The Cerebellum Generates Motor-to-Auditory Predictions: ERP Lesion Evidence

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Abstract

■ Forward predictions are crucial in motor action (e.g., catching a ball, or being tickled) but may also apply to sensory or cognitive processes (e.g., listening to distorted speech or to a foreign accent). According to the "internal forward model," the cerebellum generates predictions about somatosensory consequences of movements. These predictions simulate motor processes and prepare respective cortical areas for anticipated sensory input. Currently, there is very little evidence that a cerebellar forward model also applies to other sensory domains. In the current study, we address this question by examining the role of the cerebellum when auditory stimuli are anticipated as a consequence of a motor act. We applied an N100 suppression paradigm and compared the ERP in response to self-initiated with the ERP response to externally produced sounds. We hypothesized that sensory consequences of self-initiated sounds are precisely predicted and should lead to an N100 suppression compared with externally produced sounds. Moreover, if the cerebellum is involved in the generation of a motor-to-auditory forward model, patients with focal cerebellar lesions should not display an N100 suppression effect. Compared with healthy controls, patients showed a largely attenuated N100 suppression effect. The current results suggest that the cerebellum forms not only motor-to-somatosensory predictions but also motor-to-auditory predictions. This extends the cerebellar forward model to other sensory domains such as audition. ■

INTRODUCTION

When performing an action, such as lifting a box, an appropriate musculoskeletal system is activated. At the same time, the somatosensory consequences of this action are predicted to compute on-line corrections of the movement and subsequently to verify whether the movement is suitable for the next execution of the same action. According to the internal cerebellar forward model on motor planning and motor control (Wolpert, Miall, & Kawato, 1998), it is hypothesized that the primary motor cortex sends an efference copy (von Holst & Mittelstädt, 1950) of an action to the cerebellum. From this input, the cerebellum generates a motor-to-somatosensory prediction, which prepares the musculoskeletal system to successfully execute a further movement. Applying a corollary discharge mechanism (Sperry, 1950), the prediction is compared with an actual incoming sensation. If a match between an action and a sensation (or prediction) occurs, the same pattern is applied when repeating the movement. However, in case of a mismatch, the cerebellum receives feedback information from respective cortical areas to adjust its prediction leading to on-line corrections (for a review, see Miall, 1998). Various experimental results support the view that the cerebellum generates motor-to-somatosensory predictions by applying a forward model (Imamizu & Kawato, 2008; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007; Blakemore, Frith, & Wolpert, 2001; Wolpert et al., 1998).

Generating forward predictions is necessary not only in motor control and planning but also in sensory processing (e.g., Bendixen, Schröger, & Winkler, 2009; O'Reilly, Mesulam, & Nobre, 2008; Curio, Neuloh, Numminen, Jousmaki, & Hari, 2000). To detect the omission of a tone in a sound stream, a forward prediction of this particular tone is made (Bendixen et al., 2009). Baess, Jacobsen, and Schröger (2008) reported that a motor-to-auditory prediction leads to a strong suppression of the N100 amplitude in response to self-initiated sounds, but not in response to externally produced sounds. Hence, in its simplest form, the forward model utilizes information from agency (Frith, 2005). More precisely, if an action is self-generated, its sensory consequences can be predicted precisely. In turn, the prediction leads to the suppression of an ensuing sensation. By means of intracranial recordings, Creutzfeldt, Ojemann, and Lettich (1989) provided clear evidence that self-produced speech sounds lead to suppressed activation in the auditory cortex compared with recorded speech sounds. This study was recently replicated by the use of neural phase synchrony (Chen et al., 2011). Chen and colleagues (2011) report that the neural phase synchrony in the gamma band between Broca's area and auditory cortex in a 50-msec time window that preceded the subjects' speech onset was greater during vocalizing than during

