Cerebellar degeneration affects cortico-cortical connectivity in motor learning networks

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ABSTRACT

The cerebellum plays an important role in motor learning as part of a cortico-striato-cerebellar network. Patients with cerebellar degeneration typically show impairments in different aspects of motor learning, including implicit motor sequence learning. How cerebellar dysfunction affects interactions in this cortico-striato-cerebellar network is poorly understood. The present study investigated the effect of cerebellar degeneration on activity in causal interactions between cortical and subcortical regions involved in motor learning. We found that cerebellar patients showed learning-related increase in activity in two regions known to be involved in learning and memory, namely parahippocampal cortex and cerebellar Crus I. The cerebellar activity increase was observed in non-learners of the patient group whereas learners showed an activity decrease. Dynamic causal modeling analysis revealed that modulation of M1 to cerebellum and putamen to cerebellum connections were significantly more negative for sequence compared to random blocks in controls, replicating our previous results, and did not differ in patients. In addition, a separate analysis revealed a similar effect in connections from SMA and PMC to M1 bilaterally. Again, neural network changes were associated with learning performance in patients. Specifically, learners showed a negative modulation from right SMA to right M1 that was similar to controls, whereas this effect was close to zero in non-learners. These results highlight the role of cerebellum in motor learning and demonstrate the functional role cerebellum plays as part of the cortico-striato-cerebellar network.

1. Introduction

Degenerative Ataxias are a group of degenerative diseases which are differentiated based on the affected cerebellar tissue and/or the affected gene (Sandford and Burmeister, 2014). Cerebellar degeneration leads to symptoms such as limb ataxia, ataxia of stance and gait, dysarthria, and oculomotor disturbance as well as non-motor deficits in executive functions, working memory, language, visuo-spatial cognition and social behavior (Schmahmann and Sherman, 1998). Studies show that cerebellar degeneration causes specific impairments in different motor skill learning tasks such as visuomotor adaptation (Rabe et al., 2009; Vaca-Palomares et al., 2013) and adaptation to external force (Criscimagna-Hemminger et al., 2010; Maschke et al., 2004; Rabe et al., 2009). Also, implicit motor sequence learning is impaired in patients with cerebellar degeneration (Pascual-Leone et al., 1993) or cerebellar lesions due to stroke (Doyon et al., 1997; Gomez-Beldarrain et al., 1998; Molinari et al., 1997). Patients with cerebellar degeneration show

impairments in visuomotor associative learning (Timmann et al., 2004), and in other forms of sequence learning such as perceptual sequence learning (Dirnberger et al., 2013) and temporal sequencing (Matsuda et al., 2015). Similarly, patients with cerebellar lesions are impaired in different aspects of sequence learning involving spatial as well as temporal sequencing (Leggio et al., 2008; Shin and Ivry, 2003).

Only few attempts have been made to characterize whole-brain functional changes in patients with cerebellar degeneration when they are actively engaged in task performance. In a study by Stefanescu et al. (2015), activity in superior cerebellum (lobules V and VI) ipsilateral to the performing hand decreased for patients compared to controls while they made simple movements. Harding et al. (2016) found that Friedreich ataxia patients showed reduced activity in a working memory task compared to controls in bilateral cerebellar lobules VI, VII and VIII as well as in left insula and rostrolateral prefrontal cortex. Hence both motor and memory functions seem to affect lobule VI of the cerebellum, a region known to be involved in motor sequence learning (Bernard and

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Seidler, 2013).

Although evidence points to a critical role of the cerebellum for motor and other aspects of implicit learning, imaging studies in healthy subjects have shown that also basal ganglia nuclei and thalamus together with cortical areas such as parietal cortex and dorsolateral pre-frontal cortex are involved in motor learning (Hardwick et al., 2013). Specifically, theoretical models suggest that distinct cortico-striatal and cortico-cerebellar loops (Doyon and Benali, 2005; Doyon et al., 2003; Hikosaka et al., 2002) mediate the different stages of motor learning. A model by Doyon and Benali (2005) suggests that striatum, cerebellum, parietal cortex and cortical motor regions are mediating the early, fast learning stage. During later phases of slow learning and retention however, the model differentiates motor sequence learning and motor adaptation in terms of the brain structures involved. Specifically, the authors suggest that the striatum is involved in motor sequence learning and the cerebellum in motor adaptation. Hikosaka et al. (2002) on the other hand, differentiate learning of a spatial sequence and learning of a motor sequence. During the fast learning stage, the movements to be executed are represented by a cortical loop of pre-frontal, parietal and motor cortex. When learning is established, the motor sequence is represented by motor regions of the basal ganglia and cerebellum together with the motor cortex. Penhune and Steele (2012) recently suggested that primary motor cortex (M1), basal ganglia and cerebellum may engage in parallel interacting processes which underlie motor sequence learning. It is hypothesized that the cerebellum plays a more prominent role in externally compared to internally cued movements (Jueptner and Weiller, 1998; van Donkelaar et al., 1999, 2000).

