Sensory prediction or timing?

Clarifying cerebellar function by examining the mismatch negativity response in patients with cerebellar degeneration

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Abstract

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Title: Sensory prediction or timing? Clarifying the function of the cerebellum by examining the mismatch negativity in patients with cerebellar degeneration.

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Background and aim: Over the last few decades increasing evidence suggests that the functional domain of the cerebellum extends beyond motor control. Two functional hypotheses attempting to account for cerebellar involvement also in a range of perceptual and cognitive tasks are the sensory prediction hypothesis and the timing hypothesis. The sensory prediction hypothesis postulates that the cerebellum is critical in generating expectancies regarding forthcoming sensory information. The timing hypothesis postulates that this structure is critical for the learning and retention of temporal information, a more limited, yet specific form of prediction. Recent functional imaging and patient studies have produced evidence compatible with both of these positions. The aim of the present experiment was to contrast these two hypotheses by examining the mismatch negativity (MMN) response in patients with cerebellar cortical atrophy. While the timing hypothesis would predict a selective impairment in the MMN response to the deviants of a longer duration than the standard, the sensory prediction hypothesis would also predict similar impairments in the MMN response to deviants of higher pitch, lower intensity and a different spatial location.

Method: Patients and matched controls were presented with a stream of short sounds while watching a silent movie. A standard auditory stimulus was presented 60% of the time, composed of a fixed duration, intensity, and pitch, and presented at a fixed location. The remaining sounds deviated on one of these four dimensions (10 % each).

Key result: Compared to controls, the patients exhibited delayed duration MMN latency, as well as a similar trend for the intensity MMN. The pitch and location MMNs did not differ between patients and controls.

Conclusion: The present results fail to support a more general role in sensory prediction as predicted by the sensory prediction hypothesis, while the timing hypothesis receives partial support. Importantly, the present findings add to previous reports of timing deficits in cerebellar patients by demonstrating that this impairment is present at an early stage of auditory processing (100-200 ms), even when the task does not require an overt assessment of temporal regularities or even that the stimuli be attended.

In science it often happens that scientists say, "You know that's a really good argument; my position is mistaken," and then they actually change their minds and you never hear that old view from them again. They really do it. It doesn't happen as often as it should, because scientists are human and change is sometimes painful. But it happens every day. I cannot recall the last time something like that happened in politics or religion.

Carl Sagan, 1987

Acknowledgements

The experiment described in this thesis was carried out during a stay at the University of California, Berkeley from 2004 to 2005, and I am deeply grateful to Professor Richard B. Ivry and Professor Robert T. Knight for inviting me into their labs. The researchers and students of these labs create a vibrant and stimulating community of curiosity and critical thinking, with the sometimes sharp edges of academic ambition seemingly mellowed by the Californian climate. Whatever the secret of this special intellectual soil, I found it wondrously nourishing. I especially wish to thank graduate student Christina M. Karns. While busy developing and running her own research project, she nevertheless found time to teach a Norwegian novice the tricks of the trade and has been a very close collaborator on this project ever since. Much deserved thanks also go to Professor Leon Deouell – whose thoughtful and thorough input has been of great help both in designing the experiment and in interpreting the results – and to Anne-Kristin Solbakk, who generously gave feedback on early – and in retrospect "not-too-reader-friendly" – versions of the text, as well as provided important moral support throughout this process. I count all of the above as my additional bonus supervisors, and so I have been in the lucky position of never lacking interested and qualified people to turn to at those inevitable times when the project seemed both confusing and consuming. Thanks! I am also grateful to my supervisor Professor Magnus Lindgren, whose inspiring conversation, encouragements and many a gently push made sure that my initially somewhat nebulous speculations were solidified into concrete experimental designs. Finally, I wish to thank all the participants, who patiently endured nearly two hours of monotonous beeps in the service of science. Of these, special thanks go to the patients. I sincerely hope that the results of the present study might help elucidate the role of the cerebellum, and thus, perhaps, make a small contribution towards improving the lives of those who suffer from cerebellar dysfunction.

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Table of contents

1. Introduction

1.1. "The cerebellar cognitive revolution"

The cerebellum (Latin for "little brain") is a heavily folded brain structure covering the dorsal surface of the brainstem (see Figure 1). It consists of two hemispheres, separated by a midline structure called the vermis (Latin for "worm"). Notably, while the cerebellum accounts for only about 10% of the total mass of the brain, it has been estimated to contain more than 50% of its neurons (Houk & Mugnaini, 2003). Neuronal input reaches the cerebellum from all sensory modalities – as well as from motor and association areas of the cerebral cortex and from subcortical structures such as the hypothalamus (Schmahmann & Pandya, 1997).

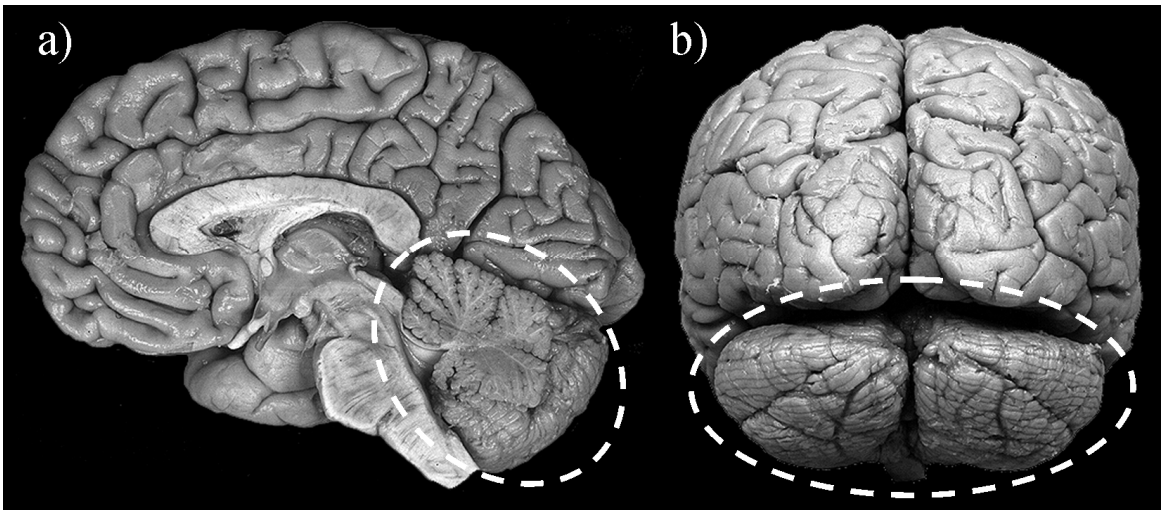

Figure 1: Photographs showing the medial (a) and posterior (b) surface of the brain with the dashed ovals indicating the cerebellum. The figure is based on photographs from The Digital Anatomist website hosted by the University of Washington, Seattle, USA: http://www9.biostr.washington.edu/da.html. Reprinted with permission.

Importantly – and in apparent contrast to the vide variety of input it receives - the internal cellular organization of the cerebellum is strikingly uniform throughout the structure (Houk & Mugnaini, 2003). This constitutes a marked difference from the cerebral cortex, where considerable variation in cellular organization can be observed across cortical areas receiving different input (Nolte, 2002).

Functionally, the cerebellum has traditionally been classified as part of the motor system. In 1809 Rolando first reported disturbances of posture and voluntary movements after ablation

of the cerebellum, and 15 years later Flourens demonstrated the importance of this structure for the coordination of voluntary movement and gait (Schmahmann, 1997[a]). While some early accounts also noted cognitive and affective deficits following cerebellar disease or agenesis (Schmahmann, 1997[a]), various motor dysfunctions are certainly the most prominent symptoms of cerebellar disorders (Houk & Mugnaini, 2003). Furthermore, based on observations of patients with acute cerebellar gunshot injuries during World War I, Holmes (1917) concluded that "no form of sensation is disturbed by cerebellar disease" (page 513). Thus, for most of the 20th century textbooks of neurology have presented the cerebellum as an organ controlling balance and movement, with reports suggesting cerebellar functional roles beyond the motor system consequently receiving less attention.

However, over the last few decades there has been a marked change in this picture, and the cerebellum is now increasingly seen as playing a part also in perceptual and cognitive processes (see reviews in Schmahmann, 1997[b]). This "cerebellar cognitive revolution" was motivated by results stemming from several lines of research. Leiner, Leiner & Dow (1986) were among the first to suggest a cerebellar contribution to cognition, based on the observation that cerebellar volume has increased in parallel with the volume of the frontal lobes across phylogenetic development (Passingham, 1975). Subsequent support for this idea was provided by anatomical studies demonstrating dense neuronal connections between the cerebellum and cortical areas involved in higher cognitive functions, such as the pre-frontal and parietal cortices (Middleton & Strick, 2000). A recent study investigating the cerebro-cerebellar connections in Macuaque monkeys and humans using diffusion tensor weighted magnetic resonance imaging (DTI-MRI) is of particular interest (Ramnani et al., 2006). Consistent with the traditional account of the cerebellum as part of the motor system, the majority of cerebro-cerebellar fibers in the Macaque originate in the primary motor area (M1), with comparatively fewer fibers stemming from pre-frontal cortex. However, in humans this picture appears to be reversed – fibers originating in pre-frontal areas now outnumber fibers stemming from M1. Thus, evolutionary and anatomical considerations suggest that in humans the cerebellum is equipped with the neural circuitry necessary to affect cognitive – as well as motor – processing.

