

1 **Can electro- and magnetoencephalography detect signals from the human cerebellum?**

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3 Lau M. Andersen^{1,2*}, Karim Jerbi^{3,4}, Sarang S. Dalal¹

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5 ¹Center of Functionally Integrative Neuroscience, Aarhus University, Denmark

6 ²NatMEG, Karolinska Institutet, Stockholm, Sweden

7 ³Computational and Cognitive Neuroscience Lab (CoCo Lab), Psychology Department,

8 University of Montreal, Montreal, QC, Canada

9 ⁴MEG Unit, University of Montreal, Montreal, QC, Canada

10

11 * Corresponding author: lmandersen@cfin.au.dk

Abstract

The cerebellum plays a key role in the regulation of motor learning, coordination and timing, and has been implicated in sensory and cognitive processes as well. However, our current knowledge of its electrophysiological mechanisms comes primarily from direct recordings in animals, as investigations into cerebellar function in humans have instead predominantly relied on lesion, haemodynamic and metabolic imaging studies. While the latter provide fundamental insights into the contribution of the cerebellum to various cerebellar-cortical pathways mediating behaviour, they remain limited in terms of temporal and spectral resolution. In principle, this shortcoming could be overcome by monitoring the cerebellum's electrophysiological signals. Non-invasive assessment of cerebellar electrophysiology in humans, however, is hampered by the limited spatial resolution of electroencephalography (EEG) and magnetoencephalography (MEG) in subcortical structures, i.e., deep sources. Furthermore, it has been argued that the anatomical configuration of the cerebellum leads to signal cancellation in MEG and EEG. Yet, claims that MEG and EEG are unable to detect cerebellar activity have been challenged by an increasing number of studies over the last decade. Here we address this controversy and survey reports in which neuromagnetic signals were successfully recorded from the human cerebellum. We argue that the detection of cerebellum activity non-invasively with MEG and EEG is indeed possible and can be enhanced with appropriate methods, in particular using connectivity analysis in source space. We provide illustrative examples of cerebellar activity detected with MEG and EEG. Furthermore, we propose practical guidelines to optimize the detection of cerebellar activity with MEG and EEG. Finally, we discuss MEG and EEG signal contamination that may lead to localizing spurious sources in the cerebellum and suggest ways of handling such artefacts. This review is to be read as a perspective review that highlights that it is indeed possible to measure cerebellum with MEG and EEG and encourages MEG and EEG researchers to do so. Its added value beyond highlighting and encouraging is that it offers useful advice for researchers aspiring to investigate the cerebellum with MEG and EEG.

1. Introduction

In addition to its well-established role in the control and coordination of motor behaviour, the cerebellum is involved in sensory processing (audition: Petacchi et al., 2005; retinotopy: van Es et al., 2019) and cognitive tasks ranging from learning and memory to higher order cognitive control processes (Ito, 1984; Thaut, 2003; Bellebaum and Daum, 2007; Strick et al. 2009; Casabona et al. 2010; Stoodley et al., 2012; Buckner et al., 2013). King et al. (2019) recently showed that the cerebellum is involved in functions as diverse as hand movements, saccades, divided attention, verbal fluency, autobiographical recall, word comprehension, action observation, mental arithmetic, emotion processing and language processing, among other functions. This is further evidence, if any were needed, that we simply cannot afford to ignore the cerebellum in studies of human brain processes. However, the utility of noninvasive electrophysiological techniques like electroencephalography (EEG) and magnetoencephalography (MEG) for measuring cerebellar responses has not been clearly established, and sometimes even explicitly discounted in textbooks (Tyner et al., 1989; Covey & Carter, 2015). Meanwhile, studies employing EEG or MEG to delineate brain networks often do not consider the cerebellum as a potential source of the measured responses. In this review, we argue for a more optimistic view on MEG's ability to detect cerebellar activity. We furthermore offer advice for how to improve cerebellar recordings with MEG, hopefully providing a valuable tool that other researchers aspiring to record the electrophysiological signals of the cerebellum can rely on.

Our current knowledge of the electrophysiological mechanisms that mediate cerebellar activity comes mainly from direct recordings in animals. Investigations of the human cerebellum consist predominantly of studies in patients with cerebellar lesions or studies tracking metabolic or haemodynamic processes such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). In contrast to electrophysiological recordings, these neuroimaging techniques only provide an indirect measure of neural activity by monitoring local metabolic or haemodynamic responses. This notwithstanding, neuroimaging studies using these modalities play a pivotal role in elucidating the functional role of the cerebellum by unraveling its contribution to numerous tasks such as motor control, visually guided behavior and many cognitive tasks (Buckner, 2013). Because they monitor the activity of the whole brain simultaneously, these imaging techniques are also used to examine the involvement of the cerebellum in potential large-scale cerebral networks and to assess the functional-role of cerebellar-thalamo-cortical pathways (Diedrichsen et al. 2019). Nevertheless, the relatively sluggish nature of haemodynamic and metabolic responses remains a severe limitation when it comes to investigating the precise temporal properties of cerebellar activity. Recording signals from the cerebellum with temporal resolution comparable to that obtained in electrophysiology (i.e., millisecond range) is crucial in order to correlate the measured activity with behavioural parameters (such as reaction times or time-varying movement parameters) but also in order to compare activation latencies between cerebellum and other brain structures and finally to assess putative fine-grained synchronization properties between the cerebellum and various nodes of the involved cerebral network. To achieve the above, one would require a non-invasive technique that