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listening to recorded speech. In contrast to self-initiated sensations, the sensory consequences of an external event cannot be predicted. This induces an accentuated sensation (Blakemore, Wolpert, & Frith, 2000; Wolpert, Ghahramani, & Jordan, 1995). As the cerebellum has been linked to sensory and cognitive functions (for reviews, see Strick, Dum, & Fiez, 2009; Baillieux, De Smet, Paquier, De Deyn, & Marien, 2008; Ramnani, 2006; Petacchi, Laird, Fox, & Bower, 2005), the question arises whether the cerebellum applies forward models in a modality-independent manner. On the basis of the idea of a motor-to-somatosensory forward model (Blakemore et al., 2000), Ramnani (2006) suggests that the cerebellum applies a forward model when receiving input not only from the motor cortex but also from other cortical areas. Ramnani (2006) proposes that the cerebellum generates predictions across various domains including sensory and cognitive domains. A recent study using combined tactography and magnetic resonance imaging provides strong evidence for this idea. The cerebro-ponto-cerebellar and the cerebello-thalamo-cerebral tracts exhibit cognitive load-dependent activity in a nonverbal auditory memory task (Salmi et al., 2010). Participants decided whether a tone in a sound stream had been previously presented. A sensory-motor task in the same study led to comparable results; however, the tracts projected via different pontine and thalamic nuclei (Salmi et al., 2010). Furthermore, the results revealed a functional segregation in the cerebellum. The posterior cerebellum was activated in a cognitive load task, whereas the anterior cerebellum was activated in a sensory motor task (Salmi et al., 2010). Although not explicitly tested, the auditory cognitive load task required a prediction concerning upcoming auditory events, possibly suggesting cerebellar involvement in generating a forward prediction. Indeed, auditory information does not only travel along the classical auditory pathway (see Shamma & Micheyl, 2010; Hackney, 1987) but also via the cerebellum, which receives direct auditory input (e.g., animal studies: Huang, Liu, & Huang, 1982; Aitkin & Boyd, 1978) and directly projects to auditory areas (animal studies: Storace, Higgins, & Read, 2011; Wang, Woody, Chizhevsky, Gruen, & Landeira-Fernandez, 1991; humans: Pastor, Vidaurre, Fernandez-Seara, Villanueva, & Friston, 2008; review on animal and human studies: Huffman & Henson, 1990). We therefore hypothesize that the cerebellum is involved in generating motor-to-auditory forward predictions, which prepare the auditory cortex for incoming auditory sensations.

Research in the auditory domain confirms that the auditory event-related N100 component is generated in the primary (Heschl's gyrus) and secondary (planum temporal) auditory cortices (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001; Zouridakis, Simos, & Papanicolaou, 1998; Näätänen & Picton, 1987). In terms of a forward model, the magnitude of the N100 is modulated when a sound is self-initiated compared with when a sound is externally triggered (EEG: Baess, Horváth, Jacobsen, & Schröger, 2011; Baess et al., 2008; McCarthy & Donchin, 1976; Hazemann, Audin, & Lille, 1975; Schäfer & Marcus, 1973; MEG: Martikainen, Kaneko, & Hari, 2005). For example, self-produced speech elicits suppressed cortical responses compared with recorded speech (fMRI: Christoffels, Formisano, & Schiller, 2007; MEG: Kauramäki et al., 2010; Aliu, Houde, & Nagarajan, 2009; Ventura, Nagarajan, & Houde, 2009; Heinks-Maldonado, Nagarajan, & Houde, 2006; Houde, Nagarajan, Sekihara, & Merzenich, 2002; Curio et al., 2000; EEG: Creutzfeldt et al., 1989, microelectrode recordings; Heinks-Maldonado, Mathalon, Gray, & Ford, 2005; Ford et al., 2001).

Accordingly, we suggest that the auditory cortex is prepared to receive sensory input when a sound is self-initiated. Hence, the processing activity directed at a sound should be reduced and in turn lead to an N100 suppression when compared with the N100 in response to an unpredictable or externally produced sound. In this process, the brain tolerates a limited amount of uncertainty. If the frequency of a self-initiated sound is modulated or the onset is shifted, the N100 suppression is maintained for self-initiated sounds (Baess et al., 2008).

In response to predictable self-initiated sounds, we hypothesize that the cerebellum is involved in generating motor-to-auditory forward predictions that lead to an N100 suppression effect. Hence, this study investigated the role of the cerebellum in generating motor-to-auditory forward predictions. We examined the N100 suppression effect elicited by self-initiated and externally produced sounds in 11 patients with focal cerebellar lesions and a group of healthy controls. If the cerebellum contributes to motor-to-auditory predictions on the basis of a forward model, we expect that patients with cerebellar lesions should show a smaller or no N100 suppression effect in response to self-initiated sounds.

METHODS

Participants

Eleven patients with cerebellar lesions (five women, mean age = 45.82 years, range = 25–61 years, all right-handed according to the Edinburgh Handedness Inventory; Oldfield, 1971) and 11 healthy controls, matched in age, sex, handedness, and educational background, participated in the experiment. All gave informed consent and were paid for their participation. They reported normal or corrected-to-normal visual acuity and normal hearing. Nevertheless, central and peripheral hearing levels were assessed in each participant. Patients and healthy controls also completed a series of neuropsychological tests and the NIH Stroke Scale to assess neurocognitive functions.

