Insights into the human cerebellum's contribution to reinforcement learning and error processing

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Zusammenfassung

In den letzten Jahrzehnten hat sich die Sichtweise auf das Kleinhirn und seine Bedeutung für das menschliche Verhalten von einer Gehirnregion, die lediglich an der motorischen Kontrolle beteiligt ist, zu einer Region gewandelt, die auch an vielen verschiedenen kognitiven und affektiven Funktionen beteiligt ist (Koziol et al., 2012). Neurophysiologische Befunde zeigten, dass das Kleinhirn mit höheren cerebralen Hirnarealen in reziproken neuronalen Schleifen verbunden ist (Middleton & Strick, 2001), was seinen potenziellen Beitrag zu diesen kognitiven Funktionen unterstreicht. Eine Konzeptualisierung dieser cerebro-cerebellären Interaktion liefert das Vorwärtsmodell (*forward model*), das davon ausgeht, dass das Kleinhirn nicht nur an der Aktualisierung sensorisch-motorischer Vorhersagen (Wolpert & Miall, 1996; Wolpert et al., 1998), sondern auch an der Aktualisierung von perzeptuellen (O. Baumann et al., 2015) und kognitiven Prozessen (Sokolov et al., 2017) beteiligt ist. Auf der Grundlage des Vorwärtsmodells wurde das Modell der Handlungsüberwachung (*performance monitoring*) entwickelt, das davon ausgeht, dass das Kleinhirn in unterschiedliche kognitive und affektive Funktionen involviert ist, einschließlich der Verarbeitung von Fehlern und des Lernens aus externalen Feedback-Informationen, welche der Optimierung und Anpassung des Verhaltens dienen (Peterburs & Desmond, 2016). Das Lernen aus Feedback im Sinne von Belohnung und Bestrafung ist eine wichtige Fähigkeit und für Entscheidungsverhalten von entscheidender Bedeutung.

Ziel dieser Doktorarbeit war es, die Rolle des Kleinhirns bei der Verarbeitung von Fehlern und dem Verstärkungslernen aus Feedback auf multimodale Weise zu beschreiben. In der ersten Studie wurde ein systematisches Review durchgeführt, um die bestehende Literatur umfassend zu sichten und Studien zu identifizieren, die feedback-basierte Lernaufgaben bei Patient:innen mit Kleinhirnkrankheiten und gesunden Kontrollen verwendeten. Sechsunddreißig Studien wurden einbezogen, und die Ergebnisse zeigten, dass etwa die Hälfte aller Patient:innen relevante Verhaltensänderungen bei verschiedenen Feedback-Lernaufgaben zeigten. Darüber hinaus zeigte das Review, dass eine Studie Hinweise auf Veränderungen im Elektroenzephalographie-Signal (EEG) bei Patient:innen mit Kleinhirnschädigung lieferte. Studien mit funktioneller Magnetresonanztomographie (fMRI) zeigten bei gesunden Proband:innen Aktivierungsmuster im Kleinhirn in verschiedenen Regionen mit konvergierenden Nachweisen im posterolateralen Kleinhirn während der Erwartung/Vorhersage sowie während der Präsentation von leistungsbezogenem Feedback.

Die zweite Studie untersuchte die Rolle des Kleinhirns bei der Fehlerverarbeitung, wie sie in dem Modell zur Handlungsüberwachung beschrieben wird. Eine Go/Nogo-Flanker-Aufgabe wurde verwendet, um Fehler zu induzieren, während ein EEG aufgezeichnet und transkranielle

Einzelimpuls-Magnetstimulation (spTMS) auf das Kleinhirn und eine extrazerebellare Kontrollregion (Vertex) in zwei verschiedenen Sitzungen appliziert wurde. Die Fehlerraten in der Aufgabe unterschieden sich nicht zwischen den Stimulationsorten, aber die fehlerbezogene Negativität (engl. error-related negativtity, ERN/Ne: Falkenstein et al., 1991; Gehring et al., 1993), eine Komponente des ereigniskorrelierten Potenzials (ERP), war bei Stimulation des Kleinhirns im Vergleich zu Vertex reduziert, was auf einen Beitrag des Kleinhirns zur Fehlerverarbeitung hindeutet.

Die dritte Studie untersuchte bei Patient:innen mit Kleinhirndegeneration das Verstärkungslernen und die Verarbeitung bzw. Kodierung von Vorhersagefehlern (engl. prediction Error, PE) in einer feedback-basierten Lernaufgabe, in welcher parallel ein EEG aufgezeichnet wurde. Die ERP-Komponenten feedbackbezogene Negativierung (feedback-related negativity: FRN: Holroyd & Coles, 2002) und P3a/P3b (Polich, 2007) wurden als neuronale/elektrophysiologische Korrelate für Verstärkungslernen analysiert. Zusätzlich wurde eine Magnetresonanztomographie (MRT) durchgeführt, um das Volumen der grauen Substanz (engl. gray matter volume, GMV) des Kleinhirns zu charakterisieren und die Auswirkungen des GMV auf die Lernleistung, FRN und P3a/P3b zu analysieren. Die Ergebnisse zeigten keinen Unterschied in der Lernleistung zwischen Patient:innen und Kontrollen. Für die Auswahl der beiden möglichen Antwortoptionen fand sich eine Reduktion des Wechselverhalten im Verlauf der Aufgabe in allen Proband:innen. Darüber hinaus fehlte die Kodierung des PE in FRN, P3a und P3b bei den Patient:innen, während sie bei den Kontrollen vorhanden war. Des Weiteren ergab die Analyse der GMV einen Verlust in weit verbreiteten Kleinhirnregionen, einschließlich der bilateralen Crus I/ II und der bilateralen Lobuli I-IV im Vergleich zu den Kontrollen. Die multiple Regression für die Patienten zeigte eine negative Korrelation zwischen dem GMV in bilateralen Crus I/ II und der FRN-Amplitude.

Zusammenfassend lässt sich sagen, dass die Ergebnisse aller drei Studien die Hypothese stützen, dass das Kleinhirn an Prozessen der Handlungsüberwachung in Bezug auf die Fehlerverarbeitung sowie das Verstärkungslernen und die PE-Verarbeitung beteiligt ist. Zukünftige Forschung muss mithilfe von Studien mit und ohne Patient:innen sowohl in aufgabenbasierten MRT-Studien als auch in Studien mit nicht-invasiver Hirnstimulation weitere Schlüsse ziehen, inwieweit das Kleinhirn an diesen Prozessen beteiligt ist.

Summary

Over the last decades, the perspective on the cerebellum and its significance for human behavior changed from a brain region exclusively involved in motor control towards a region contributing to many different cognitive and affective functions (Koziol et al., 2014). Research discovered neuronal pathways that connect the cerebellum with higher cerebral brain areas in reciprocal loops (Middleton & Strick, 2001), underlining its potential contribution to these cognitive functions. A conceptualization of this interaction is provided by the forward model which assumes that the cerebellum is not only involved in updating sensorimotor predictions (Wolpert & Miall, 1996; Wolpert et al., 1998) but also in updating of perceptual (O. Baumann et al., 2015) and cognitive processes (Sokolov et al., 2017). Based on the forward model, the model of performance monitoring was developed, which assumes that the cerebellum processes different cognitive and affective functions, including the processing of errors and learning from (external) feedback information, which serve to optimize and adapt behavior (Peterburs & Desmond, 2016). Learning from feedback information in the sense of reward and punishment is therefore an important ability and is crucial for decision-making behavior.

This doctoral thesis aimed to characterize the role of the cerebellum in processing errors and in learning from feedback in a multimodal fashion. In the first study, a systematic review was conducted to comprehensively review literature to identify studies using feedback-based learning tasks in patients with cerebellar diseases and healthy controls. Thirty-six studies were included, and results revealed that about half of all patients showed behavioral alterations across different tasks. In addition, the review showed that one study provided alterations in neural responses to feedback as revealed by electroencephalography (EEG) in patients with cerebellar damage. Studies using functional magnetic resonance imaging (fMRI) showed cerebellar activation patterns in different regions in healthy participants with converging evidence in the posterolateral cerebellum for the anticipation and presentation stage of feedback.

The second study investigated the role of the cerebellum for error processing as described in the model on performance monitoring. A Go/Nogo Flanker task was used to induce errors wile recording EEG and applying single-pulse transcranial magnetic stimulation (spTMS) on the cerebellum and an extra-cerebellar control region (vertex) in two different sessions. Error rates did not differ between the stimulation sites but the error-related negativity (ERN/Ne: Falkenstein et al., 1991; Gehring et al., 1993), a response-locked event-related potential (ERP) component, was reduced for cerebellar compared to vertex stimulation, thus pointing towards a contribution of the cerebellum in error processing.

The third study investigated reinforcement learning and prediction error (PE) processing in patients with cerebellar degeneration by conducting a feedback-based learning task while measuring EEG. The ERP components feedback-related negativity (FRN: Holroyd & Coles, 2002) and P3a/P3b (Polich, 2007) were analyzed as indicators of reinforcement learning. Additionally, MRI was measured to characterize the cerebellum's gray matter volume (GMV) and to identify potential links between GMV reduction in patients and accuracy, FRN, and P3a/P3b. The results showed no difference in accuracy between patients and controls. For the selection of the two possible response options, a reduction in switching behavior during the course of the task was found in all participants. In addition, coding of the unsigned PE in FRN, P3a and P3b was absent in patients while it was present in controls. Moreover, analysis of the GMV revealed reduction in widespread cerebellar regions including bilateral Crus I/ II and bilateral lobules I-IV compared to controls. Multiple regression analysis demonstrated a negative correlation between the GMV in Crus I/ II and the FRN amplitude.

In conclusion, the results gathered from all three studies support the hypothesis that the cerebellum is involved in performance monitoring in terms of error processing as well as reinforcement learning and PE processing when feedback is used for learning. Future research will need to further investigate the extent to which the cerebellum is involved in these processes based on studies with and without patients, both in task-based MRI studies and in studies with non-invasive brain stimulation.

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Abbreviations

ACC ..... Anterior cingulate cortex
AICA ..... Anterior inferior cerebellar artery
ARTIST ..... Automated artifact rejection for Single-pulse TMS-EEG Data
BARS ..... Brief Ataxia Rating Scale
BIDS ..... Brain Imaging Data Format
BOLD ..... Blood-oxygen level-dependence
CAG ..... Cytosine-adenine-guanine trinucleotide
CBI ..... Cerebellar-brain inhibition
CCAS ..... Cerebellar cognitive affective syndrome
CCAS-S ..... Cerebellar-Cognitive-Affective-Syndrome Scale
CRN ..... Correct-related negativity
DA ..... Dopamine
EEG ..... Electroencephalography
EMG ..... Electromyography
ERN/Ne ..... Error-related negativity
ERP ..... Event-related potential
fMRI ..... Functional magnetic resonance imaging
FRDA ..... Friedreich's ataxia
FRN ..... Feedback-related negativity
GABA ..... Gamma-aminobutyric acid
GMV ..... Gray matter volume
ICARS ..... International Cooperative Ataxia Rating Scale
IEL ..... Individual error latency
IMT ..... Individual motor threshold
INAS ..... Inventory of Non-Ataxia Signs
LTD ..... Long-term depression
LTP ..... Long-term potentiation
M1 ..... Primary motor cortex
MEP ..... Motor-evoked potential
MFC ..... Medial frontal cortex
MICARS ..... Modified International Cooperative Ataxia Rating Scale
MLM ..... Mixed linear model
MSA ..... Multiple system atrophy
NIBS ..... Non-invasive brain stimulation

OFC ..... Orbitofrontal cortex
OSF ..... Open Science Framework
PD ..... Parkinsons disease
PE ..... Prediction error
Pe* ..... Error positivity
PET ..... Positron emission tomography
PFC ..... Prefrontal cortex
PICA ..... Posterior inferior cerebellar artery
PICO ..... Patient, Intervention, Comparison, Outcome framework
PolyQ ..... Polyglutamine
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO ..... Prediction of response–outcome model
RewP ..... Reward positivity
RL-theory ..... Reinforcement learning theory
RNA ..... Ribonucleic acid
RPE ..... Reward prediction error
rsFC ..... Resting state functional connectivity
rTMS ..... Repetitive transcranial magnetic stimulation
SAOA ..... Sporadic adult-onset ataxia of unknown etiology
SARA ..... Scale for the Assessment and Rating of Ataxia
SCA ..... Spinocerebellar ataxia
SCAFI ..... Spinocerebellar Ataxia Functional Index
SCArt ..... Superior cerebellar artery
SMA ..... Supplementary motor area
SN ..... Substantia nigra
spTMS ..... Single-pulse transcranial magnetic stimulation
STDP ..... Spike-timing dependent plasticity
SUIT ..... Spatially Unbiased Infratentorial toolbox
TD ..... Temporal difference
tDCS ..... Transcranial direct current stimulation
TMS ..... Transcranial magnetic stimulation
VBM ..... Voxel-based morphometry
VTA ..... Ventral tegmental area
WCST ..... Wisconsin Card Sorting test

1 Introduction

When you walk on the street while talking to a friend and giving him the direction to the next best restaurant by moving your arm and pointing with your index finger, multiple motor representations are processed simultaneously within the brain, and coordination as well as fine-tuning of all of these functions is orchestrated with the involvement of the cerebellum. The cerebellum, also referred to as the "little brain", is located at the back of the head, beneath the cerebral hemispheres and posterior of the brainstem. It is connected to various brain regions of the cerebrum through multiple afferent and efferent pathways (Kang et al., 2021; Middleton & Strick, 1994, 2001; Palesi et al., 2017), enabling the cerebellum to be an important neuronal hub for motor control, coordination, and planning. The cerebellum's role for motor control was already identified more than 200 years ago in landmark work by researchers such as Rolando (1809), Fodéra (1823), and Flourens (1842). These researchers and many more identified symptoms of altered movement control and coordination in patients with damaged cerebellar tissue that could not be explained by other reasons, such as the mere loss of muscle strength (for a detailed review on the history of cerebellar research, see Manto, 2008). These initial clinical observations laid the foundation for cerebellar research in the following centuries, including the quest for a detailed description of the cerebellum's neuroanatomy, neurophysiology, and its interplay with other brain regions as well as its contributions to motor (Cabaraux et al., 2023; Manto et al., 2012) and even non-motor functions (Daum, Ackermann, et al., 1993; Leiner et al., 1986).

1.1 The functional neuroanatomy of the cerebellum

The neuroanatomy of the cerebellum is distinct from the composition of the cerebrum because of its uniform neuroarchitecture (Ramnani, 2006; Sillitoe & Joyner, 2007) and extensive foldings that are tighter than in the cerebrum (Diedrichsen & Zotow, 2015). The folia (lat. leaves) of the cerebellum's surface increase the total surface area of the cerebellum and enable the cerebellum to be more densely packed with almost 80 % of all neurons in the entire brain, which also contributes to more processing capacity and computing power (Herculano-Houzel, 2009, 2010). Recent research on the cerebellar surface revealed that an unfolded human cerebellum reflects around 78 % of the surface area of the neocortex in humans, whereas the unfolded macaque cerebellum reflects only around 33 % of the surface area of the neocortex in macaque monkeys (Sereno et al., 2020). This interspecies difference in ratio caused by the evolutionary development of the human cerebellum was interpreted by Sereno et al. (2020) as a key reason for the human motor and non-motor capabilities.

The human cerebellum is located in the posterior fossa of the brain and connected with the brainstem via three pairs of cerebellar peduncles (superior, medial and inferior peduncles). Macro anatomically it is constituted by two hemispheres that are each connected to a phylogenetically older structure called vermis (Leiner et al., 1991). The vermis is located medial within the cerebellum, has a worm-like shape and contains one of the four cerebellar nuclei, the fastigial nucleus. Both cerebellar hemispheres consist of ten lobules (counted from lobule I-X: see Figure 1A for an image of the cerebellum in coronal plane) that constitute the cerebellar cortex. The cerebellar cortex reveals a tree-like shape of the white matter tracts which are also referred to as the arbor vitae (lat. tree of life: see Figure 1).

The cerebellum can be divided into its three major lobes which comprise the ten lobules (see Figure 1B for an image of the cerebellum in sagittal plane) that were also identified to be functionally distinct (Voogd, 2003).

The first lobe is the anterior lobe (encompassing lobule I-V) located above the primary fissure and primarily involved in coordinating the body posture and fine tuning of muscle movements. The anterior cerebellum receives afferent signals from the spinal cord via the anterior spinocerebellar tract and is therefore also called the spinocerebellum. Damage in the anterior lobe can cause symptoms such as intention tremor, i.e., a tremor when goal-driven movements including visual feedback are performed (Kovács et al., 2019).

The second major lobe is the posterior lobe (including lobule VI-IX) which is located below the primary fissure and involved in movement planning and execution as well as many different non-motor functions (Koziol et al., 2014; Peterburs & Desmond, 2016). The posterior lobe, also called cerebrocerebellum, neocerebellum, or pontocerebellum, is the phylogenetically youngest part of the cerebellum. From the ten lobules of the cerebellar hemispheres, the lobule VI and VIIa (encompassing Crus I and II) located in the posterior lobe, are significantly larger in humans than in other species (Leiner et al., 1991). Importantly, the cerebellum receives input from the cerebrum via the pontine nuclei and subsequently via the largest peduncle, the medial cerebellar peduncle, that relays the signal to the contralateral hemispheres of the cerebellar posterior lobe.

The third cerebellar lobe is the flocculonodular lobe (lobule X), consisting of the flocculus and nodulus and located below the posterolateral fissure. It is primarily involved in coordinating eye movements, balance, and vestibular reflexes (Ito, 1982). The vestibulocerebellum comprises both the flocculondar lobe and the vermis and is the phylogenetically oldest region of the cerebellum (Klein et al., 2016). This region of the cerebellum receives afferent input from the medial and inferior vestibular nuclei via the inferior cerebellar peduncle.

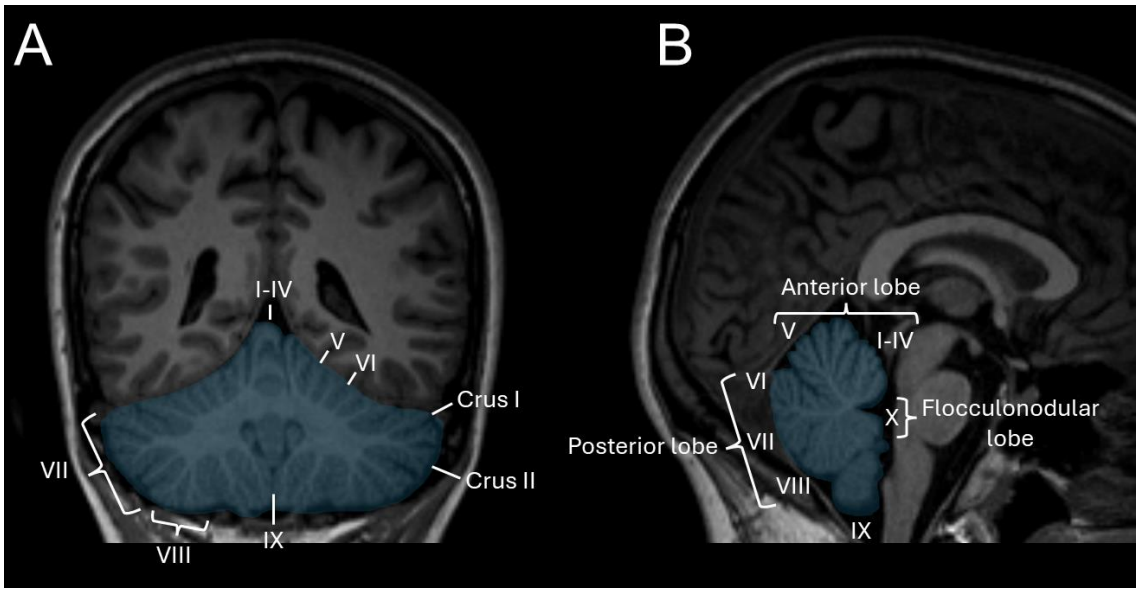

Figure 1. Panel A shows the cerebellum in the coronal plane (blue) marking the cerebellar lobules and panel B shows the cerebellum in the sagittal plane with view on the anterior and posterior cerebellar lobe. Image courtesy of my wife Bianca Berlijn-Berndt.

Importantly, the inferior cerebellar peduncle receives input from different fiber tracts, namely, the posterior spinocerebellar tract, the cuneocerebellar tract, and the trigeminocerebellar tract which are linked to the processing of proprioceptive information of the body (e.g., face, arm movements). In addition, nuclei of the inferior olive in the spinal cord send projections via the olivocerebellar tract which end as climbing fibers in the cerebellum and are, besides the mossy fibers, the major source for input signal to the cerebellum (Lang et al., 2017; Strata, 1998).

Furthermore, the cerebellum receives blood supply via three different arteries that are also involved in cerebellar stroke (Datar & Rabinstein, 2014; Macdonell et al., 1987). These arteries include the posterior inferior cerebellar artery (PICA) which mainly supplies the inferior vermis and the inferior posterior cerebellum, the anterior inferior cerebellar artery (AICA) which supplies the anterior part of the cerebellum as well as the flocculus, middle cerebellar peduncle, and the lower pontine tegmentum. The superior cerebellar artery (SCArt) supplies the superior half of the cerebellar hemispheres, the vermis, the dentate nuclei, and the upper pontine tegmentum (Tatu et al., 2012). All three arteries together build an anastomotic network on the cerebellar surface (Pasco et al., 2002).

1.1.1 Deep cerebellar nuclei

The cerebellum comprises four paired nuclei (also referred to as deep cerebellar nuclei), which all have in common that they are the only output structure for signals from the cerebellar cortex to higher cerebral areas (Habas, 2010). The fastigial nuclei are the most medial located deep

cerebellar nuclei and lie within the vermis. The caudal fastigial nuclei receive input from the vermis processing information on the eye movements such as saccades (Kleine et al., 2003) and the rostral portions receive information from the vestibular nuclei processing proprioceptive information to correct spatial movement execution (Brooks & Cullen, 2009). The globose and emboliform nuclei grouped together as the interposed nucleus are located lateral from the fastigial nuclei and receive signals from paravermal regions (Cacciola et al., 2019). The interposed nucleus sends contralateral output signals to the mesencephalic nucleus ruber (also known as red nucleus) which again sends contralaterally output to the rubrospinal tract so that the ipsilateral side of the body is innervated by the same side of the cerebellum. Fastigial and interposed nuclei are assumed to be involved in both voluntary and automatic movement coordination (Habas, 2010).

The dentate nuclei which are the most lateral and prominent cerebellar nuclei receive information from the lateral cerebellar cortex. Efferent signals are sent from the dentate nuclei to the superior cerebellar peduncle and subsequently via the dentothalamical tract to the contralateral ventrolateral thalamus which relays this signal to higher cerebral structures such as the primary motor cortex (Dum & Strick, 2003). In addition, they can be phylogenetically separated into a ventrolateral and dorsomedial part that are functionally distinct (Dum & Strick, 2003; Leiner et al., 1991; Middleton & Strick, 1994). The dorsomedial part is phylogenetically older than the ventrolateral part and similar to the dentate in other species (Leiner et al., 1991). The functional relationship of the ventrolateral dentate nucleus was investigated in a study by Dum and Strick (2003) using a herpes simplex virus to conduct retrograde trans-neuronal tracing in animals. Using this approach, they identified which cerebral structure was connected to which zone of the dentate nucleus. They found a structural correspondence of the primary motor cortex (M1) with the dorsal dentate in the mid-rostrocaudal level. Interestingly, injections in areas of the cerebrum that are supposed to be involved in non-motor, cognitive functions such as the intraparietal sulcus (Hamilton & Grafton, 2006; Tunik et al., 2007) showed correspondence in ventral parts of the caudal dentate. These findings suggest a functional dissociation for motor and non-motor functions within the organization of the dentate nuclei and a close relationship to cerebral structures (Tellmann et al., 2015).

1.1.2 Cerebellar cell structure and function

The cerebellar cortex is formed by three different layers that contain different types of neurons and fibers that were already described back in the early 20th century by Ramon y Cajal (1909). The first layer on top of the cerebellar white matter is the granule layer which contains the granule cells, unipolar brush cells as well as Golgi cells and climbing fibers. The granule cells make up about 99 % of all cells within the cerebellum (Consalez et al., 2021) and the granule and unipolar

brush cells are the only excitatory (glutamatergic) cells in the cerebellum. The projections of the granule cells end in the neighbored Purkinje cell layer where the Purkinje cells are located. The Purkinje cells are large in comparison to other cells within the brain (Bower, 2015), and their influence on the synaptic transmission is inhibitory through the neurotransmitter Gamma-aminobutyric acid (GABA) along with interneurons such as Golgi cells, stellate cells, and basket cells. The dendrite trees of the Purkinje cells located in the third, the molecular layer of the cerebellar cortex, receive excitatory input from two distinct fiber systems. First, each Purkinje cell receives signals from one climbing fiber that originates from the inferior olive which is also connected to the cerebellar nuclei. Second, each Purkinje cell receives signals from the glutamatergic mossy fibers that are connected via four to five granule cells (as so called glomeruli see Consalez et al., 2021) to parallel fibers, forming thousands of parallel fibers synapses with the massive dendrite trees of the Purkinje cells. Additionally, the stellar and basket cells located in the molecular layer, close to the Purkinje cells bodies function as inhibitory interneurons forming together synapses that project on the dendrites of the Purkinje cells using GABA. The inhibitory efferent fibers of the Purkinje cells represent the only output neurons of the cerebellar cortex and project further via the white matter to the deep cerebellar nuclei and modulate their output signal to other brain regions (Ishikawa et al., 2014).

1.1.3 Cerebellum and microzones

Purkinje cells are well organized within the cerebellar cortex and ordered according to longitudinal “microzones” that demonstrate the same output to climbing fiber input (De Zeeuw, 2021; Kostadinov & Häusser, 2022; Leiner et al., 1991; Oscarsson, 1979). These microzones are oriented in sagittal direction and perpendicular to the cortical surface of the cerebellum with a width of less than 200 µm. Each microzone’s output activity is determined by the respective activity of multiple, synchronously active Purkinje cells within the zone that elicit patterns of simple and complex spiking (Palmer et al., 2010). The excitatory climbing fibers trigger complex spiking activity at the Purkinje cells that have an upward deflection at a low frequency rate (between 0.5 Hz and 2 Hz: Kostadinov & Häusser, 2022; 1 Hz and 7 Hz: De Zeeuw, 2021). In contrast, Purkinje cells generate an endogenous and rapid firing of electrical activity called simple spiking. The rapid firing of simple spiking is characterized with a downward deflection in the activation and can exceed the frequency of 100 Hz (Palmer et al., 2010; Raman & Bean, 1999). The mossy fibers and interneurons can modulate the spontaneous firing activity of the Purkinje cells by excitatory and inhibitory synaptic transmission. In addition, complex spiking can suppress subsequent simple spiking activity by dendrite spikes (Davie et al., 2008) and Purkinje cells are able to adjust their firing rate according to the synaptic transmission of the granule cells

(Walter & Khodakhah, 2006), increasing the complexity of modulations by the electrical activity of the Purkinje cell within a respective microzone.

Functionally, microzones are categorized by the type of synaptic plasticity produced by the stimulation at the interface between parallel fibers and the Purkinje cells (De Zeeuw, 2021; De Zeeuw & Brinke, 2015). This stimulation can cause both long-term depression (LTD: Ito et al., 2014), a decrease in the strength of the postsynapse, and long-term potentiation (LTP: Gutierrez-Castellanos et al., 2017), increasing the postsynaptic strength. In addition, spike-timing can have an influence on the synaptic transmission. For instance, a stimulation of the parallel fibers can modulate the subsequent synaptic transmission in the complex spikes induced by climbing fibers which is called spike-timing dependent plasticity (STDP: Häusser & Clark, 1997). Nevertheless, LTD and LTP are the fundamental mechanisms for motor (De Zeeuw, 2021; De Zeeuw & Brinke, 2015) and non-motor learning (Kostadinov & Häusser, 2022; Tsutsumi et al., 2019). Multiple microzones together are represented as microcomplexes including projections to e.g., the cerebellar nuclei. It is assumed that thousands of microcomplexes exist within the cerebellum (Ito, 1984). The highest level arrangement, including multiple microcomplexes as the synergy of Purkinje cells, cerebellar and vestibular nuclei as well as neurons within the nucleus of the inferior olive, are called micromodules (De Zeeuw, 2021). In sum, the histological findings demonstrate a complex interplay of cells and fibers within the cerebellum that enable the cerebellum to somehow change its activation patterns and neuronal plasticity.

1.2 Cerebellum and motor control

In 1984, Masao Ito published his seminal book “The Cerebellum as Neural Control”, summarizing scientific work that had shed light on the involvement of the cerebellum in motor functions including novel insights on the inhibitory role of the Purkinje cells (Ito & Yoshida, 1964), LTD mechanisms within the cerebellum (Ito et al., 1982), and on the general neuronal circuity of the cerebellum as described by Sir John Eccles (1967) and colleagues. Ito postulated that analogous to a computer, the cerebellum acquires motor skills using computational programs termed “internal models”. These internal models contain information in form of neuronal patterns of motor representation including input from the external world (see Ito, 2008). In detail, the idea of internal models was conceptualized according to the known neuroanatomical structures that were dominantly seen to enable motor control. In this conceptualization, the motor cortex was described as a controlling unit that receives input from other cerebral areas such as the premotor cortex, supplementary motor area (SMA), and anterior cingulate cortex (ACC). Further, it was assumed that the motor cortex processes the available input information and sends efferent signals to the extremities of the body, e.g., a command to move the hand (Ito, 2008). In addition, the

motor cortex can receive and process external visual information of the body like the current hand position via occipital structures including the visual cortex to modulate its efference signal by integrating new sensory information of the current state and adjusting the hand position, if necessary, accordingly. All of these neuronal interactions are assumed to be reflected by internal models, presumably generated within the cerebellum through reciprocal connections with cerebral brain regions via the cerebello-thalamo-cerebral and cerebral-ponto-cerebellar loops (Middleton & Strick, 2001; Palesi et al., 2017). It is assumed that the cerebellum maintains this internal model as a representation of the movement (motor representation) to make fast and smooth transitions/adjustments possible (Blakemore, Goodbody, & Wolpert, 1998; Ito, 1993; Wolpert et al., 1998). Therefore, it is believed that the cerebellum generates different internal models that become/are activated depending on specific action/movement requirements in a given situation. Modelling these internal models within the cerebellar circuity has been done in many studies over the last decades (see Kawato et al., 2021) which was also feasible due to the clearly arranged cerebellar neuroarchitecture (Ramnani, 2006; Sillitoe & Joyner, 2007).

1.2.1 Forward and inverse model

Two major perspectives on these internal models are discussed in the literature, the forward, and the inverse model (Ito, 2008; Wolpert et al., 1998). According to the forward model, the subsequent movement of for instance a hand is predicted by available information of the motor commands efference copy and compared against the actual sensory consequences of the movement. In this example, mismatches in terms of a (sensory) prediction error (PE) signal between the generated predictions of e.g., the appropriate velocity and positioning of the hand are processed and adjusted according to the available sensory information. Therefore, the forward model is involved in generating predictions of outcomes. In contrast, the inverse model (Wolpert et al., 1998) generates the necessary motor command to achieve the appropriate movement (Sokolov et al., 2017; Wolpert et al., 1998). A combination of both modelling approaches was provided by Wolpert et al. (1998) called “multiple paired forward-inverse models” which constitutes the idea of two modules that are paired with each other and activated when the sensory outcome of a movement within a specific context can be predicted by one of the many paired modules. Within this model, the movement must first be evaluated to find the responsible module to optimally predict the outcome so that the suitable modules can learn from these predictions for future movements. Deviations between the sensory feedback and the generated predictions are reflected in PEs that create an internal error signal. PEs in general are smaller or even absent when the predictions align with the sensory feedback. Accordingly, a smaller PE indicates a stronger functional role of the forward model because it better models the sensory information. In addition, an inverse model delivers in each module a control signal to adjust the prediction generated by

the forward model. The models themselves are weighted within each module to estimate which contribution of which model is more successful for the given movement. In the case of high PEs within the forward model, the inverse model receives less error signals (a decreased error signal) and contributes more to the final motor command for the respective movement.

1.2.2 Timing control, sensory prediction, and the cerebellum

One functional aspect identified within the cerebellum's neurophysiology is the representation and control of timing (Breska & Ivry, 2016; Coull et al., 2011; Ivry & Keele, 1989; Ivry & Spencer, 2004; Ivry et al., 2002). Going back to the example from the very beginning, coordinating movements to show a friend the way to the restaurant involves multiple movements and therefore learning of motor sequences to appropriately time the moving of the arm, opening the hand, and pointing with the finger. Timing control was investigated in a seminal study by Ivry and Keele (1989) in which patients with a diseased cerebellum, besides patients with Parkinsons disease (PD) and patients with cerebral damage, had to perform two different tasks. First, they had to execute rhythmic movements, and second, they were instructed to discriminate different time intervals. The cerebellar patients were the only patients who showed deficits for both tasks including more variability when tapping rhythms and less accuracy in the perception of the time intervals. Building upon this initial observation, more evidence was found in lateral cerebellar activity when timing was the only source to learn the sequence of finger movements while no motor execution was necessary (Braitenberg et al., 1997; Sakai et al., 2002). The control of timing in longer time scales (several seconds) was found to be reflected in the activity of other brain regions such as the basal ganglia, the SMA, and the cerebral cortex (Spencer & Ivry, 2021). These regions partly overlap with brain regions involved in the forward model (Wolpert et al., 1998). Sensory PEs are likely generated by the inferior olive and updated within the cerebellum using available sensory input, enabling the cerebellum to learn to produce correct movements (Schlerf et al., 2012). Interestingly, findings on the cellular level suggest a pivotal role of the granule cells within the cerebellum for representing timing control because the synaptic activity and neuronal oscillation in granule cells is rapid (in a milliseconds range) and could therefore constitute the fundamental units for learning smooth and precise movements (Bareš et al., 2019).

Besides the representation of timing, research on the sensory prediction of movements demonstrated the cerebellum's involvement in tactile stimulation (Blakemore, Goodbody, & Wolpert, 1998; Blakemore, Wolpert, & Frith, 1998). In a study using functional magnetic resonance imaging (fMRI) and a device that allowed to induce self and externally generated tactile stimulation, less activation in the anterior cerebellum was found when the self-initiated movement caused a tactile stimulation than when it did not. In addition, the somatosensory cortex

demonstrated increased activity when the tactile stimulation was produced by an external source. According to the forward model, the cerebellum predicted the sensory consequences of the movement and compared the outcome with the prediction. Thus, the prediction of a self-tickle is assumed to match the predictions generated in the cerebellum and therefore resulted in less cerebellar activation compared to mismatching predictions, i.e. PEs. Also, this is suggested to be the reason why an individual's own tactile stimulation is perceived as less strong than when it is generated externally. In addition, this finding was not domain specific and similar effects supporting the forward model were found when sounds were self- vs. externally generated (Knolle et al., 2013).

In sum, the cerebellum is considered to process sensorimotor predictions and control of timing in a holistic fashion that is not dependent on a single task and motor function but an overarching function and computational program (Bareš et al., 2019; Ivry & Spencer, 2004; Spencer & Ivry, 2021).

1.3 Cerebellum and cognition

The notion that the cerebellum enables not only the learning of sensorimotor (Bareš et al., 2019; Manto et al., 2012) but also cognitive abilities (Jacobi et al., 2021; Koziol et al., 2014; Timmann & Daum, 2007) was initially discussed by Leiner et al. (1986), almost forty years ago. Leiner et al. (1986) summarized evidence of cerebellar lesion patients demonstrating different cognitive alterations. For instance, in one patient, the anticipatory use of cues to improve performance was absent and in another patient, the ability to imagine movements was altered and only vaguely mentally represented. Interestingly, they also observed that damage to phylogenetically newer regions of the cerebellum (posterior cerebellum) and damage to the tracts that connect the cerebellum to higher cerebral areas such as the cerebral-ponto-cerebellar tract did not always result in motor deficits. Aside from the application of the forward model for the motor domain, Leiner et al. discussed the possibility of extending the cerebellum’s role as an adaptive control device in the sense of the forward model (Ito, 1984) to cognitive functions. They integrated emerging observations of cognitive deficits in patients suffering from cerebellar damage in language processing during a word association task (Petersen et al., 1989). The activation of the motor execution of speech was related to activation in the superior anterior lobe whereas the word association itself showed activation in the right inferior lateral hemisphere of the cerebellum (Leiner et al., 1986, 1991). In addition, Grafman et al. (1992) used the Tower of Hanoi task to see whether impairments of problem-solving were present in patients with cerebellar degeneration compared to healthy controls. Results demonstrated that a subgroup of nine patients with pure cerebellar degeneration solved significantly less problems than the control group. Moreover, a

single-case study with a patient suffering from right cerebellar damage revealed multiple cognitive functions to be impaired, including functions such as error awareness (Fiez et al., 1992).

Besides these results in patients, large bilateral activation of the dentate nucleus was found when healthy participants solved a pegboard puzzle (S. G. Kim et al., 1994). More evidence on the involvement of the cerebellum in cognitive processes were demonstrated by Schmahmann and Sherman (1998). In their study, twenty patients with different post-acute vascular cerebellar lesions were tested with different neuropsychological tests. The patients demonstrated impaired executive functions such as shifting between different sets and problem-solving. In addition, verbal fluency was impaired and further changes in personality traits, and loss of affect were observed. Leiner et al. (1991) described a similar effect related to atrophy within the midline of the cerebellum found in the study by Gutzmann and Kühl (1987). Interestingly, Schmahmann and Sherman (1998) also observed that damage to the posterior lobe of the cerebellum and bilateral lesions were associated with stronger deficits in executive functions. These various non-motor symptoms have been labelled with the term cerebellar cognitive affective syndrome (CCAS) or Schmahmann's syndrome, encompassing alterations in executive functions, visuo-spatial processing, personality traits, logical reasoning, and language processing. These non-motor symptoms were also the foundation for the dysmetria of thought theory (Schmahmann, 1996, 2000; Schmahmann et al., 2019; Schmahmann & Sherman, 1997). Dysmetria refers to the disorder of voluntary actions resulting in impaired decisions and executions of actions that comprise the motor and non-motor (cognitive) domain.

1.3.1 Internal models of cognition

Looking closer at the cognitive functions processed within the cerebellum, it is reasonable to assume that the cerebellum also generates internal models for this domain (Ito, 1984; Sokolov et al., 2017; Wolpert et al., 1998), which have their neurophysiological equivalent in the Purkinje cells arranged in microzones, complexes, and modules (Kostadinov & Häusser, 2022; Medina, 2011). Sokolov et al. (2017) discussed the function of internal models for cognition following the forward model of sensorimotor control. Similar to this model, the forward model of cognition sees the cerebellar cortex and the deep cerebellar nuclei as the predictor, receiving information from the associative cortex as efferent copies via the pons. The predictor (deep cerebellar nuclei and cerebellar cortex) for action outcomes receives not only input by the pons but also input from the inferior olive that sends a PE signal. The inferior olive in turn receives its signal from the associative cortex in the form of sensory and cognitive information that is also provided via the thalamus. In turn, the updated information is sent back from the cerebellar cortex via the deep cerebellar nuclei to the thalamus and back to the associative cortex. An open question in this

model is where the actual comparison between the predicted future outcomes of cognitive states takes place to estimate the PE and to generate the error signal. They assumed that this comparator, responsible for determining the PE, could be located in or close to the inferior olive. Supporting evidence for the reciprocal exchange of information on cognitive states was provided by Kelly and Strick (2003). They identified a loop that enables the cerebellum to receive, predict, and send updated information back to higher cerebral structures through the neuroanatomical interconnection of the Purkinje cells in the region Crus II of the cerebellum and the middle fontal area in the cerebrum corresponding roughly to dorsolateral regions of the prefrontal cortex (PFC). In addition, many fMRI studies found supporting evidence for these connections (Buckner, 2013; Buckner et al., 2011; Stoodley & Schmahmann, 2009, 2018) for many different cognitive functions (Keren-Happuch et al., 2014).

1.4 Universal transform theory and multiple functionality hypothesis

Derived from the forward model of movement and cognition and the observed cognitive distortions caused by symptoms that were described as CCAS (Schmahmann, 2019), two competing perspectives on the way of how the cerebellum generally computes information are currently discussed, the universal transform theory (Guell et al., 2018) and the multiple functionality hypothesis (Diedrichsen et al., 2019). The major difference between these perspectives is the assumption that the cerebellum, based on its uniform neuroarchitecture including multiple similarly emerging microcomplexes, uses one universal algorithm that is capable of representing all motor and non-motor functions (universal transform theory: Guell et al., 2018). This is similar to the notion that the cerebellum computes timing and control of timing as a task-independent mechanism (Spencer & Ivry, 2021). In contrast, according to the multiple functionality hypothesis, the cerebellum is assumed to process different algorithms, each dedicated to specific motor and non-motor functions that follow specific principles (Diedrichsen et al., 2019).

1.5 Cerebellar diseases

Knowing the cerebellar cellular neurophysiology, the neuronal pathways connecting the cerebellum with other brain regions, and the concept of internal models in motor and non-motor learning helps to explain and understand which symptoms arise in the diseased cerebellum. Cerebellar diseases like cerebellar ataxia cause primarily severe motor impairments such as gait ataxia, involuntary eye movements (nystagmus) and distortions in speech (dysarthria) which are caused by different aversive events damaging the cerebellum (Manto, 2022; Manto & Marmolino, 2009). In addition, the diseased cerebellum affects non-motor functions according to the CCAS (Argyropoulos et al., 2020; Schmahmann, 1996, 2004).

A fundamental differentiation within the cluster of cerebellar disease is characterized by the anatomical distribution of neuropathological changes. In focal cerebellar ataxias, inflammatory, tumorous or vascular lesions (ischemic strokes) of the cerebellum affect a circumscribed area within the cerebellum (Manes et al., 2009), which also enables the mapping of lesions to specific symptoms, allowing to draw conclusion from the lesion location to the observed motor and cognitive symptoms (Timmann et al., 2008). In contrast, non-focal, global damage in terms of diffuse degenerative atrophy of the cerebellum is frequently caused by hereditary, acquired or sporadic-degenerative processes (Klockgether et al., 2019).

1.5.1 Focal – vascular – lesions of the cerebellum

Focal vascular lesions of the cerebellum are rare within the cluster of strokes and reflect only around 1-4 % of all ischemic stroke events. An ischemic stroke is caused by a vascular occlusion that leads through a reduction of the blood and oxygen supply of the corresponding vascular territory to a damage of the respective brain region (Iadecola & Anrather, 2011). Not so for hemorrhagic strokes, which directly damage the brain by intracranial bleeding after vessel rupture. In the cerebellum, hemorrhagic strokes are often located close to the dentate nuclei and are mostly caused by arterial hypertension (Sarikaya & Steinlin, 2012).

1.5.2 Degenerative – hereditary - diseases of the cerebellum

Non-focal degenerative cerebellar ataxias involve the entire cerebellum and can be classified into the following three main classes: hereditary ataxias, acquired ataxias, and sporadic-degenerative ataxia (Jacobi & Minnerop, 2021). Some types of degenerative cerebellar ataxia also show damage in non-cerebellar regions, although clinically the cerebellar ataxia defines the key symptom. This applies to various hereditary ataxias (e.g. SCA3), but also to sporadic forms such as multisystem atrophy, that causes widespread neuropathological degeneration (MSA: Fanciulli & Wenning, 2015). On the other hand, even degenerative cerebellar disorders classified as almost “pure” cerebellar (e.g. SCA6, sporadic adult-onset ataxia of unknown etiology (SAOA)) may show degeneration in non-cerebellar regions such as the Pons, closely connected with the cerebellum (Abele et al., 2007). Therefore, a clear distinction between degenerative diseases that predominantly damage the cerebellum vs. degenerative diseases that additionally affect non-cerebellar regions is essential in order to be able to identify the unique contribution of the cerebellum to specific motor and non-motor symptoms.