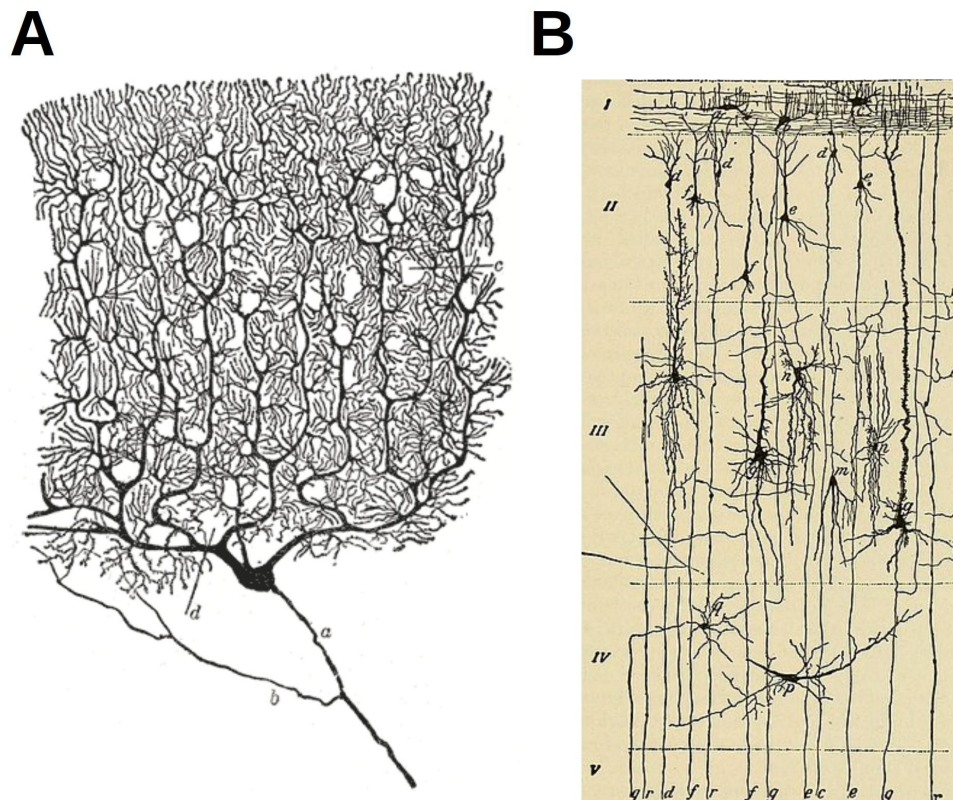
provides millisecond temporal resolution combined with whole-head coverage. EEG and MEG fulfil these requirements. While the former measures the electrical potentials on the scalp, the latter detects the minute magnetic signals generated on the surface by the same underlying cerebral generators (Hämäläinen et al. 1993). Both EEG and MEG record brain signals with millisecond resolution and currently available systems provide dense channel arrays with up to approximately 300 recording sites yielding an unprecedented spatial coverage of the head.

But do these methods provide the optimal spatiotemporal resolution at which to study the physiology of the human cerebellum? Unfortunately, the answer to this question is not straightforward. One problem lies with the poor spatial resolution of these techniques in deep structures, i.e., structures located far from the sensors. The distance from the sensor array and signal diffusion issues yield a low signal-to-noise ratio (SNR) and linear mixing at the individual recording sites. As a result, from a source estimation perspective, superficial sources (e.g., sources in primary auditory or somatosensory cortices) are easier to localize non-invasively with MEG or EEG than sources located in deeper brain structures (e.g., hippocampus or deeper substructures of the cerebellum). Furthermore, it has been speculated that the neuronal architecture of the cerebellar cortex may also be a specific limiting factor preventing detection of cerebellar sources with non-invasive methods due to signal cancellation. These potential difficulties, together with the attenuation of MEG and EEG signal strength with depth, has led to the prevailing view that MEG and EEG are not suitable for the detection of cerebellar activity. As a result, sources that appear to be localized in cerebellum are often suspected of being of artefactual in origin or simply resulting from noisy data. Nonetheless, a small but increasing number of MEG and EEG studies report activations in the cerebellum in a range of tasks. So can MEG detect cerebellar activity after all? And if so, how can we optimize its detection and how can we rule out false positives? We believe that there is now sufficient evidence in the literature to address these questions.

2. Why is the detection of cerebellar activity with EEG and MEG a controversial issue?

It has been suggested that it has been difficult to record cerebellar activity with noninvasive EEG (and by extension, MEG) since the neurons of the cerebellum are arranged in a “closed field” configuration (Bantli, 1972). However, the arrangement of Purkinje cells in cerebellar cortex (Ramón y Cajal, 1904) is very analogous to pyramidal cells in cerebral cortex (see Fig. 1) and likely contribute to the scalp EEG/MEG signal. Studies on the turtle cerebellum have demonstrated that an external magnetic field can be detected at a distance; a field of 1 pT was detected at a distance of 17 mm when a cerebellar patch of 10 mm³ was activated (Okada et al., 1987). The structure of the turtle cerebellar cortex is very similar to that of higher species, including humans (Eccles, 2013). Further evidence of the cerebellum having an open field configuration comes from the application of transcranial magnetic stimulation (TMS) to the cerebellum. This has been done in several studies (e.g.: Schutter & van Honk 2006; Koch et al., 2007; Harrington & Hammond-Tooke, 2015; Ferrari et al., 2018). The important insight is that magnetic stimulation is the converse of MEG, following the so-called reciprocity theorem (Heller & van Hulsteyn, 1992; Ruohonen & Ilmoniemi 1998). Thus, it