Focal vascular cerebellar lesions resulted from an ischemic or a hemorrhagic stroke (next to one patient with cerebellar tumor resection), thus excluding patients with posttraumatic lesions. Neuroimaging techniques, including MRI and brain CT were used to diagnose and locate the lesion. Three patients also had extracerebellar

Table 1. Basic Demographics and Clinical Information

Patient ID	*Sex*	*Age*	*Lesion Site and Etiology*	*Lesion Size (cm^3)*	*Additional Lesions*
1	m	60	Right medial PCL; PICA infarction	40.87	
2	m	31	Left ACL and superior PCL, upper pons; SCA infarction following colloid cyst resection	29.88	
3	f	46	Left medial PCL, tonsil, left lateral vermis, and right superior PCL; PICA infarction	3.38	
4	m	55	Left medial PCL, tonsil; PICA infarction	9.88	
5	f	39	Right lateral PCL; PICA infarction	0.31	
6	f	33	Bilateral vermis; right deep cerebellar nuclei, superior cerebellar peduncle; tumor postoperatively	3.1	
7	m	26	PCL bilaterally; ICH and AVM	13.53	Left superior frontal gyrus and anterior corpus callosum
8	f	50	MCL tonsil; PICA infarction	23.66	
9	m	46	Right deep cerebellar nuclei, superior and middle cerebellar peduncle, pontine tegmentum; SCA infarction	0.65	Left middle insula, right paramedian thalamus
10	f	59	Right lateral ACL; SCA infarction	14.27	
11	m	59	Left medial PCL; PICA infarction	0.86	Left anterior thalamus

m = male; f = female; ACL = anterior cerebellar lobule; PCL = posterior cerebellar lobule; LCL = lateral cerebellar lobule; ICL = inferior cerebellar lobule; MCL = medial cerebellar lobule; SCA = superior cerebellar artery; PICA = posterior cerebellar artery; ICH = intracerebral/-cerebellar hemorrhage; AVM = arteriovenous malformation.

pathologies (see Table 1 for a detailed description of the lesions). Healthy controls had no history of neurological, psychiatric, or other medical problems. The experiment was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Leipzig.

Experimental Conditions

The study contained two experimental conditions and one control condition (Figure 1). In the auditory–motor condition (AMC), participants initiated finger taps about every 2.4 sec.[1] Each tap triggered an immediate presentation of a sinusoidal sound (delay of 2–4 msec) via headphones. Participants were instructed to avoid counting to estimate the timing of the interval. The acoustic stimulation from the first experimental condition was recorded on-line and later used as the "external sound sequence" in an auditory-only condition (AOC). Thus, participants received the same set of stimuli in both conditions. However, in the AOC, no taps were required. Participants were asked to simply listen and attend to the auditory stimuli. In the motor-only condition (MOC), the participants performed self-paced finger taps every 2.4 sec. However, in contrast to the AMC, no tone was induced via the tap. This condition served as a control condition for motor activity in the AMC.

The experimental blocks were preceded by two training blocks. In the first block, participants were trained to tap every 2.4 sec. The second training block included visual feedback to indicate whether a trial was too slow (tapping interval longer than 3 sec) or too fast (tapping

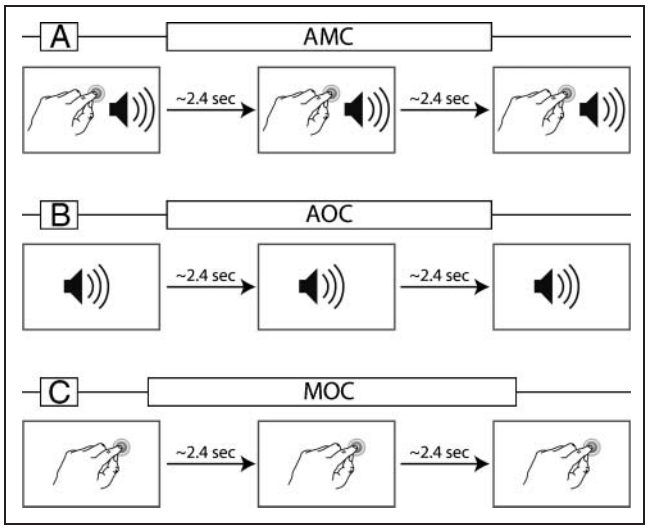

Figure 1. Schematic illustration of the three conditions. (A) AMC: Sound is self-initiated via a finger tap. (B) AOC: Tonal sequence is presented externally. (C) MOC: Taps are required, but no sound is elicited.

interval shorter than 1.8 sec).[2] This training block was run to ensure that participants had learned to estimate the time between two successive finger taps without counting. During the experimental run, visual feedback was not given.