An important group within the non-focal, degenerative cerebellar ataxias are hereditary ataxias, (Klockgether et al., 2019; Sullivan et al., 2019; van Prooije et al., 2021). Hereditary ataxia is clinically grouped into the following three categories: autosomal dominant cerebellar ataxia which encompass the many different spinocerebellar ataxia (SCA) subtypes (currently more than

40 subtypes: Diallo et al., 2021) that have a worldwide prevalence of 2.7 out of 100,000, autosomal recessive ataxias such as Friedreich's ataxia (FRDA, 3.3 out of 100,000), and x-linked ataxias (prevalence is 1 out of 4000 - 5000 people: Lanza et al., 2020; Puccio & Koenig, 2002; van Prooije et al., 2021; Zanni & Bertini, 2011). Causal treatment of these rare diseases is not available in most cases, so measures to maintain mobility and speech as well as medication to alleviate symptoms is indispensable (Klockgether et al., 2019). The different hereditary ataxias are caused by a variety of physiological abnormalities such as channelopathies that cause alterations in ion-channels, cell autophagy, mitochondrial dysfunction, and pathogenic Ribonucleic acid (RNA) gain-of-function (Sullivan et al., 2019). Many SCA subtypes as well as Huntington's disease (Stoyas & La Spada, 2012) are genetically caused by cytosine-adenine-guanine trinucleotide (CAG) repeat expansions within a coding exon that causes an abnormal polyglutamine (PolyQ) expansion repeat length. The CAG repeat length can affect the expression level of the respective gene (K. Baumann, 2015), leading to misfolded PolyQ proteins creating dysfunctional cells that cause ultimately the observed progressive degeneration within the cerebellum. In SCA1-3, the mutation of the ataxin-gene results in the pathological transcription of proteins, whereas in SCA6, alterations in the CACNA1 gene leads to Purkinje cell loss and an exclusive cerebellar degeneration (Currie et al., 2013).

Importantly, many SCA types such as SCA1-3, 5, 6 and 14-16 are supposed to cause ataxia symptoms by the dysfunction of the Purkinje cells calcium signaling causing the cells to die (Kasumu & Bezprozvanny, 2012; Leto et al., 2016). Interestingly, Purkinje cell size was associated with other neurodevelopmental diseases such as autism (Fatemi et al., 2002) and schizophrenia (Tran et al., 1998), thus extending the importance of a healthy cerebellum to a wide range of diseases that affect cognition. Since SCA is hereditary, there is a clustering of specific SCA subtypes in different parts of the world (Diallo et al., 2021; Salman, 2018).

Different SCA types and other hereditary ataxias affect the cerebellum to different degrees. Whereas patients witch a diagnosed SCA6 compared to healthy controls revealed significant reduction of gray matter volume (GMV) in the cerebellum and cerebellar nuclei as well as less blood-oxygen level-dependence (BOLD) signal measured with fMRI, patients with FRDA showed no GMV reduction, and patients with SCA3 (also called Machado-Joseph disease, Ruano et al., 2014) demonstrated only a low impact on GMV (Stefanescu et al., 2015). Besides, FRDA has been identified to affect the cerebello-cerebral pathways, leading to a reduction in structural and functional connectivity between the anterior cerebellum and frontal brain areas which also correlated with the severity of the disease (Kerestes et al., 2023). In addition, it was shown that in SCA6 patients, the dentate nuclei were significantly degenerated with a loss of iron and reduced mass in the wall and body of the dentate nuclei (Jäschke et al., 2023). These results from imaging

studies suggest that the genetic diseases have different effects on the cerebellum's structure and connections to higher brain regions.

1.5.3 Assessment of motor and non-motor symptoms in cerebellar ataxias

The effects of cerebellar degeneration in SCA patients can be observed on the level of motor and non-motor behaviors in patients, which are measured by a variety of neurological and neuropsychological tests (Agarwal et al., 2022). A well-established test to measure motor deficits caused by cerebellar degeneration is the semiquantitative Scale for the Assessment and Rating of Ataxia (SARA: Schmitz-Hübsch et al., 2006). The SARA is the most widely applied test to assess ataxia (Traschütz et al., 2023), and the total score increases with the progression of the disease (Jacobi et al., 2011; Subramony, 2007; Traschütz et al., 2023) in a range of 0 (no ataxia present) to 40 (severe ataxia present).

Besides the SARA, other tests to examine the degree of motor deficits in ataxia patients are the Spinocerebellar Ataxia Functional Index (SCAFI, *z*-transformed range from 3 no ataxia to -3 ataxia: Schmitz-Hübsch et al., 2008), International Cooperative Ataxia Rating Scale (ICARS, 19 items from 0 no ataxia to 100 severe ataxia: Trouillas et al., 1997), and Brief Ataxia Rating Scale (BARS, five items from 0 no ataxia to 30 severe ataxia: Schmahmann et al., 2009). The BARS was based on a modified version of the ICARS (MICARS) using a subset of the MICARS items to reduce the time necessary for application in a clinical setting. The BARS consists of the five dimensions Gait, Knee-tibia test, finger to nose test, examination of dysarthria, and oculomotor abnormalities. The Inventory of Non-Ataxia Signs (INAS, 30 items grouped into 16 variables with a scoring range from 0 absent non-ataxia symptoms to 16 present non-ataxia symptoms: Jacobi et al., 2013) has been created as a supplemental test to assess non-ataxic symptoms by estimating binary whether a non-ataxia symptoms is present or not.

Furthermore, non-motor symptoms are widely examined in ataxia patients since the definition of the dysmetria of thought hypothesis based on observed cognitive impairments in cerebellar patients (Schmahmann, 1996; Schmahmann & Sherman, 1997, 1998). In the most frequent SCA types 1, 2, 3 and 6, neuropsychological symptoms were observed in a wide range of non-motor functions including executive and attentional functions (SCA1-3 and mild cognitive impairment in SCA6: Klinke et al., 2010) as well as memory and learning abilities in SCA3 (Klinke et al., 2010; Roeske et al., 2013). Following these observations, the Cerebellar-Cognitive-Affective-Syndrome Scale (CCAS-S: Hoche et al., 2018) to capture non-motor deficits quantitatively was developed. This ten-item scale with points ranging from 0 to 120 (maximum points, 82 to pass all items with the minimum score) and pass-fail scores from 0 (pass) to 10 (all test failed) consists of the dimensions executive function which includes working memory and abstract reasoning,

linguistic functions such as verbal working memory, visual-spatial functions like drawing a 3-D cube, memory, and learning. For each item, a pass/fail criterion was determined besides the scoring to assess whether a CCAS in the respective patients was only possible (failing one test), probable (failing two tests), or definite (failing three or more tests). The CCAS-S revealed in patients with SCA3 more failed tests and lower scores compared to healthy controls, along with deteriorated semantic and phonemic fluency, category switching, cube drawing, and affect regulation (Maas et al., 2021). However, Thieme et al. (2022) discovered a high rate of false-positives in SCA6 and FRDA compared to controls, and only patients with SCA3 demonstrated lower performance using a German version of the CCAS-S (Thieme et al., 2020), probably due to the more widespread neuropathological changes including the cerebrum as known for SCA3. Importantly, they also demonstrated that the items of the CCAS-S were not corrected for age, education, and sex, challenging the generalizability of the CCAS-S for the assessment of non-motor symptoms in cerebellar ataxia.

Besides the application of the CCAS-S in hereditary ataxia, studies also elucidated whether the CCAS-S can differentiate between specific cognitive impairments in patients with cerebellar stroke. Interestingly, patients with an isolated cerebellar stroke in the posterior lobe of the cerebellum (mostly PICA infarct) did not show any motor but cognitive deficits, leading to the assumption that different loops for motor and cognitive functions are disturbed depending on the location of the cerebellar lesion (Stoodley et al., 2016). In addition, significant deficits in executive functions were discovered in patients with an isolated lesion of the cerebellar hemisphere and vermis applying the CCAS-S (Bolceková et al., 2017). More evidence was found in a recent study looking at patient with chronic cerebellar stroke (Chirino-Pérez et al., 2022). The results on the CCAS showed again a link between the location of the cerebellar lesion and the severity of the CCAS indicated by the CCAS-S, with worse performance when lesions were in the right posterolateral part of the cerebellum. Thus, the location of the cerebellar lesions can predict whether the motor or the cognitive deficits in terms of the CCAS were present.

There is a long history of case studies focusing on cerebellar lesions (e.g., Rolando, 1809) and a challenge is the high inter-individual variability of lesions, among other things. Both the location of a lesion and size in cerebellar stroke patients as well as the stage of degeneration are never exactly the same between patients, resulting in unexplained variance. Solutions to this challenge are the use of bigger samples to make use of the variability of lesions and stimulation techniques to induced changes in the activation of the neuronal circuity.

1.6 Non-invasive brain stimulation and the cerebellum

Non-invasive brain stimulation (NIBS) such as transcranial magnetic stimulation (TMS: Rossi et al., 2009; Rossini et al., 2015) and transcranial direct current stimulation (tDCS: Nitsche et al., 2008) is widely used to investigate the causal relationships between brain and behavior (Grimaldi et al., 2014; Manto et al., 2022). The advantage of NIBS and especially TMS is the induction of excitatory or inhibitory effects on the brain by stimulating neuronal population (Terao & Ugawa, 2002). Therefore, these methods can be used to investigate similar mechanisms as in patients with acute neurological lesions (Vaidya et al., 2019).

In TMS, an electric current is created by a stimulator that flows through a magnetic coil. Perpendicular to the electrical current, a magnetic field is induced. This magnetic field can stimulate the brain by passing the skull without resistance. The strength of this magnetic field can be up to 2.5 Tesla depending on the respective system (Kubis, 2016). In addition, the pulse duration ranges only within a few hundred microseconds and is therefore faster than the sampling rate in common electroencephalography (EEG) studies (1000 Hz = 1 ms = 1000 microseconds) allowing it to be suitable for the combination with other neurophysiological measures (Bergmann et al., 2016; Hernandez-Pavon et al., 2014; Ilmoniemi & Kičić, 2010). TMS protocols can affect the brain circuity differently depending on the frequency and intensity of the stimulation as well as on the specific TMS device and setup. For example, repetitive TMS (rTMS) can induce plasticity changes like LTP by using a high frequency of pulse application, whereas low frequencies can result in LTD (Esser et al., 2006; Wang et al., 1996; Ziemann et al., 2006). Effects of rTMS on neural plasticity were demonstrated in patients after stroke onset (Kubis, 2016; Wessel & Hummel, 2018).

Interestingly, tDCS can elicit effects by applying an electric current on the scalp surface using electrodes to change the threshold for excitability. Depending on the flow of direction (cathodal or anodal), different effects are assumed to be produced. Anodal tDCS is supposed to depolarize neurons triggering excitation, whereas cathodal tDCS is thought to hyperpolarize neurons and therefore decrease the excitability of neurons (Thair et al., 2017). Moreover, monophasic single-pulse TMS (spTMS) is suggested to disrupt processes within the brain (Pascual-Leone, 1999) when pulses with a sufficiently high power stimulate neurons, creating a distributed inhibition through GABA release (Siebner et al., 2009). Therefore, spTMS is used to induce temporary virtual lesions to identify the causal relationship between a specific brain region and cognitive process (Ruff et al., 2009). However, Shirota et al. (2012) have shown that spTMS can also elicit facilitation when stimulating the brain.

To assure that a specific brain region is targeted, landmarks on the head such as the inion at the back of the head or the position of EEG electrodes according to the 10-20 principle on the scalp are oftentimes used for orientation (Herwig et al., 2003). However, a more sophisticated approach is the use of neuro-navigation devices that allow to make use of anatomical MRI images such as T1-weighted images to precisely target a desired brain region (Caulfield et al., 2022). Depending on the shape of the coil, the magnetic field can reach deeper brain layers by a trade-off of focality (Roth et al., 2002). A standard coil that is widely used to stimulate the brain is the figure-of-eight coil, which has a more focal stimulating magnetic field compared to the so called butterfly (double cone) coil which has angled windings to create magnetic field lines that target deeper brain layers (Çan et al., 2018). Importantly, many factors such as the coil orientation and distance between the coil and the surface of the head have to be taken into account when conducting an experiment to stimulate the brain because these factors have an influence on the total stimulation power that finally reaches the brain (Cai et al., 2012). In addition, other somatosensory effects like the click sound of the TMS pulse and induced vibration can be distractors during an experimental task (Duecker & Sack, 2015). Also, when applying many pulses across many trials, heat development of the coil must be considered when conducting experiments to study cognitive processes (Rossi et al., 2009). Estimating the necessary strength to ensure a reliable depolarization (excitation) of neurons is usually done by measuring the individual motor threshold (IMT) using motor-evoked potentials (MEP: Bestmann & Krakauer, 2015; Rossini & Rossi, 1998). These potentials are measurable using electromyography (EMG) at the muscle of the extremities of the body such as the hand after stimulating the M1 region using e.g., spTMS. MEPs are elicited when neurons in M1 are depolarized, leading to subsequent motor activity in the hand. Using higher output power than the IMT, it is possible to observe the hand twitching which can also serve as an indicator that the threshold has been exceeded. Besides to the resting motor threshold at which the hand is still, the active motor threshold at which the hand is tensed can be used to determine the necessary output power for the TMS stimulation (Temesi et al., 2014)

Using two TMS coils of which one is applied on the cerebellum and one on M1, Ugawa et al. (1991) demonstrated an important neurophysiological mechanisms called cerebellar-brain inhibition (CBI: Ugawa et al., 1995). They identified that TMS pulses can trigger the cerebellum to suppress the excitability of the motor cortex in M1. The cerebellar stimulation was applied at the inion, whereas shortly (5 ms) after the stimulation, a pulse was applied over M1 which did not elicit the previously generated MEPs. It is assumed that the Purkinje cells are activated through the TMS pulse in the cerebellar cortex which in turn inhibits the deep cerebellar nuclei (dentate nucleus) as the only output source of the projections leaving the cerebellum. Hence, TMS pulses on the cerebellum can trigger cerebellar activity that suppresses excitability in M1.

Interestingly, the effect of CBI was also discussed in regard to patients with movement disorders such as ataxia because CBI could allow to identify alteration in the cerebello-thalamo-cortical loop (Groiss & Ugawa, 2012).

In conclusion, TMS can be applied to investigate specific brain behavior relations and can be used in different task-based settings while being combined with neuroimaging (Siebner et al., 2009) and electrophysiological recordings such as EEG (Belardinelli et al., 2019; Veniero et al., 2009; Verleger et al., 2009).

1.7 Adaptive behavioral control

1.7.1 Learning theories

The human ability to flexible adapt behavior in changing situations is essential for survival. Actions cause consequences, and adapting one's own behavior according to reward and punishment is therefore an indispensable ability. Thus, to appropriately act within a given situation requires a continuous learning process. Research on the formalization of learning principles dates back more than a hundred years to researchers such as Edward Thorndike, Ivan Pavlov, and Burrhus Skinner. Thorndike (1898) investigated the associative processes within cats and chicken which after a while randomly triggered one of several levers to escape from a box to receive food as reward. After multiple trials, the animals learn the association between the correct lever and the opening of the box. He observed that the associative learning behavior of these animals could be conceptualized into three general learning principles. The first learning principle was the law of readiness which states that multiple responses are combined to achieve a target goal. Second, he proposed the law of exercise in which the repetition of a learning task is assumed to increase the learning strength. Third, Thorndike postulated the law of effect, being the most important principal. According to the law of effect, the consequence of an action strengthens the action and therefore has an influence on subsequent actions (Postman, 1947). Another learning principle, classical conditioning, was established by Ivan Pavlov in 1927 based on the observation of dogs. In classical conditioning, the pairing of an unconditioned stimulus (e.g., food), that evokes an unconditioned, automatic response (e.g., salivation) with a neutral stimulus (such as a sound) that thereby transforms into a conditioned stimulus, leads to a conditioned response (e.g., salivation) to the conditioned stimulus in the absence of the unconditioned stimulus (Pavlov, 2010). Importantly, the association strength between the conditioned and unconditioned stimulus was formalized by Rescorla and Wagner (1972) in a model that explained both, the acquisition and extinction of learning associations. The change in association strength between a conditioned together with an unconditioned stimulus across a number of conditioning trials can be calculated via the model.

Both the law of effect and classical conditioning have led to the theory of operant conditioning in which not only the association (strength) between stimulus and response but also the consequence of an action was considered to have an impact on the behavior (Skinner, 1938). Skinner (1938) added the consequence to the former, purely associative learning principle extending it to a stimulus-response-consequence design. The consequence influences the probability of an action in which a positive consequence (reward) increases the likelihood of an action to be repeated whereas a negative consequence (punishment) decreases the likelihood. In addition, the removal of positive consequences of behavior (negative punishment) also decreases the likelihood of the action to happen while the removal of negative consequences (negative reinforcement) increases the likelihood again. Besides, the principal of extinction refers to the absence of the previously reinforced stimulus leading to the absence of the respective action. Operant conditioning still influences todays modelling approaches of behavior in the field of reinforcement learning (Sutton, 1988; Sutton & Barto, 2018).

1.7.2 Reinforcement learning and the dopaminergic system

Reinforcement learning has not only been used to model behavior (Sutton & Barto, 2018) but also to understand the neurophysiological underpinnings of learning and decision making in the brain (Niv, 2009). Within the brains neurocircuitry, the neurotransmitter dopamine (DA) plays a pivotal role in reinforcement learning including reward prediction error (RPE) processing (Schultz, 1998; Schultz et al., 1993). DA is produced in the substantia nigra (SN) pars compacta which has strong projections to the basal ganglia including the striatum which is the main output structure within the basal ganglia (Delgado, 2007). The striatum can be distinguished into a ventral part containing the nucleus accumbens and a dorsal part containing the caudate nucleus and putamen (Floresco, 2015). Both parts receive phasic dopaminergic input from the SN pars compacta, but the ventral striatum is assumed to be more strongly involved in motivational and reward prediction processes, whereas the dorsal striatum is more involved in motor and cognitive control (O'Doherty et al., 2004; Ullsperger, Danielmeier, & Jocham, 2014). However, it was also shown that particularly the dorsal striatum (bilateral caudate nucleus) differentiated between wins and losses in the human brain using fMRI in a feedback-based learning task (Delgado et al., 2000) challenging the functional dissociation of the ventral and dorsal striatum. In addition, when the basal ganglia were lesioned (Bellebaum et al., 2008), reward-based learning was shown to be altered in terms of deficits in reversal learning. Reversal learning describes the ability of initially learning a stimulus-response association by a specific rule that has to be learned from performance feedback and the reversal of this rule leading to e.g., another response option or stimulus to be now the correct choice. These deficits appeared to be more pronounced when the dorsal striatum was affected compared to other lesion locations. In addition, patients with lesions in the basal ganglia needed

more time to learn a second task than the controls, suggesting a general deficit caused by the damage. These results support the notion that the dorsal part of the striatum is important for learning from rewards (Balleine et al., 2007).

Interestingly, most dopaminergic neurons in the midbrain were identified to show phasic activation when rewards were presented (Schultz et al., 1993) and changes in the dopaminergic activity changes according to the generated reward predictions and outcomes (Pan et al., 2021; Schultz et al., 1993). In a pioneering study, Schultz et al. (1993) observed stronger dopaminergic activity in the stage of learning in macaque monkeys using three different tasks. In contrast, the activity was reduced when the correct action associations were already learned and therefore established. In addition, the dopaminergic activity was found to start with the presentation of the reward and not with the action to receive the reward. These findings of reward sensitivity during learning were investigated in DA neurons within the SN pars compacta and ventral tegmental area (VTA) in macaque monkeys. They showed stronger activation during the learning of pairs of novel pictures in both regions when rewards were unexpected (Hollerman & Schultz, 1998). Interestingly, the timing of the reward, besides the mere presentation, had an influence on the dopaminergic activity. DA neurons were also active when the reward was presented at an unpredicted time. Thus, when an action outcome was better than expected (positive RPE), dopaminergic activity increased, but when predictions matched with the outcome (no RPE), the dopaminergic neurons did not show any activation. However, when the reward was worse than expected (negative RPE), dopaminergic activity was reduced (Schultz, 1998; Schultz et al., 1998). In addition, GABA neurons located in the VTA were shown to directly influence DA neurons activity during reinforcement learning and reward expectation in mice by selective excitation and inhibition (Eshel et al., 2015).

Moreover, dopaminergic projections from the SN pars compacta were not only shown to affect the striatum and the VTA, but also influence other areas of the brain such as the amygdala (Costa et al., 2016; Gottfried et al., 2003), medial PFC including the ventromedial PFC and ACC (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004), the anterior insula (O'Doherty et al., 2003), the hippocampus (Foerde & Shohamy, 2011; Stachenfeld et al., 2017), and the orbitofrontal cortex (OFC: Costa et al., 2016; Rushworth et al., 2011; Sescousse et al., 2010), identifying these regions as relevant for RPE processing. In detail, the amygdala has been shown to be involved in the valuation process of sensory information such as the pleasantness of emotional stimuli, and lesioning the amygdala in macaques resulted in decreased learning from positive feedback (Costa et al., 2016). This observation was also recently shown to strongly depend on the learning environment (Taswell et al., 2023). Moreover, the context of rewards and predicting long-term rewards were both associated with hippocampal involvement (Stachenfeld et al., 2017).

Interestingly, direct projections from the deep cerebellar nuclei towards the hippocampus through the ventrolateral and dorsolateral thalamus were found in mice (Bohne et al., 2019), emphasizing a close exchange of information between the cerebellum and the hippocampus. In addition, the medial PFC and the medial OFC have been identified to encode the value of an outcome when a response was made measuring the BOLD signal. This activation also correlated with the value of the chosen reward. In contrast, the anterior parts of the PFC and ACC coded the value of response options that were not chosen (Rushworth et al., 2011).

1.7.3 Reinforcement learning, error processing, and the ACC

The ACC was identified to be an important neuronal structure for many different cognitive functions such as problem solving, error detection, and adaptive response as well as affective functions such as emotional self-control (Allman et al., 2001). The ACC has many projections to other brain regions that contribute to the different functions like the amygdala within the limbic system and motor nuclei in the brain stem. According to its functions, the ACC was subdivided into a dorsal cognitive (anterior) and a rostral-ventral affective (posterior) part (Bush et al., 2000). Therefore, damage to the anterior or posterior part of the ACC can cause different pathologies such as anxiety disorders and major depression when the posterior part is altered (Drevets et al., 2008) and worse performance in cognitive tasks when the anterior part is damaged (Di Pellegrino et al., 2007). Bilateral lesions of the ACC were also linked to akinetic mutism, a condition in which patients do not move nor speak but are awake (Devinsky et al., 1995). The ACC consists of so-called spindle cells that were only found in humans and apes, which led to the conclusion that this part of the brain just recently developed during evolution and is of great importance for higher cognitive functions (Allman et al., 2001).

The diverse functions of the ACC were brought together into a framework of error monitoring and reinforcement learning by Holroyd and Coles (2002). Holroyd and Coles proposed in their reinforcement learning theory (RL-theory) that the basal ganglia constantly change the phasic dopaminergic activity according to sensory input. This modulated mesencephalic dopaminergic activity can be seen as a temporal difference (TD) signal which serves as an input to the ACC and can be described using reinforcement learning models (Sutton & Barto, 2018). Positive TD are associated with outcomes that are better than predicted and negative TD are associated with outcomes worse than predicted, based on the previously described mechanisms of DA in the study of Schultz (1998). Hence, errors led to a decrease of the phasic mesencephalic dopaminergic activity whereas correct responses result in an increase in activity. Within the RL-theory, the basal ganglia can receive additional feedback input by the limbic system as well as input via efference copies and the response output from the spinal cord. The ACC itself serves as a detector which

receives input via different controllers such as the amygdala and OFC that changed their activity according to sensory input and additional dopaminergic input via the basal ganglia. The ACC learns from all of these signals and decides based on the TD error which response output and therefore motor command is necessary for the optimal decision.

This mechanism of the ACC was underlined by neuronal evidence measuring EEG. EEG allows to measure the continuous electrical activity in the brain using electrodes positioned at the surface of the scalp. Using this approach, it was possible to identify specific event-related potentials (ERP) in the brain's electrical activity that were sensitive to conducting errors during tasks. The discovered error-related negativity (ERN/Ne: Falkenstein et al., 1991; Gehring et al., 1993) is a negative deflection in the EEG signal that has a frontocentral scalp distribution and occurs within the time window of 0 - 100 ms after the execution of an erroneous response. Using localization techniques, the primary source of the ERN was found to be within the ACC (Dehaene et al., 1994; Herrmann et al., 2004; Hochman et al., 2009). It is assumed that the depolarization of layer V neurons within the ACC contribute to the ERN in the EEG signal (Holroyd & Coles, 2002). Therefore, according to the RL-theory, the ERN is only present when the ACC receives TD error input from the basal ganglia as a negative reinforcement signal that disinhibits the apical dendrites of the motor neurons within the ACC (Holroyd & Coles, 2002). The input from the motor controllers (containing the information about the response made) towards the ACC and the adjustment of the ACC according to the TD signal is also assumed to be the reason why the ERN peaks after the response execution. Thus, in line with the RL-theory, the ERN is the result of the error detection and TD error affecting the ACC's activity in evaluating the action outcome prediction (Holroyd & Coles, 2002).

A different perspective on the function of the ERN is provided by the conflict monitoring theory (Botvinick et al., 2001; Botvinick et al., 2004; Carter et al., 1998; Yeung et al., 2004). Here, the conflict between response options is seen to produce the ERN and the magnitude of conflict modulates the ERN amplitude (Danielmeier et al., 2009). Therefore, higher conflict leads to a subsequently higher ERN amplitude. Hajcak, Moser, et al. (2005) observed that the significance of the error also had an impact on the magnitude of the ERN. Support for the conflict monitoring theory was provided by similar activity observed in correct trials (termed correct-related negativity: CRN, Vidal et al., 2000), where conflicts also led to a smaller but present negative amplitude when correct response were made (Gehring et al., 2018). In addition, activation patterns were found in the dorsolateral PFC that is involved in top-down control and assumed to reduce the conflict signal after being monitored by the ACC (Carter & van Veen, 2007). In addition, information on the conflict signal caused by competing options is conveyed to other regions such as the lateral PFC (Carter & van Veen, 2007; Jocham et al., 2009).

The posterior medial frontal cortex (MFC) and rostral cingulate zone are assumed to generate the ERN including another ERP component called the N2 (also N200 or Nogo-N2: Folstein & van Petten, 2008; Jonkman et al., 2007). The N2 is another indicator for response conflict, response inhibition, and the processing of errors, manifesting as a frontocentral negative deflection peaking around 250 - 350 ms after stimulus onset (Folstein & van Petten, 2008). The N2 is found in tasks where responses have to be suppressed (like Go/Nogo tasks) and has been shown to be more pronounced in Nogo compared to Go trials (Nieuwenhuis et al., 2003).

Following the ERN in the response-locked signal, a positive deflection was found with a parietal distribution in the range between 200 - 400 ms after response onset (Olvet & Hajcak, 2009) and termed the error positivity (Pe[1]: Falkenstein et al., 2000). The Pe is associated with error awareness and salience (Falkenstein et al., 2000; Nieuwenhuis et al., 2001). Therefore, the ERN and Pe in the response-locked signal and the N2 in the stimulus-locked signal are seen as important indicators of error processing. However, it is still not clear whether the ERN only reflects error detection, as proposed by the RL-theory, or whether it functions as a general indicator for conflict monitoring and error processing.

Besides their findings on the previously known response-locked ERN, Miltner et al. (1997) discovered a negative deflection after the presentation of task-related performance feedback, later termed as the feedback-related negativity (FRN: Miltner et al., 1997; Nieuwenhuis et al., 2004; also called the reward positivity: RewP, Proudfit, 2015). The FRN peaks around 200 - 350 ms after feedback onset, has a frontocentral scalp distribution, and is assumed to reflect RPE processing (Gehring & Willoughby, 2002; Holroyd & Coles, 2002). The FRN has similar roots as the ERN and is thought to emerge from the neuronal activity within the ACC (Foti et al., 2015; Hauser et al., 2014; Holroyd & Coles, 2002). However, there are also studies that found activation of the FRN within the posterior cingulate cortex, superior frontal gyrus, and striatum (Foti et al., 2011; Nieuwenhuis et al., 2005). The FRN is considered to be produced by the phasic activity of midbrain dopaminergic neurons projecting on the dorsal ACC, causing disinhibition of the ACC when phasic activity decreases and inhibition of the ACC when phasic activity increases.

The FRN can be calculated as the difference between positive and negative feedback (Hauser et al., 2014). According to the RL-theory (Holroyd & Coles, 2002), the FRN is assumed to reflect the RPE as violation of the predicted feedback outcome. Therefore, the expectation is closely tied to the valence of the outcome (as positive or negative feedback) which has also been shown to

[1] Pe with a lowercase “e” is the error positivity and PE with a capital “E” is the Prediction error

have an impact on the FRN (Gehring & Willoughby, 2002; Hajcak, Holroyd, et al., 2005; Hajcak et al., 2007). When the outcomes are worse than expected, the FRN has a stronger negative amplitude than when the predictions are better than expected. The FRN was shown to be sensitive to reward expectation (Bellebaum et al., 2008; Bismark et al., 2013; Cohen et al., 2007; Weismüller & Bellebaum, 2016), violations of expectations (Bellebaum et al., 2010), outcome valence (Hajcak et al., 2006; Zhou et al., 2010), the timing of the feedback presentation (Arbel et al., 2017; Foerde & Shohamy, 2011; S. Kim & Arbel, 2019; Peterburs et al., 2016), agency (Burnside et al., 2019), and also affected in tasks where feedback was not contingent to the performance (Oliveira et al., 2007).

Besides the violation of a reward predictions formalized as signed expectations, i.e., the valence of the feedback, an unsigned expectation reflecting mere salience (or surprise: Hayden et al., 2011) was observed in the activity of midbrain DA neurons (Bromberg-Martin et al., 2010). This led to the idea that the FRN might only reflect the violation of the expectation as an unsigned PE and not encode valence (signed PE) which resulted in the prediction of response–outcome (PRO) model (Alexander & Brown, 2011). In this model, the dorsal medial PFC predicts actions and outcomes and monitors possible combinations of both. The predicted response and outcome pairs are evaluated regarding the probability of their appearance and enable response-outcome learning independent of valence. Alexander and Brown (2011) also linked their model to the forward and inverse model in the motor domain (Wolpert et al., 1998) in which each model learns to predict the optimal outcome for a given action. Learning these predictions is assumed to take place in individual neurons that generate activity reflecting all the possible action outcomes. If the sensory input reflects one of the predictions as correct, the other, incorrect prediction is suppressed, so that the activity is strongest when an expected outcome turns out to be incorrect. On the one hand, evidence was found that supports the PRO model regarding unsigned PEs (Hauser et al., 2014; Talmi et al., 2013), on the other hand, a meta-analysis on RPE processing demonstrated evidence for a signed PE (Sambrook & Goslin, 2015). Thus, the different theories on the FRN are still debated.

1.8 Executive functions and the cerebellum

The flexibility of humans to adapt their behavior to new situations involves different learning principles as mentioned before (associative and reinforcement learning) and also complex interactions within the neurocircuitry of the brain to monitor motor and non-motor functions. A concept that describes the adaptive mechanisms behind behavior as an overarching executive function is performance monitoring (Seifert et al., 2011; Ullsperger & Cramon, 2001; Ullsperger, Danielmeier, & Jocham, 2014; Ullsperger, Fischer, et al., 2014). Performance monitoring, in a

nutshell, describes the goal-directed process to adapt and optimize behavior using available information about the internal process (e.g., efference copies) and the external world. This performance related information can also be termed feedback. Combining forward and reinforcement learning principles, Ullsperger, Danielmeier, and Jocham (2014) conceptualized performance monitoring using neuroanatomical and neurophysiological evidence to establish a network model that covers multiple brain regions involved in the process of learning. For example, this network model encompasses the posterior MFC which is assumed to update action values, the ventromedial PFC which realizes the value comparison, the OFC which monitors outcomes, the anterior insula responsible for effort and conscious awareness, the frontal operculum involved in attentional control, the basal ganglia for reward-based learning (including response selection, facilitation, and inhibition) and, importantly, the cerebellum for salience, arousal and RPE processing as well as motor integration (Ullsperger, Danielmeier, & Jocham, 2014). Adding the cerebellum to this network composition underlined the close interaction of the cerebellum with many other regions of the brain that are engaged in reinforcement learning. However, this concept of performance monitoring still lacked the view on the cerebellum's capability of generating internal models to non-motor functions (Ito, 2008).

Bostan and Strick (2018) described in detail the close interaction between the basal ganglia and the cerebellum. They highlighted that the dentate nucleus projects on the striatum (putamen) and that the subthalamic nucleus located in the basal ganglia projects in a disynaptic fashion on the cerebellar cortex. Importantly, to investigate the cerebellar output towards the basal ganglia, different regions of the cerebellum were marked using virus tracing in monkeys that were associated with both motor (anterior) and non-motor (posterolateral) regions (Stoodley, 2012; Stoodley & Schmahmann, 2009) and both revealed projections to the subthalamic nucleus. In addition, they integrated new findings on the granule cells that were identified to also reflect RPE signals on the cellular level (Wagner et al., 2017). These cellular findings were underlined by research of Kostadinov et al. (2019) who identified reward sensitivity within the climbing fibers activity on the Purkinje cells, extending the previously believed role of spiking activity in the cerebellar cells to reinforcement/ reward-based learning principles. In a very recent review on reward-based learning, Kostadinov and Häusser (2022) summarized findings on simple spiking of Purkinje cells in monkeys that were associated with visuomotor associations and sensitive to the correctness of the outcome (Sendhilnathan et al., 2020). In addition, they discussed evidence of reward processing within the cerebellar nuclei (Chabrol et al., 2019). Thus, reward signals are likely processed in different cells and fibers within the cerebellar microzones and can therefore serve as a plausible neurofunctional correlate for the idea of internal models for cognitive, non-motor functions (Ito, 2008).

1.8.1 Associative learning, emotions, and the cerebellum

Furthermore, evidence on the non-motor (cognitive) functions of the cerebellum and the cerebellum's involvement in learning becomes clearer when looking back at the fundamental learning principles. Evidence in humans showed that the cerebellum is involved in classical conditioning and associative learning for motor functions using eye-blink conditioning (Daum, Schugens, et al., 1993). Patients with cerebellar lesions demonstrated impaired conditioned responses and altered learning acquisition. In addition, in non-motor associative learning (Timmann et al., 2002), patients with cerebellar degeneration revealed altered learning behavior that could not be explained by the motor execution or allocation of attention during the task. Additionally, patients with cerebellar degeneration demonstrated impaired conditioned responses pointing towards altered associative learning (Thieme et al., 2013). Moreover, using eye-blink conditioning (Gerwig et al., 2007), a strong relation between the cerebellum and fear learning was identified, coupling the limbic system and in particular the amygdala and hippocampus as core regions for fear learning and extinction to the functions of the cerebellum. Along these lines, research focusing on the cerebellum in emotion (Adamaszek et al., 2017) and social cognition (van Overwalle et al., 2020) underlined that the cerebellum is involved in these functions. For example, impairments were present in patients with cerebellar lesions toward the processing of negative emotions (Lupo et al., 2015). In addition, significant activation during the emotional perception was identified in healthy participants within the posterior lobe of the cerebellum using fMRI (Scheuerecker et al., 2007). Also, in another fMRI study, the primary emotions were demonstrated to be all distributed in distinct zones of activation within the lobules VI-IX of the cerebellum (O. Baumann & Mattingley, 2012). Beyond this, the cerebellum was proposed to contribute to mentalizing (van Overwalle et al., 2015; van Overwalle et al., 2019) such as theory of mind and social action sequence learning (Heleven et al., 2019). In a meta-analysis, the emotional self-cognition and mentalizing process were identified to be strongly linked to Crus II of the cerebellum (van Overwalle et al., 2020). Thus, the cerebellum's topographical constitution and connections to other brain regions (Stoodley & Schmahmann, 2010) strongly link it to cognitive and also affective associative learning (Timmann et al., 2010).

1.8.2 Performance monitoring and the cerebellum

Peterburs and Desmond (2016) proposed that performance monitoring consists of a composition of domain independent cognitive and affective functions that together enable behavioral adaptation through the contribution of the cerebellum. In line with reinforcement learning, they suggest that performance-related feedback is essential to adapt to new situations by activating multiple resources such as attention allocation and emotional regulation. Based upon the forward

model of cognition (Wolpert et al., 1998) and findings on the interplay between the cerebellum and cerebral regions (Middleton & Strick, 2001; Palesi et al., 2017), they assumed that successful behavioral adaption in dynamic situations relies on two stages. First, the decision to conduct an action and second, the outcome of the action that has to be evaluated to subsequently learn from it for decision-making processes in the future. Therefore, performance has to be constantly monitored and future outcomes predicted, to minimize actions that are not beneficial. The stage of receiving feedback is crucial because it is the information source to evaluate the predictions against the actual outcomes to enable learning. Therefore, adapting one's own actions based on feedback information is a continuous process. For example, standing in front the previously mentioned restaurant with a friend and realizing that the prices in the menu increased and are higher than expected, might lead to the decision to look for an alternative restaurant in the future. Peterburs and Desmond (2016) assumed that the cerebellum is involved in sensory prediction, feedback processing, error processing, response inhibition, and articulatory monitoring encompassing work on verbal working memory (Desmond et al., 1997). To support this categorization of the abovementioned subdomains of performance monitoring, they discussed several studies that discovered altered behavioral, electrophysiological, and imaging data in patients suffering from different cerebellar diseases as well as studies using NIBS in healthy participants. First, verbal working memory deficits (Desmond & Fiez, 1998; Peterburs et al., 2010; Ravizza et al., 2006) and temporary induced alterations in verbal working memory were found in in patients with cerebellar damage using TMS on the cerebellum (Desmond et al., 2005). When the right superior cerebellum was stimulated, response times during a verbal working memory task increased (Desmond et al., 2005). In addition, applying TMS on the cerebellum also revealed a disruption of phonological predictions (Sheu et al., 2019). Second, a study by Ide and Li (2011) found evidence during a stop signal task where participants had to press a button during Go trials and to suppress a response during Nogo trials which were indicated by different stimuli. Activation was not only observed in the dorsal ACC and ventrolateral PFC as suggested in the theories on cognitive control and error detection (Blasi et al., 2006; Botvinick et al., 2001) but in the SMA, Pons, medial thalamus and cerebellum analyzing the functional relationship between different brain regions. Post-error slowing, an effect that goes along with an increase in response time after the execution of an erroneous response in the behavioral data, correlated with the cerebellar activity and underlined that the cerebellum is involved in cognitive control. Third, alterations of ERP components in the EEG signal when errors were made such as the ERN and CRN were found in patients with a diseased cerebellum (Peterburs et al., 2012; Peterburs et al., 2018; Peterburs et al., 2015; Rustemeier et al., 2016; Tunc et al., 2019). In addition, evidence from an imaging study underlined that the posterolateral regions of the cerebellum and in particular Crus I and Crus II were associated with error processing as indicated by a volume

reduction of gray matter (Peterburs et al., 2015). Fourth, feedback-based learning was investigated in patients with cerebellar lesions using a probabilistic reversal learning task (Rustemeier et al., 2016). Results did not reveal a difference in the behavioral performance between both groups, but the patients revealed higher FRN and P300 amplitudes after negative compared to positive feedback which did not differ in the control group. In sum, these findings all suggest that the cerebellum is engaged in error processing and learning from external feedback and that damage of the cerebellum results in changes in performance monitoring.

2 Research goal of the dissertation

The overarching goal of this dissertation was to investigate the contribution of the cerebellum to performance monitoring indicated by reinforcement learning and error processing. To achieve this, three different studies were conducted using a broad range of methods. The first study included a systematic review on literature. The second study used a Go/Nogo Flanker task combined with EEG and TMS in healthy controls to study error processing. The third study comprised a probabilistic feedback-based learning task while measuring EEG and separate MRI data acquisition in patients with cerebellar degeneration and matched healthy controls to characterize the cerebellum's contribution to reinforcement learning and RPE coding.

Study 1:

In the first study, a systematic review on the cerebellum's contribution to feedback-based learning was conducted according to the PRISMA statement and guidelines (Page et al., 2021). The rationale of this review was grounded on the need for a brief and cohesive overview of study results that investigated feedback-based learning and also provided information on the cerebellum in healthy and diseased participants. Using an extensive PubMed search, suitable manuscripts were searched, filtered, and analyzed to identify possible overlaps in behavioral deficits in patients suffering from different cerebellar diseases. In addition, alterations in ERP components and functional imaging data during feedback-based learning in healthy participants were identified. Studies that did not focus on the cerebellum but still identified cerebellar regions to be activated in the process of feedback learning were included and discussed.

Study 2:

The second study was an experimental study that investigated contributions of the cerebellum to error processing in healthy adults by using a Go/Nogo Flanker task while measuring EEG, and coregistering it to spTMS. The idea behind this study was based upon the observation of altered error processing in patients suffering from cerebellar diseases (Peterburs et al., 2012; Peterburs et

al., 2018; Peterburs et al., 2015; Tunc et al., 2019). We wanted to stimulate the cerebellum to induce temporary "virtual lesions" and to disrupt cerebellar processes. Besides we stimulated the vertex region as a control site in a separate session. Further, we wanted to elucidate at which stage during performance monitoring the cerebellum contributes to error processing by stimulating the cerebellum at specific time points in each trial of the Go/Nogo Flanker task. Therefore, this study investigated particularly the temporal aspects of cerebellar contributions to the processing of performance errors.

Study 3:

The third study, also an experimental study, shed light on the involvement of the cerebellum in RL and RPE coding in patients with cerebellar degeneration. Patients conducted a probabilistic feedback-based learning task (Bellebaum & Colosio, 2014; Eppinger et al., 2008) while EEG was continuously measured. This task allowed RL which we modelled to investigate the relationships between possible deficits in behavioral performance such as accuracy and choice switching and altered neural response patterns in the EEG in terms of ERP components. In addition, we quantified the extent of the cerebellar damage based on structural MRI (Peterburs et al., 2015). Feedback presentation was manipulated as a within-subject factor, and we assumed that the cerebellum could be equally or differently involved in learning from and processing of immediate (500 ms) vs. delayed feedback (6500 ms).

3 Study 1: The role of the human cerebellum for learning from and processing of external feedback in non-motor learning: a systematic review

3.1 Introduction

The cerebellum has undergone a paradigm shift from a brain structure seen as exclusively involved in sensorimotor control and timing (Bareš et al., 2019; Ivry & Spencer, 2004; Johnson et al., 2019) towards a region that also contributes to many cognitive and affective processes (Leiner et al., 1991; Schmahmann, 2019; Timmann et al., 2010). Studies in patients with cerebellar damage revealed multiple cognitive deficits besides the various motor impairments such as gait ataxia and dysarthria (Schmahmann, 2019). Many consensus reviews dedicated to the roles of the cerebellum in cognitive and affective domains highlighted its vast and manyfold contribution to human behavior (Adamaszek et al., 2017; Keren-Happuch et al., 2014; Mariën et al., 2013; van Overwalle et al., 2020).