132 follows from TMS coils being capable of inducing an electromagnetic current in the
 133 cerebellum that MEG coils are also theoretically capable of detecting electromagnetic
 134 currents arising from the cerebellum. Finally, Buzsáki et al. (2012) highlight the cerebellum
 135 has an ordered structure, which would result in an open field configuration, but they note
 136 that cerebellar activation is mainly local, meaning that corresponding external magnetic
 137 fields are weak. However, in cases where synchronous activity is imposed on the cerebellum
 138 from outside itself, magnetic fields strong enough to be detected by MEG can be generated,
 139 as for example is the case in epilepsy (Kandel & Buzsáki 1993). As synchronous activity may
 140 also be imposed on the cerebellum by stimulation methods routinely used in neuroscience,
 141 all these considerations together make it the case that it, at least in principle, should not be
 142 impossible to detect cerebellum with MEG or EEG. MEG may be a more appropriate modality
 143 than EEG, however, due to the relative simplicity of MEG head models compared to EEG head
 144 models, which in turn makes source localization with MEG more precise and accurate than
 145 with EEG (Hämäläinen et. al 1993). Also, specifically for high-frequency oscillations, MEG
 146 appears to capture them with higher fidelity than EEG does (Muthukumaraswamy & Singh,
 147 2013).



148
 149 **Fig. 1: Similarities between Purkinje cells (cerebellum) and pyramidal cells**
 150 **(cerebral cortex) A)** a sketch of a Purkinje cell from the human cerebellum by
 151 Ramón y Cajal. **B)** a sketch of the pyramidal cells, showcasing different cortical
 152 layers (I-V).

153
154 One reason that the cerebellum may not be visible to EEG or MEG may arise from some
155 historical methodological limitations that have since been overcome. EEG/MEG studies
156 employing event-related averaging, inherently optimized to distinguish phase-locked evoked
157 activity, have rarely suggested cerebellum activation. Even experiments employing invasive
158 recordings in animal cerebellum only occasionally report event-related potentials (ERPs)
159 (e.g., Rowland & Jaeger, 2008); the vast majority of such studies instead report modulations
160 of oscillatory activity (see de Zeeuw et al. 2008 for a review).

161
162 This suggests that the cerebellum may primarily exhibit oscillatory modulations that may not
163 necessarily be phase-locked. Indeed, the classic experiments of Adrian (1935) [cat, 40-300
164 Hz], Dow (1938) [cat, 150-250 Hz], Ten Cate and Wiggers (1942) [cat, 50-230 Hz], and Pellet
165 (1967) [guinea pig, 200-400 Hz] all demonstrated high-frequency oscillatory activity in the
166 cerebellum. Niedermeyer & Uematsu (1974) observed low-frequency oscillations (1.5-6 Hz)
167 in three human Lennox-Gastaut syndrome patients implanted with cerebellar electrodes in
168 an experimental attempt at stimulation treatment. de Solages et al. (2008) showed that the
169 Purkinje cell layer produces 200 Hz oscillations in Wistar rats, which seem to entrain unit
170 firing; high-frequency LFPs in the molecular and granule cell layers were far less pronounced.
171 More recently, Cheron & Cheron (2018) found that stimulation of the inferior olive in mice
172 induced high-frequency oscillations (350 Hz) in the cerebellum. Intracranial recordings from
173 the human cerebellum are exceedingly rare, but Dalal et al. (2013) reviewed the sparse
174 literature describing them, and re-analysed some key historical intracranial recordings of the
175 human cerebellum, three published in Russian (Irger et al. 1949a; 1949b; 1951) and one in
176 French (Rétif 1964). In the studies by Irger et al., the human cerebellum exhibited
177 spontaneous oscillations in the beta band range (15-30 Hz) and in both the low-gamma (35-
178 50 Hz) and high-gamma (80-100 Hz) ranges. The recordings from Rétif (1964) furthermore
179 revealed evidence of 250 Hz oscillations. The few intracranial recordings from the human
180 cerebellum thus seem to correspond to the animal literature.

181
182 Perhaps the neuronal mechanisms or morphology of the cerebellum preclude robust
183 production of phase-locked evoked responses, which would have given the impression that
184 the cerebellum is silent to scalp EEG/MEG for several years until the revival of non-phase-
185 locked analyses using time-frequency techniques. Indeed, more compelling MEG findings of
186 cerebellar activity came about after techniques to perform time-frequency analysis in source
187 space became more widely available (e.g., Gross et al., 2002; Dalal et al., 2008; Pollok et al.,
188 2008; Schnitzler et al., 2009; Kennedy et al., 2011).

189
190 Sensor coverage may also be a factor. The traditional 10/20 EEG system and even state-of-
191 the-art high-density electrode caps as well as most whole-head MEG systems may simply not
192 provide sufficient spatial sampling over the regions where cerebellar signals may project,
193 e.g., the top of the neck. This problem can be partially overcome using low-tech solutions,
194 such as thoughtful placement of subjects in traditional MEG sensor arrays (perhaps with the
195 head tilted more forward than usual for better cerebellar coverage at the expense of frontal
196 coverage as in Hashimoto et al. (2003), or the use of additional free electrodes further down
197 the neck to supplement an EEG cap. With the advent of on-scalp MEG techniques such as

198 optically pumped magnetometers (OPMs) (Boto et al. 2017) and high critical temperature
199 (high- T_c) SQUIDs (Pfeiffer et al. 2019), it is also becoming possible to place sensors freely, and
200 thus place them as close as possible to the cerebellum, on the back of the head or or
201 possibly even into the mouth to approach it from the other side.