Another important impetus to the discussion of possible non-motor functions of the cerebellum came from studies using the new neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), to map the

brain areas involved in various cognitive tasks (Ivry & Fiez, 2000). Across a number of experimental paradigms cerebellar activation was found in studies investigating the neural substrates of such varied cognitive functions as attention, perception, language, working memory, episodic memory, and procedural memory (Cabeza & Nyberg, 2000). Since most of these experiments equated motor demands between the task of interest and the control condition, the functional domain of the cerebellum was increasingly seen as extending beyond motor control. According to Ivry & Fiez (2000), such neuroimaging findings "have probably provided the greatest impetus for the cerebellar cognitive revolution" (page 1001). However, as the authors note, the interpretation of cerebellar activations in neuroimaging studies is far from straightforward. Emphasizing the same methodological point, Timmann & Daum (2007) write that "it is hard to find a brain imaging task which did not yield activation changes within the cerebellum, and it is difficult to ascertain the specificity of such results, i.e., whether or not an activation is critical to the cognitive process in question" (page 160).

The study of neuropsychological function in patients with disorders affecting the cerebellum constitutes a third line of research giving rise to expanded notions of cerebellar function. In contrast to the conclusions reached early in the 20th century by Holmes (1917, 1939), several case reports – as well as more extensive group studies – now described perceptual (e.g., Ivry & Keele, 1989; Ackermann, Graber, Hertrich & Daum, 1997, Thier, Haarmeier, Treue & Barash, 1999) and cognitive deficits (e.g., Botez-Marquard, Bard, Leville & Botez, 2001; Daum, Snitz & Ackermann, 2001, Schmahmann & Sherman, 1998) in patients with cerebellar lesions. Looking back on the last two decades of neuropsychological research on cerebellar patients, Timmann & Daum (2007) conclude that, even though many of the initially reported deficits have failed to be replicated, there is nonetheless "now convincing evidence for a cerebellar involvement in some aspects of cognitive processing, most notably verbal working memory" (page 161).

Finally, cerebellar structural abnormalities have been described in varied clinical syndromes including ADHD (Berquin et al., 1998), autism (Courchesne et al, 2001), dyslexia (Nicholson et al., 2001) and schizophrenia (Nopoulos, Ceilley, Gailis & Andreasen, 1999). While the functional consequences of this pathology remains unclear (Ivry, 2003), it is noteworthy that motor impairments – while present in some degree – are not among the most prominent symptoms of these disorders. Thus, the possible cerebellar involvement in such

neuropsychiatric disorders has provided a further impetus towards investigating non-motor functions of the cerebellum.

1.2. Sensory prediction and timing

Research findings demonstrating cerebellar involvement beyond motor control have inspired a wide variety of hypotheses regarding cerebellar function, including the coordination of attentional shifts (Akshoomoff, Courchesne & Townsend, 1997, Allen, Buxton, Wong & Courchesne, 1997) and mental imagery (Parsons & Fox, 1997), facilitating retrieval from working memory (Desmond & Fiez, 1998), and various aspects of response planning (Doyon, 1997; Hallett & Grafman, 1997) and automatization (Molinari, Leggio & Silveri, 1997; Nicholson, Fawcett & Dean, 2001; Thach, 1998). However, it is worth noting that the striking anatomical homogeneity of the cerebellum is strongly suggestive of a corresponding uniformity of function (Holmes, 1939; Ito, 2005). A satisfying account of cerebellar function should therefore ideally present a common functional mechanism capable of explaining a cerebellar role in such different cognitive – and motor – domains. Interestingly, despite the seemingly disparate nature of the ideas presented above, a common feature of many of these hypotheses is an emphasis on "predictive functions – the ability to anticipate forthcoming information and ensure that actions correctly anticipate changes in the environment" (Ivry & Fiez, 2000, p. 1005).

Two alternative, but closely related, hypotheses focusing on predictive functions of the cerebellum are the sensory prediction hypothesis and the timing hypothesis. The sensory prediction hypothesis postulates that the cerebellum is critical in generating expectancies regarding forthcoming sensory information (Bower, 1997; Courchesne & Allen, 1997; Ito, 2005; Paulin, 1997; Ramnani, 2006; Wolpert, Miall & Kawato, 1998). From this perspective, the cerebellum is seen as an adaptive predictor, capable of extracting and maintaining a short-term template for predictable sensory input. Importantly, while emphasizing a cerebellar role in sensory and perceptual processes, this hypothesis also offers a possible explanation for the motor deficits seen after cerebellar damage. Wolpert et al. (1998) point out that a fundamental problem in motor control is that – due to inherent neuronal transmission delays – sensory feedback from the environment is too slow to adaptively guide movements. In effect, the sensory feedback, once it arrives at the motor control centers, is already out-of-date, describing the state of the environment at some point in the immediate past. An adaptive predictor would solve this problem by providing predictions of the likely sensory

consequences of an executed motor command. By relying on these (cerebellar) sensory predictions, rather than the slow sensory feedback, the CNS could base motor control on good estimates of the *current* state of the environment, enabling smooth online control of movement. Interestingly, in computer simulations based on these ideas, disabling the adaptive predictor leads to motor control deficits resembling those seen in humans after cerebellar damage (Miall & Wolpert, 1995). Moreover, cerebellar patients appear to be significantly more impaired on motor tasks requiring predictive control of movement than on tasks relying on feedback control (Bastian, 2006). Finally, the impairment observed in patients with cerebellar lesions in adapting to novel sensorimotor transformations (e.g. Morton & Bastian, 2004; Tseng, Diedrichsen, Krakauer, Shadmehr & Bastian, 2007) may result from an inability to establish and modify predictions regarding the sensory consequences of movement.

Neuroimaging and electrophysiological studies provide empirical support for the sensory prediction hypothesis beyond the motor domain. For instance, Gao and colleagues (1996) reported a marked increase in cerebellar activation when finger movements were used to sample tactile information compared to when similar movements were made in the absence of these sensory signals. Indeed, even when movements were minimal, the cerebellar signal remained high during passive sensory stimulation if that information was task relevant. These results suggested that the cerebellum might actually be more involved with sensory processing than with motor control. More direct evidence for sensory *prediction* was provided by Tesche & Karhu (2000). Using magnetoencephalography (MEG), they found strong cerebellar activation after the random omission of expected somatosensory stimulation. In contrast, the primary sensory cortex was only activated after actually delivered stimuli and showed no response to the unexpected omissions. The sensory prediction hypothesis is also supported by electrophysiological animal experiments demonstrating that electrical stimulation of the cerebellum modulates the responsiveness to visual stimuli in the superior colliculi – and to somatosensory stimuli in the thalamus and somatosensory cortex – provided that the electrical stimulation occurs prior to the sensory stimulation (Crispino & Bullock, 1984).

A more specific variant of the prediction idea is offered by the timing hypothesis, which postulates that the cerebellum is critical for representing the precise temporal relationship between task-relevant events (reviews in Ivry, 1997; Ivry, Spencer, Zelaznik & Diedrichsen, 2002). According to this hypothesis, the cerebellum generates temporal predictions in a

manner analogous to an hourglass, set in motion by the onset of an event and terminating at its expected offset or at the expected onset of a subsequent event. Interestingly – while also extending cerebellar function beyond motor control – the timing hypothesis was originally developed based on an analysis of the motor deficits seen in patients with cerebellar lesions. From this theoretical perspective, cerebellar symptoms such as intentional tremor and hypermetria can be interpreted as resulting from disorganization of the temporal pattern between agonist and antagonist muscles during rapid movements (Hore, Wild & Diener, 1991).

Empirical support for the timing hypothesis can be found in studies demonstrating that patients with cerebellar pathology have problems producing rhythmic movements (Ivry, Keele & Diener, 1988; Spencer, Zelaznik, Diedrichsen & Ivry, 2003) and judging the duration of intervals across different sensory modalities, including audition (Ivry & Keele, 1989; Mangels, Ivry & Shimizu, 1998), vision (Ivry & Diener, 1991; Nawrot & Rizzo, 1995) and somatosensation (Grill, Hallet, Marcus & McShane, 1994). An especially compelling demonstration of a specific cerebellar role in temporal processing is offered in a speech perception study by Ackermann et al. (1997). Patients with cerebellar dysarthria, a difficulty in speech production, were unable to discriminate words that differed solely in the duration of the intersyllabic silent period, yet showed no such deficit for words with different spectral cues. From a neurophysiological perspective, the well documented cerebellar role in eyeblink conditioning (Yeo & Hesslow, 1998) – where the adaptive timing of the response is of central importance – supports the timing hypothesis. Animals with the cerebellar cortex removed can still acquire the association, but the conditioned response is poorly timed (Perret, Ruiz & Mauk, 1993; Anderson & Keifer, 1997; Koekkoek et al., 2003).

Precise temporal regulation is necessary for a wide spectrum of motor, perceptual and cognitive processes, and can thus also offer a possible explanation for the cerebellar activation seen in various neuroimaging experiments (Ivry & Fiez, 1997; Cabeza & Nyberg, 2000). Indeed, some of the evidence marshaled in support of the sensory prediction hypothesis is also consistent with the timing hypothesis. For example, in the Tesche and Karhu (2000) study, the stimuli were presented periodically. Thus, the response to omitted stimuli can be seen as elicited by a violation of an expectancy that a stimulus will be presented *after a specific interval.* Supporting this interpretation, cerebellar activity was observed just prior to an anticipated stimulus, whether or not the stimulus was actually delivered.