A general model to understand the cerebellum's interaction with other brain regions is the forward model of cognition (Sokolov et al., 2017; Wolpert et al., 1998). The cerebellum is assumed to generate internal models that enable behavioral adaptation encompassing different internal (efference copies of motor commands) and external (e.g., visual) representations which are updated by the cerebellum and exchanged in close interaction with cerebral regions. A key cognitive function is performance monitoring which puts the processing of errors and learning from performance-related feedback, among other cognitive and affective functions, into the focus (Peterburs & Desmond, 2016). In accordance with the forward model of cognition, the cerebellum is seen to update predictions of possible outcomes by matching these predictions to information on the actual outcome to improve future predictions. These internal models as a representation of predictions are sent to higher cerebral areas via cerebello-thalamo-cerebral pathways that were identified to enable this information exchange (Bostan & Strick, 2018; Middleton & Strick, 1994; Strick et al., 2009).

Research of the last decades investigated feedback-based learning in many different tasks in the healthy and the diseased brain. In addition, cognitive functions such as verbal-working memory and other neuropsychological deficits were thoroughly investigated in patients with cerebellar diseases (Peterburs et al., 2021). However, only a few studies shed light on the cerebellum's role in performance monitoring, looking at feedback-based learning in patients with different cerebellar diseases (Peterburs et al., 2018; Rustemeier et al., 2016). Thus, a clear research line

focusing on the cerebellum in feedback-based learning is still missing. To underline the role of the cerebellum for performance monitoring as suggested by Peterburs and Desmond (2016), this review aimed to provide an extensive overview of the literature on studies using feedback-based learning tasks and providing results on the cerebellar contribution at the same time. To achieve this, studies with cerebellar results from task-based imaging studies including MRI and positron emission tomography (PET) and electrophysiological recording using EEG and NIBS to manipulate learning from feedback in patients with different cerebellar diseases and healthy participants were searched. Tasks such as the Wisconsin Card Sorting test (WCST), probabilistic learning tasks including reversal learning (Linke et al., 2010; Peterburs et al., 2018) etc. were reviewed and the different stages during feedback-based learning including the expectation and outcome stages were discussed. To enable a precise categorization of the different findings, the terminologies used across the different studies were used to develop a general taxonomy.

According to the hypotheses, it was expected that feedback-based learning in patients with cerebellar degeneration was altered compared to patients with focal vascular lesions and healthy participants. Second, altered EEG activity was expected in patients with cerebellar degeneration compared to healthy controls during feedback-based learning. Third, we expected to find activation in the cerebellum during feedback-processing especially in posterolateral regions (Stoodley & Schmahmann, 2009). Fourth, we expected NIBS of the cerebellum to alter feedback-based learning and processing in healthy participants. The study was preregistered on the Open Science Framework (OSF: osf.io/2vfg8).

3.2 Method

Studies were searched according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA: Page et al., 2021). In addition, studies were checked for eligibility using the Patient, Intervention, Comparison, Outcome framework (PICO: Schardt et al., 2007) and additional criteria were checked such as a focus on non-motor cerebellar functions, peer-reviews, availability in English etc. The PubMed Database was used as a source and search terms were created using a building block approach. In addition, studies that were known to be relevant but were not found using this approach were added to the abstract screening. In total, 1057 articles were identified using the PubMed search and 21 articles were added from other sources leading to 1078 abstracts that were screened. Abstracts were screened by two independent reviewers using a standardized screening tool to check the eligibility of the respective abstract and using the Abstrackr text-mining tool to navigate through the abstracts as well as to rate them (Wallace et al., 2012). In addition, the screening tool was modified to screen the promising full-text articles after the initial abstract screening. In the case of discrepancies between

the two reviewers, a third and fourth reviewer were involved in the screening process. In addition, the reliability between the ratings of the independent reviewers were calculated using weighted Kappa and the percentage of excluded studies (Fleiss & Cohen, 1973). The weighted Kappa after screening all abstracts was moderately high and the percentage of agreement was very high (Landis & Koch, 1977). After finishing the screening of the abstracts, leading to 62 eligible articles, 36 studies survived the full-text screening. The relevant data were subsequently extracted using an extraction tool to systemize this step. The extracted results were compared between reviewers to identify any missing details and synthesized according to the hypotheses. The risk of bias for each study was assessed checking the methodological quality and statistical analyses and their plausibility. The data were grouped according to patient and non-patient studies covering the different physiological measurements and were discussed separately. No study was identified using NIBS to stimulate the cerebellum during feedback-based learning.

3.3 Results and discussion

Among the initial 1078 abstracts, 36 studies were included, among these eleven patient studies including seven studies with chronic cerebellar lesions, two with cerebellar degeneration, one study with neurosurgical resection of tumors, and one study with different cerebellar diseases. All remaining non-patient studies were imaging studies encompassing 22 fMRI and three PET studies.

The different studies provided heterogeneous results on the performance in different feedback-based learning tasks. Five patient studies, representing in total 67 patients, provided results indicating impaired performance in feedback-learning in cerebellar patients compared to healthy controls (Drepper et al., 1999; Mak et al., 2016; Manes et al., 2009; Mukhopadhyay et al., 2008; Tucker et al., 1996). Two patient studies provided mixed results (Schmahmann & Sherman, 1998; Thoma et al., 2008), four studies covering 36 patients in the WCST (Dirnberger et al., 2010; Gottwald et al., 2004; Turner et al., 2007) and twelve patients in probabilistic feedback-based learning did not demonstrate any significant differences (Rustemeier et al., 2016). Nevertheless, Rustemeier et al. (2016) discovered a more negative FRN and P300 amplitude for negative compared to positive feedback in patients only. The effect was driven by an altered processing of positive feedback in patients. In contrast, Thoma et al. (2008) found deficits in reversal learning in patients with cerebellar stroke as well as more trials to exceed a learning criterion among classified learners within an additional learning task. The neuroimaging results covered a total of 561 healthy participants with heterogenous setups and a variety of feedback-based learning tasks including seven studies using probabilistic and reversal learning (194 participants), three studies using a monetary incentive delay task (40 participants), three studies applying non-motor

associative learning (35 participants), and five studies using different card sorting tasks (116 participants). Additionally, one study examined participants with a Markov decision task (20 participants), one used a motion prediction task (25 participants), and one used a version of the Eriksen Flanker task (16 participants). One study analyzed the functional connectivity associated with feedback learning (Edde et al., 2020). All available coordinates of significant activation within the cerebellum were manually labelled into a schematic flat map of the cerebellum that provides an unfolded overview of the cerebellar macro anatomy (Diedrichsen & Zotow, 2015).

More than half of the imaging studies (n = 14) reported bilateral activation of the cerebellum in many different regions during feedback-based learning (Balsters et al., 2013; Bellebaum et al., 2012; Berman et al., 1995; Bischoff-Grethe et al., 2009; Bjork & Hommer, 2007; Gablentz et al., 2015; Jackson et al., 2020; Kobza & Bellebaum, 2015; Lam et al., 2013; Lie et al., 2006; Nagahama et al., 1996; Shao et al., 2016; Tricomi & Fiez, 2008). Moreover, one study (Edde et al., 2020) analyzing the resting state functional connectivity (rsFC) before and after completion of a feedback-based learning task demonstrated an influence of age on the cerebellar rsFC. In addition, unilateral cerebellar activation was found in five studies for the left cerebellum (Greening et al., 2011; Linke et al., 2010; Peterburs et al., 2018; Remijnse et al., 2005; Tanaka et al., 2004) and in two studies for the right hemisphere (Balsters & Ramnani, 2011; Marco-Pallarés et al., 2007). Last, in three studies, a restricted contribution of the vermis was found during feedback-based learning (Knutson et al., 2001; Knutson et al., 2003; Späti et al., 2014). The reviewed studies highlighted a strong contribution of the cerebellum to feedback-based learning at different stages and across many tasks.

The results on the different patient samples were heterogenous and the sample sizes in the individual studies quite small which made it difficult to directly draw conclusion from the cerebellar damage towards the behavioral performance. In addition, the interval between disease onset and the measurements varied greatly, contributing to more variance in the patient sample. The lack of different patient studies using EEG to measure the neuronal activity during the performance in feedback-based learning task also made it difficult to confirm or generalize the results reported by Rustemeier et al. (2016). Nevertheless, the ERP results were interpreted to hint towards neuronal reorganization process in cerebellar stroke patients that compensate for behavioral deficits which was shown in studies looking at other stroke events and ERPs (Dejanović et al., 2015; Salvo et al., 2020).

Manipulation of feedback magnitude (Knutson et al., 2001; Knutson et al., 2003) as well as valence (Marco-Pallarés et al., 2007; Peterburs et al., 2018) and informational content (Bischoff-Grethe et al., 2009) have shown to differently activate the cerebellum. In addition, cerebellar

activation was found when predicting outcomes (Shao et al., 2016) and processing of RPEs in different studies (Gablentz et al., 2015; Greening et al., 2011; Linke et al., 2010; Remijnse et al., 2005). Also, immediate vs. future reward prediction was reflected different cerebellar activity during a decision task including feedback (Tanaka et al., 2004). Agency, i.e. whether choices were computer or self-generated, showed different cerebellar activation patterns (Shao et al., 2016). By using a search strategy, we probably did not cover studies that may have described cerebellar findings in the running text that were mentioned neither in the title nor in the abstract. In addition, we did not describe studies that found no findings in the cerebellum during feedback-based learning (Sescousse et al., 2013; Silverman et al., 2015). A problem is that many studies did not conduct whole-brain recordings using MRI or only focused on specific regions of interests and therefore neglected the cerebellum (Delgado et al., 2005; Jocham et al., 2009; O'Doherty et al., 2003)

3.4 Conclusion

In sum, the results created a heterogeneous picture of the behavioral performance in different cerebellar diseases. Reasons for this are given by the varying time between the lesion onset in the cerebellum and testing, the age at lesion onset, location of cerebellar damage and type of damage. The limited number of patient studies with cerebellar degeneration and electrophysiological recordings as well as missing studies with interventions using NIBS during feedback-based learning prevent the determination of the cerebellum's exact contribution in learning from performance feedback. The neuroimaging results underlined the involvement of the posterolateral regions of the cerebellum in feedback-based learning aside from many other cerebellar regions (Balsters & Ramnani, 2011; Balsters et al., 2013; Peterburs et al., 2018). More recent results also highlight the cerebellum's involvement during social interaction (Clausi et al., 2019; Stoodley & Tsai, 2021) which also relies on correct prediction generations.

Extended research is necessary to investigate the cerebellum's role in non-motor functions with a specific focus on its contribution to feedback-based learning and other subdomains of performance monitoring. How, where, and when the cerebellum is contributing to RPE processing and to which extent diseases of the cerebellum such as the CCAS affect this processing still remains unclear and needs to be addressed in future experimental research. Performance monitoring seems to describe and integrate old and new findings and thus provides a plausible model of the capacities and functions of the cerebellum (Peterburs & Desmond, 2016) and may ultimately help to improve and find new treatment options targeting cognitive alterations in patients with cerebellar diseases.

4 Study 2: The effect of cerebellar TMS on error processing: A combined single-pulse TMS and ERP Study

4.1 Introduction

The cerebellum contributes to non-motor, cognitive functions (King et al., 2019; Stoodley & Schmahmann, 2009) and an explanation of the complex function of the cerebellum is provided by the forward model of cognition (Sokolov et al., 2017). Cerebellar involvement in the processing of performance errors has been integrated in the model on performance monitoring (Peterburs & Desmond, 2016). Typically, the neuronal activation associated with processing of errors is observed in the EEG as a negative deflection shortly occurring after conducting an error (within 100 ms). This ERN (Falkenstein et al., 1991; Gehring et al., 1993) has a symmetrical frontocentral scalp distribution, typically measured at the electrode FCz (according to the 10:20 system). In detail, the ERN is seen as an neural correlate of error detection and response conflict processing (Botvinick et al., 2001; Yeung et al., 2004) and is generated in the ACC, a neuronal hub for reinforcement learning (Dehaene et al., 1994; Herrmann et al., 2004). Following the ERN, the Pe was observed and described as a positive deflection that appears within the time window of 200 - 400 ms post-response onset also measured at the position FCz (Falkenstein et al., 1995) and reflecting attentional awareness of errors. Studies on patients with cerebellar diseases revealed altered ERN amplitudes (Peterburs et al., 2012; Peterburs et al., 2015; Tunc et al., 2019). The ERN was increased in patients with focal cerebellar lesion (Peterburs et al., 2012) but unaffected in patients with cerebellar degeneration (Peterburs et al., 2015). In addition, only a trend-level effect on the ERN was present in the study by Tunc et al. (2019) for patients compared to controls. The behavioral performance in the abovementioned studies was also not consistently altered and impaired. Research demonstrated that particularly the posterolateral regions of the cerebellum including Crus I and II and the deep cerebellar nuclei are relevant for non-motor functions (King et al., 2019). Hence, depending on the type of disease and location affected, different consequences are expected.

Besides the analysis of patients, the manipulation of brain behavior relationships is possible using TMS, enabling the direct observation of neuronal alterations (Grimaldi et al., 2014; Vaidya et al., 2019). Single-pulse TMS has been used to facilitate and to disrupt brain activity (Pascual-Leone, 1999; Shirota et al., 2012). Importantly, spTMS can be integrated into rapid task-based studies (Verleger et al., 2009). Targeting the cerebellum using spTMS has been conducted in many studies looking at the impact on CBI (Ugawa et al., 1995) or language processing (Desmond et al., 2005; Sheu et al., 2019). In addition, cathodal tDCS on the cerebellum revealed reduced N2

activity and increased false alarms in a Go/Nogo task (Mannarelli et al., 2020). The Nogo-N2 is a stimulus-locked ERP component peaking in the time window between 250 - 300 ms in trials in which the response has to be suppressed (Folstein & van Petten, 2008). Therefore, the Nogo-N2 is seen to be an indicator of response inhibition (Larson & Clayson, 2011) and both, the Nogo-N2 and the ERN are assumed to rely on the same error monitoring system (Ferdinand et al., 2008; Folstein & van Petten, 2008; van Veen & Carter, 2002). Importantly, tDCS and TMS are different NIBS techniques and the results on tDCS are inconsistent, possibly due to poor spatial resolution (Jalali et al., 2017; van Dun et al., 2017) whereas TMS can stimulate more focally and deeper brain regions while having a high temporal resolution (Koponen et al., 2018).

The goal of the present study was to investigate the temporal characteristics of cerebellar contributions to error processing. Therefore, spTMS was applied on the left lateral cerebellum (Hardwick et al., 2014) and an extracerebellar control region (vertex, electrode position Cz, Pizem et al., 2022) in a combined Go/Nogo Flanker Task using a double cone TMS coil. Each participant took part on two different days for cerebellar and vertex stimulation. Both sessions took place separated by at least 48 hours. The task-design was inspired by the study by Verleger et al. (2009) and spTMS stimulation was applied in each trial. The pulses were shifted according to an individual error latency (IEL, i.e., individual ERN peak latency + median error response time) in Go trials which was estimated using a Go/Nogo Flanker pre-task without pulses. The three different time points for stimulation during Nogo trials were set relative to stimulus onset (at stimulus onset, 100 ms and 300 ms post stimulus onset). Focusing on the ERP components ERN and Pe in the response-locked signal, we assumed that the different stimulation timings would differently affect the time course of error processing and might reveal which timing is linked to the cerebellum's input. The Nogo-N2, Nogo-P3 and an exploratory analysis of theta in the time-frequency data were provided in the manuscript's supplemental material.

First, we expected in trials with TMS pulses pre-response increased error rates in Go trials for cerebellar compared to vertex TMS as present in patients with cerebellar degeneration (Peterburs et al., 2015). Second, we expected a decreased ERN amplitude for cerebellar compared to vertex TMS when the pulses were applied early (100 ms and 50 ms before the IEL). Third, an effect of cerebellar spTMS on the Pe was not expected. All other hypotheses regarding the Nogo ERP components and time-frequency domain were discussed in the supplemental material.

4.2 Method

In total, twenty-five young and healthy participants (age range 19-32 years, $M = 24.00$ years, $SD = 3.70$, $n = 13$ females, $n = 12$ right-handed and $n = 1$ ambidextrous) were examined and data

from nine participants were excluded, leading to the final sample of 16 participants. The sample size was based on studies with similar tasks (Danielmeier et al., 2009; Desmond et al., 2005; Panouillères et al., 2012; Sheu et al., 2019). The Go/Nogo Flanker pre-task was used to estimate the IEL and repeated when less than six errors were made (Olvet & Hajcak, 2009; Pontifex et al., 2010). Exclusion criteria were intoxication, neurological or psychiatric diseases, and metal parts in the body. All participants gave written informed consent and received monetary compensation. The hypotheses and procedure were preregistered on OSF (https://osf.io/6v9pa). In addition, the study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and received a positive vote by the Ethics committee of the Faculty of Medicine of Heinrich Heine University Düsseldorf.

4.2.1 Experimental task and procedure

The Go/Nogo Flanker main task consisted of 600 trials with 80 % (480 trials) Go trials and 20 % (120 trials) Nogo trials. In Go trials, 384 trials were congruent, and 96 trials were incongruent trials. At the beginning of each trial, arrow flankers above and below a fixation cross were presented for 200 ms. Subsequently, the fixation cross was replaced by the target arrow pointing towards the same (= congruent) or opposite (= incongruent) direction in Go trials. In Nogo trials a circle appeared indicating no button press. During Go trials, participants had to press the left or right button indicated by the central arrow within the 350 ms (or 400 ms as assessed in the pre-task). Exceeding the time led to a reminder to respond faster. The fixation cross was jittered across trials (900 - 1300 ms). Crucially, participants did not receive performance-related feedback.

A TMS pulse was applied in Go trials at the IEL (0 ms), 100 ms before (-100 ms), 50 ms before (-50 ms), and 50 ms after (+50 ms). For Nogo trials, Nogo pulses were delivered at stimulus onset, 100 ms and 300 ms after stimulus onset. Pulse timings were randomized but presented on equal number per trial type and block. To estimate the cerebellum's input to error processing, the IEL was calculated using the Go/Nogo Flanker pre-task in which no TMS pulses were applied. This task consisted of 120 trials in total, keeping the same ratio as in the main task, and the IEL was calculated by adding the median response time to the latency of the ERN for all conducted error trials. The response time window was changed from 350 to 400 ms if more than 25 % of misses were conducted in Go trials.

Participants conducted the task in front of a laptop using a response box to record responses by pressing the left and right button using only the right hand. Preparation of each participant included applying ear plugs to reduce noise caused by the TMS coil, applying an EEG cap, preparing the electrodes and covering them to avoid any contact with the TMS coil (Hernandez-

Pavon et al., 2014), and attaching electrodes to measure the EMG signal on the left hand. The IMT was measured to determine the output strength of the TMS system looking at MEPs. Following the pre-task without pulses, a task that was part of another study was started. Subsequently, the estimated IEL was used to shift the pulse timings in the main task. A specially designed mounting system kept the distance between the coil and the head constant during the task. The order for both appointments (cerebellar and vertex stimulation) was counterbalanced, with a temporal gap of at least 48 hours. The IMT was measured at both appointments and no difference was found between the appointments nor between the stimulation sites.

4.2.2 Data analysis

On the behavioral level, error rates and response times were measured in Go trials. The ERN and Pe response-locked ERP components were analyzed using the EEG data. The ERN was assessed as the local maximal negative peak in the response-locked error-correct difference wave signal (electrode FCz, Hajcak & Foti, 2008). Similarly, the Pe was quantified in the response-locked difference wave signal as the maximum positive peak between 200 and 400 ms at electrode Pz (Larson et al., 2010). The original waveforms for error and correct trials were also analyzed. The analyses of Nogo ERPs and behavioral outcomes were provided in the supplemental material. The preprocessing of the raw EEG data was done using an automated artifact rejection for Single-pulse TMS-EEG Data (ARTIST) algorithm (Wu et al., 2018). After cleaning the signal from artifacts, segments were created according to the trial type (Go/Nogo). The adapted scripts and raw data can be found in the following OSF folder (https://osf.io/jwfn9/).

Mixed linear models (MLM) were built to analyze the data following a best practice guideline (Meteyard & Davies, 2020) to find the maximal converging model. For Go trials, the four stimulation timings were changed into a two-level factor of timing with early (-100 ms and -50 ms) and late stimulation (0 ms and +50 ms). The models included stimulation site and stimulation timing as fixed effects and different random slopes. Outliers were detected using Cook's distance (Cook, 1977). Baseline differences in the Go/Nogo Flanker pre-task were checked using linear models for the error rate and ERN amplitude in Go trials for the sessions in which the cerebellum and vertex were stimulated. The categorical predictors were simple coded: stimulation site (0.5 = cerebellum, −0.5 = vertex), stimulation timing (0.5 = early, −0.5 = late), trial type (0.5 = correct, −0.5 = error), TMS-timing (response pre-TMS = 0.5, response post-TMS = -0.5). Satterthwaite's method was used to estimate the degrees of freedom and to calculate *p*-values for MLMs. *P*-values below .05 were considered as statistically significant.

4.3 Results and discussion

The analysis of the ERN revealed a reduced amplitude for cerebellar compared to vertex stimulation. In addition, results showed that this difference was modulated by the factor stimulation timing, reflecting that especially late compared to early stimulation induced a reduction on the ERN amplitude. This effect was not specific to trial type (error or correct trials).

In addition, the results in the Flanker pre-task revealed that there were no significant differences between the cerebellum and vertex sessions. Hence, the effect on the ERN in the main task was likely driven by the spTMS on the cerebellum, disrupting the inhibitory neurons of the cerebellar cortex that project on the deep cerebellar nuclei that are the only cerebellar output structure. Therefore, a disinhibition of higher cerebral structures including the ACC (Holroyd & Coles, 2002) could have been the consequence of the cerebellar stimulation. The reciprocal information exchange via the cerebello-thalamo-cerebral loop (Palesi et al., 2017) could have been facilitated, resulting in a reduction of the demand of the ACC to process errors by receiving less phasic dopaminergic input. This would also resemble recent results on the cerebellar influence on reinforcement learning (Yoshida et al., 2022) and RPE coding of cerebellar cell populations (Kostadinov & Häusser, 2022). However, the control stimulation site was vertex (Cz) which is close to the electrode position FCz that is usually measured to catch the neuronal activity also generated by the ACC. Hence, it could not be excluded that the stimulation at vertex had an influence on the activity in the ACC while increasing the amplitude of the ERN.

The temporal manipulation of early versus late stimulation demonstrated a stronger effect of late stimulation that took place on the estimated IEL and shortly after. Within the understanding of the forward model of cognition (Sokolov et al., 2017), the predictions of a certain action are compared against sensory information. The cerebellum is likely to contribute to the error signal during the comparison stage and the ERN could therefore indicate the deviation of the matching of both representations, the actual and the prediction. Therefore, late stimulation might have affected the comparison stage while early stimulation did not. In contrast to the ERN, the analysis of the Pe did not reveal any significant differences. Contrary to effects on the Pe in patients with cerebellar stroke (Peterburs et al., 2012), the absent effect on the Pe using spTMS might be related to the short induced plasticity changes that cannot replicate the long lasting effects of stroke. In addition, error awareness, as indicated by the Pe (Endrass et al., 2007), was not relevant for task completion and also not manipulated. Hence, a more sensitive task setup on the Pe might reveal difference in the Pe depending on the stimulation site and timing.

The behavioral data did not show any significant difference between the stimulation sites, challenging the direct link between the impact of the spTMS on the ERN and the performance in the task. This finding is in accordance with the missing behavioral difference in patients with cerebellar degeneration in the study of Tunc et al. (2019), in which also a Flanker task was used to induce error commissions. The analysis of the error rate with TMS pulses before and after response execution demonstrated an increased error rate when pulses were applied after the response. No difference was present for the stimulation sites which suggested that it was a change in behavior induced by the TMS pulse itself rather than a specific change depending on the stimulation site. This effect could also correspond to a startle response that decreased response times when TMS pulses occurred before responding, extending the period to make the decision. Due to the estimation of the IEL and the variability of the pulse timings for each participant, response times were not analyzed.

The interpretation of the results is limited by the complex setup and procedure of the experiment itself. The decision to stimulate the vertex region as a control condition contained the risk to stimulate other brain regions that are relevant for error processing. In addition, we used a double cone coil to stimulate deeper cerebellar brain regions by the trade-off of focality (Çan et al., 2018), increasing the likelihood to stimulate adjacent brain regions. However, sham stimulation cannot reflect the characteristic of a TMS pulse and is therefore suggested to be a poor control condition (Duecker & Sack, 2015). In addition, due to the heating of the coil over the course of the task, trials were missing particularly when the output power of the system was high which depended on the IMT. We analyzed the Nogo trials and observed remaining artifacts in the EEG signal after using ARTIST. This limited the interpretability of the results. Nevertheless, we could observe to some extent the Nogo-N2 and Nogo-P3 ERP components in the grand-average signal which were also similar to the grand averages obtained from the pre-task without pulses.

4.4 Conclusion

We shed light on the role of the cerebellum for processing errors in healthy controls using both, EEG and spTMS. Both systems were co-registered, and pulses were applied throughout the Go/Nogo Flanker task. Stimulating the cerebellum, we observed a reduction of the ERN amplitude in comparison to vertex stimulation. This finding supported the notion of the contribution of the cerebellum to performance monitoring as suggested by Peterburs and Desmond (2016). The effect of spTMS on the ERN was not related to the trial type. A second effect was identified in the temporal domain. Late cerebellar stimulation caused a stronger reduction on the ERN than early stimulation, leading to the conclusion that the contribution of the cerebellum to error processing is likely happening between the IEL onset and 50 ms later. As

predicted, the Pe did not show any effect. In conclusion, the abovementioned findings support the cerebellum's role in performance monitoring and highlighted the necessity for more studies using NIBS to investigate the cerebellum's contribution to other non-motor cognitive functions.

5 Study 3: Impaired reinforcement learning and coding of prediction errors in patients with cerebellar degeneration - a study with EEG and voxel-based morphometry

5.1 Introduction

Learning from feedback is a vital ability for survival. To achieve learning, the consequences of a decision or action must be correctly processed, evaluated, and understood. These consequences can be conceptualized as performance-related feedback and the process behind this mechanism is called performance monitoring (Ullsperger, Danielmeier, & Jocham, 2014). This performance-related feedback can be explained with the principle of reinforcement learning (Rescorla & Wagner, 1972). The cerebellum is suggested to be involved in the process of learning from feedback (Bellebaum & Daum, 2007). During learning, RPEs occur when the expected outcome (prediction) deviates from the actual outcome (feedback) which creates an error signal. This error signal is evaluated to minimize the deviation and update the RPE for future predictions. Several studies have shown that the cerebellum is involved in the processing of PEs (Ernst et al., 2019; Schlerf et al., 2012).

Studies on patients with cerebellar diseases such as SCA and patients suffering from cerebellar stroke not only show severe motor impairments (Cabaraux et al., 2023; Manto et al., 2012) but also non-motor impairments (Leiner et al., 1986; Schmahmann & Sherman, 1998). In particular regions of the posterior and lateral cerebellum such as the regions Crus I and II were associated with cognitive functions (King et al., 2019; Stoodley & Schmahmann, 2009). Alterations in the neuronal processing after cerebellar damage in cognitive tasks was demonstrated measuring EEG (Peterburs et al., 2012; Peterburs et al., 2015; Rustemeier et al., 2016; Tunc et al., 2019). Interestingly, these alterations were, among other ERP components, observed in the FRN (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004), an ERP locked to the onset of feedback. The FRN peaks within the time window of 200 - 350 ms and has been shown to code RPE reflecting striatal activity (Becker et al., 2014; Cohen, 2007). In addition, the FRN was sensitive to the modulation by several characteristics of feedback such as feedback valence (Bellebaum et al., 2010; Gehring & Willoughby, 2002; Nieuwenhuis et al., 2005), violation of expectation (Bellebaum et al., 2010; Pfabigan et al., 2011) and feedback delay (Peterburs et al., 2016). Interestingly, delaying feedback information had a beneficial influence on the performance of patients with PD (Foerde & Shohamy, 2011). RPE coding in the FRN was also observed during learning tasks with evidence highlighting an effect of positive feedback on RPE (Kirsch et al.,

2022; Weber & Bellebaum, 2024). In addition, Rustemeier et al. (2016) showed altered FRN and P3/P300 patterns but no difference in the learning performance in patients with cerebellar stroke. The P3 is a feedback-locked ERP component with a positive deflection that appears in the time window between 300 - 500 ms (Polich, 2007) and has also been shown to reflect RPE (Chase et al., 2011; Hoy et al., 2021; Weber & Bellebaum, 2024).

Importantly, the P3 can be functionally separated into a frontal subcomponent called P3a primarily associated with attention orientation and a parietal subcomponent called P3b primarily involved in memory functions such as updating contextual information (Donchin & Coles, 1988; Polich, 2007). Furthermore, patients with cerebellar degermation showed a relation between the GMV reduction in posterolateral regions of the cerebellum and the error rate and the pattern of the response-locked ERN (Falkenstein et al., 1991; Gehring et al., 1993) in an antisaccade task (Peterburs et al., 2015).

The goal of the present study was to investigate reinforcement learning in patients with cerebellar degeneration and to specifically focus on processing of RPE and associated ERP components. A probabilistic feedback-based learning task with EEG was administered on two days using different feedback timings following an action (immediate feedback = 500 ms, delayed feedback = 6500 ms). Patients with cerebellar degeneration (without extracerebellar damage) were tested, and healthy controls were matched according to age, sex, and education background. Neurological and neuropsychological testing was conducted as well as MRI measured to quantify the GMV in the cerebellum. Derived from previous studies looking at patients with cerebellar degeneration (Peterburs et al., 2012) we expected worse learning in patients compared to controls and to investigate to which extent the cerebellum might contribute to learning from delayed feedback. Additionally, we expected to see altered single trial FRN, P3a and P3b effects in patients compared to controls for high vs. low RPEs. Lastly, we expected to identify a link between GMV reduction in specific cerebellar subregions in patients and possible group differences in the accuracy, FRN and P3a/ P3b ERP components. The hypotheses were preregistered on OSF (https://osf.io/fgw8h/) and ethical approval was provided by the Ethics Committees of the Faculty of Medicine at Heinrich Heine University Düsseldorf, Germany in accordance with Declaration of Helsinki (World Medical Association, 2013).

5.2 Method

In total, we tested fifty-nine participants (28 patients, 31 healthy controls). Only patients suffering from cerebellar degeneration were included. Subtypes of SCA that also included extracerebellar degeneration were not tested. We included different SCA types (e.g., SCA6, SCA14). Exclusion

criteria were the standard MRI exclusion criteria as well as alcohol or substance abuse, any psychiatric or neurological disorder. Mild depression was not an exclusion criterion as patients with degenerative diseases frequently show mild depressive symptoms. Seven patients and six healthy controls were excluded after examining the structural imaging data, EEG data and questionnaires. For the behavioral and ERP analysis, the sample consisted of 21 patients (n = 8 female, mean age in years = 51.38, SD = 14.70) and 25 controls (n = 10 female, mean age in years 52.52, SD = 13.72). A homogeneity analysis revealed two outliers (patients sharing SCAR10 diagnosis) with severe global GMV reduction. In addition, due to missing MRI data in one patient and one healthy control, the final sample size for the voxel-based morphometry (VBM) to quantify the GMV in the imaging data was reduced (patients n = 18, control n = 24). Multiple neurological tests were administered to estimate the severity of motor impairments in patients and possible cognitive deficits. In controls, similar cognitive testing was conducted. Different questionnaires were used to assess handedness, the psychological and health state and experienced quality of life.

5.2.1 Experimental task and procedure

A probabilistic feedback-based learning task (Bellebaum & Colosio, 2014; Eppinger et al., 2008) was used while recording EEG. Measurements took place on two consecutive days with different stimulus sets and different feedback delays. In total, 320 trials were presented grouped into eight blocks of 40 trials each. At the beginning of each trial, a fixation cross was presented for 500 - 1500 ms. Subsequently, the stimulus was presented surrounded by two red rectangles to indicate a left or right button press. The stimulus was presented for 1500 ms and participants had to respond by pressing the left or right button on a response box. The choices (rectangles) remained on the screen for additional 1500 ms extending the response time window to a total of 3000 ms when no button press occurred. When participants pressed a button press (e.g., left button), the respective rectangle (left) lit up for 200 ms. Next, the feedback delay was presented as a black screen for 500 ms for immediate and 6500 ms for delayed feedback. Thereupon, the feedback was presented for a duration of 1000 ms. The performance-related feedback (stimulus-response association) was indicated by "+20ct" in green font for a correct association (positive feedback) or "-10ct" in red font as an incorrect association (negative feedback). In total, four stimuli were randomly assigned of which two were learnable and two were not and associated with random feedback presentation (50 %). These stimuli were used as distractors and increased task difficulty. The learnable stimuli had a contingency of 90 % which translates to contingent feedback (performance related feedback) in nine out of ten trials. In one of ten trials, the opposite feedback than the correct stimulus-response association was displayed to increase the difficulty to learn the

association. We determined a learning criterion of 65 % which led to a new stimulus set after the second block when the criterion was exceeded. In total, 32 participants (15 patients, 17 controls) exceeded the learning criterion in at least one of the sessions. In addition, a ninth block was added when participants exceeded the learning criterion in the eighth block. We excluded trials when responses were faster than 100 ms and longer than 3000 ms as well as trials with more than one response.

On the first day, all participants conducted the probabilistic feedback-based learning task in front of a laptop using two buttons on a response box while measuring EEG. The task was followed by neuropsychological and neurological testing. Afterwards, the MRI session took place and participants were provided with different questionnaires. On the second day, the learning task was repeated with a different stimulus set and delay period. Both stimulus sets and feedback timings were counterbalanced across the participants.

5.2.2 Data analysis

Accuracy was analyzed averaged for all learnable trials and corrected for outlier trials. In addition, we calculated choice switching to identify changes in cognitive flexibility in patients compared to controls. For the EEG data, the signal was preprocessed using standard preprocessing steps including the removal of bad and noisy electrodes, re-referencing the data to the mean of the mastoids, direct current detrending, filtering and correction of ocular artifacts using independent component analysis. Afterwards, data were segmented locked to feedback-onset. Segments were baseline corrected and an artifact rejection applied. For the single-trial analysis of the ERP components FRN, P3a and P3b, custom scripts written in MATLAB code were used. The FRN was measured at electrode FCz in the time window between 200 and 350 ms after the onset of the feedback (Bellebaum et al., 2010; Peterburs et al., 2016). The single-trial P3a (FCz) and P3b (Pz) were both measured within the time window of 300 - 500 ms post-feedback (Polich, 2007). A time window of 40 ms around the peak were used for averaging.

The PE was calculated based on reinforcement learning (Sutton & Barto, 2018) and modelled via a Rescorla-Wagner model (Rescorla & Wagner, 1972). Other variables included into the equation were the response probabilities, learning rate and exploration behaviour. To disentangle feedback valence from the PE, we took the absolute value and calculated the unsigned PE, reflecting the expectancy in each trial. Theoretical implications for calculating the unsigned PE were provided by the PRO model (Alexander & Brown, 2011).

The T1-weighted imaging data were acquired with a 3T MR scanner and converted into the Brain Imaging Data Format (BIDS: Gorgolewski et al., 2016; Zwiers et al., 2022) for the VBM. Whole-

brain VBM was preprocessed in the Computational Anatomy Toolbox (Gaser et al., 2022). The total intracranial volume was estimated for each participant. The cerebellar VBM was conducted using the preprocessing functions for isolation, segmentation, hand correction of cerebellar masks, normalization and reslicing in the Spatially Unbiased Infratentorial toolbox (SUIT: Diedrichsen, 2006). The whole-brain and cerebellar VBM images were checked after each preprocessing step and a homogeneity analysis was conducted to identify potential outliers. The final whole-brain and cerebellar gray matter maps were smoothed (Peterburs et al., 2015).

MLMs were calculated for the statistical analysis of the behavioral and EEG data following best-practice guides (Meteyard & Davies, 2020). Outlier were detected using Cook's distance (Cook, 1977). For the behavioral analysis, the between-subject factor group (patient, control) and the within-subject factor feedback timing (immediate feedback, delayed feedback), feedback valence (positive feedback, negative feedback), response type (correct, incorrect), and the scaled factor block were included as fixed-effects and random slopes, and participant was added as random effect. For the ERP components, we modeled group (patient, control), feedback timing (immediate, delayed), feedback valence (positive feedback, negative feedback) and learnability (learnable stimuli, unlearnable stimuli). In addition, the continuous predictor unsigned PE and a random intercept and slopes per participant for all within-subject factors were included. All categorical predictors were simple coded, and Satterthwaite's method was used to estimate the degrees of freedom and to calculate *p*-values. All *p*-values below .05 were considered as statistically significant.

Two-sample *t*-test were used to analyze the whole-brain and cerebellar GMV between the two groups (contrast control > patient). Multiple regression analysis was applied to analyze the cerebellar GMV and its influence on potential group differences derived from the learning task. The total intracranial volume and age were used as covariates. Family-wise error (FWE) corrected *p*-value < .5 and uncorrected *p*-value (*p*-uncorr. < .001) were used as thresholds and the regions were labelled with the probabilistic MRI atlas (Diedrichsen et al., 2009).

5.3 Results and discussion

The analysis of accuracy revealed no significant group difference between patients and controls. The main effect on feedback timing was significant. The accuracy was higher for delayed compared to immediate feedback across groups. Also, the main effect of block was significant. The accuracy was higher at the end of the task compared to the beginning for both groups.

Moreover, the analysis of choice switching, a measure of behavioral flexibility, showed the expected increased switching behavior after negative compared to positive feedback. Likewise,

choice switching was increased after incorrect compared to correct responses. Also, choice switching was higher at the beginning of the task compared to the end.

Also, decreased choice switching for both groups and feedback timings across task progression were present. In addition, for correct choices, more choice switching was found for immediate compared to delayed feedback. Increased choice switching was present for negative compared to positive feedback for both response types. For both groups, choice switching did not change for incorrect choices across task progression but for correct choices, choice switching decreased across task progression.

The analysis of the single-trial FRN amplitude revealed a significant effect for group with a more negative FRN amplitude for patients compared to controls, a significantly more negative FRN amplitude for negative compared to positive feedback and delayed compared to immediate feedback. For the unsigned PE, the FRN turned out to be less negative with higher unsigned PEs. A significant three-way interaction between group, feedback valence and unsigned PE revealed an absent coding of the unsigned PE in patients. For the controls, we found the coding of the unsigned PE for positive feedback. Highly unexpected positive feedback reflected in high unsigned PEs could have decreased the negativity of the FRN and recent findings underline the processing of positive PE in healthy controls (Kirsch et al., 2022; Weber & Bellebaum, 2024). Interestingly, Corlett et al. (2022) recently demonstrated activations in the cerebellum towards unsigned PE only using a meta-analysis. The cerebellar degeneration in the patients likely contributed to the absence of unsigned PE modulation on the FRN and caused the overall more negative FRN compared to controls. In patients, the FRN was more negative for negative feedback compared to positive feedback which is in line with results in patients suffering from cerebellar stroke (Rustemeier et al., 2016).

Similar to the FRN results, the P3a demonstrated a specific effect for positive PEs for the control group only and no modulation of the unsigned PE in patients. In addition, the learnability of the stimuli had an influence on the unsigned PE, causing a more positive P3a with higher unsigned PE. These results are again in line with recent findings on positive PE modulation in healthy participants (Weber & Bellebaum, 2024). In addition, Hoy et al. (2021) discovered a central scalp distribution of the P3 ERP component (= P3a) when focusing on the positive unsigned PE and a more posterior scalp distribution (= P3b) when taking valence into account as the signed PE. The P3a is involved in attention processes such as orientation (Polich, 2007) and the P3a was increased for positive compared to negative feedback, more positive for unlearnable compared to learnable trials and more positive for higher unsigned PE which might be explained by expectancy across participants. Positive feedback, unlearnable trials and higher unsigned PE might elicit stronger

P3a amplitudes because expectancy is lower, than for negative feedback, learnable trials and low unsigned PEs.

In addition, the P3b is seen to indicate the update of contextual information in learning (Polich, 2007) and to code RPE (Lauffs et al., 2020). Interestingly, the controls did show a modulation by the unsigned PE and a modulation by feedback valence and timing. In controls, significant effects were present for positive immediate and positive delayed feedback and unsigned PEs. The P3b amplitude was more positive with higher unsigned PEs. For negative delayed feedback we discovered an additionally effect, with less positive P3b amplitude for higher unsigned PEs. In patients, no coding of the RPE in the P3b amplitude was present. Nevertheless, the patients showed a main effect of feedback valence, with a more positive P3b amplitude for positive compared to negative feedback. Also, an effect of feedback timing was present in patients and not in controls which points towards different context updating profiles when feedback delays are manipulated. This would also explain a more positive P3b during delayed feedback in patients because of the difficulty and probably working memory efforts to keep the stimulus-response association active in longer delays. This would support the notion that stimulus-response-feedback association might have been altered in patients with cerebellar degeneration causing alterations on all ERPs during learning from performance-related feedback.

Whole-brain VBM revealed global cerebellar degeneration in patients compared to controls and cerebellar VBM demonstrated the strongest degeneration (i.e., reduction of GMV) in bilateral Crus I/ II of lobule VI and bilateral lobules I-IV. The results on the multiple regression analysis in patients showed a negative correlation between GMV and the FRN amplitude. Bilateral GMV reduction in Crus I and Crus II were associated with less negative FRN amplitudes. This observation is comparable to the findings of Peterburs et al. (2015), in which the ERN amplitude also negatively correlated with GMV reduction in patients with cerebellar degeneration in the posterolateral cerebellum. In addition, a recent meta-analysis substantiates the present correlation by highlighting activation patterns in the cerebellum for similar cerebellar regions for reward expectation and feedback (Kruithof et al., 2023).

5.4 Conclusion

In conclusion, the present study shed light on the involvement of the cerebellum in reinforcement learning and RPE processing. The results revealed altered RPE processing in patients. We discovered consistent results across the FRN, P3a and P3b including a general absence of the unsigned PE in patients compared to controls. In addition, the results on the GMV using VBM demonstrated wide cerebellar degeneration in patients and a negative correlation between the

GMV and the FRN amplitude. The present evidence underlines the importance of a healthy cerebellum in processing PE through a constant exchange within the reciprocal cerebello-thalamo-cerebral pathways that enables a direct impact of the cerebellum to higher cerebral processes that generate ERPs. Future studies need to further analyze to which extent the cerebellum is involved in the coding of the RPE using task-based fMRI in patients with cerebellar degeneration and other diseases such as cerebellar stroke and also non-invasive brain stimulation in healthy controls.

6 General discussion

The previously discussed results on error processing and reinforcement learning emphasize the contribution of the cerebellum to performance monitoring. Our studies revealed compelling evidence for cerebellar contribution to error processing (study 2) in healthy controls using cerebellar TMS and reinforcement/ feedback-based learning, both in the past literature (study 1) and in an experiment in patients with cerebellar degeneration (study 3).

Study 1 investigated the cerebellum's role in feedback-based learning using a systematic review approach. Eleven behavioral studies were included using different task parameter, patient samples, and sizes. Results demonstrated a heterogeneous picture of the available behavioral data in patients with about half the patients revealing behavioral alterations. One study using learning and EEG measures revealed altered feedback-related ERP components (FRN, P300). The neuroimaging findings were more consistent with cerebellar activation in 561 healthy participants across 25 studies. Bilateral activations of the cerebellum were reported as well as rsFC changes in one study after the conduction of a learning task including performance feedback.