202
203 Finally, source localization attempts have traditionally assumed a spherical head model fit to
204 cerebral cortex, perhaps resulting in a poor fit with cerebellar cortex. Implementations of
205 realistic head models usually neglect the cerebellum, either removing it completely or
206 including it within the same compartment as cerebral cortex. Additionally, techniques that
207 assume sources to be oriented orthogonally to the cortical surface may need refinement for
208 the cerebellum, as the cerebellum is less easily segmented. The cerebellum, due to its
209 different morphology as well as its separation of cerebral cortex by thick dura mater (the
210 cerebellar tentorium), may ultimately profit from realistic models that specifically take into
211 account its electrical properties.

212 213 **3. Previous reports and illustrative examples**

214
215 As mentioned earlier, the introduction of time-frequency analyses greatly increased the
216 number of published findings on cerebellar activity stemming from mainly MEG recordings
217 and some EEG recordings. Here, we will go through some of them in greater detail. We do
218 not intend this to be a systematic review that includes all EEG and MEG papers that have
219 been published on cerebellar activation, but rather a set of illustrative examples showcasing
220 that MEG and EEG are not blind to the cerebellum.

221 222 **3.1 Motor tasks**

223 Gross et al. (2002), based on the application of the newly developed method of Dynamic
224 Imaging of Coherent Sources (DICS; Gross et al., 2001), found coherence between
225 electromyography (EMG) resulting from a sinusoidal movement and MEG activity in the
226 contralateral sensorimotor cortex, i.e., corticomuscular coherence. They then localized the
227 brain areas coherently oscillating with sensorimotor cortex, among which they found
228 ipsilateral cerebellum, thalamus and premotor cortex (PMC) engaged in a feedback loop
229 oscillating at a rhythm of 8-10 Hz, corresponding to natural discontinuities in movement
230 (Vallbo & Wessberg, 1993).

231
232 Pollok et al. (2005) extended the network to also include supplementary motor area (SMA)
233 and posterior parietal cortex (PPC), while Pollok et al. (2008) showed that anticipated
234 movements were related to an increase in coupling directed from cerebellar to thalamic to
235 parietal areas, i.e., cerebellum to cerebrum, whereas non-anticipated movements were
236 related to an increase in coupling direction from parietal areas to cerebellar areas, i.e.,
237 cerebrum to cerebellum. Pollok et al. interpreted these two differentially directed couplings
238 as anticipatory motor control and mismatch detection, respectively. Jerbi et al. (2007) (Fig. 2)
239 found that these cerebellar couplings to motor cortex also encode the speed with which
240 hand movements are made. More recently, Marty et al. (2018) found that cerebellar activity
241 entrains to the speed and kinematics of finger movements. Wilson et al. (2010) (Fig. 3) found
242 cerebellar activity in the beta band (15-30 Hz) before and after movements. Finally, Dalal et

al. (2008) furthermore found cerebellar activity in high gamma frequencies (> 65 Hz) when subjects performed finger movements. Taken together, these studies provide consistent evidence that induced cerebellar activity can be found in MEG when simple motor movements are performed. Finally, a recent EEG study has used distributed models to reconstruct phase-locked activity (Torres & Beardsley 2019) related to simple flexions of the wrists. It remains to be seen whether the same could be done with MEG.

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Please refer to Fig. 3 in doi.org/10.1073/pnas.0609632104

Fig. 2: Strength of task-based coherence with primary cortex as a reference: subjects were to counteract the unpredictable movements of a cube rotating around its centre by moving a trackball. The kinematics of the trackball movement were registered and its coupling to the neural time series were estimated, using task-related Z-transformed coherence with M1 activity (white dot) as an outcome measure (ΔZ_{coh}). Figure from Jerbi et al. (2007).

In addition to detection of cerebellar activity in healthy participants, cerebellar activity has also been detected in patients with dysfunctional networks or motor pathologies. Using DICS, Timmermann et al. (2003) found oscillatory coherence between the EMG of the hand tremor of six Parkinson patients and their contralateral M1. Similar to Gross et al. (2002), they found evidence of coherence between contralateral M1 and ipsilateral cerebellum. Schnitzler et al. (2009) similarly found oscillatory coherence between the EMG of the hand and the contralateral M1 in eight patients with Essential Tremor. Again using DICS, they also found coherence between M1 and ipsilateral cerebellum. Similar results have been found for the tremor related to Wilson's disease (Südmeyer et al. 2006).

3.2 Audition

Using MEG, Herrojo Ruiz et al. (2017), investigated auditory feedback related to motor movements (playing the piano). They provided feedback that was either expected (related to the movement) or unexpected (unrelated to the movement). When unexpected feedback was received, cerebellum activated more strongly in the theta (3-7 Hz) and beta bands (15-30 Hz) than when expected feedback was received. Also using MEG, Cao et al. (2017), found that attenuation of self-generated tones, as indicated by the decrease of the auditory fields, was decreased when cerebellar activity was disrupted with TMS. They found that the cerebellar vermis was more active during actual attenuation, i.e. during the sham condition of the TMS. The source reconstruction was based on event-related fields (ERFs) using the eLORETA algorithm.

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Please refer to Fig. 5 in doi.org/10.1016/j.bandc.2010.03.001

Fig. 3: Pre-movement beta activation in cerebellar cortices. Beta activation in ipsilateral cerebellar cortices following a flexion-extension movement. The maximum is in the inferior portions of ipsilateral cerebellum crus II. This figure is adapted from

Wilson et al. 2010 with permission.

Using EEG, Reyes et al. (2005), found evidence of cerebellar involvement in the so-called 40 Hz auditory steady-state response (ASSR). The 40 Hz ASSR is an oscillation arising when tones are amplitude-modulated at a frequency of 40 Hz. Using the LORETA algorithm, they localized activity in the left cerebellum both when reconstructing the activity weighted and unweighted by an independent PET scan.