Experimental Procedure

Participants were comfortably seated in an electrically shielded and sound-attenuated experimental chamber. A fixation cross was displayed in the middle of a computer screen. As individual lesions affected different areas in the cerebellum, the degree and sidedness of ataxia differed in the patient sample. As patients tapped in a predefined interval, we ensured that all patients tapped in equal parts with their affected and unaffected hands. They were instructed to change the tapping (index) finger every five taps to reduce tiring in motor execution. In doing so, the motor activation pattern was similar across participants. Participants started with the right index finger and changed the response finger when indicated on the screen. Each tap triggered an instantaneous presentation of a tone (600 Hz, 50 msec in duration, sound pressure level of 70 dB SPL) via headphones (Sennheiser HD 202) in both ears in the AMC, the same presentation of the sound was used in the AOC (see above). An in-house-built, highly sensitive tapping device was used to record the finger taps. No measurable sound was emitted by the taps. In each condition, 320 trials were recorded. This resulted in 960 trials. Experimental conditions were presented in blocks of 160 trials each. Block order was restricted: The AMC always preceded the AOC, but the occurrence of the MOC was randomized across participants.

Electrophysiological Recordings

The EEG was recorded continuously from 29 Ag–AgCl electrodes according to the International 10–20 system (Fp1, Fp2, F7, F3, FZ, F4, F8, FC3, FC4, FT7, FT8, C3, T7, CZ, C4, T8, CP5, CP6, P7, P3, Pz, P4, P8, O1, O2). In addition, activity from the left and right mastoids and the sternum as the ground electrode was recorded. The EEG was sampled at a rate of 500 Hz (Refa amplifiers system, TMS International, Enschede, The Netherlands), and an antialiasing filter of 135 Hz was applied. To control for eye movements, vertical and horizontal EOGs were recorded bipolarly. The impedance of all electrodes was kept below 7 kΩ. The recordings were on-line referenced to the left mastoid.

Data Analysis: Behavioral Data

We acquired tapping intervals for the AMC and the MOC by using the Presentation software (Neurobehavioral Systems, Inc., Albany, CA). For each participant, we generated the overall performance accuracy (percent correct) separately for the AMC and the MOC. A trial was scored as correct if it fell within a time window of 1.8–3.0 sec. Additionally, we computed separate accuracy values for the left and right index finger, as well as mean values for correct (1.8–3.0 sec) tapping intervals separately for the AMC and MOC and the performing index finger (i.e., intervals tapped with the left index finger vs. the right index finger). For statistical analyses, the PASW Statistics 18 (SPSS Inc., Chicago, IL) software package for Windows was used. Two repeated measures ANOVA tested for possible differences in tapping interval means and accuracy generated with the right or the left index finger with a between-subject factor Group (patients, controls).

Data Analysis: EEG Data

The EEG data were filtered with a 0.3- to 15-Hz band-pass filter. Epochs were rejected when they exceeded 30 μV. On average, 8.6% of all trials were rejected in the patient group, and 5.7% of trials were rejected in the healthy control group. The EEG data were rereferenced to linked mastoids. ERPs were time-locked to the stimulus onset of all critical trials. Each analyzed epoch had a duration of 600 msec, including a 100-msec prestimulus baseline. Tapping intervals shorter than 1.8 sec or longer than 3.0 sec were treated as errors and excluded from further EEG analysis. Motor activity was controlled for by computing difference between AMC and MOC (AMC minus MOC; difference wave is labeled auditory–motor corrected condition [ACC]). Statistical analyses of all conditions (controlled for normal distribution) were calculated in the time window of 80–120 msec for the N100 in five ROIs (central: Fz, Cz, Pz; left lateral: F7, T7, P7; left medial: F3, C3, P3; right lateral: F8, T8, P8; right medial: F4, C4, P4). This approach allows to map the activation foci across the scalp and ensures normalization of the data on the basis of equal number of electrodes in each ROI. This approach is also pursued elsewhere (e.g., Midgley, Holcomb, & Grainger, in press; Hoshino, Midgley, Holcomb, & Grainger, 2010). The time window was defined according to the grand-averaged peak distribution within the ROIs. As forming predictions may activate specific regions in the cerebellum, we divided the patients into three subgroups according to their specific lesion site. Doing this allowed to compare left lateral versus right lateral versus bilateral cerebellar lesions. The lesion sites are also described in Table 1.