Study 2 investigated the temporal aspects of cerebellar contributions to error processing. Adult volunteers completed a Go/NoGo Flanker Task while EEG was measured and spTMS on the cerebellum and an extra-cerebellar control region (vertex) in two different sessions was applied. Pulses were applied at different points in time to identify the possible timing of cerebellar input to higher cerebral processes for the processing of errors. Results revealed no differences of stimulation site on the error rates. However, we found an effect on stimulation timing pre- and post-response, with lower error rates when pulses were delivered before the response. In addition, we found the hypothesized blunting of the ERN for cerebellar compared to vertex stimulation. For the Pe, we did not observe an effect. The interpretation of the Nogo trials regarding the ERP components N2 and P3 (stimulus-locked) and the theta power in a time-frequency analysis to investigate response inhibition, another subfunction of performance monitoring, was not possible, as the TMS pulse artifact still superimposed the signal after artifact rejection.

Study 3 elucidated the involvement of the cerebellum in reinforcement learning and RPE coding. We tested patients with a cerebellar degeneration and matched healthy controls using a probabilistic feedback-based learning task while measuring EEG. Feedback was presented either with a delay of 500 ms or 6500 ms in two different sessions. We analyzed the behavioral performance and neural response patterns sensitive to reinforcement learning and RPE processing such as the FRN and P3a/b. In addition, we measured MRI to estimate the amount of cerebellar GMV and to link it to task performance and ERP indices. In addition, neurological and

neuropsychological tests and questionnaires were used to characterize the severity of possible motor and cognitive impairments in patients and controls. Results demonstrated no group specific effect on accuracy but an influence of block and feedback timing on the accuracy across groups. Interestingly, choice switching decreased over time across groups but with the strongest decrease for the controls during delayed feedback. Moreover, in controls, modulations of unsigned RPEs in the FRN and P3a for positive feedback and in the P3b for positive and negative feedback were present. In patients these effects were completely absent.

The analysis of the GMV using VBM demonstrated global cerebellar degeneration with a particular reduction in the bilateral Crus I/ II and lobules I-IV in patients compared to controls. The correlation analysis with multiple regression revealed a negative correlation between the FRN amplitude and GMV in bilateral Crus I/ II.

6.1 Reinforcement learning and the cerebellum

The present results from study 1 and 3 both emphasize the cerebellum's contribution to reinforcement learning and extend its role in sensorimotor learning and PE processing (Blakemore, Goodbody, & Wolpert, 1998; Johnson et al., 2019; Schlerf et al., 2012) to non-motor, cognitive functions (Peterburs & Desmond, 2016). The cerebellum is strongly connected to other brain regions including those that are involved in reinforcement learning and reward processing such as the basal ganglia (Bostan & Strick, 2018) and the VTA (Watabe-Uchida et al., 2012). Understanding the cerebellum as a hub for reinforcement learning is underlined by findings on Purkinje and other cells that were shown to code reward signals (Kostadinov & Häusser, 2022).

The results of study 3 demonstrate that electrophysiological patterns were altered in patients suffering from cerebellar degeneration and that these alterations were closely linked to RPE processing. The FRN was analyzed which is seen to be indicative of reinforcement learning and to reflect striatal RPEs to enable successful behavioral adaptation (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004). The results from study 3 show altered unsigned PE coding in the FRN in patients. Altered ERP difference wave amplitudes were also shown in patients with cerebellar lesions (Rustemeier et al., 2016). Patients showed higher FRN amplitudes for negative compared to positive feedback. This difference was absent in healthy controls. The results of study 3 demonstrated overall higher FRN amplitudes in patients compared to controls. This was surprising, as we expected the FRN amplitude in patients to be less positive compared to controls. Besides, general effects for feedback valence, feedback timing and unsigned PE were present, with more negative FRN amplitudes for negative compared to positive feedback, for delayed compared to immediate feedback, and high unsigned PE compared to low unsigned PE. As described in study 1, Rustemeier et al. (2016) discussed the results on the FRN together with the

results of the P300 in patients which was also more positive after positive compared to negative feedback. The pattern of the ERP suggested that the FRN and P300 together with the P200 which alone did not yield any significant difference, could be seen as a complex that is reflecting reinforcement learning in a wider time span of the ERP. Based on these observations, we discovered the expected altered PE coding in the later P3a in patients. Only in controls, a modulation of positive feedback by the unsigned PE was present for the FRN and P3a which is in line with the recent observation of Weber and Bellebaum (2024) in a comparable probabilistic feedback learning task in healthy participants. They also found a modulation in the FRN and P3a/P3b amplitude only for positive feedback and replicated previous findings on RPE in the FRN (Kirsch et al., 2022). In accordance with the proposal of Proudfit (2015), Weber and Bellebaum (2024) concluded that the term RewP instead of FRN would be more applicable to describe these selective effects on the FRN for positive feedback. The influence of negative feedback on the FRN is assumed to reflect a N200 ERP component not sensitive to PE. Our results showed consistent findings of absent unsigned PE coding across all three feedback-locked ERPs in patients.

The probabilistic-feedback based learning task was designed to enable the participants to learn stimulus-response-feedback associations which allowed to investigate unsigned PE generation on a single-trial level. A study by Borries et al. (2013) investigated whether the violation of positive or negative expectancy had an impact on the FRN in a reversal learning task without performance related feedback as a so called confound. They assumed that behavioral adaptation processes are driven primarily by negative feedback and not positive feedback and found evidence that the FRN coded feedback valence but not the expectancy. This is in line with the RL-theory (Holroyd & Coles, 2002) and suggests that, in contrast to the PRO model (Alexander & Brown, 2011), the FRN codes signed PEs. In contrast, an EEG study on the FRN found that the FRN coded salience and not signed PEs (Talmi et al., 2013). The analysis of choice switching in study 3 underlined the idea by Borries et al. (2013). Higher choice switching after negative compared to positive feedback was found across groups. Additionally, we found evidence that the FRN is altered by feedback valence and that the expectancy is coded within the unsigned PE which was altered in patients. In contrast to the PRO model and the findings of Borries et al. (2013) in healthy controls, we used a task with contingent feedback (i.e. performance related) assigned to two stimuli and analyzed the learnability as a separate factor to see how the unsigned PE is affected throughout the task.

We did not observe an effect of learnability in the FRN, but we found evidence in the P3a amplitude as an interaction between learnability and unsigned PE. The effect was only significant for learnable trials in controls and non-significant in patients. Interestingly, Borries et al. (2013)

found the P300 a reversed pattern which was assumed to code expectancy and not the feedback valence as compared to the FRN. They concluded that the P300 reflects the updating process of relevant information for behavioral adaptation. The absent coding of the unsigned PE in patients and missing effect of learnability in the P3a hint towards an alteration of expectancy in patients. Nevertheless, we also observed valence specific differences in the P3a with more positive amplitudes for positive compared to negative feedback. Concerning the P3b, we found main effects of feedback valence and feedback timing in patients but no unsigned PE coding. However, in controls, for positive and negative feedback a modulation of unsigned PE was present for delayed feedback only. This is in line with the view that in particular the parietal P3b amplitude is involved in contextual updating processes (Polich, 2007). Analogous to the results of Rustemeier et al. (2016), the present results of study 3 extend each ERP components alteration according to high and low unsigned PE in patients towards a general alteration within the feedback-locked ERP when the cerebellum is degenerated.

The results from the whole-brain and cerebellar VBM in study 3 demonstrated the expected GMV reduction in patients compared to controls. We did not observe any extra-cerebellar differences in the whole-brain VBM between patients and controls. The multiple regression analysis revealed a less negative FRN amplitude with higher GMV reduction in bilateral Crus I/ II. This finding is in line with our prediction and the idea that cerebellar degeneration alters the inhibitory tone of the cerebellar hemispheres towards higher cerebral structures. Evidence for blunted ERP components with GMV reduction were shown in the ERN in patients with cerebellar degeneration (Peterburs et al., 2015). Astonishingly, study 2 showed also a blunted ERN for cerebellar compared to vertex spTMS stimulation which underlines the general contribution of an intact cerebellum for PE generation and updating as explained by the forward model (Sokolov et al., 2017). In addition, the cerebellar VBM results with the FRN in study 3 overlap to some extent with the findings on the FRN and the accumulated functional imaging evidence during feedback-based learning in study 1.

Moreover, the single-trial analysis did not show any coding of unsigned PE on the FRN, P3a and P3b across the patients who suffered from different cerebellar ataxia but shared exclusive cerebellar degeneration. A recent meta-analysis discovered cerebellar activation in both, the prediction (anticipation) and outcome stage across 31 different monetary incentive delay tasks in healthy participants (Kruithof et al., 2023). They discovered bilateral activations in the anterior cerebellum (lobule I-V), lobule VI, left Crus I, and in the posterior vermis for the anticipation of feedback. For the presentation of reward (feedback), they found activation differences in the left lobule VI and vermal lobule VI across a subset of 16 tasks. Different to study 1, no patient studies were analyzed, and the focus was solely on monetary incentive delay tasks. Study 1 revealed

altered behavioral performance in half of the studies. The heterogeneity of the performance-related results in study 1 were likely driven by the heterogeneity among the parameters of each individual study. For instance, selective impairment for reversal learning was found in cerebellar stroke patients in a probabilistic learning task (Thoma et al., 2008). However, no difference was found in the same sample for the performance in a modified version of the WCST. In contrast, a recent study found in patients with cerebellar ataxia using the WCST besides other neuropsychological tests a correlation between the WCST with ataxia scores (Shin et al., 2024). In addition, correlations between the VBM results with the right Crus I and II, lobule VIIb and VII and the subfactor non-perseverative error from the WCST were present. Also, rsFC changes were found using cerebellar seeds with the superior parietal and superior temporal gyrus in patients. All results point towards impaired cognitive flexibility interpreted as a disruption of the cerebello-thalamo-cerebral connectivity (Shin et al., 2024).

Comparing these results with the findings of Study 3, we see no differences on the accuracy between patients and controls and only a general effect for feedback timing, with increased accuracy for delayed compared to immediate feedback, a general effect of block, with higher accuracy for later compared to earlier blocks. For study 1, we expected a more consistent patterns on the performance in patients depending on the type of cerebellar damage. Whereas patients with cerebellar stroke were suggested to restore their initial symptoms to some extent, we assumed that patients with a progressive cerebellar degeneration could not. For study 1, we expected patients to show less accuracy in the task compared to the controls and a modulation by feedback delay as shown in patients with PD in the study by Foerde and Shohamy (2011), where immediate feedback triggered striatal activation whereas delayed feedback showed hippocampal activation using fMRI.

Besides, a study by Nicholas et al. (2023) investigated reinforcement learning and PE processing in patients with cerebellar ataxia using a probabilistic feedback-based learning in combination with a semantic learning task. Importantly, they included patients who probably also show non-cerebellar atrophy (e.g., cerebellar MSA). They observed impaired learning in patients in the probabilistic feedback-based learning task but a preserved ability to predict rewards based on episodic memory. In study 3, choice switching behavior decreased across groups over time, but the strongest decrease was present for the control group during delayed feedback. The delay period could have facilitated learning of the relevant stimulus-response associations in controls more than it did in patients, where choice switching behavior was more similar between both feedback timings. However, the present results of study 3 do not show a direct relationship between feedback delay and the cerebellum in patients which leaves open the question of whether there is a relationship at all.

6.2 Error processing and the cerebellum

The results on error processing through the application of spTMS on the cerebellum to study potential effects on the behavior and electrophysiological activity in a Go/Nogo Flanker task clearly demonstrated an impact of a ERN amplitude reduction in comparison to vertex stimulation. The ERN is related to the decrease of DA activity in the ACC (Holroyd & Coles, 2002). We observed a modulation of the ERN by late TMS timing. Late TMS timing consisted of stimulation timings at the latency of the individual error latency and 50 ms afterwards. The ACC needs information about the prediction (form e.g., the cerebellum, see forward model) and sensory consequences of the decision/ response and therefore time to generate a signal. Timings before the ERN latency did not show the blunting of the ERN in study 2. A study by Tunc et al. (2019) found a trend-level significant effect on the ERN in a similar Flanker task in patients with cerebellar degeneration pointing towards an effect of cerebellar degeneration on the ERN. Similarly, patients with basal ganglia and patients with lateral prefrontal cortex lesions conducting a Flanker task revealed reduced ERN amplitudes compared to controls (Ullsperger & Cramon, 2006). They inferred that the ERN could be an indicator of the status of the neuronal network underlying performance monitoring.

In study 2, the behavioral data did not reveal a difference between stimulation sites nor stimulation timing on the error rate, but we found a dependency on the timing of TMS pulse onset relative to the response onset with increased error rate when pulses were applied after the response compared to before the response.

In a separate analysis on the time-frequency data, we looked at the theta power which reflects prefrontal and ACC activity (Asada et al., 1999). Importantly, the findings were partially overlaid by the artefacts of the TMS stimulation. The theta activity already occurred before the response onset which could indicate the conflict-related activity after the presentation of the flanker stimulus. We did not find the modulation of theta by stimulation site and timing as predicted. Theta power was increased after cerebellar compared to vertex stimulation and stronger for early compared to late stimulation. Only the expected increased theta power for error compared to correct trials was present as predicted. Hence, in accordance with previous studies (Luu et al., 2004; Yeung et al., 2007), theta and the ERN were interpreted to underly different processes, reflecting different aspects of error processing and cognitive control.

A difference in the ERN amplitude in the Flanker pre-task was not found, underlining the effects of the spTMS on the cerebellum. The results on the Pe did not show any significant difference between cerebellar and vertex stimulation. A study in patients with cerebellar stroke did show increased Pe amplitude (Peterburs et al., 2012), suggesting a compensatory process when the

cerebellum is damaged by an isolated lesion event. Patients with cerebellar degeneration did not show any effect in the Pe (Peterburs et al., 2015) which led to the assumption that this effect is triggered by focality and therefore likely by the reorganization processes in the brain after a stroke (Grefkes & Fink, 2011).

Interestingly, Li et al. (2008) reported further cerebellar evidence in error processing. They used a stop-signal task to induce error commissions while measuring fMRI and found that the ventrolateral prefrontal cortex was strongly activated when post-error slowing occurred. Based upon this findings, Ide and Li (2011) identified regions using a similar approach that also correlated with the cerebellum. The cerebellum demonstrated the strongest association between the activity caused by errors and underlining its involvement in a circuit of cognitive control and error processing along the cerebello-thalamo-cerebral loop. Besides, using a Stroop task, Egner and Hirsch (2005) discovered involvement of frontal regions such as the superior and middle frontal gyrus during increased cognitive control. Complementary, they observed decreased activity in regions such as the bilateral prefrontal and parietal cortex when the demand for cognitive control was reduced and additionally found accompanying activation in the superior temporal and anterior cerebellum during cognitive control.

The exchange between the cerebellum and higher cerebral areas such as the ACC through reciprocal cerebello-cerebral loops might have facilitated the exchange of information in study 2. This could have increased the DA activity in the ACC, leading to less effort to detect and control errors while blunting the ERN amplitude. Thus, our results provide evidence for the involvement of the cerebellum in error processing, therefore extending the network perspective on error processing.

Besides TMS to study error processing, tDCS has been used in Flanker tasks to change the excitability of the cerebellum and to investigate response inhibition (Mannarelli et al., 2020), a cognitive process which is closely linked to error processing and also summarized under the term performance monitoring (Peterburs & Desmond, 2016). The hypothesis on the N2 ERP amplitude in Nogo trials of study 2 were based on the findings of Mannarelli et al. (2020) in which tDCS was applied before conducting the task. This is different to spTMS applied while conducting a task. They showed increased error rates when cathodal cerebellar tDCS was applied compared to sham stimulation. In addition, the N2 amplitude was reduced for cathodal tDCS compared to sham stimulation. The N2 amplitude is seen to reflect performance monitoring and decreased N2 amplitudes were associated with improved performance monitoring (Larson & Clayson, 2011). Physiologically, cathodal tDCS causes hyperpolarization of neurons and stimulating the cerebellum before the task could have inhibited the inhibitory tone in the cerebellar neurons in a

similar way as spTMS did in study 2 on the ERN in Go trials. A study by Wynn et al. (2019) demonstrated reduced error rates using cathodal tDCS on the medial cerebellum in a Go/Nogo task compared to sham tDCS. No differences were observed for the performance in a delay discounting. Further, a meta-analysis on cerebellar tDCS demonstrated that both cathodal and anodal tDCS on the cerebellum led to alteration in behavioral performance across 32 studies. Hence, no specific effect for the polarity of tDCS was present, challenging the general interpretation of effects for cathodal against anodal tDCS (Oldrati & Schutter, 2018). Importantly, the results from the Nogo trials from Study 2 using spTMS must be interpreted with caution, as the effects were still partly superimposed by artifacts. We did not find the decreased effect in the N2 amplitude for the timing shortly after stimulus onset but an increased, i.e. more negative amplitude, pointing towards more effort and suppression and aggravated performance monitoring. However, this was contradicted by the behavioral data, which did not reveal a difference in false alarm rates between cerebellar and vertex stimulation.

The stimulus-locked P300 as an indicator of attentional reorientation (Folstein & van Petten, 2008) revealed stronger positive amplitudes for early stimulations (on stimulus onset and shortly after) compared to late stimulation (300 ms post stimulus onset) for the cerebellum compared to vertex, interpreted as impeded stimulus discrimination during early stimulation. A meta-analysis investigating the impact of cerebellar TMS on different cognitive tasks (Gatti et al., 2021) indicated moderate effects of cerebellar TMS on the accuracy and response time compared to control conditions across 41 studies. The stimulation paradigm was identified to play a major role on these behavioral effects and less the investigated cognitive function.

In sum, study 2 revealed alterations in the error monitoring system using spTMS on the cerebellum. TMS application to dissociate cognitive processes while using tasks to induce errors can be seen as a promising addition to patient studies.

6.3 Reinforcement learning vs. error processing in the cerebellum

It is logical to assume that reinforcement learning, and error processing are not independent processes. Without the ability to detect and process errors, reinforcement learning principles cannot be applied. Holroyd and Coles (2002) proposed that the reinforcement learning and error processing systems are not independent and both influenced by mesencephalic dopaminergic activity. The ERN itself is seen as the results of a dopaminergic negative reinforcement learning signal which is processed in the ACC. The ERN has not only been regarded as an ERP component indicating errors but also discussed to reflect conflict monitoring (Botvinick et al., 2001; Botvinick et al., 2004) and also considered to predict reinforcement learning (Frank et al., 2005). Frank et al. (2005) showed in their study using a probabilistic feedback-based learning task that

the size of the ERN could predict to which extent participants were able to learn from negative compared to positive feedback. They additionally analyzed the FRN and classified participants into learners who had improved their performance particularly based on though negative feedback, and learners who had learned better from positive feedback. They discovered that the ERN was closely linked to avoiding negative outcomes which was also indicated by a stronger FRN amplitude. The difference in these two ERP components was put into relation of reinforcement learning and they concluded that some participants benefited more from positive, and some learn better from negative reinforcement learning.

The present results on cerebellar contributions to reinforcement learning and error processing support the idea of the forward model (Sokolov et al., 2017). We discovered evidence for modulations in both cognitive functions when cerebellar functions were disrupted. First, alterations in the error processing system were present when TMS was applied to the cerebellum (compared to vertex stimulation), a neuronal pattern that appeared to suggest facilitation of error processing as indicated by reduced ERN amplitudes. Second, when patients with cerebellar degeneration performed a feedback learning task, coding of the RPE in several ERP components as observed in healthy controls was absent. Third, cerebellar VBM revealed a link between a blunting of the FRN and cerebellar GMV reduction, which at first glance seems counterintuitive to another ERP finding, i.e., a generally increased/ more negative FRN in patients compared to controls. However, aggregating single-trial data for each participant across all trials likely resulted in lost variance which the MLM analysis was capable to explain leading to the diverse FRN pattern.

The first conclusion which can be drawn is that the cerebellum has an impact on the generation of ERP components that have their major source in the cerebrum, such as the ACC for the ERN/FRN but also on the P3a and P3b ERP components. The second conclusion is that spTMS applied to the cerebellum can alter neuronal activity during error processing. In study 2, spTMS seemed to facilitate error processing by inhibiting the cerebellar hemispheres' inhibitory tone. Third, RPE coding was absent in FRN, P3a and P3b in patients with cerebellar degeneration, pointing to alterations in several processing stages and subprocesses that these components have been linked to. Across all three studies, the evidence on the behavioral data remains heterogeneous. Study 1 revealed heterogeneous results in the literature, study 2 showed no effects of stimulation site on error rates and study 3 demonstrated no group differences in accuracy. Thus, changes in cerebellar functions that are due to either cerebellar damage or transient functional disruption appear to have rather subtle effects at the behavioral level. This is consistent with previous reports on error processing and reinforcement learning in which only certain aspects are impaired, such as reversal learning (Shin et al., 2024; Thoma et al., 2008).

6.4 Limitations

The interpretation of the results across all three studies are limited by several individual factors. For study 1, we included only studies that explicitly mentioned the cerebellum in the title or abstract into the systematic review. It is likely that we missed studies that found additional evidence in cerebellar activation during feedback-based learning that did not focus on the cerebellum and therefore did not state these results in the title nor in the abstract. In addition, we did not cover studies that used feedback-based learning tasks and did not observe cerebellar activations while using whole-brain scans (Sescousse et al., 2013; Silverman et al., 2015).

For study 2, we tested healthy participants using a sophisticated setup of EEG and TMS as well as EMG to investigate the cerebellum's contribution to error processing. We based our predictions about the ERN on patients suffering from cerebellar stroke. However, using spTMS is hardly comparable to cerebellar stroke because it only produces a temporal alteration of excitability depending on the type of TMS device, protocol, and stroke produces a more permanent damage. In addition, anatomical markers were used to navigate and stimulate the cerebellum and vertex region. It is possible that we stimulated adjacent regions due to the coil design which allowed to stimulate deeper brain regions by the cost of less focality (Çan et al., 2018). This could have caused the stimulation of other brain regions also involved in e.g., visual processing (co-stimulation of the occipital cortex) or involved in cognitive functions (co-stimulation of cerebral structures such as the ACC when stimulating vertex) that could have interfered with the investigation on error processing. We used a questionnaire to ask the participants if any phosphenes were visually present while conducting the task to make sure that the stimuli during the Go/Nogo Flanker Task were seen without any distortion. Neuronavigation has been shown to improve the accuracy of stimulating the desired brain region (Matilainen et al., 2024). Attention needs to be drawn to the heat development within the TMS coil, as studies rely on sometimes hundreds of trials to enable the analysis of learning throughout a task. This also leads to other factors such as the output power that affects heating within the coil and the integrity of the system (shutting down at some point in time) and making further pulse application impossible unless the coil is cooled down again. In addition, we encountered the challenge of persistent artifact in the Nogo trials after applying artifact removal algorithm. Also, some participants experienced headache after the application of TMS. This needs to be considered when designing tasks with many trials and TMS pulses.

In study 3, the patient sample consisted of patients suffering from different cerebellar ataxia, however, all had in common that degeneration was exclusively present within the cerebellum and participants with extra-cerebellar abnormalities, extensive white matter lesions were removed

from further analysis. We had to remove two patients with severe cerebellar atrophy which caused strong variance in the VBM and were classified in a homogeneity analysis as outliers. The small sample size could have led to an increased beta error, resulting in unidentified effects, particularly in the analysis of imaging data. Also, results of the MLMs in the single-trial ERP analyses and the multiple regression analysis are based on different statistical approaches. Whereas MLM use all underlying data points for each participant and trial to generate the maximum fitting model, the General Linear Model in VBM makes use of the aggregated datapoints. This might have resulted in lost variance resulting in deviant results on the FRNs increased negativity in patients compared to controls in the MLM and decreased FRN amplitude for GMV reduction in Crus I/ II for in patients.

In addition, the analysis of response-locked ERP components such as the ERN and Pe was limited, as the task used a rather long response time window of 3000 ms. We could not see a clear ERN in the grand average signal as for fast-paced tasks such as the Go/Nogo Flanker task in study 2. Also, several studies have shown that ERN effects are decreasing with age which was assumed to be related to a worse integration of stimulus-response associations in elderly people (Eppinger et al., 2008; Herbert et al., 2011; Pietschmann et al., 2008). Our sample consisted of rather old participants (patients mean age in years = 51.38, *SD* = 14.70; controls mean age in years 52.52, *SD* = 13.72) which probably contributed to an additional weakening of the ERN effects. Moreover, a learning criterion to change the stimulus set or to extend the experiment with an additional block at the end of 65 % accuracy was chosen arbitrarily. At which performance participants are really learning stimulus-response-feedback contingencies can be debated.

6.5 Future directions

We have come a long way from the first studies on the role of the cerebellum in motor functions (Flourens, 1842; Fodéra, 1823; Rolando, 1809) to the latest developments on the cerebellum's role in non-motor learning (Berlijn et al., 2024).

Neurodevelopmental disorders and mental illnesses are now increasingly associated with changes in the cerebellum (Lin et al., 2024; Morgado et al., 2024; Phillips et al., 2015; Stoodley, 2016). As already briefly presented in the introduction, differences in activity were found in patients with schizophrenia (Picard et al., 2008), major depression symptoms (Lin et al., 2024), posttraumatic stress disorder (Huggins et al., 2024), in patients with attention deficit and hyperactivity/ obsessive compulsive disorder and autism spectrum disorder (Morgado et al., 2024; Stoodley, 2014). Patients suffering from schizophrenia demonstrated altered cerebellar activity with increased activity in the anterior cerebellum and in lobule VI when rewards were presented in a monetary incentive delay task compared to controls (Zeng et al., 2022). In addition, decreased

functional connectivity between the cerebellum and prefrontal, cingulate, occipital and thalamic regions were shown in patients with schizophrenia and in patients with bipolar disorder (Cattarinussi et al., 2024). Also, social cognition (van Overwalle et al., 2020) and emotions such as anger and aggression (Klaus & Schutter, 2021; Wolfs et al., 2023) have been lately associated with a cerebellar contribution.

Moreover, the evolutionary development of the cerebellum is of great interest, as it has been shown that the posterolateral cerebellar hemispheres expanded analogously to the expansion of the human prefrontal cortex (Balsters et al., 2010). A recent study investigating the cerebellar development in relation to the cerebral development across 34 primate species and revealed proportional development between both the cerebellum and cerebrum but faster expansion for Crus I and II in the cerebellum (Magielse et al., 2023).

Besides the evolutionary development, ageing was shown to affect the cerebellum's rsFC, with an interesting network perspective related to age provided by Edde et al. (2020). They showed that participants categorized as young (between 18 and 30 years) revealed stronger post-learning changes in the fronto-cerebellar, temporo-cerebellar, and cerebello-cerebellar networks. Older participants (between 61 and 70 years) revealed no involvement of cerebellar networks. Moreover, only in patients with cerebellar lesion, age significantly correlated with the performance in a verbal fluency task (Peterburs et al., 2010). This finding supports the assumption that age at lesion onset might play a role in the severity of deficits in verbal working memory.

New advances in scanning the cerebellum with high resolutions MRI scanner (9.4 Tesla: Sereno et al., 2020), measuring and mapping the cerebellar nuclei and linking them to task parameters (van der Zwaag et al., 2023) enable a more precise localization of certain cognitive functions in the cerebellum. Likewise, new EEG setups to investigate the cerebellum (Todd et al., 2018) and electrophysiological localization techniques are developed to analyze the cerebellum's activity using cerebellar source localization in EEG data (Paitel & Nielson, 2023). Technologies such as (repetitive-) TMS to induce or to inhibit plasticity changes in the cerebellum need to be further explored to investigate error processing and reinforcement learning. In addition, new TMS-EEG artifact correction approaches are developed (Metsomaa et al., 2024) that improve the EEG signal and clean it from TMS-induced artifacts such as muscle artifacts for optimized preprocessing. Also, combining multiple technologies such as EEG, TMS, and task-based fMRI could be used to characterize the cerebellum in healthy participants and patients more in detail.

Furthermore, new imaging standards (Öz et al., 2023) and web-based repository systems (Gorgolewski et al., 2015) with a specific labeling system of data (Gorgolewski et al., 2016; Poldrack et al., 2024) will help to make research comparable between different studies at different

locations, allowing to make use of data from other laboratories to study the brain (Öz et al., 2023). The research on cerebellar ataxia is ongoing and new SCA types are still being discovered (Tan et al., 2023). In addition, the effects of rehabilitation on the motor impairments arising in cerebellar ataxia are investigated and show that the patients gains are still preserved after 24 weeks in half of the sample (Miyai et al., 2012). Thus, the identification of diseases and their effects on the cerebellum as well as rehabilitation continues and is far from being complete.

All three studies included in the present dissertation investigate cognitive functions that are affected by alterations in the cerebellum, whether by disease or by physiological stimulation. The practical and also partly philosophical question of whether the cerebellum processes different cognitive functions with different physiologically deterministic processes or algorithms and has a separate program for each in regard to the multiple functionality hypothesis (Diedrichsen et al., 2019) or whether there is a general process for this as indicated by the universal transform theory (Guell et al., 2018) remains open. Due to the cerebellum's uniform neuroarchitecture, it was reasonable to expect that there is a common functional process that controls different types of functions. Since the cerebellum cannot be considered as a separate entity but is in constant exchange with other brain regions that mutually influence each other, it could be difficult to conclude one general computation within the cerebellum. Looking at the whole brain, it becomes clear that a functional specialization of cell types and brain regions enables the brain to optimize processing. It is likely that the cerebellum encompasses multiple programs and that the phylogenetically older and newer structures code cognitive and motor programs in different ways. To this day, the mechanisms underlying the cerebellum's neurophysiological processes are not clarified yet and new activation patterns in different cell types for e.g., reward-based learning are found (Kostadinov & Häusser, 2022). Our results indicate the involvement of the cerebellum in cognitive functions such as error and reinforcement learning were produced in close exchange with other brain regions which would be more in line with the multiple functionality hypothesis.

In study 1, a taxonomy to understand feedback-based learning in non-motor learning is explained based on the forward model of cognition (Sokolov et al., 2017). To understand the cerebellum's significance for performance monitoring, new models and theories on the cerebellum in error-based supervised learning are continuously developed, implementing new models and findings on the cerebellar neurophysiology and functional interaction with other brain regions (Zang & Schutter, 2023).

In Study 2, we used a novel approach to investigate the ERP component ERN as an indicator of error processing by making use of concurrent cerebellar stimulation and EEG measurements. This experiment was possible due to TMS compatible EEG electrodes, a configuration with two

stimulators that have alternated the delivery of energy for the magnetic pulse, and monitoring of MEPs throughout the completion of the task to avoid any stimulation of the brainstem during cerebellar stimulation. In addition, recent developments of new algorithms to remove artifacts from the data were essential to clean the signal which would otherwise have masked the signal (Wu et al., 2018). This novel approach of using TMS to stimulate the brain while measuring EEG to analyze ERP components was also challenging and new standards were developed just recently to allow optimal measurements using TMS combined with EEG (Hernandez-Pavon et al., 2023). Other task designs have to take care of the limits of TMS, heat development when multiple single pulses are applied and the precise estimation of the location that has to be stimulated using neuronavigational approaches (Caulfield et al., 2022).

In study 3, we used a reinforcement learning algorithm to model the PE for each stimulus and in each trial. We additionally used a single-trial analysis approach to analyze the ERP components and how they are affected by the RPE. Modelling the RPE is challenge, as task-specific factors heavily influence the assumptions and expected behavioral learning curve. New statistical developments such as MLM were used to make use of each single data point within the data and enable to make the most of single-trial data. Characterizing the structural anatomy of the cerebellum using MRI allowed to correlate the electrophysiological data with the cerebellar gray matter and to study the influence of cerebellar degeneration on reinforcement learning.

6.6 Conclusion

In conclusion, this dissertation had the goal to investigate the contribution of the human cerebellum to performance monitoring while focusing on reinforcement learning and error processing. A multimodal approach was used to characterize the cerebellum's role in non-motor and external feedback-based learning in the literature, applying spTMS on the cerebellum to stimulate the cerebellar cortex and to evoke changes that lead to cognitive alterations in the error monitoring system. Additionally, we investigated reinforcement learning and RPE processing in the healthy and the diseased cerebellum. Across all three studies, we found evidence for the contribution of the cerebellum to performance monitoring using behavioral, electrophysiological and imaging data. The electrophysiological indices FRN in study 1 and 2 for reinforcement learning and the ERN in study 2 for error processing revealed alterations when the cerebellar output was changed or disrupted due to stimulation or disease. In addition, the results from the systematic review in study 1 and in study 3 with patients suffering from cerebellar degeneration provide evidence for the involvement of the posterolateral cerebellum in reinforcement (feedback-based) learning. These results underpin the need for further research to complete the picture on the cerebellum's role in performance monitoring.

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8 Affidavit

Eidesstattliche Erklärung gemäß § 5 der Promotionsordnung vom 15.06.2018 der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf:

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation wurde in der vorliegenden oder ähnlichen Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den _____ _____

Datum Adam Michael Berlijn

9 Appendix

Original article of study 1

Berlijn, A. M., Huvermann, D. M., Schneider, S., Bellebaum, C., Timmann, D., Minnerop, M., & Peterburs, J. (2024). The role of the human cerebellum for learning from and processing of external feedback in non-motor learning: a systematic review. *The Cerebellum*. https://doi.org/10.1007/s12311-024-01669-y

I was the corresponding and first author and wrote the initial draft of the manuscript. My co-authors and I planned the review, rated the abstracts, the full-text papers, and extracted the reviewed data. All authors contributed to manuscript revision, discussion and interpretation of results and approved the final version of the manuscript.

Original article of study 2

Berlijn, A. M., Huvermann, D. M., Groiss, S. J., Schnitzler, A., Mittelstaedt, M., Bellebaum, C., Timmann, D., Minnerop, M., & Peterburs, J. (2024). The effect of cerebellar TMS on error processing: A combined single-pulse TMS and ERP Study. *Imaging Neuroscience*, *2*, 1–19. https://doi.org/10.1162/imag_a_00080

I was the corresponding author, and shared the first authorship with my colleague D.H. My co-authors and I created the experimental setup. I programmed the experimental task. D.H. and I conducted the data acquisition, statistical analysis, and we wrote the first draft of the manuscript and interpreted the results. All authors contributed to results, discussion, interpretation, revision, and read and approved the final version of the manuscript.

Original article of study 3

Berlijn, A. M., Huvermann, D. M., Bechler, E., Thieme, A., Schnitzler, A., Bellebaum, C., Timmann, D., Minnerop, M., & Peterburs, J. (2024). Impaired reinforcement learning and coding of prediction errors in patients with cerebellar degeneration - a study with EEG and voxel-based morphometry. *Manuscript submitted for publication.*

I was the corresponding and first author and wrote the first draft of the manuscript. My co-authors and I planned the experimental design. I programmed the experimental task, conducted the data acquisition, statistical analysis, interpreted the results and wrote the first draft of the manuscript. All authors contributed to results, discussion, interpretation, revision, and read and approved the final version of the manuscript.

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RESEARCH

The Role of the Human Cerebellum for Learning from and Processing of External Feedback in Non-Motor Learning: A Systematic Review

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Abstract

This review aimed to systematically identify and comprehensively review the role of the cerebellum in performance monitoring, focusing on learning from and on processing of external feedback in non-motor learning. While 1078 articles were screened for eligibility, ultimately 36 studies were included in which external feedback was delivered in cognitive tasks and which referenced the cerebellum. These included studies in patient populations with cerebellar damage and studies in healthy subjects applying neuroimaging. Learning performance in patients with different cerebellar diseases was heterogeneous, with only about half of all patients showing alterations. One patient study using EEG demonstrated that damage to the cerebellum was associated with altered neural processing of external feedback. Studies assessing brain activity with task-based fMRI or PET and one resting-state functional imaging study that investigated connectivity changes following feedback-based learning in healthy participants revealed involvement particularly of lateral and posterior cerebellar regions in processing of and learning from external feedback. Cerebellar involvement was found at different stages, e.g., during feedback anticipation and following the onset of the feedback stimuli, substantiating the cerebellum's relevance for different aspects of performance monitoring such as feedback prediction. Future research will need to further elucidate precisely *how*, *where,* and *when* the cerebellum modulates the prediction and processing of external feedback information, which cerebellar subregions are particularly relevant, and to what extent cerebellar diseases alter these processes.

Keywords Cerebellum · Performance monitoring · Reinforcement learning · Cognition · Feedback-based learning · Cerebellar ataxia

Introduction

Cerebellar contributions to non-motor functions have been extensively investigated over the past decades [e.g., 1–4]. These contributions were highlighted by several consensus reviews and meta-analyses centered on the role of the cerebellum for perception [5], language [6], emotion [7], social cognition [8, 9], and higher cognitive function in general [10]. Cerebellar damage does not only impair (sensori-) motor functions [11, 12], but also affects the cognitive, emotional, and behavioral domains, albeit dependent on the localization and severity of the cerebellar disease [13, 14]. For example, damage to the posterior lobe and vermis of the cerebellum is associated with deficits in executive functions such as task-switching, which was described in terms of the cerebellar cognitive affective syndrome [CCAS: 15, for a meta-analysis see 16].

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Neuroanatomical studies revealed multiple neuronal pathways [cerebral-ponto-cerebellar and cerebello-thalamo-cerebral pathways, respectively; 17, 18] as the foundation for functional interactions between the cerebellum and non-motor cerebral areas [19–21]. The functional relationship between cerebellar and cerebral structures was initially conceptualized as a forward model of motor control that was later extended to also apply to the non-motor, cognitive domain [22]. In the motor domain, the cerebellum is thought to underlie sensorimotor integration. According to the forward model, the cerebellum predicts the sensory outcomes of movements based on efference copies of motor commands and adapts behavior based on mismatches between these predictions and the actual sensory outcomes [22–25]. A comparison between intended and actual action consequences is also thought to underlie the processing of performance errors, i.e., when instead of an intended response (e.g., button press with the left index finger) an alternative action is performed (e.g., button press with the right index finger). Cerebellar involvement specifically in error processing has been addressed in some patient studies. These studies provided initial evidence for altered error processing in patients with cerebellar degenerative disease [26, 27 for somewhat conflicting results], and with focal vascular lesions of the cerebellum [28]. Higher cognitive functions such as task-switching and adaptive control of behavior heavily rely on the detection and processing of errors. The cerebellar contribution to error processing may thus be one mechanism by which the cerebellum supports non-motor, cognitive functions.

In many situations, for example in unfamiliar conditions when an individual does not yet know which actions are correct and incorrect, performance errors cannot be identified directly at response onset, or merely based on internal information such as efference copies. In such cases, the individual must rely on external feedback, which can be provided as simple performance feedback (e.g., "correct" vs. "wrong") or as (monetary) reward or punishment. Here, external feedback can be considered a cognitive consequence of an action, and learning from such feedback for successful behavioral adaptation depends on feedback prediction. Specifically, if the actual feedback does not match the predicted feedback, the behavior needs to be changed. Given its role in generating predictions (see above), the cerebellum may be involved in generating and processing such feedback predictions errors. Indeed, recent evidence on the cellular level in mammals revealed that different cerebellar cell populations were sensitive to reward predictions and reward prediction violations [29, 30]. In this context, the large inhibitory Purkinje cells play a prominent role because they represent the only output neurons of the cerebellar cortex. Their massive dendrite trees in the molecular layer of the cerebellar cortex receive excitatory sensory input from two distinct fiber systems: glutamatergic climbing fibers originating from the inferior olive and glutamatergic mossy fibers that are connected via granular cells to parallel fibers, forming synapses with the dendrite trees of the Purkinje cells. The inhibitory axons of the Purkinje cells project in turn to the deep cerebellar nuclei, which subsequently send excitatory fibers to a broad variety of extra-cerebellar regions. In particular, the ventral part of the dentate nucleus [19] is likely involved in non-motor processes such as predicting feedback by transmitting information to higher cortical structures like the associative regions of the cerebrum [e.g., via the cerebello-thalamo-cortical pathway: 18]. Recent reviews summarize evidence from mammals during learning from feedback [30, 31] that show coding of rewards and reward predictions in several cerebellar cell populations (e.g., granular cells, Purkinje cells, nuclear neurons). It has recently been proposed that cerebellar projections to the ventral tegmental area (VTA) may play a role in reward-based learning [32]. Specifically, these projections modulate the release of dopamine in the VTA, and dopamine is critically involved in coding reward prediction errors and reward value [e.g., 33]. Moreover, dopamine is also linked to movement vigor [34], possibly providing a link between coding of rewards and translation into behavioral output. Cerebellar reward signals that are transmitted to the dopaminergic midbrain and specifically the basal ganglia, a group of subcortical cerebral nuclei critically involved in reward processing and in performance monitoring in general [35], are well in line with the idea put forward by Peterburs and Desmond [36] that performance monitoring may be a core, domain-independent function of the cerebellum.

The terminology used in previous studies on performance monitoring has been inconsistent. For instance, while Frömer et al. [37] use the term "performance monitoring" to describe the internal evaluation of one's own actions, Peterburs and Desmond [36] define performance monitoring as set of cognitive and affective functions underlying adaptive control of behavior that includes, but is not limited to, error and feedback processing. When reviewing and summarizing the existent work on the cerebellum's involvement in such processes, it is thus necessary to precisely define these terms. Figure 1 provides a taxonomy and detailed explanation of key terms and concepts in the present review. In this taxonomy, performance monitoring is a subdomain of executive control that incorporates both, the processing of internal information for response evaluation as well as the processing of external feedback stimuli.

The present review focuses on processing of external feedback to enable learning in the non-motor domain. Typical experimental tasks used in this regard include probabilistic learning tasks and reversal learning tasks with abstract visual stimuli [e.g., 38, 39] or a combination

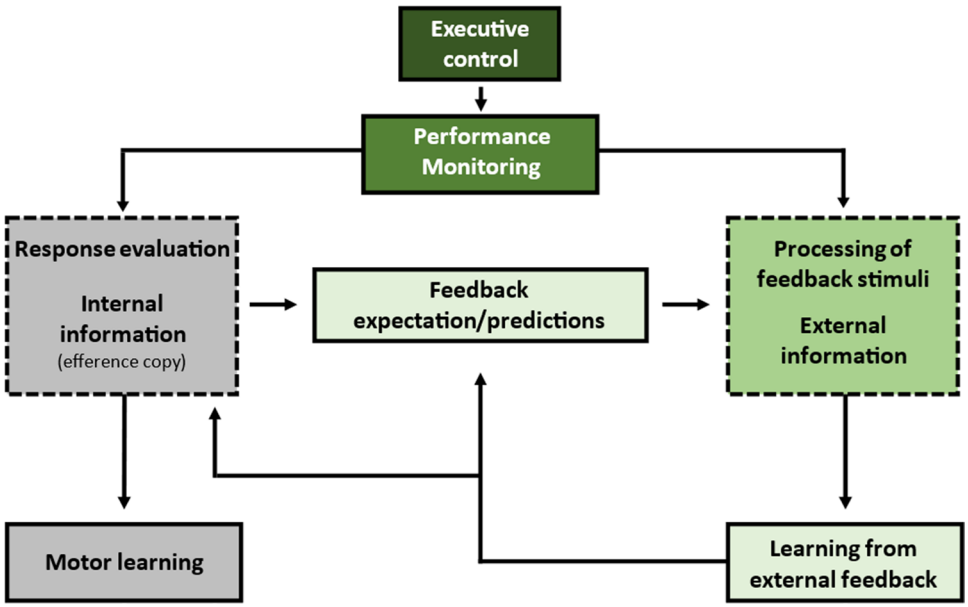

Fig. 1 Taxonomy of performance monitoring and key terms and concepts used in the present review. Crucially, the present review is focused on processing of and learning from external feedback in non-motor learning (boxes shaded in greens). Response evaluation based on purely internal information (i.e., efference copies) to optimize motor performance is not addressed (grey boxes)

of both [e.g., probabilistic reversal learning task; 40]. Figure 2 provides a schematic illustration of the sequence of stimulus presentation in one trial of a generic feedback learning task. After fixation, an abstract visual stimulus is presented, and subjects need to make a response (e.g., press one of two or more response buttons) which is followed by explicit feedback. Over the course of these tasks, feedback predictions/expectations are formed in the period between response execution and feedback presentation (anticipation stage). They are continuously adapted and may directly affect the (neural) processing of feedback stimuli in the outcome stage. Along these lines, brain activation or neural responses that arise in response to cues signaling the impending delivery of specific feedback stimuli reflect feedback predictions [e.g., monetary incentive delay task from 41].