3.3 Somatosensation

MEG-based evidence for the cerebellum's involvement in pure somatosensation was reported earlier than the evidence for its involvement in motor control. Tesche and Karhu (1997) found that median nerve stimulation elicited cerebellar event-related responses, contrary to the motor studies above where only induced responses were reported. Furthermore, they found (2000) that omissions of otherwise expected somatosensory stimulations elicited oscillatory activity following the time point when the stimulation should have happened, and that cerebellar oscillatory activity increased again before the following anticipated stimulation. Note that activity was not strictly speaking *localized* to the cerebellum in these studies, rather they estimated time courses for cerebellar sources given the assumption that there were sources there in the first place. As they also acknowledge, when time courses are estimated like this, it is possible that sources include activity generated at sources adjacent to the assumed source. Hashimoto et al. (2003), however, used a beamformer technique to localize median nerve stimulation evoked responses to the cerebellum. This study will be discussed more in-depth in a later section (Section 4) due to the importance of sensor coverage that it highlights.

In a more recent study, however, Andersen & Lundqvist (2019) (Fig. 4), using DICS, localized cerebellar oscillatory activity related to updating and maintaining expectations about somatosensation, ipsilateral to the stimulated hand in the theta and beta bands similar to the study of Herrojo Ruiz (2017) discussed above. These two studies indicate that low-frequency cerebellar oscillations may be related to updating and maintaining expectations. An important difference between the study of Andersen & Lundqvist (2019) and the motor studies discussed above is that they are indirectly dependent on a peripheral reference signal usually EMG or kinematics of hand movement. In most of the motor studies cited, first coherence between an external reference, e.g. EMG, and M1 activity is established, and second the coherence between M1 and other areas are investigated. Andersen & Lundqvist (2019), although also using DICS, instead investigated the whole brain using the power maps output by DICS.

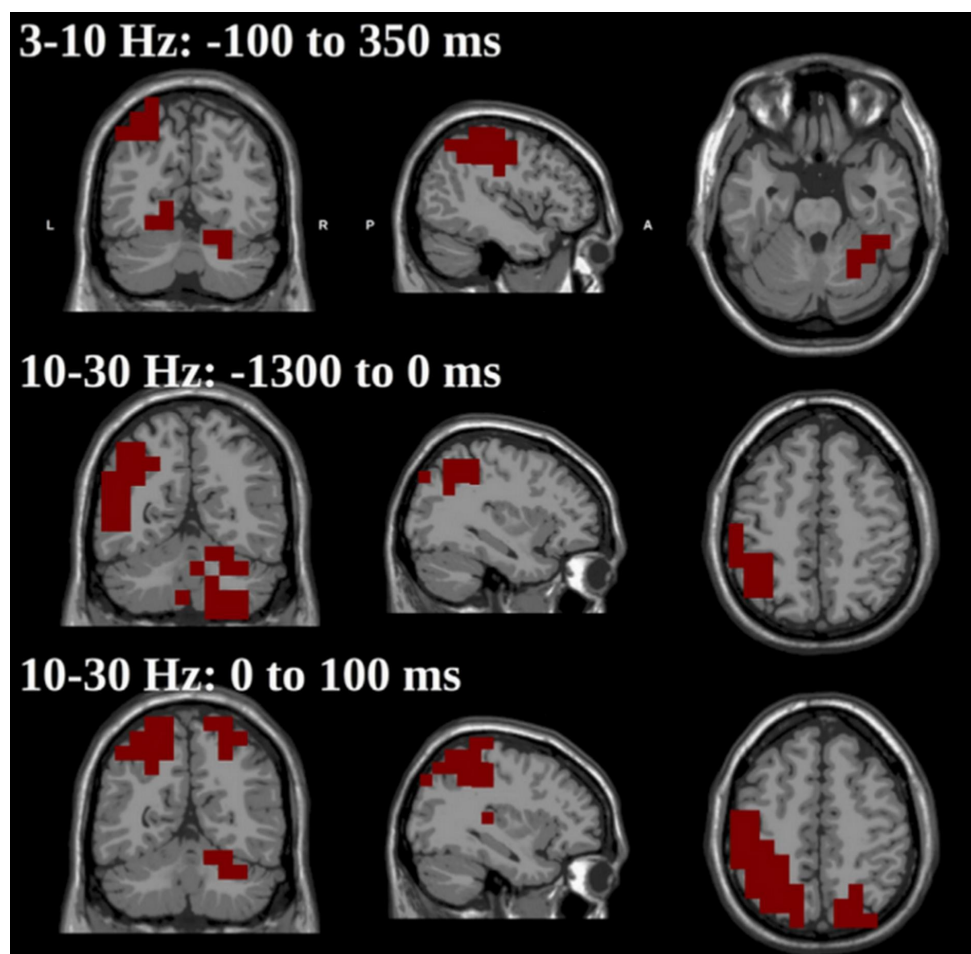
3.4 Visuomotor

Jousmäki et al. (1996) had subjects perform horizontal saccades every 3 s. Using a non-linear least squares fit, they fitted a two-dipole model in eight subjects, each with one dipole localized to cerebellum and one localized to the posterior parietal cortex. These revealed evoked responses ~170 ms after the onset of the saccade (Fig. 5). In contrast to the studies of Tesche & Karhu (1997, 2000), these dipole fits represent a source localization and not estimates of time courses. Bourguignon et al. (2013) had subjects observe an experimenter moving his finger rhythmically. Using methods similar to Gross et al. (2001), DICS, they found

330 that the motor cortices of subjects were coherently oscillating with the oscillating movement
331 of the experimenter. Furthermore, they found that the motor cortex was coherently
332 oscillating with cerebellum and V3.