While timing in this manner constitutes a form of prediction, not all prediction involves precise timing (Ivry, 2000). For instance, when driving a car, predictions concerning the (sensory) consequences of turning the steering wheel or pushing the gas pedal would have to be temporally precise, whereas the expectation that a "stop" signal will eventually change to "go" need not have this precise temporal specificity. Thus, the timing hypothesis predicts cerebellar involvement *only* in temporal predictions, that is, conditions involving expectations about the duration of events or intervals between events. In contrast, the sensory prediction hypothesis, emphasizing sensory prediction in general, does not explicitly distinguish between temporal and non-temporal predictions.

1.3. Methodological considerations and constraints

The aim of the present experiment was to contrast the sensory prediction and the timing hypotheses of cerebellar function. Importantly, a number of methodological constraints follow from the nature of this research question. First, it would be ideal to use a method allowing one to conclude that the cerebellum is a *necessary* structure for the function(s) in question. For instance, while neuroimaging studies of healthy participants might suggest cerebellar *involvement* in a wide range of functional domains, they do *not* conclusively demonstrate that the cerebellum is part of the *necessary* or *critical* neural circuitry. Conceivably, the tasks used in these studies might have been performed even in the absence of the cerebellar activation. Thus, in order to identify the *critical* neural structures responsible for a given function, studies of patients with isolated lesions provide more compelling data (Timmann & Daum, 2007). As a case in point, the critical role of the hippocampus for memory encoding was discovered by examining patients with hippocampal lesions, and would most probably not have been identified using neuroimaging technology alone (Gazzaniga, Mangun & Ivry, 2002). With regard to the cerebellum, it is worth noting that imaging studies of healthy individuals have generally suggested a wider range of functions with cerebellar involvement than have studies of patients with isolated cerebellar lesions (Timmann & Daum, 2007). Second, because of the established cerebellar role in motor control it would also be preferable to avoid any motor demands – such as button presses – in the experimental design. Third, since both the hypotheses tested in the present study concern low level sensory mechanisms, it would be an advantage to use an experimental paradigm that did not place demands on higher level cognitive processes such as attention or working memory. By fulfilling the second and third constraints one would be in a better position to attribute any observed effects to the functions

of interest – sensory prediction and timing – rather than to problems in executing motor responses, focusing or shifting attention or remembering task instructions. Finally, since the timing hypothesis predicts specific cerebellar deficits in the temporal domain, the method used should be highly sensitive to the temporal dimension.

One experimental design satisfying these methodological constraints is to compare the electrophysiological brain responses to violations of temporal and non-temporal predictions (or expectancies) in a group of patients with cerebellar pathology and a healthy control group. Studying a patient group relative to a matched control group fulfils the first constraint by examining the effects of isolated cerebellar lesions. Directly measuring brain activity instead of depending on behavioural measures fulfils the second constraint by eliminating the need for any motor responses. The third constraint, avoiding demands on working memory or attentional resources, is fulfilled by an experimental design investigating the pre-attentive detection of expectancy violations – the mismatch negativity paradigm. Finally, electro-encephalography (EEG) offers a way of measuring brain activity with a temporal resolution in the millisecond range, thus fulfilling the last constraint. The next sections turn first to a brief description of EEG and event-related potentials (ERPs), before describing the mismatch negativity paradigm in more detail.

1.4. Electroencephalography (EEG) and event-related potentials (ERPs)

Neurons communicate using a combination of electrical and chemical signalling, and part of their electrical activity is instantly reflected in voltage fluctuations at the scalp. Electro-encephalography (EEG) is the continuous measurement of these voltage fluctuations from electrodes placed on the head and connected – via an amplifier – to a computer. Importantly, EEG is thus a *direct* measure of neuronal activity; in contrast to *indirect* methods such as PET or fMRI which measure changes in the blood levels of glucose or oxygen assumed to be caused by preceding neuronal activity. Thus, while such hemodynamic techniques measure responses that are delayed by several seconds from the neuronal activity of interest, EEG measures this activity 'online' and with millisecond resolution (Gazzaniga, Ivry & Mangun, 2002).

In order to be detectable in the EEG, electrical activity must be synchronized across a large number – probably thousands – of neurons. While (pre-synaptic) action potentials or "spikes" – the neuronal 'signal' travelling along the axon – could conceivably contribute to the EEG,

these potentials are of a very short duration and are thus unlikely to be synchronized across a sufficient number of neurons. Consequently, the EEG is thought to be primarily generated by the slower post-synaptic potentials in the neuronal dendrites. These potentials consist of charged ionic currents flowing across the neuronal membrane, thus generating transient extracellular electric fields (Coles & Rugg, 1995). Provided that a sufficient number of neurons are oriented in the same direction – creating an *open field* – their synchronous activity will sum to create an electric field measurable at the scalp. In contrast, if the same number of neurons were organized either arbitrarily or concentrically – creating a *closed field* – then their electric fields will cancel out and be invisible in the EEG. Thus, whether or not brain activity is detectable at the scalp is highly dependent on the geometrical organization of the neurons, and EEG is consequently differentially sensitive to neuronal activity in different brain regions. The activity of many subcortical nuclei and brainstem structures will not be measurable at all (Coles & Rugg, 1995). Importantly, both because of the location and the massive folding of the cerebellum (Figure 1), the electrical activity of cerebellar neurons is unlikely to feature prominently in the scalp recorded EEG. Thus, EEG would not be a suitable tool for studying cerebellar function in healthy participants. Using a patient group, however, one can investigate how the cerebral cortical processing reflected in the EEG is affected by the cerebellar damage.

A given segment of continuous EEG contains signals not only from the neuronal activity associated with a particular event, but also signals from unrelated brain activity and extracerebral artefacts, such as muscle activity or eye-movements. Consequently, in order to isolate the brain activity associated with the event of interest, researchers commonly present it numerous times, extract epochs of EEG time-locked to the event and then average the activity across these epochs, presumably cancelling out any activity unrelated to the event of interest. The result of this averaging is a waveform assumed to represent the activity associated with the event, commonly called an event-related potential (ERP). Such waveforms could simply be neutrally described by noting the polarities, amplitudes and latencies of its deflections or peaks. Usually, however, ERPs are described as consisting of one or several underlying *components*. While there is no universally accepted definition of what constitutes an ERP-component (Otten & Rugg, 2005), there are two main approaches to their identification; the *psychological* and the *physiological* approach (Coles & Rugg, 1995). The psychological – or functional – approach focuses on identifying the specific feature of a waveform that is associated with the psychological process in question, often by subtracting the waveform

obtained in one experimental condition from the waveform obtained in another. The *difference wave* computed in this manner is then considered to be the component of interest, indexing the process assumed to differentiate the two experimental conditions (Coles & Rugg, 1995). In contrast, the physiological approach to component identification focuses on localizing the brain structures assumed to generate the scalp ERP. Thus, according to this approach the defining characteristic of a component is its anatomical location in the brain (Coles & Rugg, 1995). Since the brain acts an electric volume conductor, and activity generated in one brain area therefore will be present in varying degrees at all electrodes, the attempt to localize the sources generating the ERP is not straightforward. Indeed, for a given topographical pattern of voltages at the scalp, there is a nearly infinite number of configurations of sources that could have produced it (Helmholz, 1853). Nevertheless, there has been significant progress in ERP-source localization (Slotnick, 2005). Furthermore, other methodologies, from intracranial recordings to lesion studies and fMRI experiments can help resolve the localization of ERP-components (Coles & Rugg, 1995). Notably, the psychological and the physiological approaches to component identification are not mutually exclusive and many researchers use both in their attempts to characterize ERP-components (Coles & Rugg, 1995). An ERP component is commonly first identified using the psychological approach, before the attempt is made to localize its source.

1.5. Mismatch negativity (MMN)

The MMN is an electrophysiological response observed following the presentation of a discriminable change (deviant) in a sequence of regular (standard) stimuli. While MMN responses have also been reported in the visual (Czigler, Balasz & Winkler, 2002) and somatosensory (Kekoni et al., 1997) modalities, most MMN studies have used auditory stimuli. In these, the event-related potential (ERP) to the deviant sound shows a negative deflection compared to the ERP to the standard sound, peaking between 100 and 250 ms after the onset of the deviant stimulus (or stimulus feature). Interestingly, the "standard" stimulus need not be fixed: an MMN is elicited when the pitch of a sound violates a predictable sequence of descending pitch changes, as in a musical scale (Tervaniemi, Mauri & Näätänen, 1994). These results suggest that the structures generating the MMN not only retain the immediate auditory past, but may anticipate future events based on the extraction of a regularity in the past (Näätänen, Tervaniemi, Sussmann, Paavilainen & Winkler, 2001). Based on these considerations, the MMN is assumed to index the detection of a mismatch between

the auditory input and a memory-based expectation (or prediction) that evolves from the repeated presentation of the standard stimulus (Näätänen, Jacobson & Winkler, 2005).