It is also helpful to consider which types of studies can provide insight into the role of the cerebellum in feedback processing and feedback-based learning in humans: First, patient studies, for example in individuals with cerebellar lesions [e.g., 42], can characterize deficits that result from cerebellar damage.

Second, task-based fMRI studies in healthy subjects can shed light on cerebellar activations and cerebello-cerebral interactions associated with the processing of feedback stimuli, e.g., in the context of reversal learning [39]. Regarding the interpretation of cerebellar activations assessed with fMRI, it is useful to keep in mind that granule cell metabolism accounts for most of the energy consumption in the cerebellar cortex [43], and that cerebellar cortical BOLD activation consistently lags behind cerebral activation in connected regions [44]. Thus, the BOLD signal of the cerebellar cortex can be seen as predominantly a reflection of its aggregate input via the ponto-cerebellar pathway. Of note, some previous fMRI studies did not report any cerebellar activations in tasks involving feedback-based learning [45, 46] or excluded the cerebellum entirely from the data acquisition [47]. Also, a review [48] and two activation likelihood estimation meta-analyses covering a broad variety of studies on learning from reward feedback analyzing specific reward types [e.g., monetary, food, erotic: 49] and different stages (e.g., reward anticipation and receipt) and aspects (e.g., valence) of reward processing in adolescents [50] did not report any cerebellar activations.

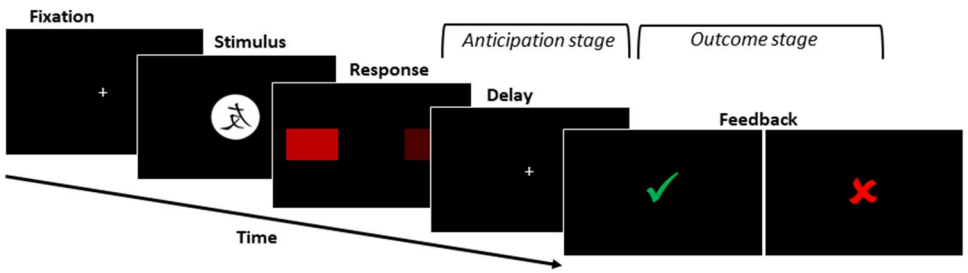

Fig. 2 Sequence of stimulus presentation in a generic feedback learning task in which abstract visual stimuli are presented upon which subjects choose between different response options and receive explicit feedback about their choice

Third, patient studies can also be combined with other methods, e.g., neuroimaging techniques such as fMRI or electroencephalography (EEG), in order to find out, in how far cerebellar damage affects brain responses to external feedback stimuli. For example, Rustemeier et al. [51] recorded brain activity in cerebellar lesion patients using EEG, assessing specific event-related potential (ERP) components that reflect feedback processing such as the feedback-related negativity [FRN: 52].

Last, studies using non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) applied to the cerebellum in the context of tasks involving processing of and learning from external feedback can also inform about cerebellar involvement in these processes. TMS can be used for both facilitation [53] or disruption of neuronal processes [54]. Most commonly, TMS is used to induce a temporary "virtual lesion" of a target brain area. TMS effects are very localized and can be observed immediately. Single-pulse TMS can be incorporated into fast-paced tasks in a trial-by-trial manner [55]. tDCS effects generally are less localized and build up over time. Since this technique alters the excitability threshold of neurons, it can also be used to facilitate (anodal tDCS) or inhibit activity (cathodal tDCS) in target brain regions [56]. Along these lines, tDCS or TMS applied to the cerebellum can directly manipulate cerebellar involvement in feedback learning and feedback processing. A meta-analysis by Gatti et al. [57] showed moderate effects sizes for cerebellar TMS on responses times and accuracy in different cognitive tasks, e.g., working memory and other tasks assessing executive functions. Regarding tDCS, Mannarelli et al. [58] showed effects of cerebellar cathodal stimulation (compared to sham) on the N2 ERP component in the EEG signal. The N2 is seen as an indicator of response inhibition which was also considered to be a subdomain of performance monitoring [36]. Hence, is stands to reason that this fronto-central ERP component and likely other ERP components originating in cingulate structures in the context of performance monitoring error-related negativity, ERN/Ne: [59, 60] and feedback-related negativity, FRN: [61], can be modulated by non-invasive brain stimulation in a task-based fashion.

In general, the substantial heterogeneity in previous findings, along with the variety of methodological approaches used in the previous works, clearly illustrates the need for a comprehensive review and systematization of cerebellar involvement in processing of and learning from external feedback. To this end, we systematically surveyed and integrated previous findings using a systematic review approach. We included patient studies to address possible alterations in behavioral performance and neuronal activation resulting from cerebellar damage. Studies using neuroimaging techniques such as fMRI and PET were also included if they involved feedback-based learning. Importantly, only studies were included in which external feedback on task performance was presented to enable human subjects (patients or healthy subjects) to adapt and optimize their behavior. Patient studies were restricted to those conducted in individuals with isolated cerebellar disease.

Aside from closing an important gap in the literature, the strength of the present review is the discussion of imaging studies that have not primarily focused on the cerebellum as a region of interest. Indeed, several previous studies collected and reported data on the cerebellum but did not discuss them in detail [e.g., 40, 62], even though these findings may provide important insights into the cerebellum's role in feedback processing and feedback learning. Ultimately, a more comprehensive understanding of cerebellar contributions to executive functions such as performance monitoring may have direct clinical relevance, as it can help inform, advance, and optimize treatment options for patients with diverse cerebellar diseases.

A preregistration of this review, including a detailed description of inclusion/exclusion criteria and hypotheses, can be found on osf.org (osf.io/2vfg8).

Hypotheses

In general, we expected findings to support direct cerebellar involvement in processing of and learning from external feedback in a non-motor context. In detail, we expected altered behavioral performance on cognitive feedback-based learning tasks in cerebellar patients. Of note, prior work hinted at the presence of compensatory processes likely relying on structural and/or functional reorganization in patients with chronic, focal cerebellar lesions [28, 63, 64]. We therefore expected altered behavioral performance on cognitive feedback-based learning tasks only in patients with progressive cerebellar degeneration as observed for error processing by Peterburs et al. [26] but not in patients with chronic focal cerebellar lesions.

Based on findings reported by Rustemeier et al. [51], we also expected to find alterations in EEG activity in patients with cerebellar degeneration compared to healthy controls during performance of tasks involving feedback processing and feedback-based learning. Specifically, we expected alterations in ERP components associated with feedback processing [e.g., FRN, 52, 61, 65], P300, [66, 67], and in time–frequency data/oscillations [68, 69]. In addition, fMRI studies conducted in patients with cerebellar damage (particularly due to progressive degeneration) should report altered activation patterns in response to feedback stimuli relative to healthy controls. Unfortunately, we did not find any other electrophysiological studies and no patient study using imaging that fulfilled our inclusion criteria.

Furthermore, we expected fMRI studies in healthy participants to yield activations in the cerebellum and/or in cerebral regions connected with the cerebellum via cerebellar-cerebral networks during tasks involving the processing of external feedback [e.g., 39]. We expected to find cerebellar activations before feedback presentation, thus in the expectation phase, and upon feedback delivery. We also expected feedback-related activity to predominantly involve posterolateral regions of the cerebellum. According to a functional cerebellar topography, these regions are more involved in complex, higher cognitive/non-motor functions [20].

Last, we would expect non-invasive cerebellar stimulation by either cathodal/anodal tDCS [see 70] or TMS (either single or double pulses that are delivered during task performance, or repetitive stimulation prior to task performance) to alter feedback processing and/or feedback learning in healthy subjects.

Methods

This systematic review followed the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [71]. A meta-analysis was not conducted due to diversity of experimental paradigms and heterogeneity in samples and methods. Eligibility criteria were assessed using the PICO framework (Patient, Intervention, Comparison, Outcome framework [72], see Table 1). Beyond the PICO framework, only full-text articles that were primary studies reporting original results (e.g., no reviews/meta-analyses) were included. Moreover, only studies collecting and analyzing quantitative data that were published in peer-reviewed journals and were available in the English language were considered. Studies focusing purely on the sensory and motor capabilities of the cerebellum and studies including patients with extra-cerebellar lesions were not included.

Information Sources

PubMed Database was used to identify relevant articles using the PubMed Advanced Search Builder and the building block approach in which keywords are grouped according to a superordinate term (see Table 2). Further, possibly relevant studies known to the authors were added to the outcome table for the third and final screening round (see below). Only studies that existed prior to the preregistration of this systematic review were used (until 01.07.2021).

Search Strategy

To identify relevant search terms, candidate search terms were created and structured according to the building block approach (see Table 2). Search terms were thematically grouped into three distinct key concepts: cerebellum, feedback processing, and performance monitoring. We then manually screened titles in the reference list of Peterburs and Desmond [36] for search terms related to each concept. Each list of candidate search terms was then expanded by adding relevant MeSH (Medical Subject Headings) terms and/or other relevant synonyms related to each key concept (see Table 2). After candidate search terms had been identified, we searched each key concept one at a time by applying an OR operator between search terms, followed by combining all concepts including the respective keywords with the AND operator for the combined search. In addition, search results were filtered in PubMed to only include studies published in English with human subjects. The initial search led

Table 1 PICO framework

Population
Humans
Adult participants (≥ 18 years old)
Healthy subjects and patients with a cerebellar disease/lesion
Intervention
Studies using feedback paradigms like: Reversal learning task, Probabilistic feedback learning task, Wisconsin Card Sorting Test, Weather prediction task, etc
Studies using fMRI, EEG, TMS, tDCS and other methods investigating the cerebellum
Comparators
Healthy and/or clinical comparison groups
Outcomes
Behavioral data: Accuracy, response times
Electrophysiological data: Event-related potentials (ERPs; FRN, ERN, P300), Neural oscillations
Neuroimaging data: Brain activation patterns

Individuals from the healthy control group must not present with any neurologic, psychological, or neuropsychiatric disorder. Individuals from the clinical control group must be diagnosed with a purely cerebellar disease/stroke

Table 2 Building block approach for the search strategy

Concept 1: Cerebellum
"Cerebellum"[Mesh] OR "Cerebellar Ataxia"[Mesh] OR Cerebellum OR Cerebellar OR Cerebellar ataxia OR Cerebellar hemispheres
Concept 2: Feedback processing
"Feedback, Psychological"[Mesh] OR "Formative Feedback"[Mesh] OR feedback OR "Feedback processing*"[tw] OR "reinforcement learning*"[tw] OR "prediction error*"[tw] OR "reward-based learning*"[tw] OR "associative learning*"[tw] OR "reversal learning*" [tw]
Concept 3: Performance monitoring
"performance monitoring*"[tw], "action monitoring*"[tw] OR "adaptive behavior*"[tw] OR "rule retrieval*" [tw] OR "executive functions*" [tw]
Final Search:
Concept 1 AND (Concept 2 OR Concept 3)

Two additional filters were used within the PubMed environment (Humans, English). The final search took place on the 1st of July 2021, 17:49 CEST with 1057 results

to $n = 839$ studies. However, five studies considered relevant and cited by Peterburs and Desmond [36] were not found with this search strategy.

Thus, we added additional keywords to our initial search strategy: Cerebellar hemispheres, reversal learning, rule retrieval, and executive functions. Using the final extended search strategy, we were able to identify $n = 1057$ articles from the PubMed database as eligible for abstract screening. In addition, we now identified three [73–75] out of the five studies which were previously not detected. The building of the final search can be seen in Table 2. Additionally, we added $n = 21$ articles from other sources for abstract screening that were not covered by our search strategy, which led to $N = 1078$ articles that were screened.

Screening

Abstracts and full-text articles were independently read by two reviewers (A.M.B. and S.S.) using the Abstrackr text-mining tool [76]. The settings "priority order" and "double selection" were used in the Abstrackr environment. Priority order re-orders the articles starting with the ones with greatest likelihood to be included after each round. Hence, Abstrackr continuously calculated predictions about which articles might be relevant based upon the reviewers' prior decisions and ordered them accordingly. Moreover, both reviewers used the same screening tool (see supplement Table S1) to first review all available abstracts and then the remaining full-text articles as suggested in the best practice paper by Polanin et al. [77]. The screening tool consists of several questions targeting the most important aspects of the abstract. This was done to ensure that both reviewers kept inclusion and exclusion decisions as objective as possible.

Additionally, we labelled the excluded articles according to the respective number of questions asked within the screening tool. We provided the reason for the exclusion of each article in the PRISMA Flow chart (see Fig. 2). A third (principal investigator J.P.) and fourth (D.M.H.) reviewer were consulted when discrepancies between the assessments of the two initial reviewers were found. The screening process started with a pilot round ($n = 20$ articles) so that questions and problems during the screening could be discussed at an early stage and to ensure that the Abstrackr algorithm was able to sort the articles as intended according to the pilot ratings. Following the pilot round, three main rounds were conducted (first round: $n = 300$, second round: $n = 300$, third round: $n = 458$).

Extraction

Data collection was combined with full-text screening and performed after all reviewers found a given article eligible. Two independent reviewers (AB and SS) were involved in the data extraction process (extraction tool, see supplement Table S2). To systemize data extraction, we developed a data extraction form (see supplement Table S3). The data extracted by each reviewer were compared, and major discrepancies such as missing details were discussed until resolved. Differences between extracted data in each extraction category emerged in only a few cases ($n = 6$) and were mainly related to the summary of the main and key results. Inaccuracies in the description of the sample size occurred in four cases and were corrected. The extracted raw data for each included study can be found in the supplemental material (Table S9). The collected data were synthesized in a comparative qualitative analysis in accordance with our research goals and hypotheses. Risk of bias was assessed evaluating the described sample size, statistical power (high power allowing the researchers to find and to discuss also small significant effects, if present), and the general methodological quality of the study (e.g., use of appropriate control group or condition, appropriate reporting of descriptive and inferential statistical results, correcting for multiple comparison). A study was additionally assumed to have a lower risk of bias if the hypotheses were preregistered. However,

none of the included studies were preregistered. The threshold of statistically significant reported results of each study was $p < 0.05$.

Risk of Bias

The objectivity of the selection process was ensured by using the questions of the screening tool, which helped the reviewers to systematically approach and assess the abstracts and full-text articles irrespective of their role and status in the research team (PhD student and student assistant) and their prior knowledge of the topic.

Interrater Reliability

Consensus between raters was continuously assessed throughout the screening and data collection process. Regular meetings were held to ensure that arising questions were addressed during the selection process. In case of discrepancies between raters, these were discussed with the principal investigator until consensus was reached. Interrater reliability was calculated at multiple time points during the screening process using weighted Kappa as well as the percentage of excluded studies. At the end of the selection process, interrater reliability was calculated to assess if the agreement between the raters was sufficiently high. Of note, due to the nature of the prioritizing option in Abstrackr, articles with low likelihood to be relevant were mostly rated in the later rounds of the screening process, which affected the calculation of weighted Kappa [78]. Weighted Kappa calculates the interrater reliability between two or more raters and is therefore affected by the distribution of ratings. We calculated weighted Kappa after each round to see if the screening patterns of both reviewers were consistent and agreement was high (first round = 0.41, second round = 0.50, third round = 0.97). The overall weighted Kappa was moderately high [0.62, 79, see supplement Table S4], while the percentage of agreement between the reviewers was very high (see supplement Table S5).

Synthesis

For qualitative literature synthesis, selected studies were grouped into patient and non-patient study (including behavioral, electrophysiological, neuroimaging, see supplement Table S6). As we aimed to understand the role of the cerebellum for feedback processing and feedback-based learning across studies with different kinds of samples, studies including only healthy participants were reported separately from studies with patient groups. Importantly, we included and synthesized results from methodologically diverse studies in order to draw the most comprehensive picture possible of the role of the cerebellum for processing of and learning from external feedback in the non-motor domain.

Results

A total of 1078 abstracts were screened, and 62 articles were selected for full-text reading, leading finally to 36 articles that were included into the review (Fig. 3). The majority of the studies were excluded because they did not include a feedback-based learning task (see Fig. 3 for more details on the exclusion reasons). Among the 36 included studies, we identified $n = 11$ patient studies of which one assessed feedback processing by means of EEG in addition to feedback learning. Of the eleven patient studies, most (7/11) provided data from patients with chronic cerebellar lesions, two included patient samples with cerebellar degeneration [80, 81], one study included patients who underwent neurosurgical resection of tumors located exclusively in the cerebellum [82], and one study included samples with different cerebellar diseases [15], e.g., neurodegeneration, stroke, inflammation of the cerebellum, supplement Table S7). Patient studies included data of a total of $N = 131$ patients. The remaining 25 studies included only healthy participants and were all imaging studies (fMRI: $n = 22$; PET: $n = 3$). A short description of each study can be found in the supplement Table S8.

Task Descriptions

In the following, a brief overview of the main types of feedback learning tasks used in studies covered by this review is provided. Importantly, all tasks had to contain (trial-by-trial) external feedback that participants could use to optimize their task performance. In the descriptions we will use the terms used by the authors of the studies. These are not necessarily mutually exclusive, as, e.g., a probabilistic learning tasks is also an associative learning task. In our description, we will, however, make clear, what the role of feedback is in these tasks.

In the *Wisconsin Card Sorting Tests (WCST)* and its *modified versions (MCST),* cards depicting geometric objects that differ in properties such as shape, size, and color are drawn from several decks and matched to a sample card. How a card should be matched follows a rule that changes over the course of the test, so participants must monitor and adjust their decisions based on feedback provided by the experimenter that indicates a correct or incorrect choice. Test performance is measured as the number of categories completed, the number of perseveration responses (repeating a certain response option), and the number of perseverative errors (i.e., repeating the error).

In *non-motor associative learning tasks* that include external feedback information [e.g., 80, 81], the association

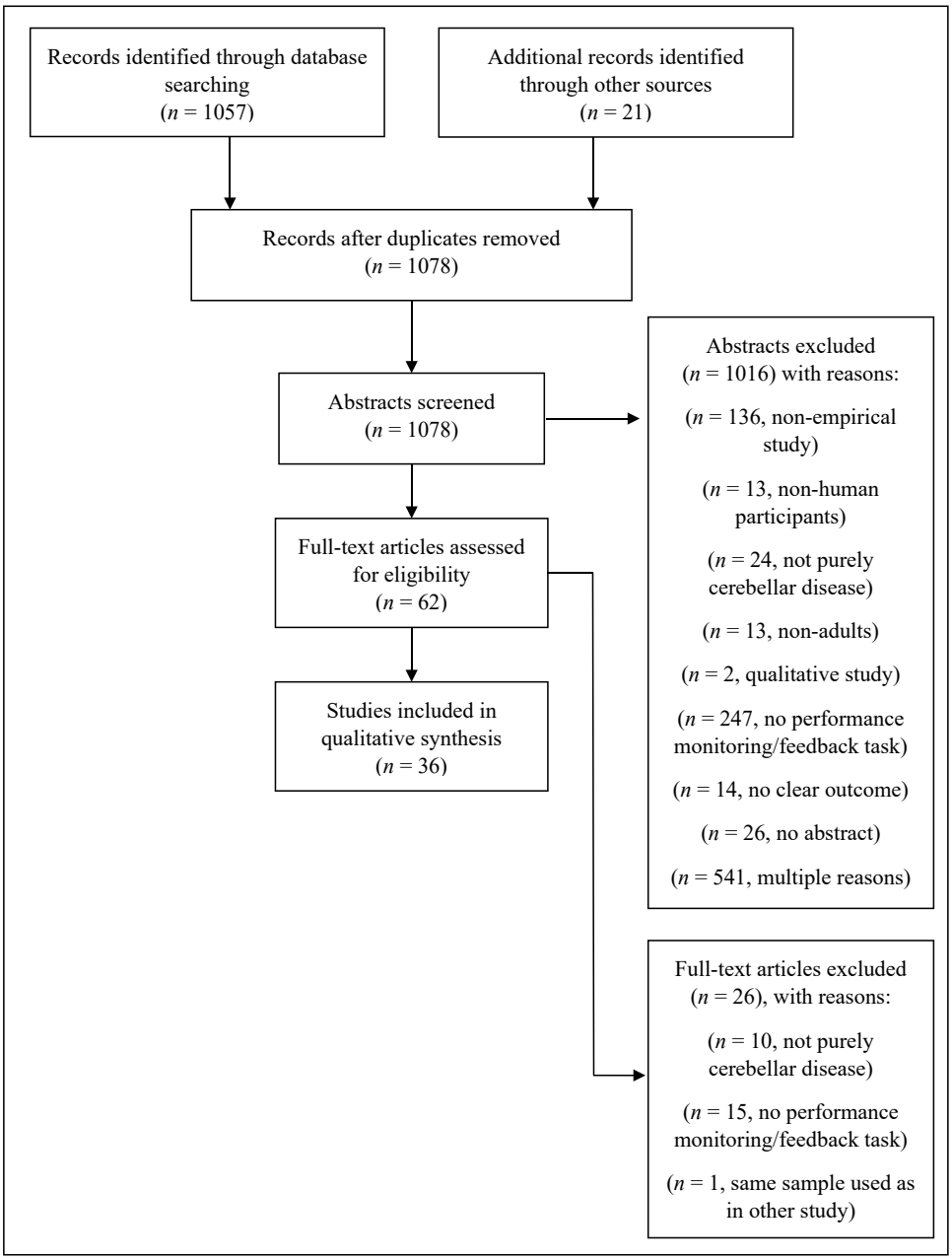

Fig. 3 Preferred reporting items for systematic reviews and meta-analyses flow diagram (PRISMA statement)

between response options and specific stimuli must be learned by trial and error. A correct choice is indicated by a sound and an erroneous choice by the dis- and reappearance of the stimulus which indicates that a different button must be pressed.

In *probabilistic learning tasks*, a specific case of associative learning, the reward contingencies for a stimulus-response association are not 100 percent so that correct responses are not invariably followed by positive feedback/reward but instead in some cases by negative feedback/non-reward. This increases task difficulty and preserves a degree of exploration behavior. Probabilistic learning can involve *reversal learning* which means that stimulus-response contingencies change throughout the task so that responses that were previously (probabilistically) associated with positive feedback are now associated with negative feedback and vice versa, and response strategies must be adapted accordingly.

In *monetary incentive delay (MID) tasks*, the prediction and anticipation of rewards or punishments can be varied as well as the chance of delivery of the respective outcome (outcome may or may not appear accordingly) indicated by incentive cues reflecting reward probability and magnitude. These incentive cues are presented before the target stimulus and response time window. Performance can be improved based on the provided feedback of winning or losing the

indicated reward [for a review on the MID, see 83]. Importantly, studies using this task typically focus on reward anticipation or expectation, e.g., by assessing brain responses to the incentive cues.

Studies in Patients with Cerebellar Damage

Out of the eleven patient studies, five reported worse performance in the respective cognitive feedback-based learning tasks in cerebellar patients compared to healthy controls [80–82, 84, 85], $n = 67$). Two studies reported no clear evidence for or against cerebellar involvement [15, 86], $n = 16$). Four studies did not find performance differences between patients and controls, or relative to the norm values for the respective versions of the WCST/MCST [87–89], $n = 36$) and no differences between patients and controls in a probabilistic learning task [51], $n = 12$). Importantly, not all patient studies provided the same information on the subscales of the WCST. For instance, the percentage of perseverative errors as an index of deficient feedback-based learning was only reported in five studies (out of eight), and some only provided a mean for the categories completed [84] or z-score of overall performance [15], see Table 3). As outlined above, only five studies reported impaired performance. Deficits were found in feedback learning in patients with cerebellar degeneration [80, 81] who exhibited difficulties in identifying correct associations and needed more time to reach a specific learning criterion as compared to healthy controls. Furthermore, MCST and WCST findings showed fewer completed categories and/or more perseverative errors in patients (MCST in cerebellar stroke patients: [84], WCST in cerebellar lesion patients: [85],WCST in patients with resected cerebellar tumors: [82]. Interestingly, Mak et al. [82] and Mukhopadhyay et al. [85] both reported fewer categories completed and more perseverative errors in patients. However, a significant difference in the percentage of perseverative responses between patients and controls was only found by Mak et al. [82], while the difference was non-significant in the study by Mukhopadhyay et al. [85].

The study by Thoma et al. [86] did not report altered MCST performance in patients with chronic stroke of the cerebellum relative to a matched control group. However, this study revealed a selective impairment in reversal learning based on reward feedback. While patients showed comparable learning success prior to reversal, and better learning of stimuli associated with larger relative to smaller rewards, patients demonstrated poor reversal learning. Moreover, in a subsequent probabilistic learning task, a subsample of patients who were classified as "learners" based upon their prior performance needed more trials to exceed a learning criterion when learning new stimulus-stimulus-outcome associations compared to healthy controls. Rustemeier et al. [51] did not find significant performance differences between patients with post-acute cerebellar lesions and healthy controls in a similar probabilistic learning task.

Despite the lack of performance differences in the probabilistic learning task between patients with chronic cerebellar stroke ($N = 12$) and controls in the study by Rustemeier et al. [51], EEG data revealed significant differences in the ERP. Patients showed higher (i.e., more negative) amplitudes in the FRN for negative compared to positive feedback and a more pronounced (i.e., more positive) P300 for positive compared to negative feedback. In contrast, FRN and P300 were not sensitive to feedback valence in controls. In addition to the initial probabilistic task, the researchers also applied a task with fixed reward contingencies to control for potentially confounding effects of feedback frequency on feedback processing. The results largely replicated the pattern described above. Of note, further analyses appeared to indicate that ERP alterations in patients particularly affected processing of positive feedback, although this effect was not consistently observed in both tasks.

Table 3 WCST/MCST results

Study	Year	Task	Categories completed	Pesevera-tion respones	Non-per-severative errors	Perse-veration errors	Errors	Overall score
Schmahmann	1998	WCST	"-"	"-"	"-"	"-"	"-"	n.s
Gottwald	2004	MCST	n.s	"-"	"-"	"-"	"-"	"-"
Turner	2007	WCST	"-"	"-"	"-"	n.s	"-"	"-"
Mukhopadhyay	2007	WCST	$P < C$	n.s	"-"	$P < C$	"-"	"-"
Thoma	2008	MCST	n.s	"-"	n.s	"-"	"-"	"-"
Manes	2009	WCST	$P < C$	"-"	"-"	"-"	"-"	"-"
Dirnberger	2010	WCST	"-"	"-"	n.s	n.s	"-"	"-"
Mak	2015	WCST	$P < C$	$P < C$	"-"	$P < C$	$P < C$	"-"

WCST Wisconsin Card Sorting Test, *MCST* Modified Card Sorting Test, $P < C$ (Controls significantly better than patients), *n.s.* non-significant difference, "- "=not available

Neuroimaging Results

All neuroimaging studies were performed in healthy participants (total $N=561$) but differed with regard to task designs, sample sizes, technical setup, and applied statistical analyses (see supplement Table S8). Importantly, all studies used trial-by-trial feedback for choice behavior. The coordinates of significant cerebellar (peak-) activations for ten studies and the respective analysis were transformed from Talairach into the MNI space using the MNI 2 Talairach Converter program [version 1.2.0, 2020/08/25, 90]. For each study, the coordinates are provided in the supplemental material (see Table S9). To make the distribution of significant cerebellar findings for each study more accessible, we labelled the extracted coordinates using the label4MRI package (version 1.2) in R (R Core Team, version 4.0.3) and RStudio ([91], version 1.3.959) and the AAL atlas taxonomy [92]. Subsequently, each study was assigned a symbol and the significant findings were inserted into a schematic flat map of the cerebellum inspired by the flat map from Diedrichsen and Zotow [93]. Importantly, this figure serves only as a rough illustration and does not represent the exact distribution of the significant voxels in the cerebellum of the calculated contrasts for each respective study (Fig. 4).

The main experimental paradigms in the imaging studies were as follows: seven studies used probabilistic/reversal learning ($n=194$), three studies used an MID task ($n=40$), three studies used a non-motor associative learning task ($n=35$), three studies used WCST/MCST ($n=70$), two studies used a modified version of a card game (Risk taking task, $n=20$; Card-guessing task, $n=26$), one study used a Markov decision task ($n=20$), one study used a modified version of the dynamically adapted motion prediction task ($n=25$), and one study used a modified version of the Eriksen-Flanker Task ($n=16$).

Substantial bilateral cerebellar activations were reported in fourteen studies [38, 42, 73, 75, 94–103], and resting state functional connectivity changes were shown in one study after conducting a task involving rule learning through feedback [104].

Berman et al. [42] contrasted the WCST with a control task (sensorimotor task = matching-to-sample task) and revealed stronger activations in the right (lateral) hemisphere as well as the left posterior hemisphere of the cerebellum. Lie et al. [75] contrasted different executive subdomains in the WCST and discovered increased bilateral cerebellar activations for matching information, error detection, and feedback processing. Ernst et al. [96] found significantly

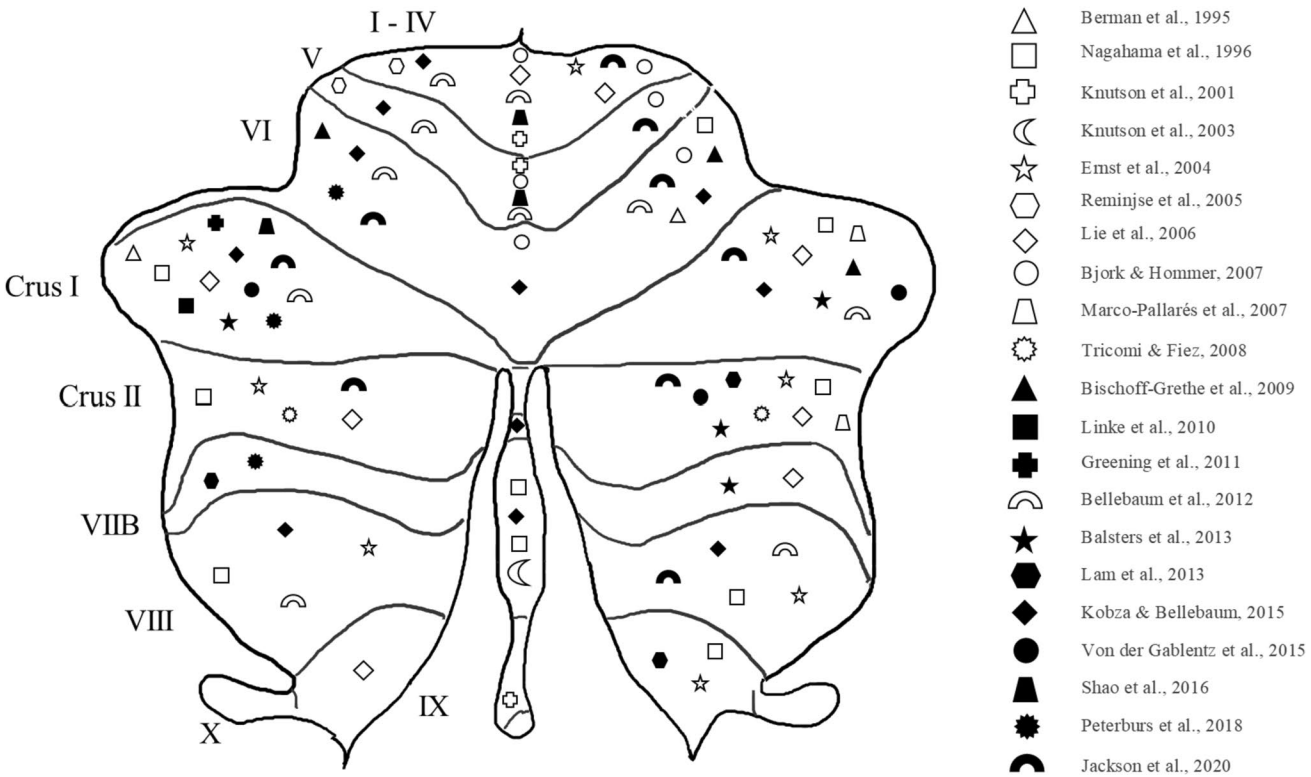

Fig. 4 Schematic illustration of the assignment of significant findings from each included imaging study (when coordinates were provided, $N=21$) to its respective region in a 2D flat map of the cerebellum according to the design in Diedrichsen and Zotow [93]. Importantly, the coordinates in $n=4$ studies were not provided

stronger bilateral cerebellar activation (left and right Crus I and lobule VIII, left Crus II) in a risk-taking Task (RTT: gambling card game) compared to a control task involving no decision making. A second run of the RTT also revealed significant bilateral cerebellar activation and right cerebellar peduncle activation when the data on the second run of the RTT were compared to the first run. In addition, Nagahama et al. [101] showed that the bilateral cerebellum was significantly more activated for the MCST relative to a matching-to-sample task. It has to be noted that brain activation in these two studies was averaged across task runs and thus did not reflect exclusively feedback-related activity. In contrast, more recent fMRI work by Tricomi and Fiez [103] did investigate feedback-related brain activations. Increased activation of the bilateral medial inferior cerebellum was found for negative relative to positive feedback trials in feedback-based paired association word-learning task [103]. Interestingly, Bischoff-Grethe et al. [94] reported increased bilateral cerebellar lobule VI activation following positive feedback and right cerebellar lobule VI activation following negative feedback compared to uninformative feedback.

Moreover, Bjork and Hommer [95] showed modulation of cerebellar activations by reward probability in an anticipatory period in which a motor response was necessary: activation in the left vermis IV and V was increased for high vs. low reward probability, and in vermis VI for medium compared to low reward probability. In addition, the right cerebellar lobule VI was active during reward presentation for high compared to low reward probability trials. In accordance with these findings, Lam et al. [100] also found that reward probability of a combination of cards had an influence on cerebellar activations. Here, the right lateral cerebellum was more active for high predictive value vs. low predictive value.

Bellebaum et al. [38] used a probabilistic learning task to contrast active and observational learning. Left lobules IV and V were more strongly activated for expected rewards compared to unexpected rewards in active learners. Observational learners showed increased activation in left lobules IV and V for unexpected feedback compared to active learners. In active learners, only right Crus I was significantly more active for expected non-rewards compared to unexpected rewards, whereas observational learners showed significant activations in bilateral Crus I and II, lobule VI and VIII. Contrasting active with observational learners revealed increased activation in the left lobule IV and V. The reversed contrast yielded more activation in right lobule VI. Activation related to prediction error coding across groups was found in left Crus I and right lobule VI. For active learners only, significant activations were also found in bilateral lobules VIII and right lobule VI. In observers, prediction error related activations were found in bilateral Crus I, right vermis IV and V as well as the left lobule IV and V. These findings thus suggest that the cerebellum may be differentially involved in feedback processing as a function of agency.

This notion was supported by Kobza and Bellebaum [99] who used a different probabilistic learning task (card-guessing task) to contrast active and observational feedback-based learning. Using the uncertainty associated with the card as parametric modulator for fMRI analyses, the researchers found activation in right lobule VI, right vermis VI, and left Crus I in observers. Additionally, when action-independent prediction errors were used as a parametric modulator, significantly increased activation in the right cerebellar lobule VIII and right Crus I were found in the active subsample. Action-dependent prediction errors used as parametric modulators revealed increased activation in right cerebellar vermis VII and left anterior lobules IV/V and left lobules VI and VIII in the active subsample. In addition, the comparison of active against observational for the action-dependent prediction errors demonstrated increased activation in the right vermis VII and left vermis III.

In another card-guessing task [102], participants had to first choose a face-up card out of three and subsequently another face-down card out of three with the instruction to choose the same card as the already determined one. Next, they had to bet credits on whether the cards matched. Feedback was presented as either a win or loss of money. In a second condition, the computer selected the cards and winning or losing was pseudo-randomized, but participants still had to bet credits. Bilateral activation of the cerebellum (labeling according to the provided coordinates: lobules IV and vermis IV and V) was found during the betting stage for the contrast previous winning vs. previous losing outcomes. Shao et al. [102] also reported stronger activation in the left Crus I during the betting stage for computer-generated choices compared to self-generated choices and after previous wins compared to previous losses.

In a modified version of the Eriksen-Flanker task that included reversal learning [97], participants had to respond to a central letter that was surrounded by flanker letters with either a left or right button press. They were informed by feedback if their stimulus-response association was correct or incorrect. The association itself switched across time according to a jittered interval. When a previously correct stimulus-response association switched, the first incorrect feedback was declared as "switch feedback". Von der Gablentz et al. [97] found increased activation in bilateral cerebellar lobule VIIa for incorrect feedback vs. switch feedback. In addition, the cerebellar vermis was found to be more active for switch feedback relative to correct feedback.

Balsters et al. [73] assessed cerebellar activations during learning of first and second order rules to investigate whether the cerebellum would be engaged only when rules specified

the properties of actions (i.e., first order rules = arbitrary stimulus-response mappings), or whether it would also be engaged in learning rules relating to cognitive control independent of action properties (i.e., second order rules which were devoid of motor information). Importantly, this study focused on brain activity in response to instruction cues that specified these rules, rather than the feedback provided in each trial. The most interesting finding in the context of the present review therefore is that the cerebellar lobules Crus I and Crus II were engaged in processing rule-related information irrespective of action properties.

Partially in line with this, Jackson et al. [98] also showed cerebellar activation in a modified second-order rule learning task. Here, the sample consisted of old and young participants. A local peak activation in the right lobule VI was found in older adults for the second order rule in correct trials compared to control trials. Nevertheless, clusters in Crus I and II were also active, but no local peak activation was found. In young adults, bilateral Crus II, right Crus I, and right lobule IV-VI and VIII were activated. Older adults showed more widespread activation compared to young adults. In addition, increased activation of left Crus II and lobules III and VI was discovered in older adults for feedback cues in all learning blocks compared to control blocks. In young adults, areas of peak activation were present in the bilateral lobule VI and bilateral Crus I in response to feedback cues during all learning blocks compared to control blocks.

Age-related differences in cerebellar activity were also demonstrated in a study by Edde et al. [104] in which a modified version of the dual-task paradigm [105] was used. Resting state functional connectivity (rsFC) data were acquired before and after the task with the cerebellum as a region of interest. Young adults (18–30 years of age) demonstrated post-learning activation changes within 44 pairs of brain regions. Forty-two pairs were connections of cerebellar with non-cerebellar regions. Distinct cerebellar networks were fronto-cerebellar, temporo-cerebellar, cerebello-cerebellar. Older adults (61–70 years of age) on the other hand showed fewer learning-related changes in rsFC than young adults and no involvement of cerebellar networks.

Activations restricted to the vermis were discovered in three studies [41, 106, 107]. Späti et al. [107] found increased vermis activation for losses relative to gains in a motion prediction task in which the reward contingencies were fixed. Knutson et al. [41] demonstrated significant activation in the cerebellar vermis for large vs. small rewards/punishments and found significant vermis activation during the anticipation of potential gain vs. no outcome and potential loss vs. no outcome in a subsequent study [106].

Activations restricted to the left cerebellum were found in five studies [39, 40, 62, 108, 109]. For reversal learning in probabilistic feedback tasks, three studies showed increased activation of the left cerebellum for affective switching, i.e., the inhibition of responses towards the previously rewarding stimulus that were now punished and the execution of responses towards the new rewarding stimulus compared to the baseline [40, 62, 108]. Moreover, using a reversal learning task, Peterburs et al. [39] found left-sided activations in lobule VI and VIIa.

Tanaka et al. [109] investigated reward-based learning in terms of predictions and prediction errors using a Markov decision task. In this task, one of three shapes was presented, and participants had to respond with either left or right button press. Feedback was provided as a monetary win or loss. The left lateral cerebellum was activated for future relative to immediate reward predictions. Also, increased activation of the medial cerebellum during immediate reward prediction was found.

Activations restricted to the right cerebellum were found and described in two studies [105, 110]. Marco-Pallarés et al. [110] reported significant cerebellar activations in right Crus I and II for positive compared to negative feedback. Rule information was manipulated in a dual-task study [105] in which a conditional learning task and a verb-generation task were both conducted simultaneously. Significant activation was found in right Crus I for highly informative cues, and a trial-by-trial analysis revealed that this activation decreased faster as learning progressed. In contrast, cerebellar activation in Crus I in response to less informative cues did not decrease with learning progression.

Discussion

The main goal of this systematic review was to identify and summarize findings pertaining to cerebellar involvement in processing of and learning from external feedback in a non-motor context, following the guidelines of the PRISMA statement [71]. Thirty-six studies met our criteria and were included. Among these were several patient studies, one of which addressed altered electrophysiological activity during feedback processing in patients with cerebellar lesions, and a larger number of fMRI imaging studies (either task-based studies or studies assessing cerebello-cerebral functional connectivity changes associated with feedback learning) conducted in healthy subjects. We did not find any study that used non-invasive brain stimulation techniques to target the cerebellum in the context of feedback-based learning tasks published prior to July 2021, i.e., prior to the preregistration of this systematic review.

Feedback Learning Performance in Patients with Cerebellar Diseases

The reviewed studies were very heterogeneous regarding tasks and sample characteristics. Likewise, findings were inconsistent: five patient studies reported impaired learning in cerebellar patients [80–82, 84, 85], $n = 67$), while four studies did not find performance differences between patients and controls [51, 87–89] $n = 48$), and two studies reported mixed findings [15, 86], $n = 28$). Aggregating patient samples within these three groups of studies yielded comparable overall sample sizes, further hampering a clear statement regarding the presence or absence of alterations of feedback-based learning in patients. Even within one single study, not all patients demonstrated consistent deficits, as outlined by Tucker et al. [81). Most patients had presented with cerebellar strokes with long intervals between lesion onset and study participation, and this passage of time may have allowed for some functional reorganization. In line with this, Schmahmann and Sherman [15] described improved or normalized executive task performance in "chronic" compared to "acute" cerebellar focal lesions. In addition, it has been shown that targeted rehabilitation may allow for substantial compensation regarding motor [111, 112] and cognitive deficits [113–115]. In contrast, cognitive performance in patients with neurodegenerative cerebellar diseases likely decreases with disease progression, similar to motor symptoms in different types of cerebellar ataxia [116–118]. Aside from time since lesion, lesion location in cerebellar stroke, and severity of cerebellar degeneration, other factors such as the age at lesion onset [119] have also been linked to the severity of cognitive deficits [see 120 and 121 for an overview on stroke related factors].

Only one of the included patient studies recorded electrophysiological data to assess feedback processing [51]. While behavioral data in this particular study did not show differences between cerebellar lesion patients and controls regarding learning from external feedback, the ERP components FRN and P300 indicated altered neural processing of negative and positive feedback in patients. Rustemeier et al. [51] concluded that these altered ERP patterns reflected impaired outcome prediction, although somewhat contrary to this notion, learning performance in patients was similar to controls. Given that in most patients, several years had elapsed between stroke onset and study participation (see supplement Table S7), functional reorganization and/or compensatory processes might help explain this discrepancy.

