary motor cortex (M1), the supplementary motor area (SMA), cerebellum (CB), parts of the basal ganglia - in detail the globus pallidus (GP) and putamen (PU) - as well as the thalamus. On the one hand there is evidence that dysfunctions of a network are embedded in the cortico-striatal pathway (Ibáñez et al., 1999; Islam et al., 2009; Oga et al., 2002; Wu et al., 2010). For instance, abnormal dopaminergic function within the cortico-striatal circuity has been described in dystonia (Simonyan et al., 2017). In

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addition, dysfunctions in the cerebello-cortical pathway have been detected as well. Neuronal activity in the cerebellum in writer's cramp (WC) is increased (Hu et al., 2006; Preibisch et al., 2001), and therefore the cerebellar influence on the motor cortex possibly leads to a deficit in cortical inhibition and stronger dystonic symptoms (Bradnam et al., 2015). Just recently, Gallea et al. (2018) confirmed the hypothesis of cortico-cerebellar abnormalities in WC. They found an abnormal decrease of GABA-A receptor density in the right cerebellum and the left sensorimotor cortex resulting in the loss of inhibitory cortical control (Gallea et al., 2018). Even in resting-state networks WC patients show a divergent neuronal activation compared to healthy controls. Thus, a reduced positive subcortico-cortical functional connectivity in combination with an increased negative cortico-cerebellar functional connectivity was evident (Dresel et al., 2014). Since primary dystonia is considered a network disorder (Blood et al., 2006; Delmaire et al., 2009; Gallea et al., 2018; Hinkley, 2013; Islam et al., 2009; Oga et al., 2002; Simonyan et al., 2017; Wu et al., 2010; Zeuner et al., 2015) the investigation of the functional connectivity between the nodal points of the network may give new pathophysiological insights. Thus, the aim of the present study was to investigate the movement-dependent pathophysiology of WC while focusing on the effective connectivity within the motor network activated during a finger-tapping task. In contrast to previous studies that focused on isolated brain regions, the purpose of our study was to examine the affected network in a more holistically manner. This approach is crucial to get a closer understanding of the diverging interaction among motor areas in patients with WC compared to healthy subjects. Based on previous literature, we firstly assumed a movement-dependent abnormal activation within the cortico-striatal network comprising the motor cortex, the putamen and the globus pallidus in patients with WC compared to healthy controls (Ibáñez et al., 1999; Oga et al., 2002; Simonyan et al., 2017; Wu et al., 2010). Secondly, we expected diverging cortico-cerebellar network activation (Bradnam et al., 2015; Gallea et al., 2018). We implemented dynamic causal modeling (DCM) to address the question whether the underlying neuronal motor network during finger-tapping is identical in writer's cramp and healthy controls and if so, whether single connections between network regions are different. DCM is a method for network analyses employing effective connectivity and has been introduced by Friston et al. (2003). The advantage of DCM is the possibility to estimate hidden neuronal states based on measuring brain activity, e.g. blood oxygenation level depended (BOLD) signal. Changes within a network analysis depend on the motor performance (Pool et al., 2013). Hence, comparing the functional connectivity of patients suffering from dystonia with matched controls may be confounded by impaired motor performance in dystonic patients. In order to exclude such a confounding factor, we investigated in this study the activity of the motor network, while tapping with the non-affected in WC Patients and controls. We recently demonstrated that WC patients performed a finger-tapping task with the non-affected hand equivalent to controls. Regardless, changes in the motor network were still evident in dystonic patients while performing this motor task with the non-dominant hand (Zeuner et al., 2015).

2. Materials and methods

2.1. Subjects

The results of the structural and functional MRI analysis have been published by Zeuner et al. (2015) previously. In this study, we included fifteen patients suffering from writer's cramp (6 women, mean age of 51.6 ± 11.1 years, range: 35–69) with a mean disease duration of 15.7 ± 8.9 years (range: 3–36 years). Four patients disclosed simple writer's cramp showing symptoms only during writing, while all further patients suffered from complex writer's cramp and even demonstrated dystonic symptoms when performing fine motor tasks other than writing. Further, nine patients exhibited mirror dystonia. The diagnosis of dystonia was established by medical history and by using the Writer's Cramp Rating Scale (Wissel et al., 1996) and the Arm Dystonia Disability Scale (Fahn, 1989). The Arm Dystonia Disability Scale (ADDS) contains seven items that together estimate the impairment of manual skills reported by patients. A score of 100% indicates normal motor function. The final score represents the percentage of normal manual activity. Therefore, a lower ADDS score means the patient suffers from more severe functional impairment. According to the Arm Dystonia Disability Scale, writer's cramp patients exhibited difficulties in other fine motor tasks such as using a computer mouse, using the keyboard of a computer, battening shirts, blouses, using silverware for eating, grasping objects or difficulties with homework or in the job. The mean of the ADDS was equal to 56.4% (± 14.1% SD).

We further used the Writer's Cramp Rating Scale (WCRS) (Wissel et al., 1996) to examine the clinical presentation. Patients were videotaped while writing the German sentence "Die Wellen schlagen hoch" ("The waves are surging high") ten times without a break between consecutive sentences, and the severity of writer's cramp was analyzed from the video segments (Wissel et al., 1996). A higher total WCRS score (with a maximum score of 30 points) means the patient showed more severe dystonic signs during handwriting. The mean in our sample was equal to 8.8 (± 4.6). Table 1 displays an overview of patients' characteristics. Eighteen age-matched healthy individuals (7 women) with a mean age of 51.1 ± 8.4 years (range: 33–68) served as controls. All participants were right-handed, ascertained through the Edinburgh Inventory (Oldfield, 1971), but in our study they performed

Table 1
Characteristics of included patients suffering from writer's cramp.

Patient ID	Age (y)	Symptom duration (y)	Type of writer's cramp	Last injection (months)	Duration BoNT treatment (y)	Total ADDS score (%)	Total WCRS score	Mirror dysonia
P101	69	9	Complex	4	8	60	10	Yes
P106	49	10	Complex	n.a.	n.a.	68.57	5	Yes
P107	43	9	Complex	60	3	64.29	22	Yes
P108	36	11	Simple	n.a.	n.a.	55.71	8	Yes
P110	60	14	Simple	n.a.	n.a.	51.43	6	No
P112	36	3	Complex	17	0.7	42.85	7	No
P115	56	14	Simple	5	10	60	10	No
P119	35	21	Complex	36	0.5	48.9	14	Yes
P120	58	25	Complex	72	0.25	60	5	Yes
P122	59	13	Complex	120	0.5	51.43	6	No
P123	68	25	Complex	132	0.5	25.71	8	No
P125	55	4	Complex	18	3	81.43	5	Yes
P127	51	19	Complex	3	4	72.86	3	Yes
P128	57	34	Complex	10	2	34.29	12	Yes
P129	42	22	Simple	6	1	68.57	11	No