The amplitude of the MMN is related to the magnitude of the deviation, increasing monotonically as the difference between the standard and the deviant increases (e.g. along pitch, Tiitinen, May, Reinikainen & Näätänen, 1994; Yago, Corral & Escera, 2001; duration, Amenedo & Escera, 2000; location, Deouell, Parnes, Pickard & Knight, 2006, or stimulation rate, Sable, Gratton & Fabiani, 2003). For some stimulus dimensions (pitch and location), a similar relationship has been found between the degree of deviance and the latency of the MMN peak, with shorter latencies observed for larger deviants (Pakarinen, Takegata, Rinne, Huotilainen & Näätänen, 2007). Thus, the amplitudes and latencies of the MMN can provide objective measures of the representation of a specific dimension in sensory memory (Tiitinen *et al*., 1994; Näätänen & Alho, 1997), making the MMN a promising tool for investigating the integrity of sensory processing and prediction in clinical groups (Näätänen, 2003).

ERP source localization as well as fMRI studies indicate that the main generators of the MMN are associated with primary and secondary auditory cortex in the superior temporal gyrus (e.g. Alho, 1995; Halgren et al., 1995; Rosburg, 2003), along with secondary generators in the frontal (Giard, Perrin, Pernier & Bouchet, 1990; Deouell, Bentin & Giard, 1998; Molholm, Martinez, Ritter, Javitt & Foxe, 2005; Tse, Tien & Penney, 2006; for review see Deouell, in press) and possibly parietal cortex (Molholm et al., 2005). Involvement of the temporal and frontal cortical areas has received additional support from studies demonstrating reduced MMN amplitude in patients with lesions in frontal and temporal cortex (Alain, Woods & Knight, 1998; Alho, Woods, Algazi, Knight & Näätänen, 1994).

While there is increasing evidence for a cerebellar contribution to auditory processing (Petacchi, Laird, Fox & Bower, 2005), the role of the cerebellum in the MMN is less established. Studies in rabbits have showed distinct electrical responses in the cerebellum in response to auditory (pitch), visual, and somatosensory deviants (Ruusuvirta, 1996; Astikainen, Ruusuvirta & Korhonen, 2000; Astikainen, Ruusuvirta & Korhonen, 2001), but whether these are similar to the properties of the MMN is not clear. In humans, two imaging studies have reported cerebellar activation in duration MMN paradigms (Dittman-Balçar, Juptner, Jentzen & Schall, 2001; Schall, Johnston, Todd, Ward & Mitchie, 2003). Finally, one patient study reported a diminished somatosensory mismatch response to deviant tactile

stimuli applied to the affected (ipsilesional) hand of six patients with unilateral cerebellar lesions compared to stimuli applied to the unaffected hand (Restuccia, Della Marca, Valeriani, Leggio & Molinari, 2007). In contrast, two of the patients showed normal MMN responses on an auditory task using a pitch deviant. However, as the authors discuss, the modality difference might be related to the fact that the auditory stimuli were presented bilaterally, possibly enabling the intact cerebellar hemisphere to compensate for the damaged one.

1.6. Aim and predictions of the present study

The present study aimed to contrast the sensory prediction and the timing hypothesis by testing patients with bilateral cerebellar atrophy on an MMN task which employed four types of stimulus deviation: duration, pitch, intensity, and location. It was reasoned that the sensory prediction and the timing hypotheses would offer differential predictions for the results of this experiment: While the timing hypothesis would predict a selective impairment in the patients' MMN to duration deviants, the sensory prediction hypothesis would predict a more general form of impairment in the MMN responses to both temporal and non-temporal deviants. While these differential predictions are straightforward, one complication needs to be considered. A reduced MMN to all deviants – the prediction derived from the sensory prediction hypothesis – could also be explained within the framework of the timing hypothesis if the *temporal predictability* of the stimuli contributes to establishing the memory trace of the standard (and hence also to the generation of the MMN in response to any deviation from the standard). In line with this possibility, Takegata and Morotomi (1999) reported a reduction in the MMN amplitude to a pitch deviant when the interval separating successive stimuli was varied compared to when this interval was fixed. Thus, the sensory prediction was not only of a stimulus of a particular pitch, but also of one that would occur at a particular time. Should the patients have difficulty anticipating the timing of a stimulus, their MMN to non-temporal deviants might also be abnormal. To address this concern, the stimuli were either presented periodically with a constant stimulus onset asynchrony (SOA) or aperiodically (variable SOA). If temporal information contributes to the memory trace of the standard, then the timing hypothesis would predict that reducing the periodicity of the stimuli would reduce the MMNs to all deviants in the healthy control group. The patient group, however, would be expected to show less or no effect of periodicity manipulations, reflecting an impaired ability to utilize the temporal regularity.

2. Methods:

2.1. Participants:

Seven patients with bilateral cerebellar degeneration and 10 age-, gender- and education-matched controls volunteered for this experiment. The data of 3 control participants were discarded because of excessive ocular artefacts or technical problems, leaving 7 patients and 7 controls in the final set of participants (6 male, 1 female in each group). Table 1 provides a summary of clinical information regarding the patients.

Table 1: Demographic and clinical data for the patients

Patient ID (sex)	Age	Education	Ataxia type / etiology	Years since diagnosis	ICARS score	MMSE score	WAIS-III IQ
AC01 (F)	59	18	Unknown	6	29.0	30	127
AC04 (M)	50	18	SCA3	10	49.8	28	96
AC06 (M)	66	20	Unknown	14	42.8	27	80
AC07 (M)	39	16	SCA2	15	36.5	29	97
AC08 (M)	52	14	Unknown	9	20.8	29	105
AC09 (M)	66	17	OPCA	7	17.8	29	108
AC10 (M)	75	12	Unknown	44	45.0	30	91
Mean	58.1	16.4	-	15.0	34.5	28.8	100.6
(sd)	(12.1)	(2.7)	-	(13.2)	(12.3)	(1.1)	(14.8)

SCA: Spinocerebellar Ataxia (types 2 and 3); OPCA: Olivopontocerebellar Atrophy; ICARS: International Cerebellar Ataxia Rating Scale; MMSE: Mini Mental Status Examination; WAIS-III: Full scale IQ score from the Wechsler Adult Intelligence Scale, 3rd edition.

This is a heterogeneous group in terms of age, etiology, disease duration, and symptoms. While advanced cerebellar degeneration can be associated with atrophy in the brainstem or basal ganglia (Klockgether et al., 1998), the radiological assessment of the patients' scans, when available, did not reveal atrophy outside the cerebellum. Even in the one case of olivopontocerebellar atrophy (OPCA), the extracerebellar signs were minimal. All patients were evaluated on a battery of tests to assess neurological function and neuropsychological status. As can be seen in the table, the mean ataxia rating on the International Cerebellar

Ataxia Rating Scale (ICARS, Trouillas et al., 1997) was 34.5 with a range of 17.55 to 49.75, indicating that all of the patients were at least moderately ataxic and some exhibited more advanced symptoms. The mean full-scale IQ for the patients (WAIS-III) was 100.6. Control participants were selected to match the patients in terms of age (patients: 58.1, sd; 12.1; controls; 59.3, sd; 12.7) and education level (patients: 16.4, sd; 2.7; controls; 17.4, sd; 2.7).

The procedures employed in this study conformed to the Declaration of Helsinki, and were approved by the institutional review board at the University of California, Berkeley. Prior to the experiment, participants provided informed consent. The exact aims were explained at the end of the experimental session to avoid directing the participant's attention to the sounds. Participants were paid for their participation.

2.2. Stimuli and procedures:

Participants were seated comfortably in a sound-attenuated room and instructed to watch a subtitled movie for which the soundtrack was turned off. They were told that a continuous series of sounds would be presented during the movie and that they should ignore these.

The primary experiment consisted of 10 blocks of approximately 7 min each. Within each block, 515 sounds were presented. Standard stimuli were presented 60% of the time and had a fixed spectrum, intensity, duration, and location. The standard was a harmonic tone, composed of three sinusoidal partials of 500, 1000 and 1500 Hz. Compared to the first partial, the intensity of the second and third partials were reduced by 3 and 6 dB, respectively. Standard stimuli were presented from a speaker located 15 degrees to the right of the centre of the monitor and were 250 ms in duration (including 10 ms rise and fall times). Tone duration was chosen in order to avoid confounding the perception of intensity and duration. For durations up to about 200 ms, longer stimuli of equal physical intensity are judged as louder (Scharf, 1978; Cowan, 1984), and likewise, more intense stimuli of equal physical duration are judged as longer (Lifshitz, 1933). Since confounding the stimulus dimensions would be problematic in light of the questions motivating this experiment, stimuli of relatively long duration compared to most MMN experiments were used. To ensure that the tones were clearly audible, the intensity of the standard was set on an individual basis to be 50 dB above the person's detection threshold. This threshold was determined at the start of the experimental session using a simple ascending and descending staircase procedure. Thresholds, and – correspondingly – the intensity of the standard used in the experimental

session were not significantly different between patients (72.5 dB SPL, sd 6.6) and controls (67.8, sd 5.0 dB, $t(12) = -1.51$, $p > .10$).