There is indeed evidence from various studies in cerebellar stroke patients that ERPs, in particular the P300 component, reflect functional improvement over the course of the disease [122–127]. However, the P300 in these cases was not obtained in feedback-based learning tasks. Additionally, stroke patients who recovered best from the injury demonstrated more symmetrical distribution of the EEG power spectrum compared to patients with poorer recovery across a period of six months (period between the stroke onset and the first examination was on average 28.16 days, $SD = 7.15$ days; [128]. Taken together, these findings suggest that EEG in general, and ERPs in particular, might be a useful tool to track changes in neural processing that occur during immediate post-stroke recovery, also in the context of cerebellar lesions.

Cerebellar Activations in Neuroimaging Studies

We reviewed functional imaging data of 25 studies (total sample of $N = 561$), all in healthy participants, demonstrating activations in the cerebellum and cerebellar-cortical networks during and after tasks involving feedback processing and feedback-based learning. Meta-analyses of functional imaging data with the cerebellum as the region of interest [10, 20], data on functional connectivity [129] or a combination of task-based and functional connectivity data [130], and task-specific parcellation [131] of the cerebellum provide the foundation for interpreting the different results. Buckner et al. [129] demonstrated functional coupling between lobules VI and VII and cerebral networks involved in cognitive control. Stoodley and Schmahmann [20] showed that bilateral Crus I, left lobule VI and VIIB were most active in tasks requiring executive control. Consistent with this, Keren-Happuch et al. [10] reported that the bilateral Crus I, left Crus II, right lobule VI and midline lobule VII were most active during executive processing. More recently, King et al. [131] parcellated the cerebellum into task-specific regions, but clear differentiation of executive tasks with a focus on feedback processing was lacking. The present review attempts to fill this gap, identifying studies with increased cerebellar activation while performing tasks involving processing of and learning from external feedback (e.g., WCST, MCST, RTT) compared to control tasks or conditions that control for several aspects of the respective version of the task [42, 75, 96, 101].

Our review of imaging findings found significant activation in bilateral Crus I and II (see Fig. 3 and Table S9) associated with feedback learning. For instance, Balsters and Ramnani [105] showed significantly increased activation of Crus I for "high learning cues" in which feedback information always reflected the performance in the current trial compared to "low learning cues" which did not. Performance under dual task conditions improved over time, which was interpreted as automatization of rule learning. Likewise, Balsters et al. [73] showed increased activation of Crus I and II during rule learning, highlighting that the posterolateral cerebellum was engaged in processing external, rule-related information irrespective of action properties

which is in line with its function as a "prediction machine" within the forward model.

According to our findings, imaging data obtained in non-motor associative learning tasks underlined the significance of several aspects of feedback. First, the context of feedback is important. Tricomi & Fiez [103] investigated whether brain activation patterns differed for feedback that was informative but only arbitrarily related to performance compared to feedback that provided information about goal achievement. Regarding the cerebellum, the most interesting finding was that activations for negative relative to positive feedback were increased when feedback was tied to goal achievement. Second, feedback valence has been shown to differentially activate the cerebellum [e.g., 110]. Interestingly, positive compared to uninformative feedback was associated with increased bilateral activation in cerebellar lobule VI, and right cerebellar lobule VI was significantly more activated for negative compared to uninformative feedback demonstrating the significance of feedback information content [94]. These latter results may be taken to suggest that information content rather than valence is driving cerebellar activity. Along these lines, it could be speculated that the cerebellum may filter out irrelevant information before calculating the respective prediction.

In terms of expectations and prediction errors, previous feedback experiences may affect the anticipation of upcoming feedback, as has been shown for the electrophysiological indices FRN and P300 [132] as well as for the activity of several non-cerebellar brain regions including the anterior cingulate cortex (ACC) and basal ganglia [133, 134]. In this regard, Knutson et al. [41, 106] manipulated the anticipation of reward and punishment size (large vs. small and gain vs. no outcome) and demonstrated that both were associated with increased activation of the cerebellar vermis. This is in line with several studies demonstrating that particularly unexpected feedback was associated with significantly more activation in the cerebellum and suggests that the cerebellum is involved both during feedback prediction and the processing of prediction errors [40, 62, 97, 108].

In addition, cueing the certainty of feedback as a manipulation of expectancy yielded increased vermal activation and stronger right cerebellar activation during the processing of certain wins compared to certain losses. In a somewhat similar manner, higher predictive values of card combinations compared to lower ones led to stronger activation of the right lateral cerebellum [100]. Hence, the anticipation of an outcome could be modulated by cerebellar structures at an early stage before external feedback information is available. Evidence for early processing of feedback information was already found in the stimulus-preceding negativity, a negative slow wave in ERP that occurs before feedback presentation and is suggested to reflect the anticipation of meaningful information [135, 136]. However, no study has yet investigated whether the cerebellum may contribute to the stimulus-preceding negativity, which might be conceivable considering the cerebellar forward model.

Shao et al. [102] showed increased bilateral cerebellar activations (lobules IV) in the betting stage of a card-guessing game when subjects had won in preceding trials compared to when subjects had lost in preceding trials. Moreover, stronger activation in left Crus I was present when outcome expectation had to be articulated into a distinct value, and when participants had experienced more previous self-executed choices and previous wins. Interestingly, the effect of the interaction of agency (either the participant or the computer made the card selection) and outcome (positive or negative feedback) was stronger for computer-generated choices than self-generated ones, particularly after winning compared to losing, suggesting that the cerebellum is also involved in processing agency as a factor determining the optimal decision. Somewhat in line with this notion, action dependent and independent outcome prediction errors were associated with increased cerebellar activity in a subsample of active learners and for action dependent prediction errors when compared to observers [99]. In addition, predictions of future compared to immediate rewards were again associated with activation in the left lateral cerebellum, revealing that the time scale of the reward had an influence on how the cerebellum generated the prediction [109]. Also, feedback valence is an important aspect for adaptive control of behavior, given that only negative but not positive feedback indicates the need for change. Peterburs et al. [39] showed increased activation of cerebellar lobules VI and VIIa/Crus I for negative compared to positive feedback, and in left lobule VIIa/Crus I for the first positive feedback after switching compared to the final negative feedback before a switch. The authors pointed out that in a prior study by Lam et al. [100], no cerebellar activity was found for the feedback valence contrast likely due to the simplicity of the task itself. Therefore, task difficulty may impact how predictions are updated in the forward model [22] and could be a cause for substantial variance across the reviewed task and the respective cerebellar activation patterns. Aside from objective valence, the subjective value [33] and the timing of the feedback [137] have been shown to affect the neuronal circuits activated during learning. However, cerebellar involvement in feedback processing has not yet been investigated as a function of these factors.

Limitations

There are several limitations to our review that need attention. Importantly, we did not include unpublished work or grey literature because we focused on peer-reviewed articles that were retrievable on PubMed following the PRISMA guidelines. Since we anticipated that it would be difficult

to find appropriate studies using only this search strategy, we did consult the most relevant reviews on this topic and identified additional studies that did not report significant cerebellar findings in either the title or the abstract.

Another important limitation of this review concerns the fMRI studies. Our search strategy included the cerebellum as a key concept, among a few others, but we did not include studies that may have conducted whole brain analyses and reported no activity in the cerebellum during feedback-based learning. This is a crucial shortcoming since the chain of reasoning is solely built upon the significant cerebellar effects reported in the included studies. Nonetheless, many studies investigating feedback-based learning have focused on cortical [e.g., 138] and subcortical regions like the basal ganglia [e.g., 133, 139] and did not include the cerebellum as region of interest. However, there are also imaging studies that conducted whole-brain analyses in healthy participants and did not find or report any activation for contrasts similar to the ones described in the results section of this review [see 49, 50]. In addition, the study by Tricomi and Fiez [103] reported that the cerebellum was only partially scanned and thus further activations in the cerebellum might have remained undetected. Nevertheless, our search strategy revealed a large number of studies that reported cerebellar effects which could provide starting points for future studies.

To minimize the risk of bias, we used our screening tool and extracted data of studies that survived our inclusion criteria irrespective of the sample size and statistical method. However, the reported effects were mainly based on small sample sizes, especially in the patient populations, and therefore may have possibly limited statistical power (see supplement Table S7). In addition, the lack of studies using EEG, resting state and task-based fMRI as well as studies using non-invasive brain stimulation to stimulate the cerebellum to investigate cognitive feedback-based learning is an issue, and such results are clearly needed to complete the picture of cerebellar involvement in processing of and learning from external feedback.

Last, only studies published prior to July 2021 were included in the preregistration. However, since the peer review and publication process has taken more than 1 year, several new studies have become available. To address this limitation, we will include a brief summary of recent findings and development pertaining to the topic of this review in the following section.

Recent Developments

In a very recent activation likelihood estimation meta-analysis on the cerebellum's role in reward anticipation and outcome processing, Kruithof et al. [140] found bilateral activation patterns in the anterior lobe, lobule VI, left Crus I and posterior vermis across 31 studies using monetary-incentive delay tasks. In addition, activations were observed in the left lobule VI and the declive (vermian lobule VI) during processing of reward outcomes in 16 tasks. These results overlap with and complement the presently reviewed imaging findings. In a recent original study, Nicholas et al. [141] used a probabilistic feedback-based learning task and a semantic memory task in patients with cerebellar ataxia to investigate reinforcement learning in terms of prediction and prediction errors. Patients were impaired at reward learning from trial-and-error feedback but showed a preserved ability to learn to predict reward based on episodic memory. Regarding effects of cerebellar TMS on performance monitoring, a recent study reported a reduction of the ERN [142]. Due to the functional link between ERN and FRN [61], these findings certainly motivate investigations of the effects of cerebellar TMS on feedback processing as indexed by the FRN.

Conclusions

Findings concerning the notion of altered learning from external feedback in a non-motor context in patients with cerebellar diseases are inconsistent, with roughly half of the patients showing alterations when compared to healthy controls or normative performance. This could be attributed to heterogeneity, e.g., time elapsed since lesion onset, age at lesion onset, type and location of cerebellar damage, but also small sample sizes. In contrast, degenerative diseases of the cerebellum are associated with more pronounced performance deficits compared to chronic focal lesions, although data in this regard were limited [80, 81]. Electrophysiological or imaging data in patients on the role of the cerebellum in feedback processing is extremely sparse but points to cerebellar damage being associated with altered coding of feedback valence and prediction errors [51]. Imaging data in healthy subjects yielded a much more uniform picture, with cerebellar activations found in different regions depending on task type and respective contrast. Contrasts that specifically examined feedback anticipation or feedback receipt indicated that posterolateral regions of the cerebellum play a key role in performance monitoring [e.g., 39, 73, 98, 104, 105]. However, it must be noted that a number of imaging studies in healthy subjects failed to find cerebellar activations during feedback learning [49, 50], and fMRI data on feedback learning in cerebellar patients are missing to date. Therefore, the results of this systematic review must be interpreted with caution.

Notwithstanding, we believe that performance monitoring is a relevant concept for understanding the interplay between cerebral and cerebellar structures [36], and that this concept fits well into the proposed forward model [22, 24]. Future studies therefore should not underestimate the contributions of the cerebellum to higher cognitive functions, and researchers should consider including the cerebellum

as a region of interest when conducting imaging studies on feedback-based learning. We also highlight the need for more studies that use either electrophysiological measures or neuroimaging in patients with cerebellar diseases in order to better characterize the contributions of the cerebellum to processing of and learning from external feedback. It is conceivable that some of the typical deficits that patients with CCAS [15] present with, e.g., impaired verbal fluency, working memory, or affect regulation, may be at least partially rooted in aberrant processing of and learning from feedback, given that feedback processing is a critical step for generating predictions, and predictions, in turn, are helpful not only in working memory [e.g., 143], but also in social interactions [e.g., 144, for a review on the cerebellum and prediction for social contexts, see 145]. Therefore, a more comprehensive understanding of cerebellar contributions to executive functions such as performance monitoring, can help to establish and optimize treatment options for patients with diverse cerebellar diseases.

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Authors' Contributions A.M.B., D.M.H., and J.P. planned the review. J.P. supervised the project. A.M.B. wrote the first draft of the manuscript. A.M.B. and S.S. rated the abstracts, the full-text papers, and extracted the reviewed data. All authors contributed to manuscript revision and discussion and interpretation of results. All authors approved the final version of the manuscript.

The study protocol was preregistered on osf.org (osf.io/2vfg8).

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Declarations

Ethical Approval Not applicable.

Competing Interests The authors declare no competing interests.

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Research Article

The effect of cerebellar TMS on error processing: A combined single-pulse TMS and ERP study

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ABSTRACT

The present study investigated temporal aspects of cerebellar contributions to the processing of performance errors as indexed by the error-related negativity (ERN) in the response-locked event-related potential (ERP). We co-registered EEG and applied single-pulse transcranial magnetic stimulation (spTMS) to the left posterolateral cerebellum and an extra-cerebellar control region (vertex) while healthy adult volunteers performed a Go/Nogo Flanker Task. In Go trials, TMS pulses were applied at four different time points, with temporal shifts of -100 ms, -50 ms, 0 ms, or +50 ms relative to the individual error latency (IEL, i.e., individual ERN peak latency + median error response time). These stimulation timings were aggregated into early (-100 ms, -50 ms) and late (0 ms, +50 ms) stimulation for the analysis. In Nogo trials, TMS pulses occurred 0 ms, 100 ms, or 300 ms after stimulus onset. Mixed linear model analyses revealed that cerebellar stimulation did not affect error rates overall. No effects were found for response times. As hypothesized, ERN amplitudes were decreased for cerebellar stimulation. No significant differences were found for the error positivity (Pe). Similar to TMS application to probe cerebellar-brain inhibition in the motor domain, the inhibitory tone of the cerebellar cortex may have been disrupted by the pulses. Reduced inhibitory output of the cerebellar cortex may have facilitated the processing of error information for response selection, which is reflected in a decreased ERN.

Keywords: Error processing, cerebellum, cognitive control, EEG, single pulse TMS, performance monitoring, executive functions

1. INTRODUCTION

The cerebellum is assumed to be strongly involved in making predictions, processing error information, and adjusting behavior not only in the motor but also in the cognitive domain (King et al., 2019; Sokolov et al., 2017). Specifically, it has been suggested to generate internal models of movement and thought that are crucial for efficiency and precision in adaptive control (Ito, 2008; Koziol et al., 2014; Wolpert et al., 1998). These internal models reflect the process of error detection and correction in

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which the cerebellum functions as a comparator, comparing the actual and predicted outcomes of actions and adjusting the predictions accordingly. Along these lines, performance monitoring, which includes error and feedback processing, has been proposed to be an overarching function of the cerebellum (Peterburs & Desmond, 2016).

Performance monitoring can be indexed by the error-related negativity (ERN) in the event-related potential (ERP) in the electroencephalogram (EEG). The ERN, a relative negativity that typically peaks within 100 ms after an erroneous response, is interpreted to reflect processes related to the detection of errors (Falkenstein et al., 1991; Gehring et al., 1993) or response conflict (Botvinick et al., 2001; Yeung et al., 2004). The ERN has a symmetric, frontocentral scalp distribution, and its neural generator is likely in the anterior cingulate cortex (ACC) or supplementary motor area (Dehaene et al., 1994; Herrmann et al., 2004). It has been proposed that the ACC is critical for detecting conflict and conveying conflict-related information to other brain regions such as the lateral prefrontal cortex (Cohen et al., 2000). The ACC is also a key structure for evaluating actions and their outcomes, thus playing a critical role for reinforcement learning (Holroyd & Yeung, 2011).

Findings from studies in patients with cerebellar diseases suggest that the cerebellum contributes to the processing of errors and response conflict. Specifically, the ERN was shown to be reduced in patients with focal post-acute vascular lesions of the cerebellum (Peterburs et al., 2012) and cerebellar degenerative disease (Peterburs et al., 2015). The latter patient group also exhibited increased error rates, and the ERN reduction and behavioral impairment were linked to gray matter volume loss in posterolateral cerebellar regions (Peterburs et al., 2015). In contrast, patients with post-acute cerebellar lesions did not show altered behavior. However, another ERP component related to error processing, the error positivity (Pe), a relative positivity occurring 200–400 ms post-response that has been linked to more conscious aspects of error processing (Falkenstein et al., 1995), was increased (Peterburs et al., 2012). Interestingly, the Pe was unaffected in patients with progressive cerebellar degeneration (Peterburs et al., 2015). This result pattern could be indicative of a compensatory mechanism that may help maintain behavioral performance in patients with longstanding lesions but is absent in patients with cerebellar degenerative disease. In contrast, Tunc et al. (2019) investigated error processing in patients with different types of spinocerebellar ataxia (SCA) and failed to find behavioral impairments beyond a slowing of response times. However, they did report a trend-level reduction of the ERN in patients compared with healthy controls, which conforms to previous findings (Peterburs et al., 2015). The less pronounced neurophysiological differences and discrepancy in behavioral results compared with the study by Peterburs et al. (2015) may be attributed to sample differences (e.g., SCA subtypes with extra-cerebellar degeneration included in the study by Tunc et al., differences in extent and location of cerebellar degeneration). Cerebellar degeneration in Crus I, Crus II, and the deep cerebellar nuclei may cause stronger effects on error processing than the degeneration of other, more motor control related regions of the cerebellum, such as the anterior regions (see King et al., 2019 for a detailed overview on different cognitive functions reflected in different regions of the cerebellum).

While these patient studies provided strong evidence for a role of the cerebellum in error processing, testing patients is not the only option to probe such cerebellar involvement. An alternative approach that offers the possibility of direct manipulations of brain activity is to use non-invasive stimulation of the cerebellum. Transcranial magnetic stimulation (TMS) is a widely used non-invasive brain stimulation technique that can be applied to a variety of brain regions (for a review, see Grimaldi et al., 2014) to establish causal links to behavior (see Vaidya et al., 2019). Single-pulse TMS (spTMS) is assumed to be useful for both facilitation (Shirota et al., 2012) and disruption of neuronal processes (Pascual-Leone, 1999) and can be used in fast-paced task designs (Verleger et al., 2009). A number of studies have targeted the cerebellum with TMS, among other techniques, to investigate cerebellar-brain inhibition (Ugawa et al., 1995; Fernandez et al., 2018). For instance, Ugawa et al. (1995) demonstrated that the motor cortex could be influenced by stimulating the cerebellum. The cerebellar cortex inhibits the deep cerebellar nuclei, which are the only output source of cerebellar projections to higher cortical regions via the thalamus (Palesi et al., 2017). The TMS pulse triggers activity of the cerebellar cortex that suppresses motor cortical excitability in M1 via increased inhibition of the cerebellar nuclei. Notably, effects of cerebellar TMS have also been reported in the non-motor domain. Stimulation of the right superior cerebellum led to increased response times in a verbal working memory task (Desmond et al., 2005) and disrupted phonological prediction (Sheu et al., 2019). We, thus, assume the influence of spTMS on the cerebellum to be similarly disruptive for other cognitive domains like the processing of performance errors.

Mannarelli et al. (2020) used cathodal transcranial direct current stimulation (tDCS) to the cerebellum before healthy participants performed a Go/Nogo task. In contrast to the facilitating effects of anodal tDCS, cathodal tDCS causes a hyperpolarization of neurons, making upcoming action potentials harder to trigger. After cerebellar tDCS compared with sham stimulation, the Nogo-N2, a negative ERP component peaking around 250–300 ms post stimulus onset (Folstein & van Petten, 2008), was reduced. The N2 has been linked to response inhibition and cognitive control, with decreased amplitudes indicating improved performance monitoring in terms of cognitive flexibility (Larson & Clayson, 2011). In addition, false alarm rates were increased. These results provide the first evidence that cerebellar neuromodulation alters behavioral and ERP indices of performance monitoring and cognitive control. In particular, it has been suggested that the stimulus-locked N2 and the response-locked ERN may reflect activity of the same underlying error monitoring system (Ferdinand et al., 2008; Folstein & van Petten, 2008; van Veen & Carter, 2002). Hence, perturbing cerebellar function by non-invasive brain stimulation should also affect error processing and the ERN, and this is what the present study aimed to demonstrate. However, it must be noted that findings on effects of cerebellar tDCS on cognition and motor behavior have been rather heterogeneous and inconsistent (Jalali et al., 2017), and the exact mechanisms on the cell or network level are still unclear (van Dun et al., 2017). TMS, on the other hand, allows for a more focal and controlled stimulation that can reach deeper regions in the brain by generating pulses in a time resolution of less than 1 ms (Koponen et al., 2018). Therefore, the present study made use of cerebellar spTMS (and stimulation of vertex as a control site) in a Go/Nogo Flanker Task (Voegler et al., 2018) to investigate effects on error processing. Guided by the previous patient studies (Peterburs et al., 2012, 2015), our main focus was on the response-locked ERP components ERN and Pe. The stimulus-locked ERP components Nogo-N2 and Nogo-P3 investigated in the previous tDCS study in healthy subjects (Mannarelli et al., 2020) were not the focus of the present work, so data on and analyses of these components are only provided as Supplementary Material. For a more comprehensive neurophysiological account, we have also exploratively analyzed induced theta power in the time-frequency domain as an index of cognitive control (e.g., Cavanagh & Frank, 2014). Information on preprocessing, results, and discussion with respect to these dependent variables is provided in the Supplementary Material (see Figs. S11–S14).

We selected the left lateral cerebellum for stimulation with a double cone TMS coil because of several studies pointing towards the significance of posterolateral cerebellar regions for executive functions, which also encompass error processing (King et al., 2019; Sheu et al., 2019; Stoodley & Schmahmann, 2009). The experiment was conducted on two different days resulting in a fully within-subject design (each participant underwent both cerebellum and vertex stimulation). We followed the study design by Verleger et al. (2009) in which an spTMS pulse was delivered in each trial of a Flanker Task. As outlined above, spTMS has a high temporal resolution, and it can thus help elucidate causal links between brain and behavior. Thus, spTMS can also help elucidate temporal aspects of cerebellar contributions to error processing. Verleger et al. (2009) temporally shifted the pulses depending on an individually estimated peak latency of the lateralized readiness potential, a potential reflecting motor cortex activity leading up to voluntary movements, which was measured before the TMS blocks. In the present study, pulses were delivered at four different time points relative to the individual error latency (IEL, i.e., individual ERN peak latency + median error response time) in Go trials, and at three different time points relative to stimulus onset in Nogo trials.

Similar to deficits found in patients with cerebellar degeneration (Peterburs et al., 2015), we expected increased error rates in Go trials for cerebellar TMS compared to vertex TMS, but only when pulses were delivered before the responses, due to disturbance of the internal forward-model generated within the cerebellum (see Ramnani, 2006). Concerning the ERN, patients with cerebellar damage showed reduced negativity in the error-correct difference signal in the typical ERN time window (Peterburs et al., 2012, 2015). Consequently, we expected a reduced ERN for cerebellar TMS compared to vertex for pulses that were applied 100 ms and 50 ms before the IEL, since these time points should precede the onset of error processing. Since the Pe in patients with cerebellar lesions was interpreted to be the result of long-term compensatory processes of the brain (Peterburs et al., 2012), we did not expect effects of cerebellar spTMS on the Pe. Further, more exploratory hypotheses regarding response inhibition in Nogo trials as reflected in Nogo-N2 and Nogo-P3 and an additional analysis on the induced theta power are provided and discussed in the Supplementary Material.

2. METHODS

2.1. Sample

Twenty-five young and healthy participants were recruited through newspaper advertisements and postings at Heinrich-Heine-University Düsseldorf. Data from nine participants had to be excluded from the analyses: two participants attended only the first appointments necessary for study completion, further two participants complained of mild headaches during the task and dropped out, a miscalculated TMS onset value was used in another two participants, two participants made too few errors in the main task, and another misunderstood the task. Concerning the pre-task, which was used to determine the individual error latency (IEL, see below), we aimed to repeat the Go/Nogo Flanker until participants who committed at least six errors in all conditions, because at least six error trials are needed to reliably measure the ERN (see Olvet & Hajcak, 2009; Pontifex et al., 2010). For one participant we only discovered post hoc, after trial inspection and removing double responses, that only five error trials in one condition remained (see Table S1 in the Supplementary Material). As the ERN was clearly visible after averaging the five error trials, we decided to include the participant in further data analysis. The final sample thus consisted of 16 participants. The required sample size was estimated based on studies which used cerebellar spTMS in a different task (n = 17, Desmond et al., 2005; n = 10, Panouillères et al., 2012; n = 23, Sheu et al., 2019), or spTMS at another location in a Flanker task (n = 20, Danielmeier et al., 2009; n = 21, Klein et al., 2014; n = 8, Soto et al., 2009; n = 12, Verleger et al., 2009). Participants were healthy adults (age range 19–32 years, M = 24.00 years, SD = 3.70, n = 13 females, n = 12 right-handed and n = 1 ambidextrous; for more details, see Table S1 in the Supplementary Material). As TMS uses electromagnetic pulses, exclusion criteria were metal parts within the body (e.g., implants, pacemakers, shards of metal, pumps for medication), spinal fractures, acute heart attacks, or pregnancy. Further exclusion criteria were current psychiatric disorders, neurological disorders, alcohol or substance abuse, and intake of medication affecting the central nervous system. Participants were paid 40 Euros for participating in the two appointments. All participants gave written informed consent. The study was preregistered on the Open Science Framework (OSF: https://osf.io/6v9pa) and was approved by the Ethics Committee at the Faculty of Medicine of Heinrich Heine University Düsseldorf in accordance with the Declaration of Helsinki.

2.2. Questionnaires

Participants had to fill in a demographic questionnaire as well as the "Mehrfachwahl-Wortschatz-Intelligenztest" (IQ: M = 98.75, SD = 10.88; Lehrl et al., 1977), a multiple-choice vocabulary intelligence test.

2.3. Go/Nogo Flanker task

Participants completed a modified Go/Nogo Flanker task coded in the software *Presentation* (version 20.0, Build 02.20.17, Neurobehavioral Systems, Inc.). Figure 1 provides a schematic illustration of the time course and sequence of stimulus presentation in each trial. The main task consisted of 600 trials in four blocks. Go trials made up 80 % of all trials (480 trials), while Nogo trials made up 20 % of all trials (120 trials). In 80 % of Go Trials (384 trials), the flanker arrows aligned with the central target arrow (congruent trials), while in the other 20 % of Go trials (96 trials), the flankers pointed in the opposite direction (incongruent). Each trial started with the onset of arrow flankers positioned above and below a fixation cross for 200 ms. During Go trials, the fixation cross was replaced by the central target arrow to which participants had to respond by pressing the corresponding (left or right) button on a response pad with the index or middle finger of their right hand, respectively. Participants were instructed to respond as fast and as accurately as possible. If participants did not press one of the two buttons within the response time window of 350 ms (alternatively 400 ms, when the miss rate was too high in the flanker pre-task), a reminder to respond faster was displayed. No feedback was provided concerning the correctness of the response. During Nogo trials, the fixation cross was replaced by a filled circle, to which participants should suppress their response and not press a button. As in Go trials, the flankers together with the circle were displayed in the response time window for 350/400 ms. Thereafter, a fixation cross without flankers was displayed for 500 ms. During the subsequent inter-trial interval, the fixation cross was presented for a further 900–1300 ms (jittered).

Since the aim of the present study was to disturb error processing on a trial-by-trial basis using TMS pulses applied to the cerebellum and to elucidate temporal aspects of cerebellar involvement in error processing, it was critical to determine the time point at which cerebellar input was needed for error processing. More specifically, cerebellar input could be needed at the very onset of error processing or a bit later when error processing is already underway. To temporally approximate the onset of error processing individually for each participant, we

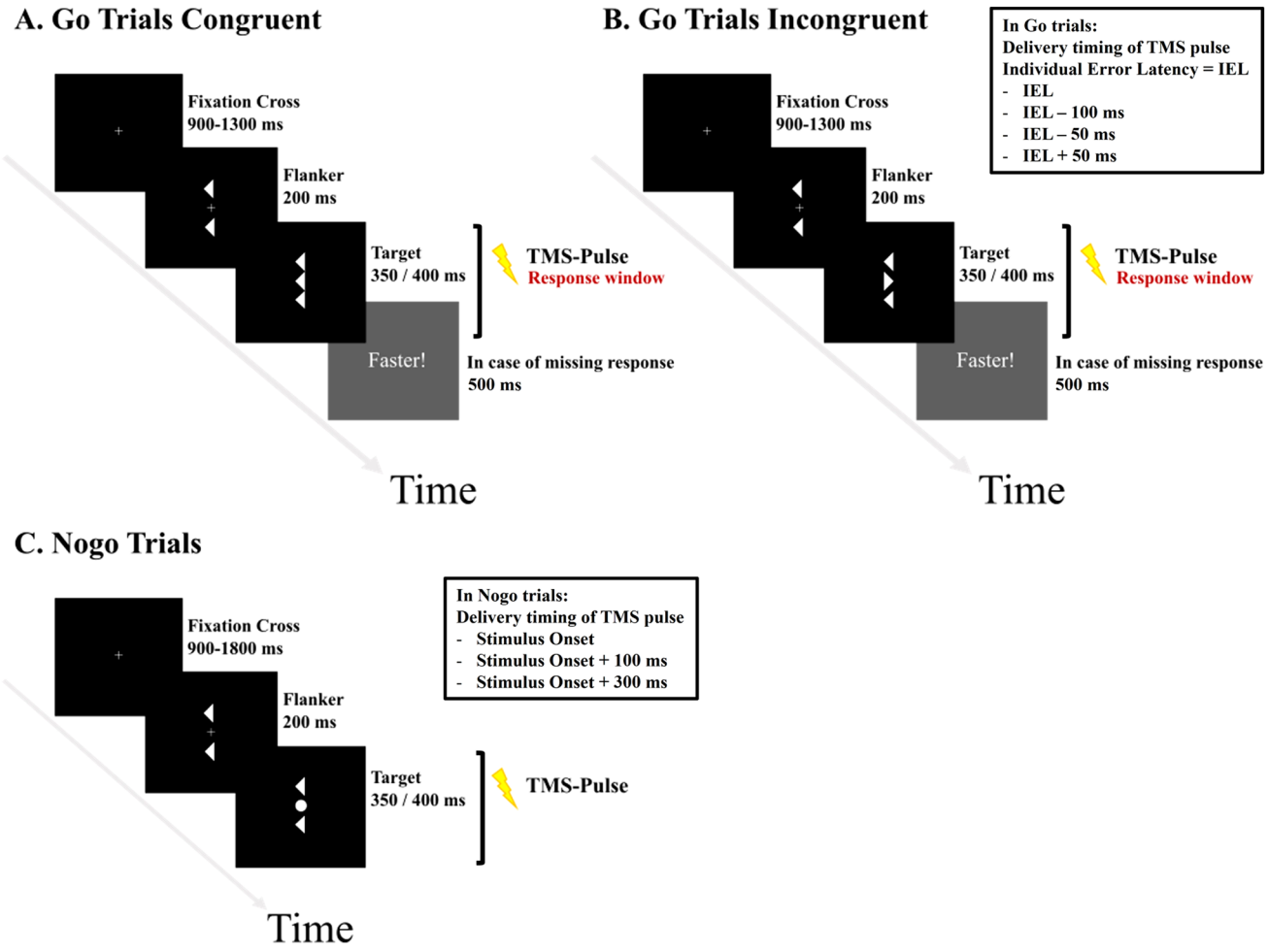

Fig. 1. Schematic illustration of time course and sequence of stimulus presentation in a trial of the Go/Nogo Flanker Task. Go trials with congruent flankers (A) and with incongruent flankers (B) relative to the target arrow in the center. Only one single pulse was applied in each trial. TMS pulses were delivered for Go trials shortly before the IEL (-100 ms, -50 ms), at the IEL, or shortly after the IEL (+50 ms). (C) In Nogo Trials, the target stimulus indicating the need to inhibit the response was a circle. TMS pulses were delivered at stimulus onset or shortly after target onset (+100 ms or +300 ms).

determined the IEL using a Flanker pre-task without pulses. This Flanker pre-task consisted of the same ratio of Go and Nogo Trials as the main task (120 trials in total, 80 Go and 40 Nogo trials). The IEL was calculated by adding the median error response time to the latency of the ERN in the response-locked ERP. If a participant was unable to respond within the standard response time window of 350 ms in more than 25 % of trials in the pre-task, the task was repeated with an increased response time window of 400 ms. This was done to ensure that enough valid trials were recorded. In total, three participants required the longer response time window.

Throughout the Flanker main task, monophasic single TMS pulses were applied within each trial. The time points at which TMS was applied differed for Go and Nogo trials. In Go trials, TMS pulses were delivered at the IEL (0 ms) as well as 100 ms before (-100 ms), 50 ms before (-50 ms), and 50 ms after (+50 ms). In Nogo trials, TMS pulses were delivered at fixed time points, that is, at stimulus onset as well as 100 ms and 300 ms after stimulus onset (+100 ms and +300 ms, respectively). Pulse timings relative to the IEL in Go and relative to stimulus onset in Nogo trials were randomized throughout the task but occurred an equal number of times per trial type and block.

2.4. Procedure

Upon arriving at the laboratory, the participants were seated in a brightly lit room in front of a laptop (DELL®

Precision M4800, 15.4 inch with a resolution of 1920 × 1080 pixels and a refresh rate of 60 Hz) with a response box (Cedrus RB-740, Science Plus Group, Groningen, NL) positioned before it. The distance between response box and laptop was kept constant. Only two keys were relevant for the task and had to be pressed with the index (left key) and middle finger (right key) of the right hand. A third key was used to navigate through pauses and instruction slides. After positioning the participants and putting earplugs in their ears, the EEG cap was aligned on the head, and the scalp electrodes were prepared. The electrodes on the cap were further covered with a plastic wrap to avoid any direct contact between electrodes and the TMS coil which could cause artifacts (Hernandez-Pavon et al., 2023). EMG electrodes were attached to the left hand, and the TMS stimulators were started and triggered via the laptop so that pulses were sent for the determination of the individual motor threshold (IMT). After IMT determination, the coil was firmly aligned and fixed with a custom mounting structure. Thereafter, the Flanker pre-task was started, in which no pulses occurred. Subsequently, another experimental task with spTMS was completed, which is not part of this manuscript. While participants were completing this task, we calculated the individual ERN peak latency and median response time for errors as described above. Subsequently, the IEL was calculated and used as an input value for the Flanker main task. Afterwards, the Flanker main task was performed. Participants underwent cerebellar and vertex stimulation in separate appointments. They were aware that both sessions included stimulation, but they were not explicitly informed about the specifics of the two stimulation sites. They were also naïve to the study's intent. The two appointments took place with a temporal gap of at least 48 hours (M = 82.13 days, SD = 143.36 days, range from 2 to 373 days). Due to a defect in the TMS stimulators, the second measurement had to be postponed for a long time, resulting in time gaps of 362 to 373 days for 3 subjects. Correcting for the delay of these subjects, the time interval between the two appointments was on average only 16.00 days (SD = 20.52 days, range from 2 to 74 days). The order of the stimulation sites was counterbalanced.

2.5. TMS-EEG-EMG interface

2.5.1. EEG system

A TMS compatible amplifier (BrainAmp MR plus, BrainProducts GmbH, Munich, Germany) was used with a cap containing 32 flat multitrodes. The flat electrodes minimize the distance between the coil and the skull surface. The following electrode sites were used: Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC1, FC2, FC5, FC6, Cz, C3, C4, CPz, CP1, CP2, CP5, CP6, T7, T8, Pz, P3, P4, P7, P8, Oz, O1, and O2. BrainVision Recorder software, version 1.21 (BrainProducts, Munich, Germany) was used for recording. Impedances were kept below 5 kΩ. Data were sampled at 1000 Hz.

2.5.2. EMG system

Two surface EMG Ag/AgCl-electrodes (20 × 15 mm, Ambu, Ballerup, Denmark) were placed on the left M. abductor pollicis brevis in resting condition to record the muscle activity in terms of motor evoked potentials (MEPs) that reflect the corticospinal excitability throughout the estimation period of the IMT. This also allowed us to check that no MEPs would be triggered by the TMS pulses during the tasks. The signal was amplified with a Digitimer D360 (Digitimer Ltd, Hertfordshire, UK). The frequency band of the filter was 100–5000 Hz and digitized at a sampling rate of 5 kHz (Signal version 6.02, Cambridge Electronic Design Ltd., Cambridge, UK).

2.5.3. TMS system

We estimated the IMT with a custom script in *Presentation* that sent a code to a single TMS stimulator (Magstim® 200²) every 10 seconds to elicit a pulse. The double cone coil was aligned so that we could stimulate the right motor cortex (region M1). After an MEP was detected in the EMG signal using the independent trigger mode in the software *Signal*, 5 consecutive trials (out of 10) were counted to determine whether the position also clearly stimulated the motor cortex. The output power of the device was then reduced until only 5 out of 10 trials elicited an MEP. The estimated IMT with additional 20 % power (corresponding to 120 % motor threshold) was used as the output power for the TMS system for both appointments. Nevertheless, we measured the motor-threshold on both appointments to see if there was any variability. Checking the IMT revealed no significant difference between the first (M = 38.20 %, SD = 7.84 %) and second appointment (M = 37.68 %, SD = 7.97 %), $t(37)$ = 0.20, p = .840, and no significant difference between the cerebellar (M = 37.80 %, SD = 8.15 %) and vertex (M = 38.11 %, SD = 7.64 %) stimulation appointments $t(37)$ = -0.12, p = .905. The TMS coil was either placed at the level of the left lateral cerebellum (3 cm left and 1 cm inferior to the inion; Hardwick et al., 2014) or at

the vertex position which corresponds to electrode position Cz of the international 10–20 system (Pizem et al., 2022, see Fig. 2 for an illustration, and Figs. S15 and S16 for real photographs in the Supplementary Material) with the voltage flow in the inferior direction. After the coil was correctly aligned, it was fixed with a custom stand so that the same position was maintained over the course of the session. In addition, we used a fabric elastic band to ensure that the coil-to-head distance was kept constant (forehead for the cerebellar TMS or chin for the vertex TMS). The distance of the coil to the head surface was observed during the task and adjusted during the pause between the individual, since even small changes lead to a decrease in the induced magnetic field strength (Hernandez-Pavon et al., 2023).

The BiStim TMS stimulators were manually charged before the first trial, and the independent trigger mode was selected in Signal for the subsequent tasks to trigger the stimulators. Then, the single-pulses were observed in the EMG-signal to ensure that no MEPs were evoked, particularly when stimulating the cerebellum. If MEPs had occurred, the session would have been interrupted, and the coil would be realigned, in order to avoid co-stimulating the brainstem. However, this did not occur during our study. Additionally, the coil position was constantly monitored and readjusted between the blocks and tasks if substantial movement had occurred to ensure that the distance between coil and scalp was consistent. Since the recharge period of a single Magstim® 200² stimulator exceeded the duration of a single trial, we alternated activation of two BiStim stimulators. Unfortunately, due to overheating of the stimulators, trials were lost in 3 participants towards the end of the task, for the TMS system no longer sent any pulses while the task and EEG measurements were still running. The time of termination was checked in the EEG signal, so that all trials without TMS pulses were excluded from analysis. The heat development in the stimulators was related to both

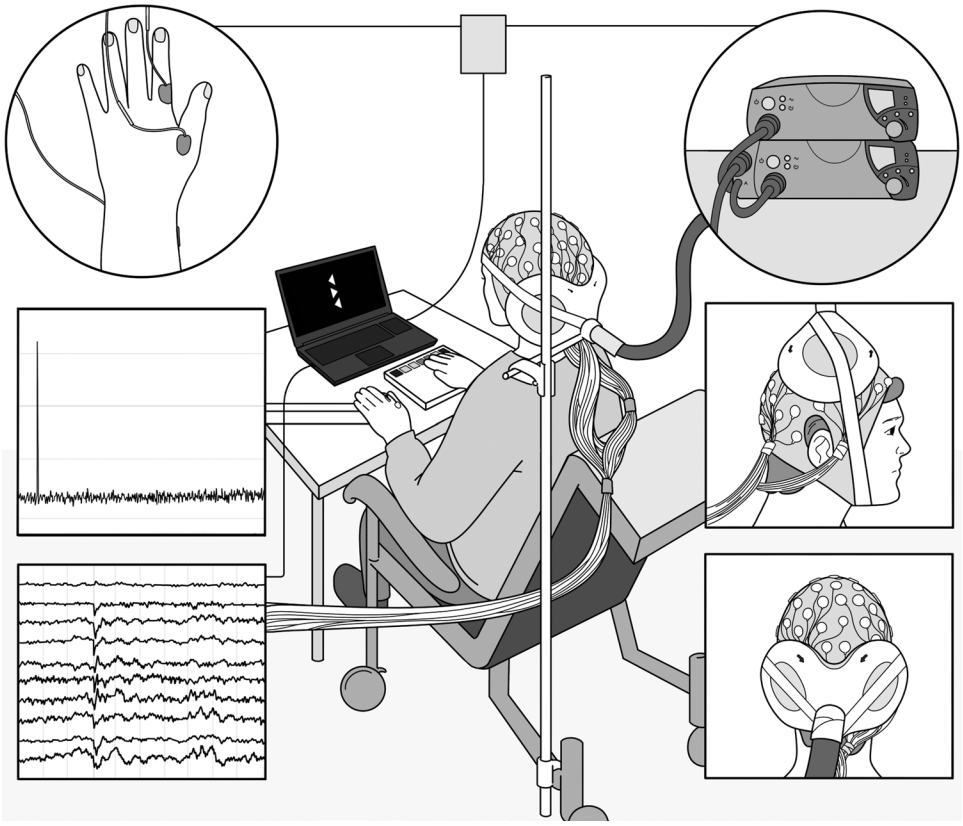

Fig. 2. Illustration of the TMS-EEG Setup for cerebellar and vertex stimulation. Top left circle shows the placement of the electrodes for recording of the EMG signal. Below, the TMS pulse is shown in the EMG signal. Bottom left, continuous measures of the EEG signal. Top right, TMS generators are shown. Below, the TMS coil orientation for vertex stimulation is shown and, in the bottom, right, the coil alignment for the cerebellar stimulation is presented. The voltage flow indicated by the arrows is aligned inferiorly. A double-cone coil was used for stimulation.

the high number of single pulses and the output power which varied greatly among the participants (see Table S1 in the Supplementary Material).

In case of a port conflict due to close proximity of two marker codes sent by the presentation laptop to the EEG system (i.e., codes sent within 5 ms), which may be the case for the response codes and matching TMS pulse codes, the later code was delayed until the port conflict no longer arose. The respective code timings were corrected in the EEG marker file using a custom script in MATLAB. Time points were not changed for the TMS pulse codes because the timing in the marker file always fitted the timing of the real TMS pulse. Instead, trials with a TMS pulse differently timed than the planned onset due to marker code delay were excluded.

2.6. Individual error latency estimation based on the flanker pre-task

ERN latency was determined by peak detection performed in BrainVision Analyzer software, version 2.1 (BrainProducts, Munich, Germany). All trials containing two or more responses were removed beforehand. Preprocessing for peak detection was performed as follows: First, data were re-referenced to the average signal of all electrodes, and the signal at FCz was re-established. Next, a DC detrend was performed, followed by low-pass filtering with a cut-off of 30 Hz and a slope of 12 dB/oct, high-pass filtering with a cut-off of 0.1 Hz and a slope of 12 dB/oct, and a notch filter set to 50 Hz. Subsequently, automatic ocular correction ICA was performed, and data were segmented into epochs of 600 ms, starting 200 ms before and ending 400 ms after erroneous responses. The baseline-corrected data (with the 200 ms period preceding response onset as baseline) underwent artifact rejection (only 3 trials were rejected across all participants and sessions) with the following settings: maximum difference of values over 100 µV or activity lower than 0.1 µV within an interval of 100 ms, voltage steps exceeding 50 µV/ms, or values above 100 µV or below -100 µV. Segments were then averaged, and peak detection was performed on a time window of 100 ms after the response, searching for a negative peak at site FCz.