For all statistical analyses, the SAS 8.20.20 (Statistical Analysis System, SAS Institute, Inc., Cary, NC) software package was used. Visual inspection confirmed an early negativity with a whole-head distribution in both auditory conditions (ACC and AOC). An ANOVA was carried out on mean amplitudes in a preselected time window. Only significant main effects and significant interactions with p values smaller or equal to .05 are reported for critical conditions and interactions. The omnibus ANOVA included the within-subject factors Condition (ACC/AOC) and ROI (5) and the between-subject factor Group (patients, controls), resulting in a $2 \times 2 \times 5$ design. To account for functional differentiation in the cerebellum, an omnibus ANOVA was

carried out, including the between-subject factor Group (left lateral, right lateral, bilateral) and the within-subject factors Condition (ACC/AOC) and ROI (5). Where necessary, the Greenhouse–Geisser correction was applied to the results reported below.

RESULTS

Behavioral Data

In the AMC, the control subjects correctly tapped in 93.7% (*SD* = 12.2%) of the cases and in the MOC in 88.4% (*SD* = 12.2%). The patients produced correct intervals in 89.5% (*SD* = 12.7%) of the trials in the AMC and in 80.2% (*SD* = 14.9%) of the trials in the MOC. Statistical analysis of participants' tapping performance revealed no significant main effects or interactions (all *p*s > .1), indicating no behavioral differences between the groups. The controls tapped on average every 2152.3 msec (*SD* = 427.7 msec), whereas the patients tapped every 2186.4 msec (*SD* = 697.3 msec). Although the variance is greater in the patients than in the controls, both groups showed a periodic tapping performance.

ERP Data

The statistical analyses of the ERPs (Figure 2A) of both groups confirm a pronounced N100[3] in both conditions (Condition [$F(1, 20) = 28.43$, $p < .0001$]; Condition × Group [$F(1, 1) = 9.10$, $p < .01$]). In the control group (Figure 2B), the self-initiated sounds elicited a large N100 suppression when compared with the N100 elicited to externally generated sounds (condition [$F(1, 9) = 33.04$, $p < .0001$]). The mean N100 amplitude in response to self-initiated sounds (ACC: mean = −2.96 μV) was significantly less pronounced than the one elicited by externally produced sounds (AOC: mean = −6.07 μV).

In the patient group, we did not find a suppression effect in response to self-initiated sounds, confirming our hypothesis (Figure 2C). The mean N100 amplitude elicited by self-initiated sounds (ACC: mean = −4.31 μV) was not significantly suppressed compared with externally produced sounds (AOC: mean = −5.17 μV).

Furthermore, the results show a global distribution (Figure 3) of the suppression effect in the control group (Condition × ROI [$F(1, 3) = 19.06$, $p < .0001$]), which is significant in all ROIs (left medial [$F(1, 9) = 35.05$, $p < .0001$], left lateral [$F(1, 9) = 15.67$, $p < .01$], central [$F(1, 9) = 34.75$, $p < .001$], right medial [$F(1, 9) = 26.15$, $p < .001$], right lateral [$F(1, 9) = 17.17$, $p < .01$]).

When comparing the three lesion subgroups, neither a significant difference nor a significant interaction was found. This indicates that lesion site does not differentially contribute to the N100 suppression effect. When we analyzed each group separately, we confirmed no suppression effect in either group (see also Figure 4). For all patients, independent of lesion site (see different marking for the subgroups), the suppression effect is greatly reduced or not