The remaining 40% of the sounds differed from the standard on one of four dimensions: pitch (10% higher than the standard, i.e. composed of 550, 1100 and 1650 Hz partials), duration (150 ms longer than the standard), intensity (10 dB softer than the standard) or sound location (30 degrees to the right of the standard speaker). Each deviant differed on only one of these dimensions, with each occurring 10% of the time. This mixed-deviant procedure has been shown to produce robust MMNs (Deouell, Bentin & Soroker, 2000; Näätänen, Pakarinen, Rinne & Takegata, 2004). The order of the tones within a block was randomized with two constraints. First, all blocks began with a series of 15 standard stimuli**.** Second, the same deviant was never presented twice in a row.

In order to investigate the effect of the temporal predictability of the stimuli, two different timing schemes were used. In the five periodic blocks, the stimulus onset asynchrony (SOA) was fixed at 800 ms. In the five aperiodic blocks, the SOA was randomly selected to be one of three equiprobable durations (650, 800 or 950 ms), with the constraint that a given SOA never occurred more than twice in a row.

In addition to the 10 primary blocks, two duration control blocks were included, one at the beginning and one at the end of the experimental session. In these blocks, the duration of the standard and deviant were reversed, so that the duration of the standard was set to 400 ms and the duration of the deviants was set to 250 ms. The control blocks were included to provide an alternative baseline (standard) ERP response to use in the analysis of the duration MMN. That is, a *control duration MMN* was obtained by comparing the ERP elicited by a 400 ms deviant sound in the main blocks to the ERP arising from a physically identical stimulus used as a standard in the control blocks. This control was included given prior work showing that the MMN may be artificially inflated when a shorter standard is subtracted from a longer deviant (Jacobsen & Schröger, 2003). The SOA was fixed at 800 ms in the control blocks. In pilot work, similar "reversed" blocks were used to control for stimulus differences in the other dimensions. This work indicated that stimulus differences had negligible effects on the MMNs elicited in response to pitch, intensity, and location deviants. Consequently, in order to reduce the total duration of the recording session, these control blocks were not included in the final experimental design.

The entire session, including the preparation for the EEG recordings, lasted approximately 2 hours. Participants were provided with short breaks between the test blocks.

2.3. EEG recording and averaging:

EEG was continuously recorded at 512 Hz by an Active 2 system (Biosemi), using 64 sintered Ag/AgCl electrodes in an electrode cap laid out according to the extended 10–20 system with three additions (nose, left and right mastoid). The electrooculogram (EOG) was monitored from electrodes near the outer canthi and below the left eye. EEG was referenced to an average-reference computed offline, using the 64 cap electrodes and the mastoids, excluding occasional malfunctioning electrodes. During recording, a 128 Hz low pass filter was applied to avoid aliasing of high frequencies. Offline, the EEG was filtered with bandpass of 1–20 Hz (24 dB/octave) suitable for the frequency range of auditory late evoked potentials and the MMN. For ERP averaging, the EEG was divided into epochs of 750 ms starting 100 ms before stimulus onset, and the epochs were averaged separately for the responses to the standards and for the 4 types of deviant stimuli in each SOA condition. Epochs including an EEG or EOG voltage exceeding +/-75 μV, as well as those from the first 15 stimuli of each block were omitted from the averaging. The baseline was adjusted by subtracting the mean amplitude of the 100 ms pre-stimulus period of each ERP from all the data points in the epochs. On average, the ERPs were based on 215 trials for each of the eight deviants (four dimensions x 2 SOA conditions), and this value did not differ between controls (range: 194 – 229) and patients (range: 185-242). The ERP for the standard is based on approximately six times as many trials as the deviants, except for the duration control ERP which is based on approximately twice as many trials as the duration deviant ERP.

2.4. Statistical analysis

In order to examine the possibility that any group differences in the MMN could be due to differences in auditory processing prior to deviance detection, the P1, N1, and P2 components of the ERP to standard sounds were analyzed. Latencies and amplitudes of these components in the periodic and aperiodic condition were measured at electrode FCz. The P1-component was defined as the most positive peak occurring in the first 100 ms after stimulus onset, the N1-component as the most negative peak between 50 and 150 ms, and the P2 component as the most positive peak between 100 and 250 ms. Latencies and amplitudes were tested

statistically by separate Group (2 levels: patients and controls) by Periodicity (2 levels: periodic and aperiodic SOA condition) ANOVAs for each component.

The MMN was identified by subtracting the waveform elicited by the standard from that of each deviant. In the case of the duration MMN, an additional *control duration MMN* was identified by subtracting the response to the 400 ms standard used in the two control blocks from the response to the duration deviant in the regular periodic blocks.

Three frontal electrodes (F3, Fz and F4) were pre-selected for statistical analysis. MMN latencies were measured as the most negative peak occurring between 100 and 250 ms after the onset of deviance from the standard stimulus. Note that while the onset of deviance coincided with stimulus onset for the non-temporal deviants, in case of the duration deviant the deviance (delayed termination) occurred 250 ms after stimulus onset, and hence the expected MMN window was between 350 and 500 ms after stimulus onset. In order to facilitate comparison across deviant types, MMN latencies for duration changes were corrected in relation to the onset of deviation (e.g., the duration of the standard tone was subtracted from the peak latency). MMN amplitudes were integrated over 50 ms (± 25 ms around the individual peak latencies). Two-tailed *t*-tests were used to determine whether MMN amplitudes differed significantly from 0 μV.

In order to compare the MMN latencies and amplitudes between groups and SOA-conditions, three-way ANOVAs (Group x Periodicity x Electrode) were conducted separately for each deviant type. The Greenhouse-Geisser correction was applied when appropriate (the original degrees of freedom and corrected p-values are reported). Sources of significant interactions were examined with additional post hoc ANOVAs. Since the control block 400 ms standard had only been recorded in a periodic SOA condition, the duration MMN made by subtracting the 250 ms standard from the 400 ms deviant was used for the initial analyses. However, all analyses on the duration MMN that did not involve the Periodicity factor (or were restricted to the Periodic SOA condition) were repeated with the control duration MMN.

Although the sample size is small, it was also examined whether the degree of clinical severity was related to abnormalities in the ERP data. For these analyses, Pearson product moment correlation coefficients were computed between the score on the ICARS evaluation and the MMN latency and amplitude data measured at electrode Fz.

3. Results:

3.1. Auditory evoked potentials to standard tones

Standard stimuli elicited a waveform consisting of the P1, N1 and P2 components in both patients and controls (see Figure 1). There were no significant main effects or interactions involving Group on P1 latency. In contrast, the P1 amplitude yielded a significant Group x Periodicity interaction ($F(1, 12) = 4.83$; $p < .05$). Separate ANOVAs for each group revealed that the P1 amplitude was larger in the aperiodic compared to periodic condition for the controls (Periodicity: ($F(1, 6) = 6.03$; $p < .05$). There was no significant amplitude difference between these two conditions for the patient group ($F < 1$).

Latencies and amplitudes of the N1 and P2 peaks did not differ between groups or periodicity conditions. While the waveforms suggest a somewhat reduced P2 amplitude in the patients relative to the controls (fig. 1), this difference failed to reach significance ($F(1, 12) = 1.48$; $p > .10$).

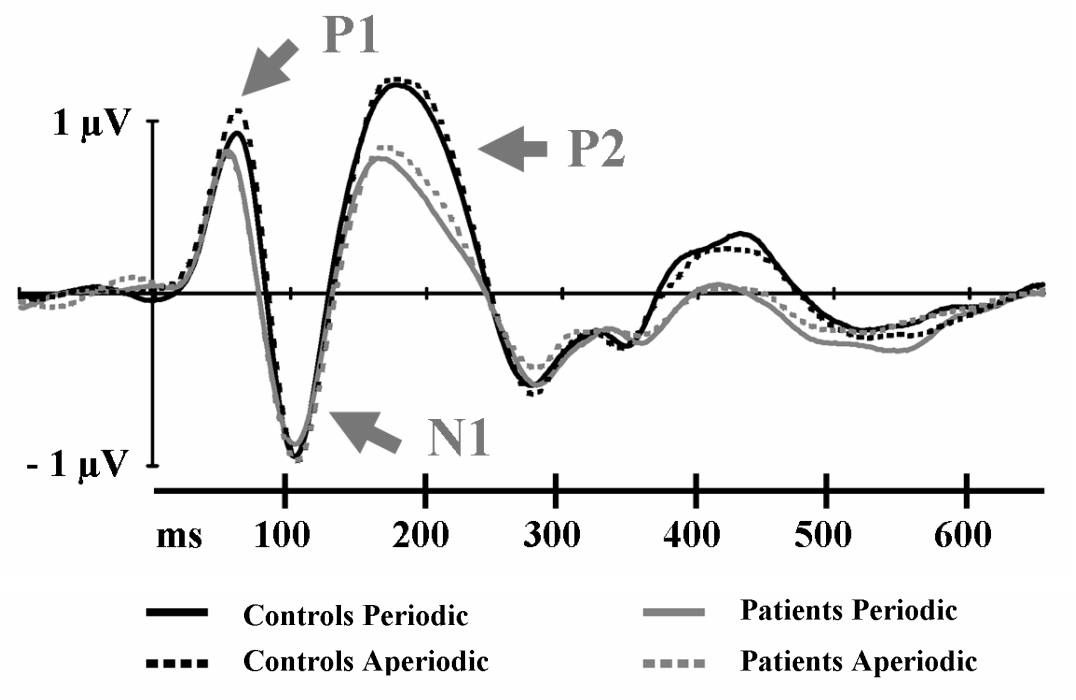

Figure 1: Grand average ERPs to standard sounds recorded at the frontocentral FCz electrode.