2.7. Dependent variables

Behavioral outcome variables were error rates and response times in Go trials. For the EEG data, we analyzed the ERN for Go Trials in the response-locked ERP. In an exploratory analysis, the Pe (Go trials) was also analyzed. The ERN was defined as the local maximal negative peak in the error-correct difference signal within a time window of 100 ms post-response at site FCz (see Hajcak & Foti, 2008). The Pe was defined as the maximum positive peak in the difference signal within the time window between 200 and 400 ms post-response at Pz (see Larson et al., 2010). Follow-up analyses with the original waveforms were conducted to further elucidate if effects were specifically driven by altered ERP amplitudes for errors or correct responses. In addition, analyses of false alarm rates and Nogo-N2 and Nogo-P3 ERP components as well as analyses of induced theta power in the time-frequency domain are provided in the Supplementary Material.

2.8. Preprocessing of the TMS-EEG data

Preprocessing of the spTMS-EEG co-registered EEG raw data was conducted using the EEGLAB Toolbox (version 2021.1) in MATLAB (version R2021a) (MathWorks, Natick, Massachusetts, USA) and the Automated aRTIfact rejection for Single-pulse TMS-EEG Data (ARTIST) algorithm created by Wu et al. (2018). This algorithm provides an efficient and objective approach to preprocess raw EEG data and has proven to be superior to manual artifact rejection by experts and other algorithms such as TESA (Rogasch et al., 2017; Wu et al., 2018). Some of the default settings were adapted because the signal at electrode FCz, which had been used as online reference during EEG recording, needed to be re-established. In addition, the high pass filter of 1 Hz was kept, and the low pass filter was changed from 100 Hz to 30 Hz. The notch filter was changed from 60 Hz to 50 Hz. Electrode Iz was removed before applying the ARTIST algorithm because of low signal quality. The ARTIST algorithm creates segments around a given code which marks the onset of the TMS pulse. Here, segments were created with a length of 2500 ms, spanning 1000 ms before and 1500 ms after TMS pulse onset. Next, response onsets were checked by a custom script using MATLAB to ensure that only valid trials were included into the analysis (see above, some responses and therefore the respective response codes had overlapped with other codes within trials and were therefore delayed). In addition, we manually rejected trials without a TMS pulse (due to overheating or close proximity of two TMS pulses, see above) before re-referencing and segmenting the data. Following this, the ARTIST algorithm preprocessed the data in three distinct stages. In the first stage, large-amplitude artifacts were removed by applying DC drift correction, the removal and

interpolation of the TMS pulse artifact (15 ms prior to the TMS marker code onset until 5 ms after), downsampling of the data, and the removal of the TMS decay artifacts in a first ICA run. In the second stage, the AC line noise was removed, and the band-pass filter was applied. Then, the signal was segmented around the TMS pulse onset, and segments that exceeded the default thresholds were removed. The final step within the second stage was the removal and interpolation of poor channels. ARTIST interpolated on average 1.13 channels (*SD* = 1.13) per participant and stimulation site. In addition, on average, 44.13 trials (*SD* = 50.93) were rejected, including both trials which were manually rejected due to overheating (*M* = 29.25, *SD* = 39.67, range = 5–169) and trials which ARTIST rejected (*M* = 14.88, *SD* = 14.72, range = 1–63), with slightly more excluded trials in total for cerebellar (*M* = 47.56, *SD* = 54.69) compared to vertex (*M* = 40.69, *SD* = 48.41) stimulation (*N* = 16). In the third stage, poor independent components were removed in a second ICA run. The data average was referenced, and the baseline was corrected. The output data were imported into BrainVision Analyzer 2.1, and further segmentation was performed according to trial type (Go/Nogo). For Go trials, segmentation was done for response and stimulus onset separately for error and correct trials. The adapted scripts and raw data can be found in the following OSF folder: https://osf.io/jwfn9/

2.9. Statistical models

We deviated from our preregistration and ran mixed linear model (MLMs) analyses in R (R Core Team, version 4.0.3) using RStudio Team (2020: version 1.3.959) and the lme4 package (version: 1.1.25, Bates et al., 2014) in place of traditional repeated-measures ANOVA. This enabled us to analyze factors with missing values and use the participant as a random factor to further explain variance in the data. Meteyard and Davies (2020) proposed in their best practice guidelines for MLMs that the maximum model should be chosen, including all within-subject main and interaction effects as random effects. The maximum model should be only chosen if no errors in the model fit, in terms of converging errors or singular fits, appear, which would cause an overfitting of the model. To avoid this, the models were checked using an iterative process in which the within-subject highest order interaction was first included as random factor and the random slopes rejected subsequently in case of model fit errors. All our models included stimulation site and stimulation timing as fixed effects, but for some models, these factors were additionally included as random slopes depending on the model fit. In addition, Cooks distance (Cook, 1977) was calculated to identify potential outlier subjects before running the MLM analysis using the influence.ME package (version 0.9–9; Nieuwenhuis et al., 2012).

Before setting up our models for ERP analysis in Go trials, we grouped the four stimulation timings into a two-level factor, resulting in "early" and "late" stimulation. For this purpose, the -100 ms and -50 ms trials were combined into "early" and the 0 ms (at IEL) and +50 ms trials into "late." This allowed us to pool more error trials together, to better take into account the variability of the IEL within and across participants, and to compare the effect of stimulation timing on error processing over a broader time period.

To check for baseline performance differences between the two sessions in the Flanker pre-task, we calculated Linear models (LMs) comparing error rates (Go trials) and ERN amplitude between the cerebellar stimulation and vertex stimulation session (see Fig. S1 and Table S3 in the Supplementary Material).

To analyze behavioral performance in the Flanker main task for Go trials, we set up an MLMs for error rates including stimulation site (cerebellum, vertex), stimulation timing (early, late), and the interaction between these factors as fixed effects and added stimulation site and the interaction with stimulation site and stimulation timing as random slopes and participant as random effect in the model.

$$\text{Error rate} \sim \text{site} * \text{timing} + (1 + \text{site} + \text{site} : \text{timing} \mid \text{participant})$$

For response times, we included all responses to see whether there was a difference in response times between correct and error trials. In the final model, we included trial type (correct trials, error trials) as fixed effect and as random slope into the model equation.

$$\text{Response time} \sim \text{site} * \text{timing} * \text{trial type} + (1 + \text{site} * \text{trial type} \mid \text{participant})$$

In a third MLM, we analyzed error responses by their timing relative to TMS onset to identify a possible influence of the pulse itself on the error rates independent of the trial type. Here, the model was specified using the error rates as the dependent variable, stimulation site (cerebellum, vertex) and TMS timing (response preTMS, response postTMS) as fixed effects and random slopes:

$$\text{Error rate} \sim \text{site} * \text{TMStiming} + (1 + \text{site} + \text{site} : \text{TMS timing} \mid \text{participant})$$

For ERP analyses for Go trials, we analyzed the ERN and Pe peak amplitudes obtained from the difference wave as the dependent variables.

$$\text{ERN\_diff}(\text{amp}) \sim \text{site} * \text{timing} + (1 + \text{site} + \text{timing} \mid \text{participant})$$

$$\text{Pe\_diff}(\text{amp}) \sim \text{site} * \text{timing} + (1 + \text{site} \mid \text{participant})$$

In addition, we analyzed the original waveforms, entering the amplitudes at the time points corresponding to the ERN latency in the difference signal. We added fixed effects of stimulation site (cerebellum, vertex) and timing (early, late) and trial type (correct trials, error trials) for the analysis as well as the interaction between the fixed effects as well as the three factors as random slopes and participant as a random effect. In addition, the optimizer was changed from the default to Nelder-mead to cope with an occurring convergence error as suggested by the best practice guideline by Meteyard and Davies (2020).

The final, maximum model specification was as follows:

$$\text{ERN}(\text{amp}) \sim \text{site} * \text{timing} * \text{trial type} + (1 + \text{site} + \text{timing} + \text{trial type} + \text{site} : \text{timing} \mid \text{participant})$$

We simple-coded the categorical predictors stimulation site (0.5 = cerebellum, –0.5 = vertex), stimulation timing (0.5 = early, –0.5 = late), and trial type (0.5 = correct, –0.5 = error). Also, TMS-timing (response pre-TMS = 0.5, response post-TMS = –0.5) was simple-coded for the additional analysis of the error rate. We used the lmerTest package (version: 3.1.3, Kuznetsova et al., 2017) in R using Satterthwaite's method to estimate the degrees of freedom and to generate *p*-values for MLMs. We considered *p*-values below .05 as statistically significant. Statistical models for the analyses of false alarms, Nogo-N2, and Nogo-P3 are provided in the Supplementary Material.

3. RESULTS

3.1. Error rates

MLM analysis revealed no significant effects of stimulation site or timing on error rates (all $p \geq .384$, $n = 15$, see Fig. 3A). However, exploring the influence of TMS timing relative to response execution (i.e., whether a pulse had occurred prior to a response on a given trial or after the response) revealed a highly significant main effect of TMS timing ($\beta = 5.02$, $t(15.00) = 13.30$, $p < .001$, see Fig. 3B). Error rates were higher in trials in which pulses had occurred after the response (i.e., response pre-TMS: $M = 13.69$ %, $SD = 4.47$ %) compared to trials in which pulses had occurred prior to the response (i.e., response post-TMS: $M = 8.66$ %, $SD = 4.59$ %), irrespective of stimulation site. The main effect of stimulation site was only marginally significant ($\beta = –1.11$, $t(15.00) = –2.03$, $p = .061$). The interaction between stimulation site and TMS timing relative to response was not significant ($\beta = –0.79$, $t(15.00) = –0.80$, $p = .437$ $N = 16$, see Fig. 3B).

3.2. Response times

For response times, there was a significant main effect of trial type ($\beta = 25.66$, $t(14) = 10.05$, $p < .001$). Overall, responses were faster in error trials ($M = 239.40$ ms, $SD = 19.53$ ms) compared to correct trials ($M = 265.07$ ms, $SD = 18.41$ ms). The main effects of site and stimulation timing as well as the interaction between these factors were not significant (all *p*-values $\geq .119$, $n = 15$, see Fig. 3C).

3.3. EEG results

3.3.1. ERN based on the difference wave (ERN-diff)

Figure 4A provides response-locked grand-average ERP difference waves (error minus correct) at electrode FCz according to stimulation site (cerebellum, vertex) and stimulation timing (early, late), along with scalp topographies for the time points of maximum negativity in the ERN time window. Figure 4B displays corresponding response-locked grand-average ERPs for errors and correct responses.

There was a significant main effect of stimulation site ($\beta = 0.93$, $t(13.00) = 2.82$, $p = .015$). The ERN was less negative for cerebellar ($M = –5.56$ µV, $SD = 2.81$ µV) compared to vertex stimulation ($M = –6.49$ µV, $SD = 2.98$ µV). The main effect of timing was non-significant ($\beta = –0.02$, $t(13.00) = –0.05$, $p = .962$). The interaction of stimulation site and timing was significant ($\beta = –1.36$, $t(12.99) = –2.52$, $p = .026$). Simple slope analyses of the stimulation site for early and late stimulation timing yielded a significant slope (see Fig. S4 in the Supplementary Material) for late stimulation ($\beta = 1.61$, $t = 3.78$, $p < .001$). For early stimulation, the slope was non-significant ($\beta = 0.25$, $t = 0.59$, $p = .563$). The interaction between site and timing seemed to be driven by the late stimulation: for cerebellar TMS, the negativity was reduced for late ($M = –5.21$ µV, $SD = 2.72$ µV) compared to early stimulation ($M = –5.90$ µV,

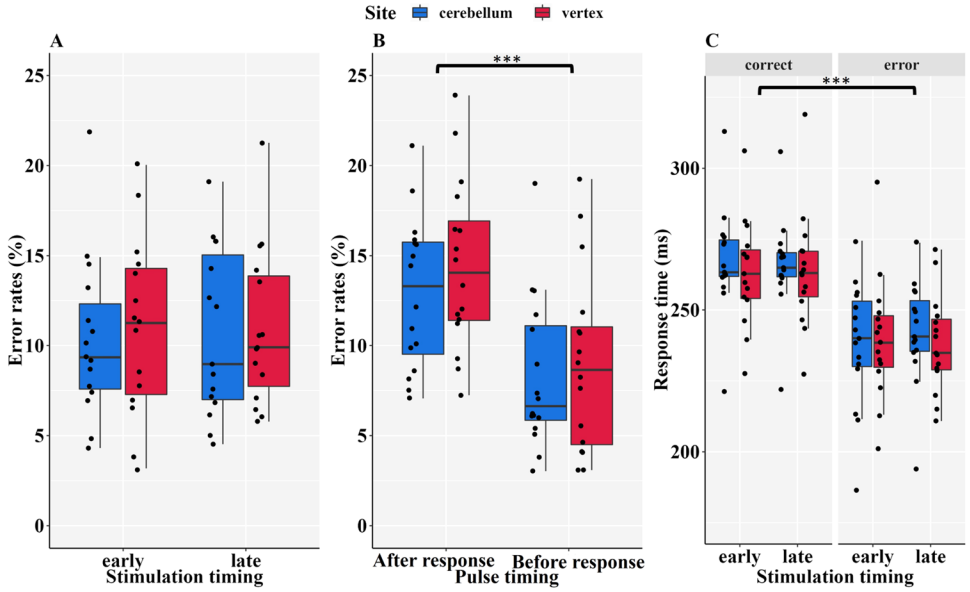

Fig. 3. (A) Mean error rates in Go trials according to stimulation site and stimulation timing. The analysis did not yield any significant effects of stimulation site or stimulation timing on error rates. (B) Mean error rates in Go trials according to stimulation site and pulse timing relative to response onset (i.e., whether a pulse had occurred prior to a response on a given trial or after the response). Asterisks indicate the significant main effect of pulse timing relative to response onset: error rates were higher in trials in which pulses had occurred after the response compared to trials in which pulses had occurred prior to response. (C) Mean response times in Go trials according to stimulation site and stimulation timing. Asterisks indicate the significant main effect of trial type: response times were shorter for errors compared to correct responses. The dots were jittered horizontally, the central line reflects the median and the whisker the first and third quartiles (the 25th and 75th percentiles) in all plots.

SD = 2.97 μV), and in contrast, vertex stimulation led to increased negativity for late (*M* = –6.82 μV, *SD* = 2.85 μV) compared to early stimulation (*M* = –6.16 μV, *SD* = 3.17 μV; see Fig. 5A for the boxplots of the ERN amplitudes as well as Fig. S4 for the interaction plot in the Supplementary Material).

3.3.2. ERN in the original waveforms

To elucidate whether the decreased negativity in the difference waves for cerebellar compared to vertex stimulation was specifically driven by altered neural responses to errors or correct responses, the original waveforms were analyzed (see Fig. 6). We found a significant main effect of trial type (β = 6.01, *t*(12.99) = 8.18, *p* > .001), with increased negativity for errors (*M* = –5.46 μV, *SD* = 3.98 μV) compared to correct responses (*M* = 0.55 μV, *SD* = 3.30 μV). All other main effects were non-significant (all $p \geq .079$). The interaction between trial type, and site was significant (β = –0.93, *t*(38.99) = –2.95, *p* = .005). Crucially, the three-way interaction between site, timing, and trial type was also significant (β = 1.36, *t*(38.99) = 2.16, *p* = .037). To resolve this interaction, we performed simple slope analysis. Results showed only a marginal significant slope for error trials on the stimulation sites and during late stimulation (β = 0.98, *t* = 2.06, *p* = .052). The slope was positive, indicating that the ERN was more negative in vertex (*M* = –5.78 μV, *SD* = 4.23 μV) compared to cerebellar stimulation (*M* = –5.13 μV, *SD* = 3.76 μV).

All other simple slopes for trial type, stimulation site, and stimulation timing were not significant (all $p \geq .200$).

3.3.3. Pe-diff

Analysis of the Pe in the difference waves did not yield any significant effects (all $p \geq .198$; see Fig. 5B for the boxplots of the Pe amplitudes).

4. DISCUSSION

This study investigated the role of the cerebellum in error processing using spTMS to stimulate the cerebellum while co-registering EEG. With the help of a Flanker pretask, we estimated individual ERN peak latencies and

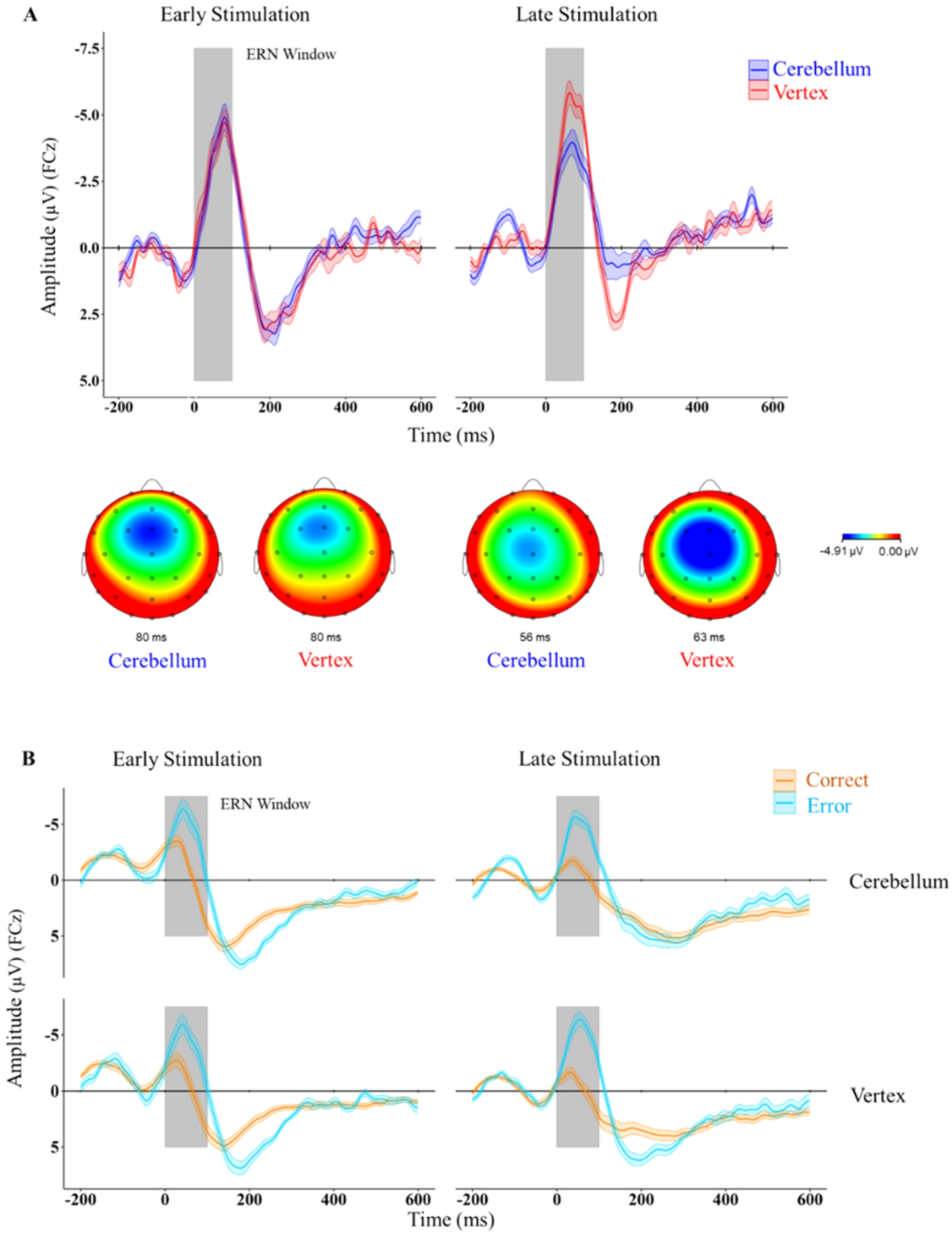

Fig. 4. (A) Response-locked grand-average ERP difference wave (error minus correct) at electrode FCz according to stimulation site (cerebellum, vertex) and stimulation timing (early, late), along with scalp topographies for the time points of maximum negativity in the ERN time window. (B) Response-locked grand-average ERPs for errors and correct responses at electrode FCz according to stimulation site (cerebellum, vertex) and stimulation timing (early, late) and trial type (correct, error). Smoothing around the lines in panel (A) and (B) indicate the standard error. The shaded area indicates time window for ERN quantification (0–100 ms post-response).

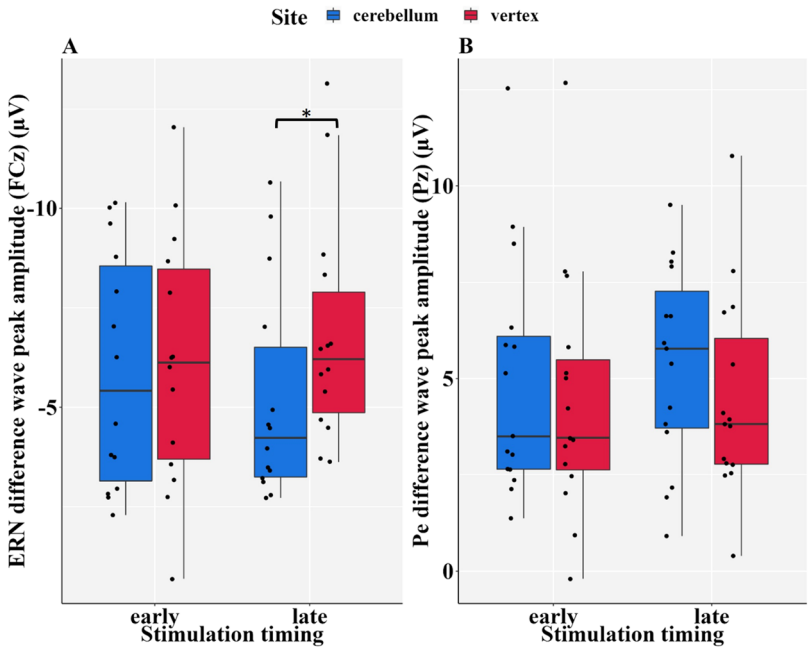

Fig. 5. (A) ERN peak amplitudes in the difference wave (error – correct) at electrode FCz as a function of stimulation site (cerebellum/vertex) and stimulation timing (early/late). Asterisks indicate the significant interaction effect between site and stimulation timing with the highly significant slope for late stimulation timing only. (B) Pe peak amplitudes in the difference wave (error – correct) at electrode Pz as a function of stimulation site (cerebellum/vertex) and stimulation timing (early/late). The dots were jittered horizontally. The central line reflects the median and the whisker the first and third quartiles (the 25th and 75th percentiles).

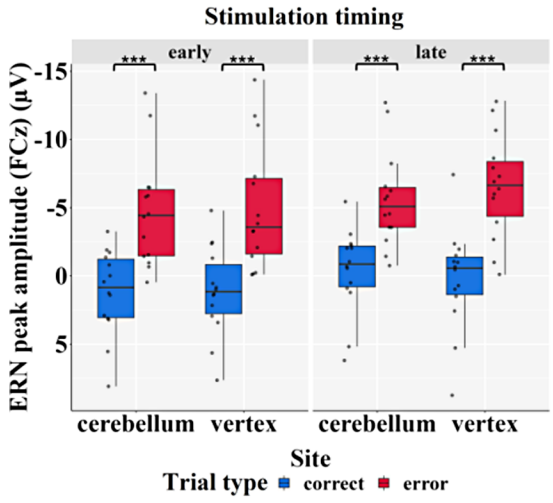

Fig. 6. ERN peak amplitudes as derived from the original waveforms at electrode FCz as a function of trial type (correct, error), stimulation site (cerebellum, vertex), and timing (early, late). Asterisks indicate significant main effects of trial type in both, cerebellar and vertex stimulation. All dots were jittered horizontally. The central line reflects the median and the whisker the first and third quartiles (the 25th and 75th percentiles).

median error response times to calculate the Individual Error Latency (IEL) as an approximation of the onset of error processing for each study participant. TMS pulses were then applied at different time points around the IEL in each trial of the subsequent Flanker main task. We expected to observe differences in error rates as well as in response-locked ERP components (specifically ERN, Pe) for cerebellar compared to vertex stimulation.

In line with our predictions, analysis of the ERP difference waves revealed that the ERN was reduced for cerebellar compared to vertex stimulation. This difference was also modulated by the timing of stimulation, with blunting particularly present for late compared to early stimulation. Analysis of the original ERP waveforms to determine whether the reduced negativity in the difference signal was particularly driven by altered neural responses to either errors or correct responses revealed that this effect was not specific to either response type.

Importantly, ERN magnitude in the Flanker pre-task was comparable between the day of cerebellar (M = –6.37 μV, SD = 2.09 μV) and vertex stimulation (M = –5.97 μV, SD = 2.18 μV, see Table S3 in the Supplementary Material). While we cannot exclude that active vertex stimulation

slightly increased the ERN (M = –6.49 μV, SD = 2.98 μV), ERN magnitude was substantially reduced for cerebellar stimulation (M = –5.56 μV, SD = 2.81 μV). Thus, the reduction of the ERN magnitude appeared to be driven mostly by spTMS applied to the cerebellum and not the vertex region, although vertex contributions cannot be fully excluded.

In general, the observed effect of stimulation site may indicate that monophasic single-pulse TMS disrupted inhibitory functions of the cerebellar cortex towards the deep cerebellar nuclei. This may have caused disinhibition, thereby facilitating information exchange with higher cortical structures through the cerebello-thalamo-cortical loop (Palesi et al., 2017). Here, the anterior cingulate cortex (ACC, Rubia et al., 2007), which is highly involved in the generation of the ERN (Dehaene et al., 1994; Holroyd & Coles, 2002), may be of particular interest. According to the reinforcement learning theory (Holroyd & Coles, 2002), the ERN is generated when a reduction of dopaminergic input from the VTA, possibly reflecting prediction errors, disinhibits deep cingulate cortical neurons. Recent findings show that the cerebellum may contribute to the generation of prediction errors. For instance, electrophysiological findings in mammals show that different cerebellar cell populations are sensitive to reward predictions and prediction violations (Heffley et al., 2018; Hull, 2020), and by the presence of direct cerebellar projections to the VTA that can modulate dopamine release in the striatum (Yoshida et al., 2022). Regarding the present results, with facilitated cerebello-cerebral information exchange, less phasic dopaminergic input towards the ACC may have reduced the cognitive demand for error processing (Holroyd & Coles, 2002).

In the conflict-monitoring theory (Botvinick et al., 2001, 2004), the ACC is seen as a monitoring system detecting conflicts (such as between opposing response options) and signaling the need for cognitive control. Here, facilitated cerebello-cerebral information exchange may have promoted conflict detection, leading to a reduced need for cognitive control that could be reflected in a reduced ERN. Adjustments in cognitive control related to conflict adaptation have previously been associated with increased functional interaction between prefrontal regions, superior temporal regions, and the anterior cerebellum (Egner & Hirsch, 2005). In addition, right cerebellar activation along with frontal and parietal activations were observed in the presence of persistent conflict leading to the interpretation that the cerebellum is involved in visuospatial attention processes during conflict to maintain high activation (Casey et al., 2000). However, somewhat contrary to both interpretations, error rates in the present study were not affected by cerebellar spTMS, and it could be argued that reduced cognitive demand or facilitated conflict detection should have led to increased accuracy/decreased error rates.

By taking advantage of the temporal resolution of spTMS, the present study addressed the question *when* cerebellar input is used during error processing. Our results show that late TMS pulses, that is, pulses that were applied to the cerebellum at IEL onset or shortly after, were more effective in that they were associated with a decrease in ERN magnitude in the error-correct difference signal. Early pulses, that is, pulses applied within 100 ms prior to IEL onset, left the ERN unaffected. A possible explanation for this pattern could be that the cerebellum receives information about the action through sensory input pathways and compares the actual information with the predicted outcome as stated in the forward model (Sokolov et al., 2017). Along these lines, cerebellar input for error processing is needed as this process is already underway. The peak of the ERN might correspond with the reconciliation of the predicted and actual action representation, that is., the use of the cerebellar input. Cerebellar spTMS may facilitate continuous information exchange with frontal regions by disinhibiting the cerebellar output signal. Thus, ERN generation would depend on this interplay of multiple regions, extending the existing framework (Falkenstein et al., 1991; Gehring et al., 1993) towards involvement of the cerebellum.

Analysis of the Pe in the difference signal did not reveal any significant effects of stimulation site or timing, which is in line with our hypothesis (see Fig. S5 of the grand averages in the Supplementary Material). The Pe likely reflects the conscious detection of an error (Endrass et al., 2007; Orr & Carrasco, 2011), and it is conceivable that error awareness might have been low due to the lack of feedback information in our rapid Go/Nogo Flanker task. Unfortunately, we did not implement any assessment of error awareness in the present study, so this notion remains speculative. Regardless of this, Pe alterations in the context of cerebellar damage were found in one previous study (Peterburs et al., 2012) in which patients with chronic cerebellar lesions were investigated. Here, an increase in Pe amplitudes—in concert with decreased ERN and preserved performance accuracy—was interpreted to reflect a compensatory mechanism. Importantly, spTMS to the cerebellum elicits a temporary effect while a stroke is associated with permanent tissue damage. Therefore, we can only roughly compare spTMS-induced "virtual lesions" of the cerebellum with degenerative or focal cerebellar diseases (Çan et al., 2018).

Analysis of the behavioral data showed no significant effects of site or timing. The lack of a site effect was unexpected, given that we had hypothesized an increase in error rates for cerebellar stimulation based on results observed in patients with cerebellar degeneration in an antisaccade task (Peterburs et al., 2015). However, another previous study also failed to find altered error rates in patients with cerebellar degeneration using a more comparable flanker task (Tunc et al., 2019). The present findings also resemble to some extent results obtained in patients with basal ganglia lesions, in whom the ERN was reduced in the absence of behavioral deficits in a flanker task (Ullsperger & von Cramon, 2006). In general, altered neural responses despite preserved behavior therefore are not particularly unusual. Interestingly, such a pattern of results has also been reported for feedback-based learning (Rustemeier et al., 2016) and in the acquisition phase of learning stimulus related contingencies in cerebellar lesion patients (Thoma et al., 2008), However, impaired learning performance in these patients was present when the task required reversal of learned stimulus-response-outcome contingencies (Thoma et al., 2008). Based on these observations, it could be speculated that the simple Flanker task used in the present study may not have been sensitive enough to detect more subtle performance differences as a function of stimulation site. It is conceivable that impaired cerebellar function may specifically affect behavioral flexibility, as suggested by findings of impaired feedback-based learning in cerebellar lesion patients only when the task involved reversal learning (Thoma et al., 2008). Behavioral flexibility is not tested in the Flanker task. Future studies could therefore investigate feedback-based learning and/or reversal learning in the context of cerebellar TMS.

When analyzing error rates according to TMS timing relative to response execution, we observed increased error rates in trials in which pulses had occurred after the response compared to trials in which pulses had occurred prior to response, irrespective of stimulation site. Thus, this effect is not informative about cerebellar contributions to error processing. Given that there were no baseline differences in error rates (based on flanker pre-task runs, see Fig. S1), this effect cannot be attributed to differences in baseline performance. It could, however, be speculated that the pulses themselves (regardless of where they were delivered) may have elicited a small startle response that could have slowed down subsequent responses. Along these lines, decreased error rates for trials in which pulses had occurred prior to the response could reflect a speed-accuracy trade-off, if increased accuracy after pre-response pulses coincided with increased response times. Unfortunately, response times could not be meaningfully analyzed according to TMS timing relative to response onset because stimulation timing was determined based on the IEL.

4.1. Limitations

This complex and technically advanced procedure led to some unique challenges and limitations that are relevant when interpreting the present results.

To begin, stimulation location was based on anatomical landmarks and not neuro-navigated. Moreover, the pulses were generated using two Magstim 200² in the Bistim configuration to overcome the challenge of the recharge period of the individual stimulators that is determined by the used output power, which varied greatly across the participants (see Table S1 in the Supplementary Material). Nevertheless, individual trials still had to be removed before analysis because no pulse had occurred. This was mostly due to the development of heat in the coil which caused the system to shut down so that the task was still running, and EEG was still recorded but no pulses were delivered. Here, the number of trials and breaks between the blocks need to be considered when planning a similarly fast-paced task in which monophasic single pulses are delivered across several hundreds of trials. Monophasic pulses are more likely to cause overheating due to the higher electrical charge compared to biphasic pulses (see Klomjai et al., 2015). Here, an external cooling system could help reduce heating issues.

Furthermore, the stimulation sites were the cerebellum and the vertex region, but we cannot exclude the possibility that stimulation also affected other brain regions. The direction of the magnetic field lines of the double cone coil are well-established to target deeper brain layers (Çan et al., 2018), but at the expense of a less focal stimulation in comparison to a figure-of-eight coil. Therefore, it may have caused stimulation of other, adjacent regions. This has been shown to be especially critical for vertex stimulation, which caused decreases in the BOLD signal in the default-mode network (see Jung et al., 2016). Regardless, we expected vertex stimulation to be a better control condition than sham because of a more comparable experience for participants regarding vibrations, coil click sounds, magnetic field build (Duecker & Sack, 2015), and discomfort. Some of the participants told us that they experienced the stimulation as uncomfortable, and that focusing on the task was

difficult because of the frequency of the pulses. Two participants dropped out in the cerebellar stimulation condition after the first block because they found the stimulation very unpleasant. The short trial period and jitter as well as the total number of trials might have contributed to this. Nevertheless, no systematic differences in ratings of these side effects were present between the two sessions, demonstrating that TMS pulses were perceived as similar for the stimulation sites (see Table S2 in the Supplementary Material).

In addition, Nogo trials and the analysis of response inhibition related ERP components were not the main focus of this work. This was partially due to the unexpectedly strong impact of TMS-induced EEG artifacts that hampered data analysis and result interpretation. In the grand-average ERPs for Nogo trials, the TMS induced artifacts did not completely disappear after preprocessing (see Fig. S7 in the Supplementary Material), and ERP components of interest, especially the Nogo-N2, occurred in close temporal proximity to pulses. We were able to identify the Nogo-N2 and Nogo-P3 to a certain degree, with grand-average patterns resembling those described in the literature (e.g., Rietdijk et al., 2014). The pulse artifact itself was cut out of the segment by the ARTIST algorithm, but there was still noise present that was likely caused by aftereffects (e.g., decay artifact) superimposed on the signal. Visual inspection of the grand-averages showed that the artifact was temporally shifted depending on pulse timing and more visible for vertex compared to cerebellar TMS, likely due to spatial proximity to analyzed electrode sites. Nevertheless, the grand-averages were also very similar to those obtained in the Go/Nogo pre-task without TMS pulses (see Fig. S2 for Go and Fig. S3 for Nogo ERPs in the Supplementary Material).

5. CONCLUSION

The present study investigated the role of the cerebellum for error processing using spTMS to stimulate the cerebellum while co-registering EEG. Applying cerebellar TMS caused a blunting of the ERN, directly supporting cerebellar involvement in performance monitoring. Of note, this effect was not specific to erroneous responses but generalized also to correct responses. Most importantly, our study also provides a first glimpse into temporal aspects of cerebellar contributions to error processing. The effect of cerebellar TMS on the ERN depended on pulse timing and was evident only when stimulation occurred around the onset of the IEL or shortly after. Finally, Pe as an index of late, more cognitive, awareness-related aspects of error processing, was not affected by cerebellar TMS.

In general, the present study adds to a growing body of research supporting cerebellar involvement in error processing and performance monitoring. More studies applying brain stimulation techniques are needed to further develop this line of research and investigate other aspects of performance monitoring such as feedback processing and feedback-based learning to better understand the role of the cerebellum for adaptive control of (non-motor) behavior.

DATA AND CODE AVAILABILITY

The data and code are openly available through the Open Science Framework at https://osf.io/jwfn9/

AUTHOR CONTRIBUTIONS

A.M.B., D.M.H., S.J.G., M.M., and J.P. planned the study. A.M.B. programmed the task. A.M.B. and D.M.H. set up the experiment, collected data, created the preprocessing pipeline, and analyzed the data. M.M. constructed the interface between the TMS and EEG system. J.P. supervised the project. A.M.B. and D.M.H. wrote the first draft of the manuscript. All authors contributed to results discussion and interpretation, and manuscript revision, and read and approved the submitted version.

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DECLARATION OF COMPETING INTEREST

The study protocol was defined prior to the experiment and preregistered on osf.org (osf.io/6v9pa).

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SUPPLEMENTARY MATERIAL

Supplementary material for this article is available with the online version here: https://doi.org/10.1162/imag_a_00080

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Impaired reinforcement learning and coding of prediction errors in patients with cerebellar degeneration - a study with EEG and voxel-based morphometry

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Abstract

This study investigated cerebellar involvement in reinforcement learning and prediction error (RL-PE) processing. Participants with pure cerebellar degeneration and matched healthy controls performed a probabilistic feedback-based learning task while brain activity was recorded using electroencephalography (EEG). Structural magnetic resonance imaging was used to quantify cerebellar gray matter volume (GMV). Data from 21 cerebellar and 25 control participants were included in the analysis. The feedback-related negativity (FRN) in the event-related potential (ERP) was analyzed on single trial level as an indicator of dopaminergic activity reflecting RL-PE coding in the forebrain. In addition, the ERP components P3a and P3b were assessed. Learning performance did not differ between patients and controls. Crucially, while in controls, coding of the unsigned RL-PE was found in the FRN and P3a for positive and in the P3b for positive and negative feedback, these effects were absent in patients. Voxel-based morphometry revealed widely distributed cerebellar GMV reduction in patients, most pronounced in bilateral Crus I/ II and bilateral lobules I-IV. Multiple regressions in patients revealed a negative correlation between GMV in bilateral Crus I and II and FRN amplitudes. The present study extends previous evidence for cerebellar involvement in RL-PE processing in humans and advances our understanding of the cerebellum's role in performance monitoring and adaptive control of behavior.

Key words: reinforcement learning, reward prediction errors, performance monitoring, cerebellum, neurodegeneration, ataxia

Introduction

Reinforcement learning is a key cognitive ability that enables humans to process performance-related external feedback and to adapt their decisions and actions accordingly (1). It relies on the processing of reward prediction errors during reinforcement learning (RL-PEs) which arise when an action is followed by an unexpected reward/punishment or by omission of an expected reward/punishment. Reinforcement learning is associated with a distributed network of cortical and subcortical cerebral structures, especially midbrain/striatum and the anterior cingulate cortex (ACC: 1). However, previous findings also point to RL-PE processing in the cerebellum (2–5). The cerebellum had previously been suggested to form (sensory-) predictions for action outcomes in terms of error-based learning, thus functioning as a forward model (6,7). Cerebellar involvement in reinforcement learning is substantiated by neuroanatomical findings identifying reciprocal cerebello-cerebral pathways (8) that enable the cerebellum to exchange information with higher order, associative brain regions also involved in processing rewards (e.g., ACC). Furthermore, initial human cerebellar lesion studies support a role in learning from (9) and processing of positive and negative feedback, i.e., rewards and punishment (10). Recent rodent studies support this by showing reward sensitivity for instance within cerebellar climbing fibers (11) and the mossy fiber-granule cell pathway (12, for a review see 4).

Structural damage of the cerebellum can be caused by a wide range of disorders and frequently leads to impairment of voluntary motor coordination, known as cerebellar ataxia (for a review, see 13). In addition, nonmotor symptoms such as affective and cognitive alterations have been observed in cerebellar disorders (14–19). Several studies have reported altered performance monitoring in patients with cerebellar damage (e.g., patients with cerebellar stroke: 10,18,20; patients with cerebellar degeneration: 17,21). Performance monitoring can be defined as a set of cognitive and affective functions that enables adaptive control of behavior and includes processes such as error and feedback processing (22). One initial study (9) revealed impaired reversal learning (i.e., re-learning once an initially learned rule for stimulus-response associations had changed) in patients with cerebellar stroke. Rustemeier et al. (10) and Huvermann et al. (20) found altered feedback processing in patients with cerebellar stroke. Using a probabilistic feedback learning task while recording EEG, both studies obtained event-related potentials (ERPs) and quantified distinct components of the ERP as indices of performance monitoring and reinforcement learning, e.g., the feedback-related negativity (FRN, 23,24; also named reward positivity: RewP, 25). The FRN is a negative deflection that peaks approximately 200 – 350 ms after feedback onset (23,26). The FRN has been shown to be sensitive to feedback valence (with more negative amplitudes for negative compared to positive feedback; 26–28) and violation of expectation (28,29). Additionally, the FRN was found to code RL-PEs

during learning (30,31) and is assumed to reflect striatal activity linked to reward processing and reward expectancy 23,32; see 33 for a detailed review).

Consistent with Thoma et al. (9), Rustemeier et al. (10) did not show impaired reinforcement learning in patients with cerebellar stroke. However, they did observe altered neural processing of feedback. Specifically, the differentiation of positive and negative feedback as reflected in the negative-positive difference signal in the FRN time window was increased in patients compared to controls, which could be indicative of aberrant coding of surprise and thus, ultimately, altered coding of RL-PEs. However, RL-PEs were not directly modelled in this study.

Of note, the FRN is not the only ERP component that is modulated by expectancy. The P3/P300 (a positive deflection peaking between 300 and 500 ms after stimulus onset, 34) was also found to be sensitive to expectancy (10,28,35). Indeed, both subcomponents of the P3, the frontal P3a and the parietal P3b, were found to be sensitive to RL-PE coding (31,36–38).

Altered reinforcement learning in patients with cerebellar lesions is consistent with fMRI findings showing cerebellar activations during feedback-based learning (e.g., 39; see 40, for a comprehensive systematic review, and 41, for a meta-analysis on reward anticipation and reward outcome processing). The present study aimed to further characterize the cerebellum's role in reinforcement learning by investigating patients with progressive cerebellar degeneration, and by focusing on coding of RL-PEs. To this end, the FRN as an index of RL-PEs reflecting dopaminergic activity in striatum and ACC was assessed. Importantly, previous research has shown that feedback timing is an important factor for feedback processing: FRN amplitudes (in the negative-positive difference signal) decreased with increasing delay between response and feedback (42), consistent with a shift away from striatal processing for delayed compared to immediate feedback (43). Along these lines, it is conceivable that cerebellar involvement in feedback processing and RL-PE coding is modulated by feedback timing.

The present study used a probabilistic feedback learning task in which feedback was present either immediately (500 ms post-response) or with a 6500 ms delay. Relationships between (possibly altered) behavioral performance, FRN and P3a/b, and cerebellar gray matter volume (GMV) were investigated using structural imaging data. Patients with cerebellar degeneration were hypothesized to show decreased accuracy in the task relative to healthy controls. Second, differences in accuracy as a function of feedback timing were expected in patients, with decreased accuracy for immediate feedback. In contrast, we did not expect differences in accuracy as a function of feedback delay in controls (42). We also expected reduced choice switching in patients compared to controls, consistent with decreased behavioral flexibility (9). In addition, altered FRN, P3a and P3b amplitudes in patients compared to controls for immediate feedback and for trials with high unsigned RL-PEs (low expectancy) but not low unsigned RL-PEs (high expectancy)

were expected. Last, we investigated whether GMV in patients as revealed by whole-brain and cerebellar voxel-based morphometry (VBM) would link specific cerebellar subregions to alterations in behavior or neural response patterns. Based on the cerebellar functional topography (45) and previous findings on error processing (17,18), posterolateral regions were hypothesized to be most critical.