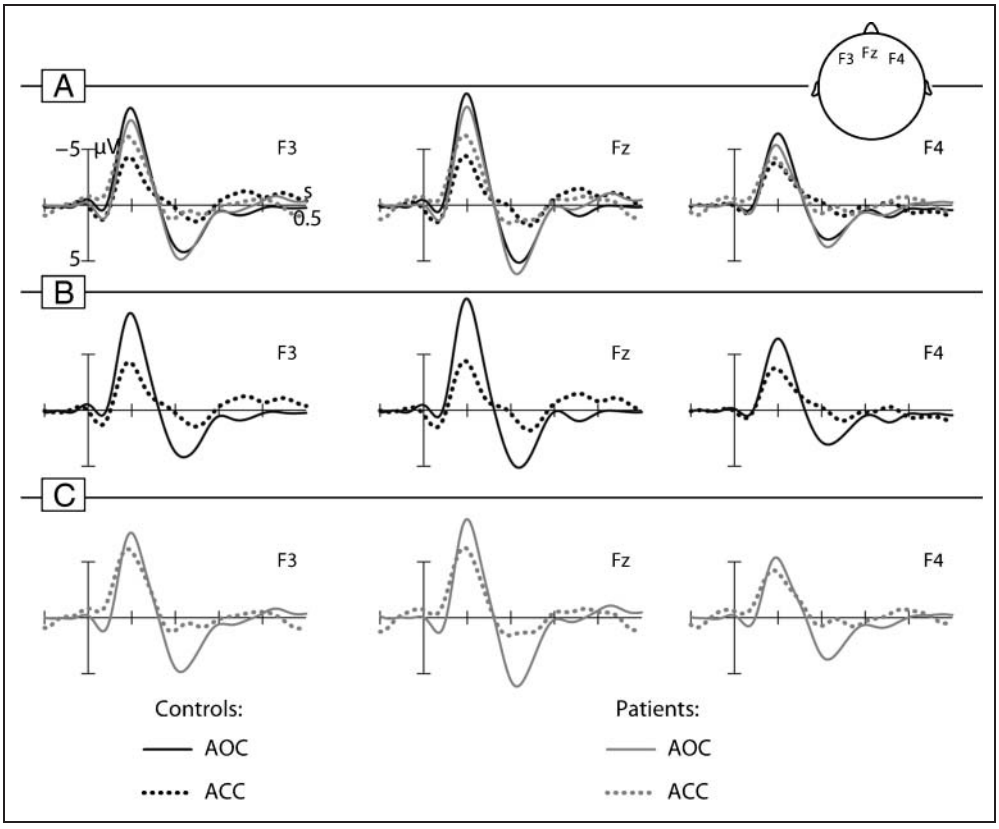

Figure 2. ERP responses. (A) Direct comparison of healthy controls (black) and cerebellar patients (red). ERPs elicited in AOC (black solid line) and ACC (black dotted line). (B) Group average of healthy controls (n = 11). ERPs elicited in AOC (black solid line) and ACC (black dotted line). (C) Group average of patients (n = 11). ERPs elicited in AOC (red solid line) and ACC (red dotted line).

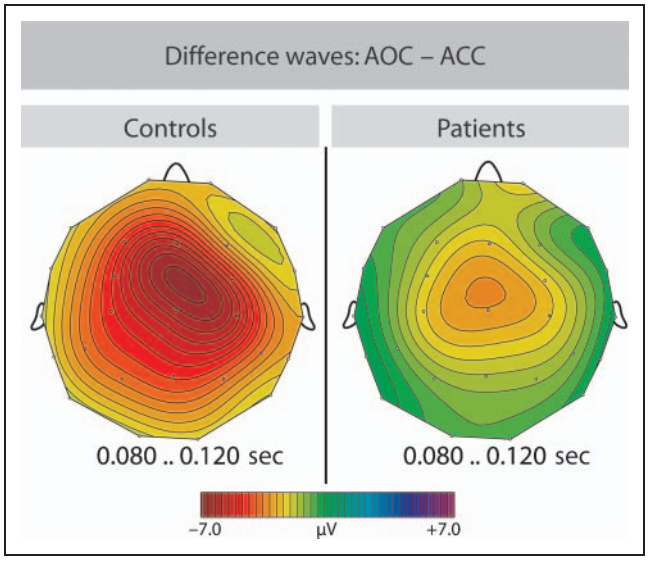

Figure 3. Grand average scalp maps showing the spatial distribution of the difference waves (AOC − ACC) in the analyzed N100 time window.

present at all, whereas the matching controls show a significant suppression effect. However, the patient sample size is too small to fully investigate this question, as the subgroups contain either three or four patients only.

DISCUSSION

The current study aimed to test the cerebellar forward model by investigating its role in generating motor-to-auditory predictions and thereby extending a motor-to-somatosensory prediction account (Blakemore et al., 2001; Wolpert et al., 1995) to another sensory modality. In the auditory domain, the N100 ERP component is sensitive to the process of generating an internal prediction as evidenced in the N100 suppression effect elicited by self-initiated but not externally produced sounds (Baess et al., 2008; Martikainen et al., 2005; Ford et al., 2001; McCarthy & Donchin, 1976; Hazemann et al., 1975; Schäfer & Marcus, 1973). In the current study, we addressed the question of whether the cerebellum is involved in motor-to-auditory predictions by investigating the N100 suppression effect generated by self-initiated and externally produced sounds in a group of patients with focal cerebellar lesion and matched healthy controls. The results confirm that healthy controls show the expected N100 suppression effect elicited by self-initiated sounds replicating previous results (EEG: Baess et al., 2008, 2011; McCarthy & Donchin, 1976; Hazemann et al., 1975; Schäfer & Marcus, 1973; MEG: Martikainen et al., 2005). In contrast, patients with cerebellar lesions do not show an N100 suppression effect elicited by self-initiated sounds. This suggests that cerebellar patients are compromised in generating a prediction of an auditory event that is triggered by a self-generated action. Thus, the current findings suggest that the cerebellum is a key structure in generating motor-to-auditory predictions via a motor-to-auditory forward model.