3.2. Mismatch negativity (MMN)

Both the control and the patient group produced identifiable MMNs to all deviant types in both the periodic and aperiodic conditions (see Figures 2 and 3). The MMN potentials showed the expected scalp distribution, with maximum negative amplitude over frontal electrodes and reversed polarity at posterior temporal electrodes (see Figure 2).

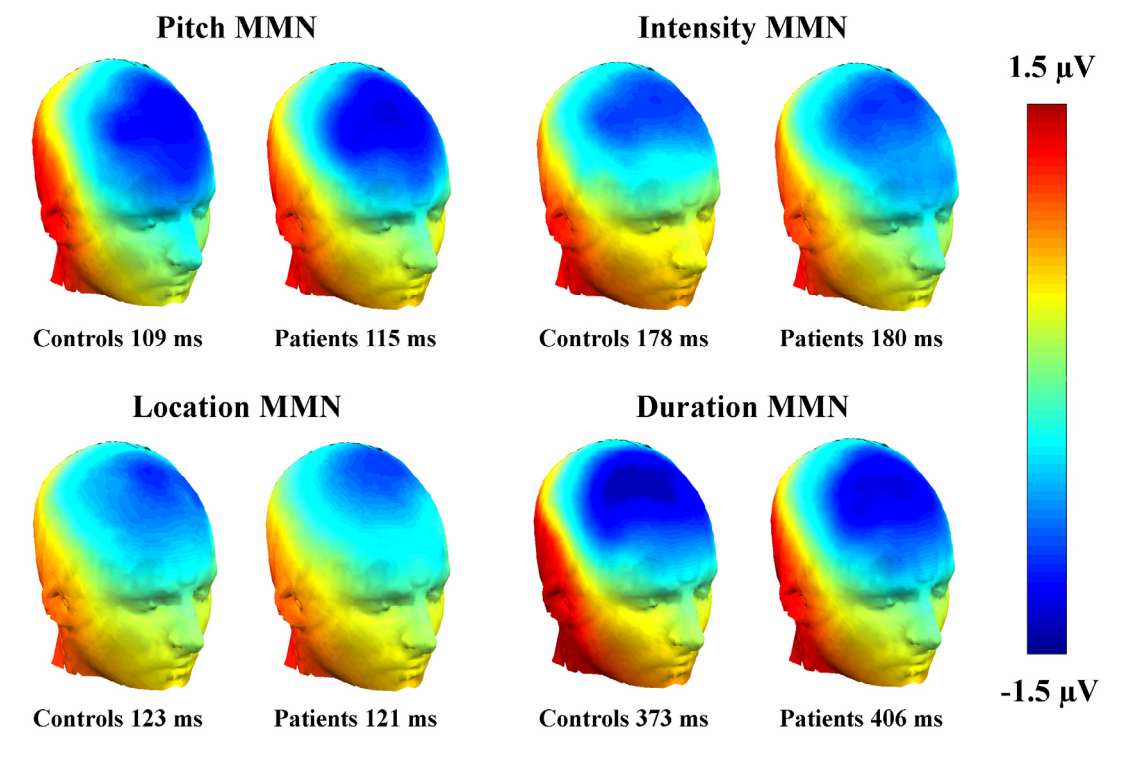

Figure 2: Scalp maps showing the spatial distribution of the grand average MMNs at peak latency (measured at Fz) in the periodic SOA-condition.

As can be seen in Figure 3, the MMN to location deviants had a clear double peak, consistent with previous reports (Tata & Ward, 2005; Deouell et al., 2006). The first peak reached maximum amplitude around 120 ms and the second around 195 ms. Given this double-peaked response, we manually determined the latencies and amplitudes of each peak and conducted our analyses on these measures.

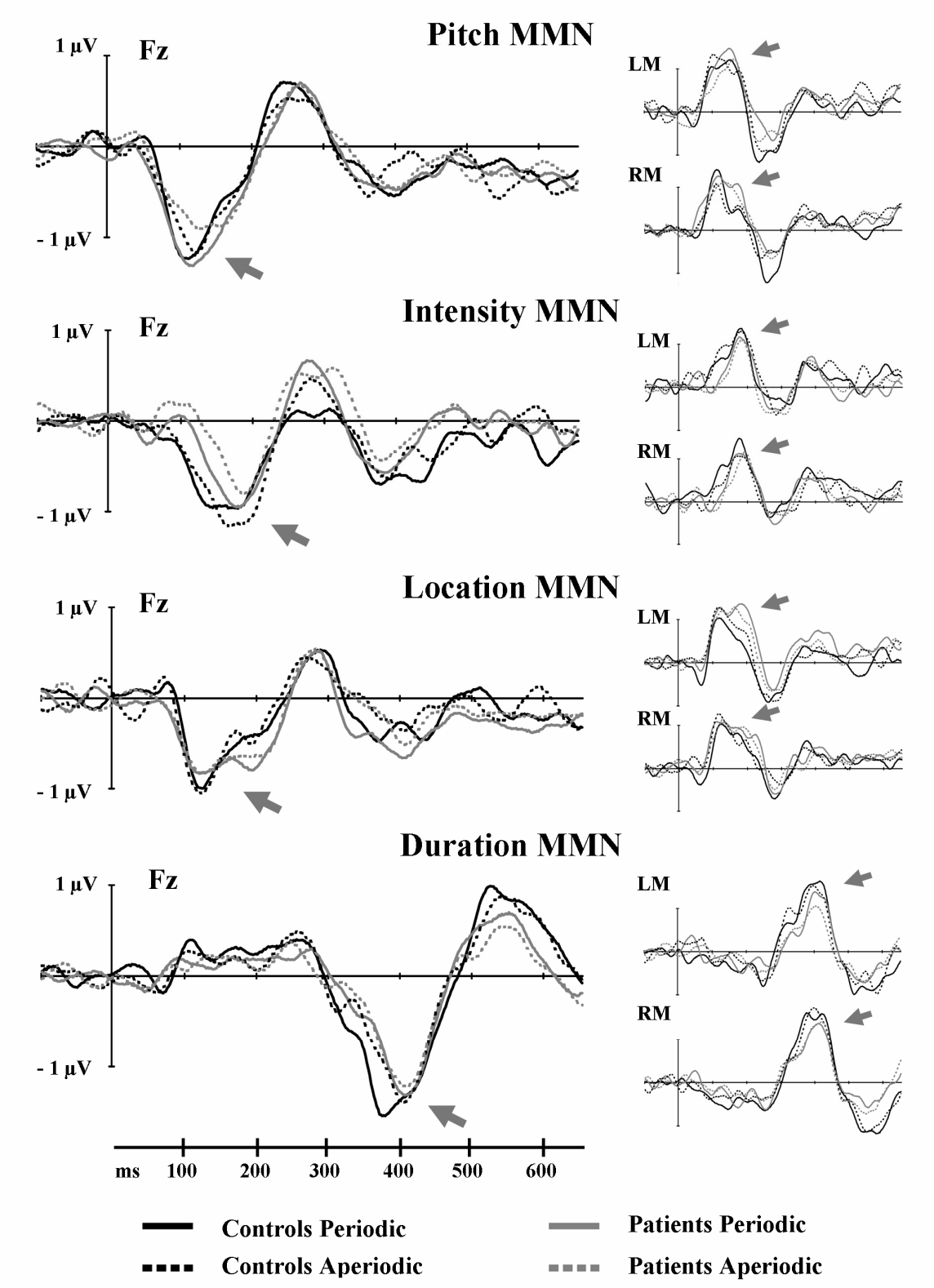

Figure 3: Grand average difference waves showing MMN responses to the four different deviant types recorded at electrode Fz and the left (LM) and right (RM) mastoid. Responses for controls and patients in the periodic and aperiodic conditions are overlaid. Arrows indicate the MMN.

MMN-latencies and amplitudes for the controls and patients are provided in Figure 4. Two-tailed t-tests showed that for both patients and controls the MMN amplitude differed significantly from zero for all conditions and deviant types ($p < .05$). As noted in the Methods section, a *control duration MMN* was also calculated by subtracting the 400 ms stimulus used as a standard in the control blocks from the physically identical 400 ms duration deviant of the main block. Similar to previous findings (Jacobson and Schröger, 2003), this control duration MMN was reduced in amplitude compared to the duration MMN calculated by subtracting the 250 ms standard used in the main blocks from the 400 ms duration deviant (see Figure 4). Importantly, however, this control duration MMN also differed significantly from zero for both groups ($p < .05$).