333
334 Using EEG in a visuomotor task, Cebolla et al. (2016) compared the alpha-mu (~8-12 Hz)
335 oscillations in astronauts when they were either in a weightless state (in space) or on Earth.
336 They found greater desynchronization of the mu rhythms when the astronauts were visually
337 attending to target stimuli when the astronauts were in space compared to when they were
338 on Earth. Using a LORETA-style algorithm, cerebellum was revealed to contribute to this
339 difference, possibly reflecting activation necessary for postural stabilization.

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341



342
343 **Fig. 4: Differences in cerebellar activation between expected and unexpected**
344 **stimulations.** Subjects had their right index finger stimulated rhythmically (every 3 s).
345 Every now and then a stimulation was omitted. The contrasts shown here indicate

346 brain regions exhibiting significantly more power for *repeated stimulations* (a
347 stimulation following another stimulation) than for *first stimulations* (a stimulation
348 following an omission), where 0 ms refers to stimulation onset. This figure is adapted
349 from Andersen & Lundqvist (2019) under the CC BY 4.0 licence.

350

351 3.5 Cognition

352 High-gamma oscillations (~60-180 Hz) in the cerebellum have also been implicated in
353 decision making and introspection about decisions, perception and movement. Guggisberg
354 et al. (2008) found high-gamma oscillations in the cerebellum when participants make
355 decisions related to numerical representation, explicit memory and self-representation. They
356 specifically found that the left cerebellar hemisphere, together with the inferior parietal
357 lobule, were the key structures involved with internally cued decisions. Guggisberg et al.
358 (2011) found that the cerebellum was part of a network activated when participants were
359 asked to introspect the timing of three kinds of events: phoneme perception, their own
360 response decision, or the movement manifesting that decision. Both of these studies made
361 use of the time-frequency beamformer technique introduced by Dalal et al. (2008), together
362 with group statistics based on statistical non-parametric mapping (SnPM; Singh et al., 2003).

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Please refer to Fig. 2 in

doi.org/10.1097/00001756-199611250-00032

364

365 **Fig. 5: Dipole position projected onto MRI.** Dipoles are localized to cerebellum and
366 posterior parietal cortex

367

368 3.6 Epilepsy

369 A few reports of cerebellar activation in epilepsy patients also exist. Mohamed et al. (2011)
370 found, using MEG, cerebellar activity 14 s after ictal onset in the motor cortex in a four-year
371 old boy. They discuss the possibility that the delayed cerebellar activity may play a
372 modulatory role in seizure termination. Lascano et al. (2013), however, found evidence of a
373 cerebellar lesion as the primary seizure generator in a 14-month old girl from high-density
374 scalp EEG, which was subsequently confirmed by intracranial EEG performed immediately
375 prior to surgical resection as well as freedom from seizures post-operatively. Finally, Elshoff
376 et al. (2013) tested sources underlying the frequency spectrum in EEG epochs of 10 s
377 recorded during seizures. Using DICS, they found cerebellar activity in 5 out of 11 patients.
378 The patients were between 1 and 19 years old (mean age: 9.6 years).

379

380 3.7 Summary

381 Taken together, these studies show that cerebellar activity can, under certain circumstances,
382 be detected with MEG and EEG. Many of the studies rely on an external reference, e.g.,
383 movement and observed movement, for establishing coherence between areas, and it is the
384 coherence between oscillations that is detected rather than a standard task-related source
385 activation. The studies of Jousmäki et al. (1996), Hashimoto et al. (2003), Cao et al. (2017)
386 and Torres & Beardsley (2019) are also noteworthy for their detection of event-related fields
387 in the cerebellum, where most other studies detect oscillatory responses.

4. How can we enhance our ability to monitor cerebellum with MEG?

In this section, we will cover methodological approaches that can enhance the chances of detecting cerebellar activity with MEG. We describe approaches that have successfully been used to detect cerebellar activity and discuss further promising strategies.

4.1 Optimizing design (superficial targets and initial localization)

The signal of more anterior parts of the cerebellum is going to be comparatively small, purely due to the distance to the MEG sensors. If possible, one could aim to target cerebellar areas that are superficial, relatively speaking. This would of course require that studies based on other modalities had implicated the specific cerebellar region. For inspiration, one could look at the detailed functional mapping of King et al. (2019). A related strategy would be to use a paradigm that robustly elicits a cerebellar response that can also be robustly localized. Using such a paradigm, a cerebellar source could be initially localized and thereafter its time course could be estimated for more subtle manipulations and variations of the localization paradigm. The question is though whether such a paradigm exists. A possible candidate might be the eye-blink conditioning paradigm. In eye-blink conditioning, performing an eye-blink is conditioned to the onset of tone (Conditioned Stimulus) which is followed by an air-puff to the eye (Unconditioned Stimulus). This conditioned response is dependent on an intact cerebellum (McCormick & Thompson 1984). Kirsch et al. (2003) found evidence of cerebellum's involvement in this response using MEG. Note however that their strategy is similar to that of Tesche and Karhu (1997, 2000) where they estimate the time course of assumed cerebellar sources.

4.2 Coverage of MEG sensor array or EEG coverage

A recent study of Todd et al. (2018) extended the 10-20 layout with extra electrodes below electrode Oz. They very interestingly found that these "cerebellar" electrodes picked up high-frequency oscillations (> 100 Hz) that were unique to these electrodes and not found on the occipital electrodes above nor the splenius muscle electrodes below. This highlights the importance of actually covering the cerebellum such that signal can be picked up in the first place.