Several studies provide experimental evidence that the cerebellum predicts somatosensory consequences of motor actions (for review, see Blakemore & Sirigu, 2003; Ito, 1970). Wolpert et al. (1998) and Jordan and Rumelhart (1992), for example, postulate that the cerebellum generates a somatosensory forward representation of a motor action, which in turn predicts the state changes of a limb. By comparing estimated state changes with actual state changes, the forward model provides essential information for movement control. In an fMRI study and a later PET study, Blakemore and colleagues (Blakemore et al., 2001; Blakemore, Wolpert, & Frith, 1999; for a review, see Blakemore et al., 2000) investigated the somatosensory activity during self-produced and external tactile stimulation. They reported decreased activity in the somatosensory cortex to self-produced tactile stimuli, which presumably resulted from a motor-to-somatosensory prediction generated by the cerebellum. In addition, they found that, when self-produced sensory stimulation was delayed, the somatosensory prediction became less accurate, and the activity in the cerebellum decreased.

In the last two decades, research has provided ample evidence that the cerebellum is not only involved in motor

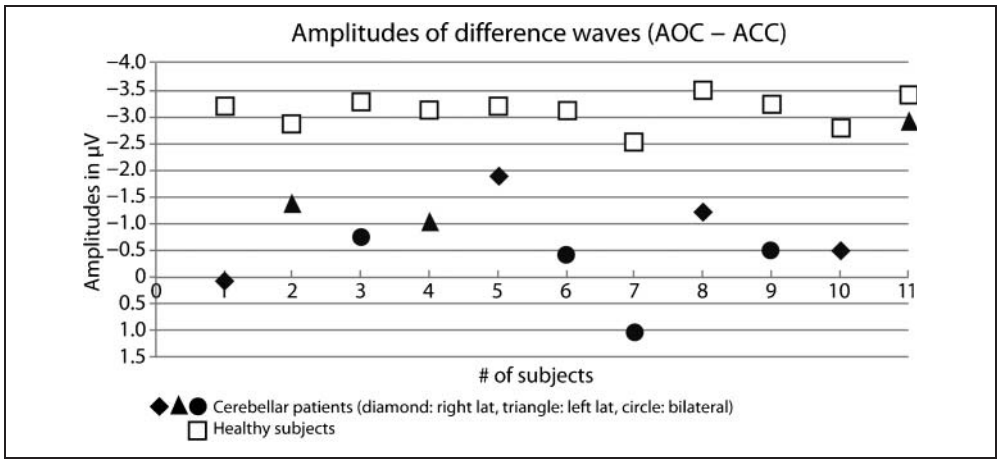

Figure 4. Scatter plot shows individual amplitudes of difference waves (AOC − ACC). Cerebellar patients are grouped into the three different subgroups according to their lesion site: diamonds = right lateralized; triangle = left lateralized; circle = bilateralized.

control and planning but also in sensory processing and cognition (e.g., Hodge et al., 2010; Strick et al., 2009; Baillieux et al., 2008; Ivry & Baldo, 1992). Because of its cellular organization, which is invariant across its entire structure (Bloedel, 1992), it has been proposed that the functional diversity of the cerebellum is a result of its different input and output structures. Most cortical areas, including prefrontal and primary motor areas, send afferents to specialized regions in the cerebellar cortex. There they form closed loops with respective cortical target areas (Middleton & Strick, 1994, 2001). This view supports the idea that a cerebellar forward model is applied independent of a specific processing modality.

None of the previous studies exploring the role of the cerebellum in generating sensory predictions have investigated the role of the cerebellum when an auditory event is self-produced. If an event is self-produced, the input to the cerebellum is modulated by motor activity. Although we included a MOC to account for motor activity during the self-initiation of sounds, we investigate neither purely sensory nor purely motor input but rather sensorimotor input to the cerebellum. As cerebellar patients fail to show an N100 suppression effect in response to self-initiated sounds, our results provide evidence that the cerebellum generates an auditory prediction from sensorimotor information by using a motor-to-auditory forward model. More specifically, we suggest that, by receiving an efference-copy-based motor activity induced by a finger tap to the auditory input, the cerebellum predicts the sensory consequences of an auditory stimulus. The predicted auditory consequences are sent to the auditory cortex. Consequently, the auditory cortex is prepared for the incoming sensation and directs less activity to the processing of this stimulus (Creutzfeldt et al., 1989). This view is consistent with ideas proposed by Ramnani (2006), who suggests that the cerebellar forward model receives input not only from the motor cortex but from all cortical areas. He discusses that the cerebellar forward model describes a function that can be applied to different modalities: motor and sensory modalities. Although we controlled for motor activity by means of a motor control condition, the current study does not provide evidence of a sensory-to-sensory forward model, but rather of a motor-to-sensory forward model. To investigate a purely sensory forward model, it is necessary to test predictions that are not based on self-initiation, but rather on an external stimulus that functions as a cue.