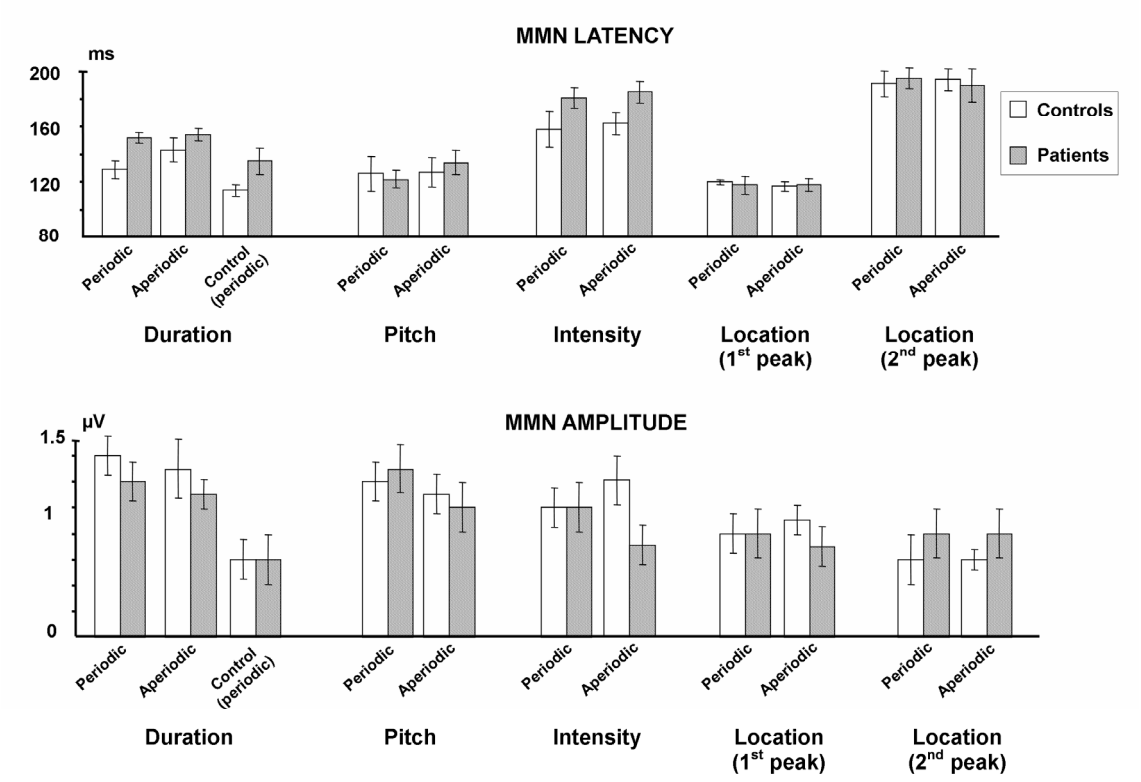

Figure 4: Bar graphs showing mean MMN latencies and amplitudes. Error bars represent the standard error of the mean.

We conducted separate three-way (Group x Periodicity x Electrode) ANOVAs for each deviant type, using the latency data as dependent variable in one set of analyses and the amplitude data in a second set.

3.2.1. Latencies

Latencies of the pitch and location MMN did not differ between patients and controls (F-values < 1). In contrast, the MMN latency was delayed in the patients compared to the control group for the duration deviant (Group: $F(1, 12) = 5.72$, $p < .05$), and we observed a similar trend for the intensity MMN (Group: $F(1, 12) = 4.32$; $p = .06$). Consistent with the primary analysis of the duration MMN, a significant increase in the patients' latency was also observed when the periodic *control* duration MMN was used in the analysis (Group: $F(1, 12) = 5.80$; $p < .05$).

There were no significant main effects or interactions involving Periodicity for the latencies of the pitch, intensity and location MMNs. Importantly, however, the main effect of Group on duration MMN latency was qualified by a significant Group x Periodicity interaction ($F(1, 12) = 6.26$; $p < .05$). This interaction was due to a shortened latency for the control participants in the periodic relative to the aperiodic condition ($F(1, 6) = 12.17$; $p < .05$), an effect that was not observed in the patient group ($F(1, 6) < 1$).

3.2.2. Amplitudes

There were no significant main group effects on the MMN amplitudes to pitch ($F(1, 12) < 1$), duration ($F(1, 12) < 1$), intensity ($F(1, 12) < 1$) or location (first peak: $F(1, 12) < 1$), second peak: $F(1, 12) = 1.30$; $p = .28$) deviants. Across groups, pitch MMN amplitude was increased in the periodic compared to the aperiodic condition (Periodicity: $F(1, 12) = 13.07$; $p < .05$), while periodicity did not affect the MMN amplitude to duration (Periodicity: $F(1, 12) < 1$), intensity (Periodicity: $F(1, 12) < 1$) or location (Periodicity: $F(1, 12) < 1$ for both the early and late peak) deviants. There were no significant interactions involving Group or Periodicity for any of the deviant types.

3.3. Exploratory correlations

Correlations between MMN-measures and cerebellar symptom scores are given in Table 2. While ataxia scores were not significantly correlated with the MMN latencies to any of the deviants, we did observe a positive correlation between the amplitude of the duration MMN and the ataxia score: patients exhibiting the most severe signs of ataxia produced lower amplitude MMN responses to the duration deviant. This relationship was significant in the aperiodic condition ($r = .83$, $p < .05$), with a similar trend in the periodic condition ($r = .73$, $p = .06$) reflecting the fact that the MMN amplitude values were very similar within individuals

for the two conditions. A marginally reliable correlation was also observed between the ataxia scores and the amplitude of the control duration MMN (r = .75, p =.05).

Table 2: Correlations between ataxia scores and MMN latencies and amplitudes at Fz

Deviant type	Latencies	Amplitudes
Duration Periodic	.26	.73 (p = .06)
Duration Aperiodic	.05	.83 (p < .05)
Duration Control	-.50	.75 (p = .05)
Pitch Periodic	.11	.58
Pitch Aperiodic	-.54	.60
Intensity Periodic	-.45	.68 (p =.09)
Intensity Aperiodic	-.48	.58
Location 1 Periodic *	-.58	.46
Location 1 Aperiodic *	-.50	.18
Location 2 Periodic **	-.36	.12
Location 2 Aperiodic **	-.32	-.27

* First peak of Location MMN; ** Second peak of Location MMN. Unless indicated, p > .1.

Predominantly positive correlations between ataxia scores and MMN amplitudes to the other deviants failed to reach statistical significance. The scatter plots in Figure 5 show the relationships between ataxia scores and duration MMN latencies and amplitudes. While visual inspection of both panels suggest that degree of cerebellar damage is related to both MMN measures, this failed to reach significance for the latency measures (also when removing the apparent outlier with the lowest ataxia score).

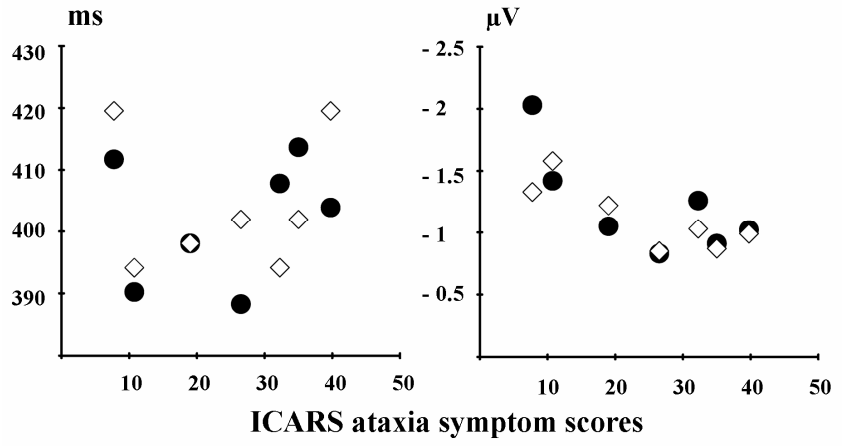

Figure 5: Scatter plots showing the relationship between ICARS ataxia symptom scores and duration MMN latencies (left panel) and amplitudes (right panel). Filled circles indicate periodic and open diamonds indicate aperiodic SOA-condition.

4. Discussion:

The goal of the present study was to contrast two related hypotheses of cerebellar function by investigating the MMN to temporal and non-temporal deviants in patients with cerebellar degeneration and a healthy control group. Based on the sensory prediction hypothesis, the patients should show impaired MMNs to all deviant types. In contrast, the timing hypothesis predicts a selective impairment in the MMN to temporal duration deviants. Additionally, the timing hypothesis predicts that controls should benefit when the stimuli are presented periodically, an effect that should be absent or reduced in the patient group. Before turning to a discussion of the main MMN results, it should be mentioned that in both groups standard stimuli elicited comparable auditory evoked potentials consisting of the expected P1, N1 and P2 peaks suggesting intact initial cortical activation. Thus, the observed group differences in the MMN measures are unlikely to be due to differences in information processing prior to the generation of the MMN.

4.1. Main results

The main finding of this study was that cerebellar degeneration was associated with selective abnormalities in the MMN response to the duration deviant (as well as a similar trend for the intensity MMN, to be discussed below). Specifically, the latency of the MMN to the duration deviant was delayed in the patients relative to the control group, especially in the periodic condition. A further observation was that duration MMN amplitude was related to cerebellar symptom scores; patients with more advanced pathology produced more attenuated responses. These results suggest that the cerebellum contributes to pre-attentive duration estimation. Importantly, the patients produced significant duration MMNs, indicating that they were not insensitive to the temporal deviation, despite their cerebellar damage. Indeed, duration MMN amplitude did not differ significantly between the patient and the control group. Taken together, the findings of delayed latency but preserved amplitude in the patients are consistent with a coarser or unreliable temporal representation (Ivry et al., 2002). An unreliable temporal memory trace entails that patients would require a larger temporal difference between standard and deviant for detecting the change. Considering that deviance consisted of sound *prolongation*, this means that deviation would be detected later, resulting in an increased MMN latency.