Hashimoto et al. (2003) investigated somatosensory fields evoked by median nerve stimulation using the Yokogawa MEGVISION with 160 axial gradiometers. Using a beamformer method (Sekihara et al. 2001), they were able to reconstruct fields as arising from the medial part of the cerebellum. As can be seen in Fig. 6, sensor coverage extended below the cerebellum, including the upper cervical spine. This seems to have been done by having subjects tilting their heads forwards relative to the helmet. This meant that some frontal coverage was sacrificed at the expense of being able to sample the cerebellum. This is a simple strategy that may be highly beneficial.

Figure cannot be shown because of copyright issues.
Please refer to Fig. 1 in [doi.org/10.1016/S1388-2457\(03\)00233-5](https://doi.org/10.1016/S1388-2457(03)00233-5)

Fig. 6: Tilting the head to obtain better sensor coverage of the cerebellum. 160-channel Yokogawa System. Notice that the subject has tilted his head, such that the cerebellum was more fully covered. Figure from Hashimoto et al., 2003 with permission. (A=Anterior, P=Posterior, L=Left, R=Right).

4.3 Careful artefact removal

Cerebellar responses are susceptible to masking by or confounding with neck muscle EMG. It is therefore recommendable to record EMG from the major neck muscles. Especially, Minimum-Norm-Estimate-like source reconstructions (Hämäläinen & Ilmoniemi, 1994) would benefit from this, since these will allocate all magnetic fields recorded by the sensors to the assumed source space. If the source space includes cerebellum, and neck muscle activity is not removed before source reconstruction, the neck muscle activity is likely to be source reconstructed as spuriously arising from the cerebellum. Even in the presence of artefacts, beamformer methods will be useful since these reconstruct source activity independently at each assumed source location. This is done by creating a spatial filter that minimises contributions from other sources, brain and noise alike.

4.4 Long-range coupling

A successful strategy for localizing cerebellar activity has been to localize it based on its coherence with a “far-away” signal such as the EMG of the foot or the hand as discussed in Section 3. Using long-range coupling adds a level of trustworthiness to the connectivity assessments, since short-range connectivity assessments have many interpretational pitfalls (Bastos and Schoffelen 2016; Schoffelen and Gross 2009). The paradigms of Gross's and Jerbi's groups have been very successful in applying this strategy (see Section 3). The kinds of paradigms that can be run with these kinds of strategies might be limited to sensory and motor paradigms, however.

4.5 Reducing neocortical activity using Cortical Signal Suppression

Samuelsson and Hämäläinen (2019) have developed the method of Cortical Signal Suppression (CSS). The overall idea of this method is based on using unique features respectively of planar gradiometers and of magnetometers, as in the Neuromag system. Colloquially said, planar gradiometers are “near-sighted”, being maximally sensitive to signals arising from the cerebral cortex, whereas magnetometers are also sensitive to signals from beyond the cerebral cortex. By projecting out the signal shared between the magnetometers and planar gradiometers from the signal of the magnetometers alone, one can obtain a magnetometer signal that uniquely represents non-cerebral cortex. Applying this method to the Auditory Steady State Response (ASSR), they were able to decrease the ASSR signal arising from cerebral cortex by 97%, while in turn increasing the ASSR signal arising subcortically by 10%. The method has not been applied to investigate cerebellar activity yet. Another interesting aspect about this method is that it does not require any special data acquisition procedures. Thus, already acquired data sets are likely to benefit from re-analysis using CSS if cerebellum or sub-cortical sources are expected.

4.6 Improving anatomical models of cerebellum

In beamformer applications, the orientations of the sources are normally not included in the source model. Instead, the direction that maximizes the beamformer's output SNR is

typically chosen as the source orientation, determined through an optimization based on singular value decomposition (Sekihara et al., 2004). However, Hillebrand and Barnes (2003) found that the signal of the beamformer could be improved if anatomical constraints were introduced, such that sources were correctly oriented in the source model. The improvement in signal, however, is critically dependent on the co-registration error between MEG and MRI and the precision of the estimate of the orientation of the sources. Hillebrand and Barnes (2003) conclude that these errors need to be smaller than 2 mm and 10° respectively for these anatomical constraints. Regarding the co-registration error, several different strategies have been developed to reduce the error to less than 2 mm, e.g., photogrammetry (Clausner et al. 2017), structured-light scanner (Zetter et al. 2019; Homöle & Oostenfeld, 2019), and head casts (Meyer et al. 2017).

Regarding the estimation of source orientations, the typical anatomical constraint for MEG is to assume sources are orthogonal to the cortical surface extracted from anatomical T1 MRI scans. However, high-quality cortical surface extraction from 1.5T or 3T MRI is less tractable for the cerebellar cortex due to its thinness, leading to the unfortunate consequence that most available source analysis pipelines that depend on cortical surface information simply drop the cerebellum from the source space entirely. 7T MRI can yield sufficient resolution for reasonable extraction of the cerebellar cortical surface (Boillat et al., 2018). Alternatively, it has been suggested that neural fiber orientations may be derived from customized diffusion-weighted MRI (DWI) sequences at 3T; preliminary investigations suggest that this method can help distinguish activations of the visual cortex from the cerebellum (Dalal et al., 2018).