To investigate the role of the cerebellum in generating predictions independent of the processing modality, one has to study sensory-to-sensory prediction. Restuccia and colleagues (Restuccia, Della Marca, Valeriani, Leggio, & Molinari, 2007; Restuccia et al., 2001) used a sensory MMN paradigm in an EEG study to investigate preattentive change detection in incoming electrical somatosensory stimuli. The underlying process is based on the comparison of a predicted and an actual future event. Patients with unilateral cerebellar lesions displayed an abnormal sensory MMN paradigm compared with the ERP response in controls, indicating that the cerebellum initiates sensory consequences of upcoming events (Restuccia et al., 2001, 2007). In a second EEG study with cerebellar patients, Moberget and colleagues (2008) tested two hypotheses. Whereas a timing hypothesis states that the cerebellum is crucial for precise temporal predictions, the sensory prediction hypothesis postulates that the cerebellum is crucial in generating predictions about upcoming sensory events. The study investigated MMN responses to four types of deviants: duration, intensity, pitch, and location. Cerebellar patients differed from controls in their response to duration and intensity deviants, suggesting an involvement of the cerebellum based on precise timing. This does not yet provide a definite answer to the question whether the cerebellum also generates predictions across domains, for example, in the purely sensory or the cognitive domains, which should be of great interest for future research.

In conclusion, the current study sought to answer the question of whether the cerebellum is involved in generating motor-to-auditory forward predictions. We tested patients with cerebellar lesions in an auditory task utilizing self-initiated and externally produced sounds. When comparing ERP responses to self-initiated and externally produced sounds, we found that cerebellar patients, in contrast to healthy controls, did not display a significant N100 suppression effect. This result suggests that the cerebellum generates motor-to-auditory forward predictions by applying a motor-to-auditory forward model. Hence, it also indicates that the cerebellum contributes to generating predictions in various sensory modalities. However, the theoretical groundwork on the cerebellar involvement in auditory perception during speech processing, a purely sensory modality, has been provided by Kotz and Schwartze (2010). They state that auditory information is directly sent to the cerebellum, which encodes the temporal relationship between incoming events. This information is transmitted to the frontal cortex, thereby establishing a basis for temporally explicit prediction mechanisms (Kotz & Schwarzte, 2010).

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Notes

1. The interval of 2.4 sec is motivated by the tapping and timing literature; 2.4 sec is a multiple of 600 msec, which is considered a reliable measure of spontaneous motor tempo (Drake, Jones, & Baruch, 2000; Fraisse, 1982). Furthermore, there is evidence that two sounds occurring within an interval of more than 1.8 sec are no longer perceived as a chain of

events, but rather as discrete events (Fraisse, 1982). To reduce habituation effects, we aimed for a discrete temporal structure. Therefore, we chose the first multiple of 600 msec following 1.8 sec.

2. We choose to set a minimum and a maximum length of a tapping interval based on two reasons: First, the correct interval was motivated by the timing literature, which states that 600 msec is considered a reliable measure of spontaneous motor tempo (Drake et al., 2000; Fraisse, 1982). We therefore set the boundaries of the correct tapping rate at ±600 msec. Second, we wanted to ensure that the two experimental conditions were as similar as possible. Although the sounds in the AOC also had a regular structure as they appear approximately every 2.4 sec, they were not predictable in terms of precise timing. Hence, the precise predictability is the only difference when comparing the AOC and the auditory-corrected motor condition.

3. Statistical analyses of the P200 component revealed a significant main effect of Condition [$F(1, 20) = 19.39$, $p < .0003$] and a significant interaction of Condition × ROI [$F(1, 3) = 17.62$, $p < .0001$]. However, no significant main effect of Group was found. The analysis reveals that the P200 response in both groups is similar: Healthy controls display a significant main effect of Condition [$F(1, 9) = 8.01$, $p = .0178$] and a significant interaction of Condition × ROI [$F(1, 3) = 7.28$, $p < .01$]. Group analysis of the patients revealed a significant main effect of Condition [$F(1, 9) = 11.50$, $p = .0069$] as well as a significant interaction of Condition × ROI [$F(1, 3) = 10.53$, $p < .01$]. Interestingly, the attenuation in the P200 was not only present in the control group but also in the cerebellar lesion group, showing that the N100 suppression effect is selectively impaired.

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