In previous work, we directly assessed causal interactions within this hypothesized cortico-striatal-cerebellar network using dynamic causal modeling. Our results demonstrated that learning negatively modulated connections from M1 to cerebellum (Tzvi et al., 2014) and from premotor cortex (PMC) to cerebellum (Tzvi et al., 2015) suggesting that interactions between motor cortical areas and cerebellum are critical for implicit motor sequence learning. The aim of the present study was to use an effective connectivity approach to investigate how cerebellar degeneration affects interactions within the cortico-striato-cerebellar network and how these changes relate to the commonly reported motor sequence learning deficits. Using voxel-based morphometry and tract-based statistics, studies investigating spino-cerebellar ataxia (SCA) – one form of cerebellar degeneration showed that white- and grey-matter degeneration is not limited to cerebellar structures but also found in cerebellar pathways as well as extra-cerebellar structures (Alcauter et al., 2011; Brenneis et al., 2003; Franca et al., 2009; Hernandez-Castillo et al., 2016; Lasek et al., 2006; Mercadillo et al., 2014). The patients included in this study were heterogeneous in terms of the specific cerebellar degeneration. Therefore, we also analyzed whole-brain grey matter volume changes in the patient group to identify the brain areas which were most consistently affected in the patient group. Based on the evidence above, we hypothesized that patients relative to healthy controls will be impaired in motor sequence learning and show reduced activity in brain regions related to motor learning. With respect to changes in causal interactions within the motor learning network, we expected that patients show both altered intrinsic connectivity patterns and weaker modulatory effects associated with their motor learning deficits.

2. Materials and methods

2.1. Participants

Sixteen cerebellar ataxia patients (5 females; age: 28–71; mean age: 49) volunteered to participate in the study. The patients were recruited from the outpatient clinic of the Department of Neurology of the University Hospital of Lübeck after being diagnosed by an expert neurologist for cerebellar disease (M.N.). In Table 1 the diagnosis of each

Table 1
Patients characteristics.

ID	age	gender	disease	MMSE	SARA	DD (years)
Z_01	37	male	SCA1	30	8	10
[a]Z_03	44	female	SAOA	30	8	–
Z_04	48	female	SAOA	30	9	4
Z_05	71	male	SCA6	29	11	7
[a]Z_06	68	male	SCA17	28	13.5	8
Z_07	34	female	SAOA	30	7	–
Z_08	60	male	SAOA	30	7	6
Z_10	39	female	SCA3	29	17	13
Z_11	54	female	SAOA	30	9	9
Z_12	61	male	SAOA	28	7	9
[a,b]Z_13	28	male	SCA4	30	20	8
Z_14	46	male	SCA7	30	12	3
Z_15	58	male	SAOA	28	9.5	3
Z_17	51	male	SAOA	30	14	5
Z_20	49	male	SAOA	29	9.5	3
Z_22	39	male	SAOA	28	14.5	2

SCA = spinocerebellar ataxia; SAOA = sporadic adult onset ataxia; DD = Disease duration; MMSE = mini-mental state examination; SARA = Scale for the Assessment and Rating of Ataxia.
[a] Patients excluded from analysis
[b] This patient was diagnosed using a genetic linkage analysis to confirm the SCA4 haplotype (Hellenbroich et al., 2003; Hellenbroich et al., 2006)

patient is specified. Patients were diagnosed with a specific SCA type as evident by a genetic test or as SAOA (sporadic adult onset ataxia). None of the patients were receiving neurological or psychiatric medication. Upon recruitment, patients were first tested for their general cognitive abilities using the "mini-mental state examination" (MMSE; Pangman et al., 2000). The level of ataxia was then rated using the "Scale for the Assessment and Rating of Ataxia" (SARA; Schmitz-Hubsch et al., 2006). Only patients who scored 28 points or more on the mini-mental test and < 18 points on the SARA score were eligible to participate. Sixteen neurologically healthy controls (4 males; age: 30–70; mean age: 52) were recruited from the general community as a control group. Two Ataxia patients could not perform the task in the scanner and therefore were excluded from all further analyses. One Ataxia patient and two healthy controls were excluded from the fMRI analysis due to excessive head movements and/or data acquisition errors. The final sample thus comprised 13 patients and 14 healthy controls. All participants were right-handed and had normal or corrected to normal vision. Informed written consent was given by the participants prior to study participation. The study was approved by the Ethics Committee of the University of Lübeck.

2.2. Experimental paradigm and task design

Participants performed a modified version of the serial reaction time task (SRTT) (Nissen and Bullemer, 1987) while lying supine in the magnetic resonance imaging (MRI) scanner after a short familiarization with the task. The visual stimuli were delivered to the participants through MR-compatible goggles. In each trial, four squares were presented in a horizontal array, with each square (from left to right) associated with the following four fingers: middle finger left hand, index finger left hand, index finger right hand, middle finger right hand. Subjects were instructed to respond to the red coloured square (see Fig. 1A) with the corresponding button on an MRI-compatible keypad, one for each hand, as precisely and quickly as possible. Unbeknownst to the participants, stimuli were presented in either a random order or as a 12-items-sequence ("1-2-1-4-2-3-4-1-3-2-4-3"). Random orders were generated using Matlab (Natick, MA) such that items were not repeated. The task consisted of 3 sessions with two blocks each. Each block contained 8 repetitions of the 12-element sequence (i.e. 96 trials) as well as 24 randomly presented stimuli before the sequence material and right after (see Fig. 1A). The inter-stimulus interval was 2000 ms. A 20 s