4.7 Speculation for the future

Several technologies are being developed where the ambition is to create whole-head arrays of on-scalp, or nearly on-scalp, of MEG sensors. One alternative is to use high- T_c SQUIDs (Pfeiffer et al. 2019; Öisjöen et al. 2012). Successful recordings of somatosensory and auditory fields have been made using these (Andersen et al. 2017; Andersen et al. 2019; Pfeiffer et al. 2019). At present, arrays of up to 7 high- T_c SQUID magnetometers have been created. These can virtually be placed on the scalp (<1 mm). Another alternative, optically pumped magnetometers (OPMs), are already commercially available for assembly into small-scale systems suitable for MEG. Recordings with 20 OPMs have been conducted and can also be placed close to the scalp ~ 6.5 mm (Borna et al. 2017; Boto et al. 2017). Since the pickup coil size of the magnetometers can be made smaller when moving towards the scalp, the spatial resolution will increase. This allows for sampling magnetic fields related to more focal brain activity than could be obtained with state-of-the-art MEG. As discussed earlier, one oft-mentioned reason that the cerebellum is purportedly not visible to MEG is that it is more finely folded than the cerebral cortex, resulting in signal cancellation. With finer spatial resolution, the problem of signal cancellation may be mitigated. Interestingly, the aforementioned Yokogawa system (Hashimoto et al. 2003) had a smaller pickup area 189 mm^2 than current CTF-systems (254 mm^2) and Neuromag systems (441 mm^2). In comparison, the size of the pickup coils in high- T_c SQUIDs is 81 mm^2 (Andersen et al. 2017; Andersen et al. 2019; Pfeiffer et al. 2019). These new technologies are likely to usher in a new exciting age for recordings of cerebellar MEG. In fact, a report already exists of OPMs being used to record evoked fields arising from the cerebellum (Lin et al., 2019). It furthermore seems likely

that on-scalp technologies may be used to recover evoked responses from the cerebellum when doing classical median nerve stimulation as Hashimoto et al. (2003) did. On-scalp MEG may also improve SNR for high-frequency oscillations (Krishnaswamy et al. 2017) since it samples brain activity more sparsely than conventional MEG that samples the brain from a distance.

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4.8 Summary and general recommendations

There are thus several strategies to employ to detect cerebellar activity. For any paradigm, however, one should increase the signal-to-noise ratio by acquiring as many trials as feasible. This necessitates a relatively simple paradigm without too many conditions. The results can be validated by ascertaining that any motor- or somatosensation-related responses arise from ipsilateral cerebellum. However, this requires both sides (e.g. left and right hands) to be tested – running counter to the idea of reducing the number of conditions. Experimental designs must therefore be optimized between these competing considerations.

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4.9 MEG's sensitivity to other structures outside neocortex

In this section, we briefly consider evidence for MEG's sensitivity to structures outside of neocortex. Our intention with this is to dispel the notion that MEG and EEG are exclusively generated by pyramidal cells near the surface of the cerebral cortex.

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The auditory brainstem response is perhaps the most well-known evidence that sensors on the scalp are capable of measuring subcortical activity (Jewett et al., 1970). The auditory brainstem responses consists of responses to brief auditory stimuli, generated sequentially by the cochlea, auditory nerve, superior olivary complex, lateral lemniscus, and inferior colliculus. It is routinely measured in the clinic with scalp electrodes, as a hearing test or measure of neural integrity. MEG sensors have also been able to capture the auditory brainstem response in experimental settings (Erné & Hoke, 1990; Parkkonen et al., 2009).

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Ruzich et al. in their recent review (2019) found 37 MEG studies between the years 2005 to 2018 that revealed robust hippocampal activity. Similarly, Pizzo et al. (2019) found evidence that using independent component analysis (ICA) hippocampal and amygdala activations could be found with MEG (6 out of 14 patients). Data from some patients (4 out of 14) even revealed evidence of a thalamic signal. These activations were independently verified using simultaneous intracranial EEG recordings. Even though less than half had detectable signal, this demonstrates the possibility to record from otherwise deep regions. Supporting this Attal & Schwartz (2013), using a combination of simulations and real data, showed that MEG is sensitive to signal arising from hippocampus, amygdala and thalamus. They emphasize the need to have anatomically precise source spaces, precisely orientation-constrained dipoles and a realistic estimate of dipole moment densities in different regions. We echo them in our advice to use anatomically precise models of the cerebellum. Thus, there is nothing about the depth *per se* that leaves cerebellum outside MEG's sensitivity range.

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5. Conclusion

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We conclude that it is indeed possible to detect MEG signals from the human cerebellum.

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Many studies using diverse methodologies have showcased MEG signals in different sensory domains such as audition, vision and somatosensation and during movements. There is also MEG-based evidence of the cerebellum being involved in more cognitive operations such as updating and maintaining sensory expectations, and in decision making. Some limitations do exist at the moment however. The prime one is that the signal-to-noise ratio is low due to the larger distance between much of the cerebellum and the sensors (compared to the cerebrum). This means that we are likely to miss true activations of the cerebellum if the signal-to-noise ratio is low. Under favourable circumstances, e.g. high number of trials, optimized paradigms, facilitating coupling approaches, suppression of cortical activity, etc., this review indicates that cerebellar activation *can* be detected, just as many other deeper brain structures can, e.g. hippocampus, amygdala and thalamus. Even when we robustly detect cerebellar activation, however, we still face the limitation of spatial resolution - with MEG it is hard to detect where exactly within the cerebellum we are. More precise anatomical models of the cerebellum may be useful for constraining the source reconstructions possible with MEG. MEG studies of the cerebellum however have the immense utility of being able to resolve brain activity as it unfolds in real time compared to the sluggish responses of fMRI. This may be paramount in understanding the complexities and details of cerebellar function and dysfunction.

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