The selective sensitivity of the duration MMN to cerebellar damage is consistent with the predictions of the timing hypothesis. Further support for this hypothesis is provided by the results of periodicity manipulation in the duration deviant condition. In the control group, periodicity shortened the latency of the duration MMN, while in the patients, the MMN response to the duration deviant was not affected by the periodicity manipulation. A lack of sensitivity to periodicity manipulation was also seen in that the P1 for standards was larger for aperiodic than periodic stimulation in controls, but had equal amplitude across conditions in patients.

4.2. Contradictory findings and limitations

While some aspects of the periodicity results provide support for the timing hypothesis, other aspects are problematic. The timing hypothesis would predict that the patients show a global deficit – i.e. across all deviant types – in utilizing the high temporal predictability offered by periodic stimulation. Contrary to this prediction, the patients showed normal amplitude augmentation for pitch changes in the periodic condition, while the MMNs to intensity and location deviants were not affected by periodicity for either patients or controls. Thus, while the current results are clearly inconsistent with the general sensory prediction hypothesis, they provide only partial support to the timing hypothesis as defined in the introduction. The results strongly support a deficit in encoding temporal information embedded within a stimulus (i.e., its duration), but remain inconclusive regarding the inter-stimulus temporal information (i.e., intervals).

A second finding at odds with the timing hypothesis was the observed trend towards increased intensity MMN latency in the patients. It might, however, be possible to explain the delayed detection of both duration and intensity deviants as resulting from a common deficient timing mechanism. As mentioned in the Methods section, for sounds shorter than about 200 ms perceived stimulus intensity is influenced by stimulus duration, being approximated as the integral of energy over time (Scharf, 1978; Cowan, 1984). Consequently, a standard duration outside this temporal window was deliberately chosen to ensure that the duration MMN, related to the sound offset, was not affected by sound intensity. However, the latency of the intensity MMN (around 170 ms from sound onset) suggests that stimulus intensity is determined well before the stimulus ends, and within the temporal window where intensity and duration interact. Perhaps, with an unreliable timer, the integration of stimulus energy over time may take longer than usual, resulting in delayed detection of the intensity deviant.

This conjecture is obviously post-hoc and needs to be directly addressed in future research.

It is also important to note that the duration deviant was the only "graded" deviant, in the sense that the degree of deviance increased over the extent of stimulus presentation (since we only used deviants longer than the standard). That is, as the long deviant continued past the expected offset time at 250 ms, the listener could detect the difference at various points of time during the subsequent 150 ms. In contrast; the other deviants were "instant" – and rather large. Thus, one cannot exclude the possibility that the use of smaller deviants would have revealed group differences in the MMN response to non-temporal deviants. To overrule this possibility, a parametric study utilizing several deviance magnitudes for each deviant feature will be needed (Pakarinen et al., 2007).

4.3. Comparison with earlier studies

The present experiment revealed a specific deficit for the cerebellar patients in the MMN to the duration deviant. This finding is in agreement with two neuroimaging studies reporting cerebellar activation in an auditory MMN paradigm using duration deviants (Dittmann-Balçar et al., 2001; Schall et al., 2003). Importantly, the present results in patients with cerebellar lesions strongly suggest that the previously observed activations are part of the *critical* network for the generation of the duration MMN, a conclusion that would not have been warranted on the basis of imaging studies alone. Furthermore, the present finding of a *preserved* MMN to pitch deviants in the patient group replicates the results from the only other study that was found to have investigated the MMN in patients with cerebellar pathology (Restuccia et al., 2007). Interestingly, such sensitivity to temporal (duration) – but not to spectral (pitch) – cues in auditory perception is also consistent with the observations on cerebellar dysarthria mentioned in section 1.2. (Ackermann et al., 1997).

More specifically, the present results suggest that the patients have a heightened duration discrimination threshold, rather than an absolute deficit in temporal perception. Direct comparison of the present results with previous studies of overt duration discrimination in cerebellar patients (reviewed in Diedrichsen, Ivry & Pressing, 2003) is not straightforward, since precise indexes of discriminatory ability cannot be calculated without overt responses. Nonetheless, these duration discrimination results are consistent with the present MMN findings, indicating that cerebellar pathology increases the variability of temporal processing (e.g., an elevated discrimination threshold). Furthermore, it is possible to use the results from

these discrimination studies to estimate the patients' elevated discrimination threshold for a 250 ms tone (the duration of the standard) and then compare this number to the observed latency delay in the present experiment. A common measure in psychophysical studies is to calculate the Weber ratio, dividing the discrimination threshold by the mean. Across a set of duration discrimination studies (Casini & Ivry, 1999; Ivry & Keele, 1989; Mangels et al., 1998; Nichelli, Alway & Grafman, 1996) the Weber ratio for controls has fallen in the range of 0.05 to 0.11 whereas for patients with cerebellar degeneration, the range has been from 0.08 to 0.18 (elevated thresholds of about 70%). These differences would lead one to expect that the patients' discrimination threshold for a 250 ms tone would be increased by between 7.5 and 17.5 ms relative to the controls, a range that is close to their 20 ms increase in duration MMN latency. The somewhat larger value observed in the present experiment may be related to the fact that discrimination thresholds are larger with filled intervals (the duration of a tone) than with empty intervals (the time between two tones), as were used in these cited studies (e.g., Grondin, 1993). Importantly, the present findings add to these previous studies by demonstrating that the cerebellar patients' impaired time discrimination is present at an early stage of auditory processing (100-200 ms). Furthermore, unlike these previous studies, the present task did not require an overt assessment of temporal regularities or even that the stimuli are attended. Thus, the observed effects are unlikely to be due to attentional or motor difficulties in the patient group, and can more confidently be attributed to an impaired timing mechanism.

On a methodological note, the observation of periodicity effects – if somewhat inconsistent – emphasize that periodicity may be a relevant factor when interpreting cerebellar function in imaging and patient studies. For instance, the two imaging studies reporting cerebellar activation in an auditory duration MMN paradigm used a fixed SOA (Dittmann-Balçar et al., 2001; Schall et al., 2003). A fixed SOA was also used in the study reporting a diminished somatosensory MMN to deviations in stimulation of the affected compared to the unaffected hand in patients with unilateral cerebellar damage (Restuccia et al., 2007). The present results suggest that these effects might be related to the periodicity of the stimuli; it would be interesting to see if similar results would be obtained with a variable SOA.

The present experiment was focused on contrasting the sensory prediction and timing hypotheses by investigating the MMN in cerebellar patients and healthy controls. However, there was also an interesting group difference in the effect of periodicity on P1 amplitude. The

control group showed enhanced P1 amplitude in the aperiodic compared to the periodic condition, an effect that was absent in the patients. While clearly speculative, it is tempting to relate this result to previous work on P1 suppression, which has been reported to be reduced in patients with Machado-Josephs disease (or SCA3), a form of cerebellar cortical degeneration (Ghisolfi et al., 2004). P1-suppression is commonly interpreted as a measure of sensory gating, and is observed as a marked reduction in the P1 (or P50) potential evoked by the second compared to the first of a pair of auditory stimuli separated by a fixed ISI (usually 500 ms). A reduced P1 to the second stimulus can also be demonstrated by pairing it to a preceding somatosensory stimulus, suggesting that P1-gating is not due to a passive refractory mechanism, but instead to an active (and potentially cross-modal) inhibitory process (Perlstein, Simons & Graham, 2001). In the present experiment, the fixed SOA might have enabled the controls to suppress (or "gate out") the irrelevant tones in the periodic condition, whereas such suppression would be more difficult in the less predictable aperiodic condition. The absence of a difference between conditions in the patient group might thus provide indirect support to the idea that the cerebellum plays an important role in filtering out predictable irrelevant stimuli, as has been suggested by researchers studying the cerebella and cerebellar-like structures of lower animals (Devor, 2000; Bell, 2002). An interesting question for further research is whether difficulties in filtering out temporally predictable task-irrelevant stimuli might partly account for the attentional difficulties reported in patients with cerebellar lesions (Gottwald, Mihailovic, Wilde & Mehdorn, 2003).

5. Conclusion

In conclusion, the present experiment demonstrates that the mismatch paradigm can reveal important and meaningful data clarifying the functional role of the cerebellum. The results provide support for a cerebellar contribution to the automatic processing of the temporal (and possibly also intensity) properties of auditory stimuli. These findings, together with the absence of robust group differences in the MMNs to the non-temporal pitch and location deviants, suggest a rather specific cerebellar role in sensory prediction. Thus, the present results fail to support a general role in sensory prediction as predicted by the sensory prediction hypothesis. The timing hypothesis, as defined in the introduction, receives partial support. While the results strongly suggest a cerebellar role in the processing of temporal information embedded within a stimulus (i.e., its duration), they remain inconclusive regarding the inter-stimulus temporal information (i.e., intervals). Also, the observed trend towards a delayed intensity MMN was unpredicted by the timing hypothesis, but might be

related to an interaction between temporal and intensity information in intensity discrimination of short sounds. Importantly, the present findings add to previous reports of timing deficits in cerebellar patients by demonstrating that this impairment is present at an early stage of auditory processing (100-200 ms), even when the task does not require an overt assessment of temporal regularities or even that the stimuli be attended.

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