The study protocol and hypotheses were preregistered on the Open Science Framework (OSF: https://osf.io/fgw8h/)

Methods

Sample

Fifty-nine participants were recruited of which 28 were patients and 31 healthy controls. Information on the a priori power analysis for the preregistered repeated measures ANOVA is provided in the supplement. For the patient group, only individuals with pure forms of cerebellar degeneration were included, such as spinocerebellar ataxia type 6 (SCA6), for details see Table 1.

Patients were recruited from the ataxia clinics of the Departments of Neurology at the University Hospitals Düsseldorf and Essen, Germany. Exclusion criteria for patients were alcohol and illicit substance abuse, presence of other neurological disorders or psychiatric disorders except for mild depression. As participants received structural MR imaging, typical exclusion criteria for MRI studies applied, such as prosthesis, metallic clips, pacemakers, insulin pumps, claustrophobia, and pregnancy. All patients underwent neurological and neuropsychological assessment (for details, see Table 2 and Table S1 in the supplement). Healthy participants were recruited via newspaper advertisements and postings at the respective university and/or clinic. Control subjects were matched to the patients regarding sex, age, and educational attainment. Exclusion criteria for control subjects were presence or history of any neurological disorders, psychiatric disorders other than sufficiently treated depression (e.g., antidepressants/psychotherapy; this was due to the high prevalence of depression in the patients), and alcohol or illicit substance abuse. In addition, MRI exclusion criteria also applied. All control participants underwent neuropsychological testing but did not receive a neurological examination.

After inspecting the structural MRI data (T1- and T2-weighted scans; not available for one patient and one control subject) and EEG data as well as evaluating the questionnaires, a total of thirteen participants had to be excluded from data analyses (seven patients, six controls). One patient and one control subject were excluded due to severe white matter hyperintensities/lesions as rated by three reviewers (A.B., A.R., M.M.) including an experienced neurologist (M.M.) using the Scale for Age-Related White Matter Changes (ARWMC, scoring with 3, 46). Two individuals from the control group (hydrocephalus, lacunar lesion within the cerebellum) and one patient (hydrocephalus) were excluded based on incidental findings. One

patient and one control subject were excluded due to current psychological disorders (major depression and agoraphobia, respectively). Inspecting the EEG data, another six participants (four patients and two control subjects) had to be excluded due to poor signal quality (n = 3), excessive movement during the experimental task (n = 1), or technical issues resulting in data loss (n = 2).

In total, data from 21 patients (n = 8 female, mean age in years = 51.38, SD = 14.70) and 25 healthy controls (n = 10 female, mean age in years 52.52, SD = 13.72) were included in the behavioral and ERP analyses. VBM was performed using a subset of n = 18 patients because one patient (sub-pat-28) had not been able to participate in the MRI session and two patients with SCAR10 (sub-pat-23, sub-pat-24) revealed massive atrophy in the cerebellum and were identified in a homogeneity analysis as extreme outliers (see Figure S3 for a boxplot and Figure S4 for a gray matter slice for each patient in the supplement). For the group comparison, a subset of n = 24 control subjects was used because MRI data were not available for one individual. Detailed demographic information about each included patient can be found in Table 1.

The present study was conducted in accordance with the ethical principles for medical research involving human subjects outlined in the revised version of the Declaration of Helsinki (47), and had received ethical clearance by the Ethics Committees of the Faculty of Medicine at Heinrich Heine University Düsseldorf, Germany, and of the University Hospital Essen, Germany.

Neurological and neuropsychological assessment

Severity of ataxia symptoms in patients was assessed using the Scale for the Assessment and Rating of Ataxia (SARA; 48). To assess possible cognitive and/or affective impairments, the German version (49) of the Cerebellar Cognitive Affective Syndrome Scale (CCAS; 50) was used in both groups. In addition, the intelligence quotient (IQ) was estimated based on performance in a multiple-choice vocabulary test, i.e., the MWT-B (*Mehrfachwahl-Wortschatz-Intelligenztest Version B*; 51). The BDI-II (Beck Depression Inventory 2; 52) was used to measure severity of depression, and handedness was assessed using the EHI (Edinburgh Handedness Inventory: 53). Group means and comparisons for the different tests and questionnaires are provided in Table 2. Table S1 in the supplement contains further neurological scores and results on questionnaires regarding motor and nonmotor symptoms as well as general quality of life.

Task

Participants completed two versions of a probabilistic feedback-based learning task as described by Eppinger et al. (54), Bellebaum & Colosio (55), and Huvermann et al. (20) in two sessions that took place on two consecutive days. EEG was recorded concurrently. The task versions differed in feedback delay and stimulus sets (see below) but were otherwise identical.

Table 1 - Patient characterization

Number	Type of disease	Age (years)	Sex	EHI – LQ
sub-pat-01	SCA6	54	m	100
sub-pat-03	SCAR8	29	m	100
sub-pat-04	SCA6	66	f	100
sub-pat-05	SCA14	64	m	73.33
sub-pat-06	SCA48	38	m	100
sub-pat-08	SCA27B	29	m	100
sub-pat-09	SCA27B	70	f	100
sub-pat-10	SCA14	65	f	100
sub-pat-13	SCA14	43	m	100
sub-pat-14	SCA14	40	m	100
sub-pat-16	SCA14	61	m	100
sub-pat-17	CACNA1A	55	m	100
sub-pat-18	SCA14	38	f	100
sub-pat-19	SCA27B	67	m	100
sub-pat-20	SCA14	62	f	100
sub-pat-22	SCA6	71	m	100
sub-pat-23	SCAR10	32	f	100
sub-pat-24	SCAR10 (ANO10)	33	f	100
sub-pat-26	SCA6	66	m	100
sub-pat-27	Early-onset cerebellar ataxia[1]	43	m	100
sub-pat-28	SCA14*	53	f	20

Note. SCA = Spinocerebellar ataxia (autosomal dominant), ADCA III = Autosomal dominant cerebellar ataxia type III (pure cerebellar degeneration, no known gene mutation), SCAR10 = Spinocerebellar ataxia - autosomal recessive, CACNA1A = calcium voltage-gated channel subunit alpha1 A mutation, m = male, f = female, [1]Genetic defect not yet found. *Patient did not take part in the MRI session. Handedness was measured using the EHI obtaining the lateralization quotient (LQ).

The task consisted of eight blocks with 40 trials each, thus 320 trials in total. Figure 1 illustrates the time course and sequence of stimulus presentation in one trial of the task. Each trial began with a fixation cross presented for 500-1500 ms. Next, one of four abstract stimuli was presented for 1500 ms, and participants were asked to respond by pressing the left or right button on a response box. The choice options were represented by red rectangles which stayed on screen for further 1500 ms, if no response was given. Once a response was given, the respective rectangle was highlighted for 200 ms to visualize the given response, followed by a black screen for 500 ms in the task version with immediate feedback condition, and for 6500 ms in the task version with delayed feedback. Last, feedback was displayed for 1000 ms. Feedback was either displayed as a monetary reward of "+20ct" in green font as positive feedback or "-10ct" in red font as negative feedback. Two stimuli were linked to random feedback (50 % positive and 50 % negative feedback independent of response) and served as distractors, while for the other two stimuli, choosing the correct

option (left or right, respectively), resulted in positive feedback 90% of the time and in negative feedback 10% of the time. These two stimuli will henceforth be referred to as "learnable".

Table 2 - Results of the neurological and neuropsychological assessment

Function and test	**Patients (*M*/*SD*)**	**Controls (*M*/*SD*)**	***p*-value**
Premorbid intelligence (MWT-B)	108/10.81	111.4/9.84	.282
Severity of ataxia (SARA)	9.17/3.47	NA	
Neuropsychological deficits (CCAS-Scale)	1.33/1.46	1.48/1.76	.945
Depressed mood (BDI-II)	8.38/5.73	3.12/2.82	< .001

Note. *t*-tests for parametric and Wilcoxon rank test for non-parametric distribution were calculated. $N = 21$ patients, $N = 25$ controls.

In case a participant had learned so fast that they exceeded the learning criterion of 65 % correct responses for the learnable stimuli by the second of eight blocks, a new stimulus set was provided to increase the number of pre-learning trials. This was the case in 32 participants (15 patients, 17 controls). If a participant did not exceed the learning criterion until the eighth and last block, a ninth block was added to generate post-learning trials. This was the case in one patient and one control subject for one task version. Trials with responses made within 100 ms after stimulus onset, responses given later than 3000 ms after stimulus onset, or multiple responses were excluded from analysis.

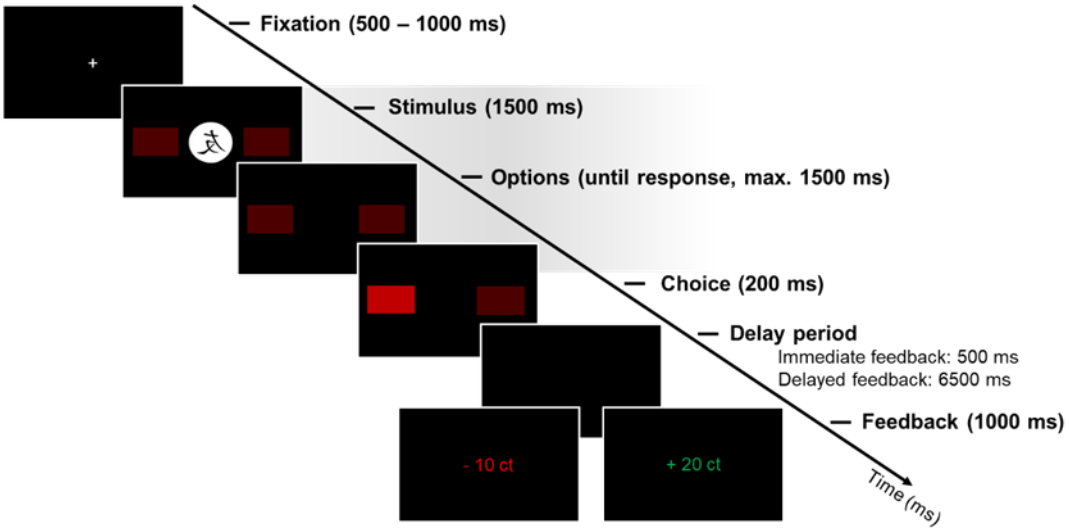

Figure 1. Schematic illustration of the time course and sequence of stimulus presentation in one trial of the probabilistic feedback-based learning task. Each trial started with a fixation cross, followed by a stimulus along with two response options (left or right) presented for 1500 ms. Responses had to be made within 3000 ms after stimulus onset as indicated by the grey shading. The response was highlighted on screen for 200 ms. Subsequently, feedback was provided after a delay period of either 500 ms (immediate feedback) or 6500 ms (delayed feedback), with positive feedback indicated by "+ 20 ct" in green color and negative feedback with "-10 ct" in red color. Feedback was displayed for 1000 ms.

Procedure

Participants were seated in a brightly lit room in front of a laptop (DELL® Precision M4800, 15.4 inch with a resolution of 1920 x 1080 pixels and a refresh rate of 60 Hz). Left and right button presses were made with a response box (Cedrus RB-740, Science Plus Group, Groningen, NL) placed in front of the laptop. A third key was used to navigate through instruction slides and pauses. Across both sessions, the distance between response box and laptop was kept constant. After positioning the participant, the EEG cap was fitted, and the electrodes were prepared. Subsequently, standardized task instructions were given, and five practice trials were presented before the first block of the experiment started. Following the completion of the probabilistic feedback-based learning task (approx. 30 min for the immediate feedback version, or 60 minutes for the delayed feedback version), demographic data, neuropsychological and neurological testing and MRI data were obtained. The entire test session on the first day took approx. 2.5-3 hours. On the second day, the other version of the probabilistic feedback-based learning task was conducted, either with immediate or delayed feedback and a different stimulus set to avoid any spill-over effects between the sessions. Version order and stimulus set were balanced across participants. The test session on the second day took approx. 1.5-2 hours.

EEG acquisition and preprocessing

EEG was recorded from 28 active Ag/AgCl electrodes on an actiCAP (BrainProducts GmbH, Munich, Germany) with the following electrode sites: Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, T7, T8, Pz, P3, P4, P7, P8, PO9, PO10, O1, O2, Oz. The electrode FCz served as on-line reference, and AFz was used as ground electrode. Both mastoids were recorded for later re-referencing. Horizontal (hEOG) eye movements were measured with an electrode positioned next to the other canthus of the left eye and vertical (vEOG) eye movements/blinks were recorded using electrode position Fp1, respectively. BrainVision Recorder software (version 1.21; BrainProducts, Munich, Germany) was used for recording. Data were amplified with a BrainAmp DC amplifier, and impedances were kept below 25 kΩ. Data were sampled at 1000 Hz**.**

First, the EEG signal in each data set was visually inspected for noisy electrodes which were removed before re-referencing. On average, 2.93 (*SD* = 1.33) electrodes (mostly occipital) had to be removed in eleven participants. The signal was then re-referenced to the mean of the mastoid electrodes so that FCz could be restored as an active electrode. Direct current (DC) detrending and a Butterworth filter with a low cut-off of 0.1 Hz (time constant: 1.59), a high cut-off of 30 Hz, and a notch filter of 50 Hz were applied. As a next step, oculomotor artifacts were corrected for using ocular correction independent component analysis as implemented in BrainVision Analyzer 2 (version 2.2, Brain Products GmbH, Gilching, Germany) using hEOG and vEOG for each participant. Data were then segmented into epochs of 800 ms, starting 200 ms

before and ending 600 ms after feedback onset. Next, baseline correction was applied based on the 200 ms preceding feedback onset, and automatic artifact detection was performed. Here, segments with a voltage step above 50 µV/ms, values over 100 µV or below -100 µV, a difference of more than 100 µV between values, or an activity lower than 0.1 µV within an interval of 100 ms were excluded.

On average, M = 6.53 % (SD = 9.28 %) feedback-locked segments were rejected per participant. Last, data were exported via generic data export and then imported into MATLAB (version R2020b: MathWorks, Natick, Massachusetts, USA) to run custom scripts to further process ERP components at single-trial level.

In the single-trial ERPs, we analyzed the amplitudes of FRN and P3a/b by determining the latencies in the average per person for each condition: The FRN was defined as the local maximal negative peak within the time window between 200 and 350 ms post-feedback at site FCz (29,42). For the P3a and P3b, a time window of 300 – 500 ms was used to find the maximal positive peak. Single-trial peak amplitudes were calculated using a time window around the peak for averaging the amplitude. For the FRN, P3a (electrode FCz: 55), and P3b (electrode Pz: 34), a time window of 20 ms before and after the peak was used (40 ms length for averaging). If no peak was detected in the respective average, the trial was coded as an outlier.

Prediction error modelling

A reinforcement learning model was used to estimate the prediction error δ associated with positive and negative feedback in each trial (PE: 56). Many previous studies have used this approach (e.g., 57–61). The action values Q and PE δ were modelled using a Rescorla-Wagner model (62). For the estimation of the PE δ, the information from the individual trial including the received feedback R and the given response a of each participant were used:

$$Q_{a,t+1} = Q_{a,t} + \alpha * \delta_t$$

$$\delta_t = R_{a,t} - Q_{a,t}$$

A softmax function (56) was used to model response probabilities by estimating the probability of the chosen action and its respective action value Q for each action option a and time point t (trial):

$$p_{a_1,t} = \frac{e^{\beta * Q_{a_1,t}}}{e^{\beta * Q_{a_1,t}} + e^{\beta * Q_{a_2,t}}}$$

The model was fitted using the fmincon function implemented in MATLAB (version R2020b). The fmincon function minimized the negative sum of log-likelihoods minus a gamma distribution of β with a shape parameter of 2 and scale parameter of 3 to adjust for high β (60,63). The learning rate α was separately estimated for positive and negative feedback and each stimulus. We allowed α to assume any value between 0 and 1. In addition, we calculated an inverse temperature β for exploration behavior assuming any value

between 0 and 50. In the statistical analysis, valence and the unsigned PE were used as separate predictors, as the signed PE correlates with feedback valence.

Voxel-based morphometry

Imaging data were acquired with a 3T MR scanner (MAGNETOM Trio, a Tim System, Siemens Healthineers AG, Forchheim, Germany) using a 12-channel head coil. This included 3D T1-weighted magnetisation-prepared rapid acquisition gradient-echo (MPRAGE) sequence (voxel size 1 mm^3). The complete MRI protocol can be found in the OSF folder. DICOM files were transformed into the Brain Imaging Data Format (BIDS: 64) by using the *BIDSmapper* and *BIDScoiner* applications (65).

VBM (66,67) was used to characterize GMV loss in patients relative to controls, and to relate possible group differences found in the feedback-based learning task and/or in EEG measures to specific cerebellar regions using multiple regression. For the whole-brain VBM, we used the Computational Anatomy Toolbox (CAT12: 68) implemented in the Statistical Parametric Mapping software package (SPM12: Wellcome Department of Cognitive Neurology, London, UK) in MATLAB (version R2020b). The default preprocessing procedure was used, and we calculated the total intracranial volume (TIV) for each participant. In addition, we checked the homogeneity of the whole-brain data for all participants. Last, the preprocessed gray matter images were smoothed using an 8 mm full-width half-maximum (FWHM) gaussian kernel.

For the cerebellar VBM, we applied an optimized approach to isolate the cerebellum using the Spatially Unbiased Infratentorial toolbox (SUIT: 69). We followed previous analysis protocols to conduct VBM in SUIT (17,70) and visually inspected the preprocessed images for each subsequent analysis step to ensure sufficient data quality. First, the cerebellum and brainstem were isolated using the standard isolation and segmentation procedure in SUIT which created gray and white matter maps as well as the respective masks.

For six datasets, we additionally used T2-weighted images (Sampling Perfection with Application optimized Contrasts using different flip angle Evolution: SPACE) and fluid attenuated inversion recovery (FLAIR; see supplemental material for MRI protocol details) to optimize the isolation and segmentation procedure of the cerebellum because of poor results after visual inspection of an initial isolation and segmentation run. The T1-weighted images were oriented according to the AC-PC line, and the T2-weighted images were subsequently registered on the reoriented T1-weighted images. After optimizing these six datasets, results improved. In the next step, all cerebellar masks were hand-corrected by an expert (B.B.) using MRIcron (https://www.nitrc.org/projects/mricron). This step was conducted to correct the automatically generated masks for any occipital cortex within the cerebellar mask and to add any missing cerebellar matter. Afterwards, the isolated and segmented gray matter maps were spatially normalized to the SUIT template

using the normalization procedure with Dartel. Next, we resliced the spatially normalized gray matter maps using Dartel into SUIT-space with 1mm^3 voxel size and with a 2 mm FWHM gaussian kernel.

Statistical analysis

Accuracy in each version (immediate/delayed feedback) of the probabilistic feedback learning task was calculated as the mean percentage of correct responses for all learnable trials per block corrected for misses (> 3000 ms), multiple responses, and too fast responding (within 100 ms following stimulus onset). In addition, choice switching was calculated on the single trial level by checking whether the response in the next trial with the same stimulus was the same or different compared to the current trial.We deviated from the preregistration and conducted mixed linear model (MLM) analysis instead of analysis of variance (ANOVA) because we decided to analyze the RL-PE which is a single-trial predictor and cannot be analyzed using ANOVA. MLMs are robust against missing values and can additionally model each participant as a random factor to explain more variance. MLMs were conducted in R (R Core Team, version 4.0.3) using RStudio (version 1.3.959) and the lme4 package (version: 1.1.25, 71). Meteyard and Davies (72) advise in their best practice guidelines to use the maximum model including all within-subject main and interaction effects as random effects as long as no errors in model fit occur (e.g., convergence errors or singular fits). The *buildmer* (version 2.8) package was used to find the maximum model by fitting the MLM in an ordered stepwise manner by deleting terms that led to convergence errors. In addition, the optimizer was changed from default to bobyqa when the buildmer model did not converge after using the *lmer* function to check the model. Outlier detection was conducted using Cook's distance.

For the behavioral data, we determined accuracy as the percentage of correct responses (i.e., selection of the option with a higher chance of positive feedback) for learnable trials. Non-learnable trials were not considered in the analysis. The between-subjects factor group (patients, controls) and the within-subject factors feedback timing (immediate, delayed) and block (block 1-8, scaled using the built-in *scale* function) were included as fixed-effects and the within-subject factors main effects and interaction as random slopes per participant:

Accuracy ~ group*feedback timing*block + (1+feedback timing*block|participant)

To investigate behavioral flexibility, choice switching was analyzed with the factors group, feedback valence, feedback timing, response type, and block (block 1-8, scaled), and the within-subject factors were again used as random slopes per participant

Choice switching ~ group*feedback timing*feedback valence*response type*block + (1+feedback timing +feedback valence+response type+feedback valence:response type|participant)

Third, for the single-trial ERP analyses, separate models were calculated for FRN, P3a, and P3b amplitudes as dependent variables. We calculated the unsigned prediction error (unsigned PE) using the unsigned value of each PE to separate the sign from the PE and subtracting the value from 0.5 to center the range (-0.5 minimum and 0.5 maximum value). The between-subjects factor group (patient, control) and the categorical within-subject factors feedback timing (immediate, delayed), feedback valence (positive, negative), and learnability (learnable, unlearnable) were included. In addition, we modelled the continuous predictor unsigned PE. Their main effects and interactions were used as fixed effects. To account for individual differences, a random intercept per participant and random slopes per participant for all within-subject factors main and interaction effects were used:

FRN ~ group*feedback timing*feedback valence*unsigned PE*learnability + (1+feedback timing*feedback valence+learnability|participant)

P3a ~ feedback timing*group*unsigned PE*feedback valence*learnability + (1+feedback timing+ feedback valence|participant)

P3b ~ feedback timing*group*unsigned PE*feedback valence*learnability + (1+feedback timing+ feedback valence+unsigned PE+feedback valence*unsigned PE|participant)

All categorical predictors were simple coded: group (0.5 = patient, −0.5 = control), feedback timing (0.5 = delayed feedback, -0.5 = immediate feedback), feedback valence (0.5 = positive feedback, -0.5 = negative feedback), learnability (0.5 = learnable, -0.5 = unlearnable), response type (0.5 = correct, -0.5 = false). The *lmerTest* package (version: 3.1.3 , 73) in R including the Satterthwaite's method to estimate the degrees of freedom and to generate *p*-values for MLMs was used. *P*-values below .05 were considered as statistically significant. Interactions were resolved using the *probe_interaction* function to estimate simple slopes based on the moderating factors of interest.

The preprocessed whole-brain volumes and cerebellar gray matter volumes were analyzed using two-sample *t*-tests and for the patients, the cerebellar GMV was correlated (separately for positive and negative correlations) for significant group differences derived from the learning task. The total intracranial volume and age were used for all analysis as covariates of no interest within the framework of the general linear model (GLM) as implemented in SPM12. First, we compared the cerebellar GMV for the whole-brain data between patients and controls (contrast control > patient) using two-sample *t*-test. Second, we used the cerebellar GMV for the same contrast. Third, for the multiple regression analysis we aggregated the single-trial FRN across all trials for each patient as a covariate of interest. All regressors were demeaned before entering the final model. For the statistical threshold, we used the Family-wise error (FWE) corrected *p*-value < .05 for the between-subjects comparison and an uncorrected *p*-value ($p < .001$) for the multiple regression. Last, the contrasts were masked using the SUIT atlas with 1 mm resolution, and the cerebellar

lobules were labelled using the probabilistic MRI atlas of the human cerebellum according to Diedrichsen et al. (74).

Results

Accuracy

MLM analysis revealed a significant main effect of feedback timing (β = -4.52, $t(44.00) = -2.11$, $p = .041$). Across groups, accuracy was increased for delayed ($M = 73.66$ %, $SD = 22.02$ %) compared to immediate feedback ($M = 68.81$ %, $SD = 22.10$ %). The main effect of block was also significant (β = 5.50, $t(44.00) = 7.09$, $p < .001$), with lower accuracy at the beginning of the task (first block: $M = 59.79$ %, $SD = 20.56$ %) than at the end (last block: $M = 78.38$ %, $SD = 23.05$ %). All other main and interaction effects were nonsignificant (all $p \geq .087$; $n = 46$, see Figure 2A and Table S2 in the supplement for the complete results).

Choice switching

The analysis of choice switching revealed a significant main effect of feedback valence (β = -0.42, $t(37.94) = -9.59$, $p < .001$). Choice switching was reduced for positive compared to negative feedback (see Figure 2B for the plot and Table S2 in the supplement). In addition, choice switching was reduced after correct compared to incorrect choices (β = -0.34, $t(40.37) = -4.63$, $p < .001$). Also, the main effect of block was significant (β = -0.06, $t(7167.74) = -3.98$, $p < .001$). Choice switching was more frequent at the beginning of the task compared to later.

Moreover, the three-way interaction between feedback timing, group, and block was significant (β = -0.12, $t(7414.71) = -1.98$, $p = .048$; see Figure 2B. Simple slopes were resolved using the factors feedback timing and group as moderators. The analysis revealed two significant timing effects for both groups: decreased choice switching for immediate (controls: β = -0.06, $SE = 0.02$, $t = -2.72$, $p = .007$; patients: β = -0.08, $SE = 0.03$, $t = -3.35$, $p < .001$) and delayed feedback with task progression (controls: β = -0.13, $SE = 0.02$, $t = -5.12$, $p < .001$; patients: β = -0.06, $SE = 0.03$, $t = -2.37$, $p = .018$).

Across groups, the interaction between response type and feedback timing was also significant (β = 0.16, $t(5010.70) = 2.55$, $p = .011$). Simple slope analysis using response type as the moderating factor showed that for correct choices, the effect was significant (β = 0.14, $SE = 0.04$, $t = 3.60$, $p < .001$), indicating more choice switching for immediate compared to delayed feedback. For incorrect choices, the effect was nonsignificant ($p = .905$).

In addition, the interaction between response type and feedback valence across both groups was significant (β = 0.18, $t(32.51) = 2.09$, $p = .044$). Simple slope analysis using response type as the moderating factor

revealed reduced choice switching for positive compared to negative feedback for incorrect (β = -0.51, *SE* = 0.08, *t* = -6.65, *p* < .001) and correct responses (β = -0.33, *SE* = 0.04, *t* = -8.29, *p* < .001).

Last, the interaction between response type and block was significant (β = -0.12, *t*(6913.05) = -4.08, *p* < .001). Simple slope analysis using response type as the moderating factor revealed a non-significant effect for block (*p* = .692) for incorrect choices, indicating a constant rate of choice switching throughout the task. In contrast, the effect for correct responses was significant (β = -0.11, *SE* = 0.01, *t* = -10.02, *p* < .001), with reduced choice switching in late compared to early blocks.

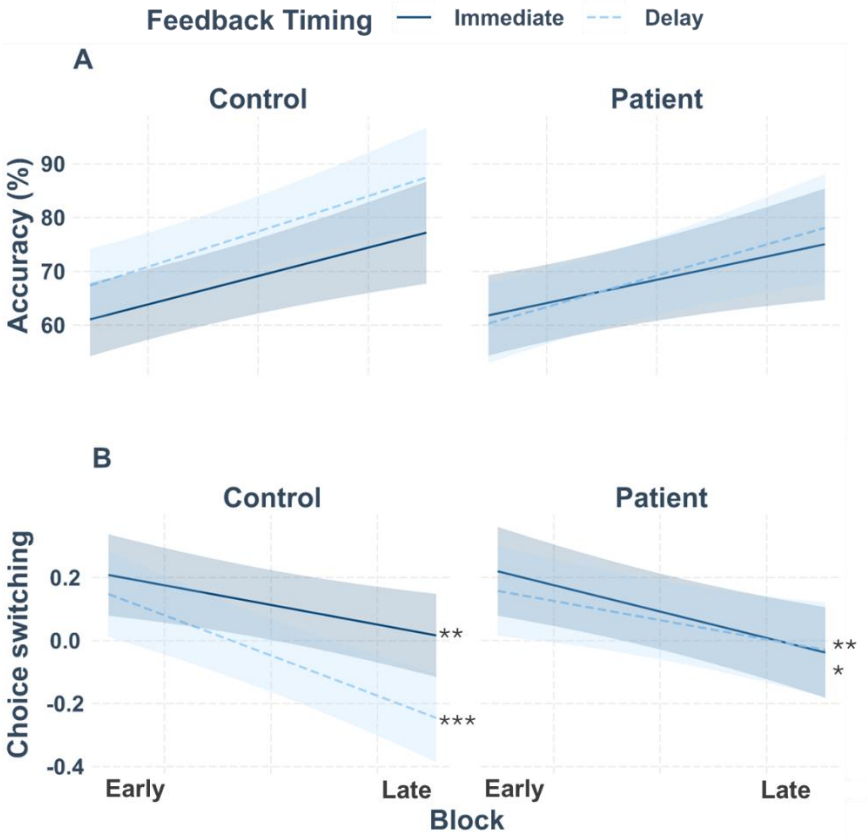

Figure 2. Interaction plots for accuracy (A) and choice switching (B) with the categorial factors group, feedback timing, and the scaled factor block. (A) For accuracy, a significant main effect of feedback timing indicated higher accuracy for delayed compared to immediate feedback across groups. (B) For choice switching, asterisks indicate the significant effects of decreased choice switching across the progression of the task. The strongest effect was found in controls for delayed feedback. The smoothing around the lines indicates the 95% confidence interval for *N* = 46.

Feedback-related negativity (FRN)

Feedback-locked grand-average ERPs at electrodes FCz according to group (controls, patients), feedback timing (immediate, delayed), feedback valence (positive, negative), and unsigned PE (high, low) are

provided in Figure 3. A figure depicting grand-average ERPs (at FCz) including only feedback timing and valence for each group is provided in the supplement (see Figure S1).

For single-trial FRN amplitude, a significant main effect of group emerged (β = -1.61, $t(44.25) = -2.64$, $p = .011$), indicating a more negative FRN in patients ($M = 2.10$ µV, $SD = 7.54$ µV) compared to controls ($M = 3.61$ µV, $SD = 8.04$ µV). In addition, the main effect of feedback valence was significant (β = 0.65, $t(43.61) = 3.85$, $p < .001$), with more negative amplitudes for negative ($M = 2.63$ µV, $SD = 7.75$ µV) compared to positive feedback ($M = 3.10$ µV, $SD = 7.91$ µV). The main effect of feedback timing was also significant (β = -1.14, $t(44.45) = -2.50$, $p = .016$). The FRN was more negative for delayed ($M = 2.28$ µV, $SD = 8.10$ µV) compared to immediate feedback ($M = 3.52$ µV, $SD = 7.53$ µV). Last, the main effect of unsigned PE was also significant (β = 0.35, $t(3000.76) = 2.22$, $p = .027$), reflecting a less negative FRN for higher unsigned PE relative to low PE.

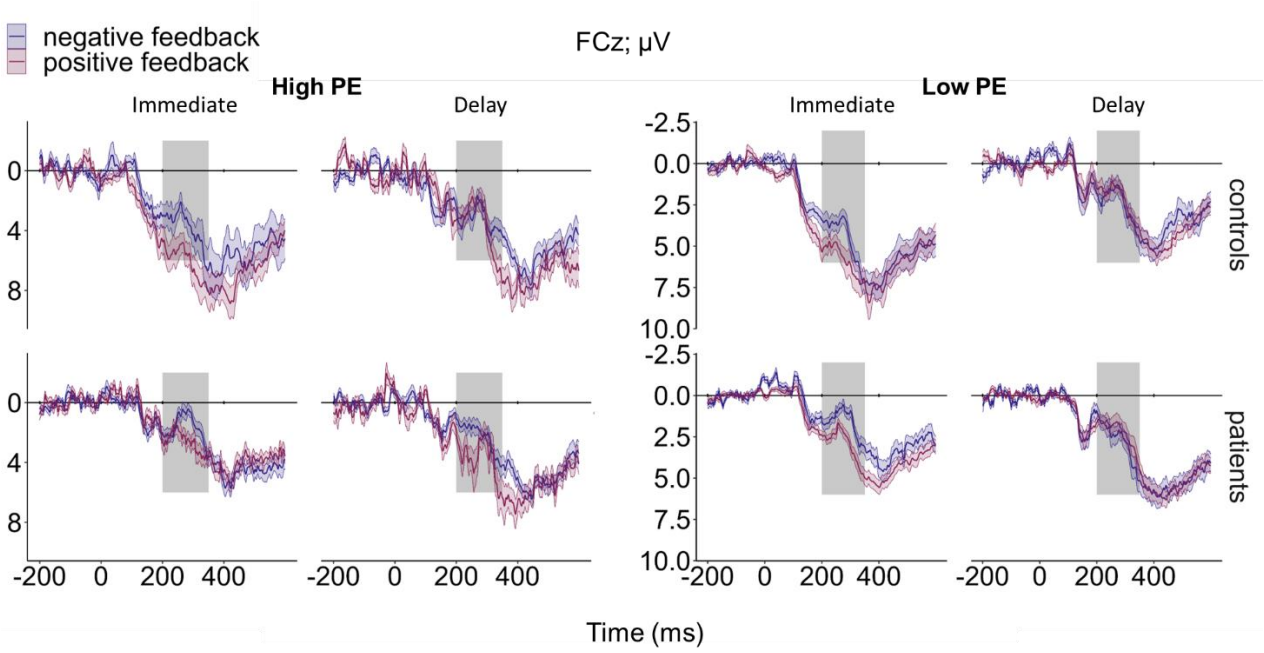

Figure 3. Feedback-locked grand-average ERPs at electrode FCz according to group (patients, controls), feedback timing (immediate, delayed), feedback valence (positive, negative), and unsigned PE categorized into high unsigned PE (> 0.5) and low unsigned PE (≤ 0.5). The gray rectangle indicates the time window for the FRN (200 – 350 ms).

Further, we discovered a significant three-way interaction between group, feedback valence, and unsigned PE (β = -1.36, $t(5672.17) = -2.04$, $p = .041$, see Figure 4A for the interaction plot). Simple slope analyses with the moderating factors group and feedback valence revealed a significant effect on the unsigned PE for controls when feedback was positive (β = 0.98, $SE = 0.30$, $t = 3.26$, $p = .001$). More positive FRN amplitudes were present for higher unsigned PE. All other effects were nonsignificant (all $p \geq .256$).

In addition, the interaction between group and feedback timing was also significant (β = 2.06, $t(44.45)$ = 2.26, p = .029 see Figure 4B for the interaction plot). Simple slope analyses with the moderating factor group revealed a significant effect for controls (β = -2.23, SE = 0.63, t = -3.54, p < .001), indicating that the FRN was more negative for delayed (M = 2.49 μV, SD = 8.25 μV) compared to immediate feedback (M = 4.72 μV, SD = 7.68 μV). For patients, the effect for feedback timing was nonsignificant (p = .848).

The interaction between feedback valence and feedback timing was also significant (β = -0.81, $t(45.29)$ = -2.34, p = .024, see Figure 4C). Simple slope analysis revealed that the effect for immediate feedback was significant (β = 1.05, SE = 0.23, t = 4.61, p < .001), indicating a more negative FRN for negative (M = 3.05 μV, SD = 7.52 μV) compared to positive feedback (M = 3.89 μV, SD = 7.53 μV). The effect for delayed feedback was nonsignificant (p = .526). All other main and interaction effects were nonsignificant (all $p \geq$ .079). A full table of the statistical output can be found in Table S4 of the supplemental material.

P3a

Analysis of the single-trial P3a revealed a significant main effect of feedback valence (β = 0.57, $t(45.88)$ = 4.03, p < .001). The P3a was increased for positive (M = 5.41 μV, SD = 7.86 μV) compared to negative feedback (M = 5.03 μV, SD = 8.10 μV). Also, the main effect on learnability was significant (β = -0.43, $t(26984.07)$ = -4.45, p < .001). The P3a was more positive for unlearnable (M = 5.52 μV, SD = 8.00 μV) compared to learnable trials (M = 4.98 μV, SD = 7.92 μV). In addition, the main effect of the unsigned PE was significant (β = 0.56, $t(3715.93)$ = 3.81, p < .001). The estimate of the effect indicated a more positive P3a for higher unsigned PEs. All other main effects were non-significant (all p-values ≥ .087, see later time window (300 – 500 ms) in Figure 3A for the grand averages and Table S4 in the supplemental material for the detailed results).

Further, a significant three-way interaction between group, feedback valence, and unsigned PE emerged (β = -2.53, $t(26811.17)$ = -3.95, p < .001, see Figure 3B for the grand-averages separately for high and low PE and Figure 5A for the interaction plot). Simple slope analysis with the moderating factor group revealed a significant effect for positive feedback for controls (β = 1.95, SE = 0.28, t = 7.01, p < .001), with more positive P3a amplitudes for higher unsigned PEs. All other simple slopes were non-significant (all p-values ≥ .196).

A significant three-way interaction was also present with the factors group, learnability, and unsigned PE (β = -1.18, $t(18997.71)$ = -2.10, p = .036, see Figure 5B for the interaction plot). Simple slope analysis with the moderating factor group revealed a significant effect for learnable trials in controls (β = 1.56, SE = 0.29, t = 5.28, p < .001), with more positive P3a amplitudes for higher unsigned PEs. All other simple slopes were non-significant (all p-values ≥ .124).

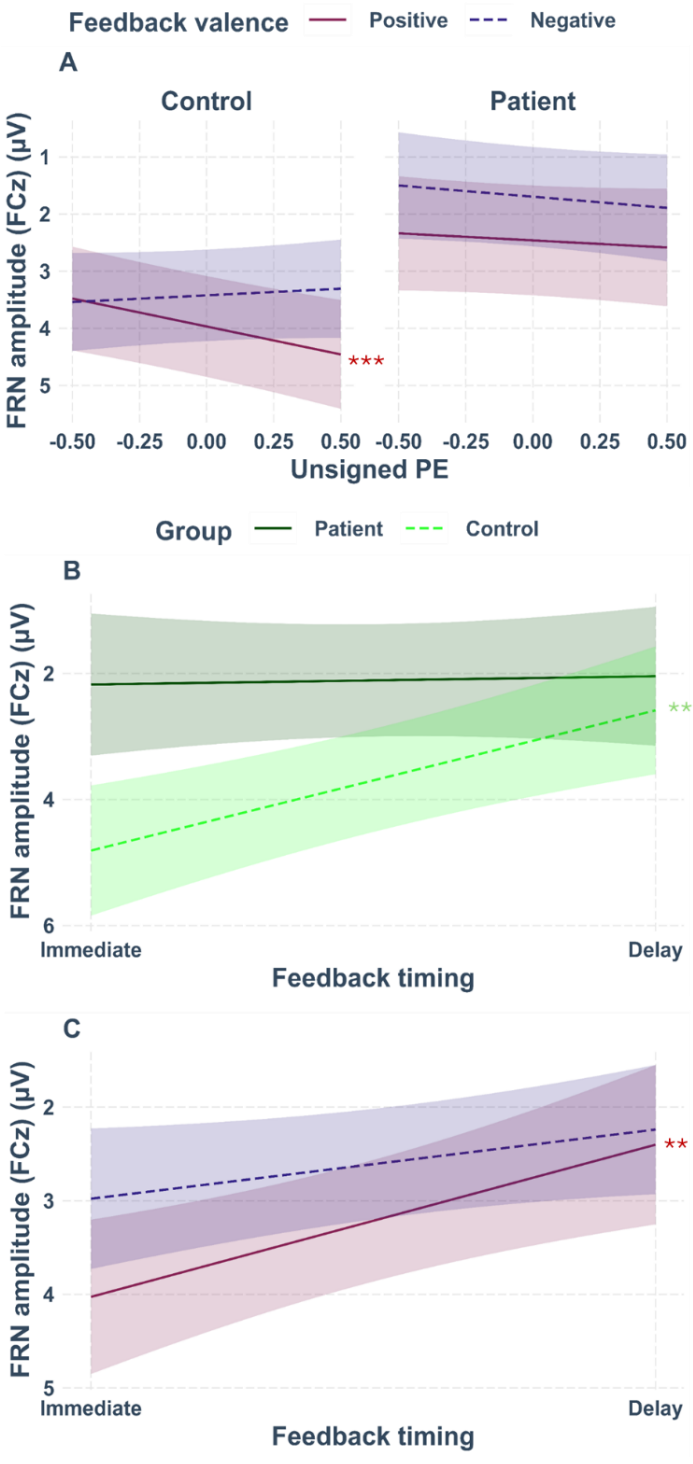

Figure 4. Interaction plot for single-trial FRN amplitudes at electrode FCz. Panel A shows the significant interaction between group, feedback valence, and unsigned PE. The slope for positive feedback modulated by the unsigned PE in controls was significant. Panel B shows the significant interaction between feedback timing and group. The slope for the controls modulated by feedback timing was significant. Panel C shows the interaction between feedback timing and feedback valence. The slope for positive feedback modulated by feedback timing was significant. Asterisks indicate significant effects. The smoothing around the lines indicates the 95% confidence interval for $N = 46$.

The interaction between unsigned PE and learnability was also significant ($\beta = 0.64$, $t(18997.71) = 2.29$, $p = .022$). Simple slope analysis revealed a significant effect for learnable trials only ($\beta = 0.99$, $SE = 0.21$, $t = 4.60$, $p < .001$), with increasing P3a amplitudes with higher unsigned PE across groups. The effect for unlearnable trials was not significant ($p \geq .091$).

In addition, the interaction between unsigned PE and feedback valence was significant ($\beta = 1.01$, $t(26811.17) = 3.15$, $p = .002$). Simple slope analysis demonstrated a significant effect for positive feedback only ($\beta = 1.12$, $SE = 0.21$, $t = 5.43$, $p < .001$), with increased P3a for higher unsigned PEs. The remaining statistical results are provided in the supplemental material Table S5.

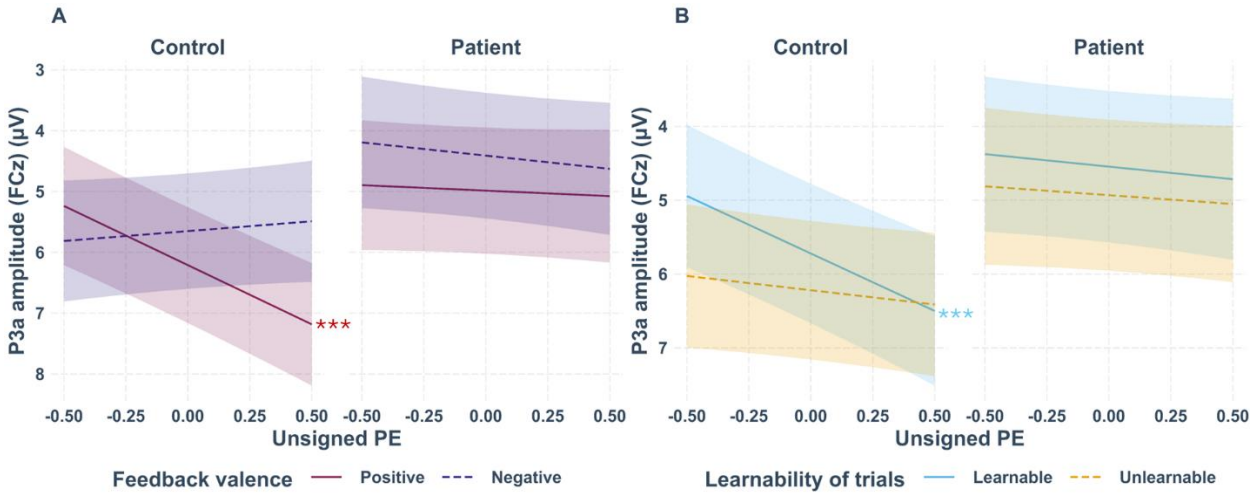

Figure 5. Panel A shows the interaction plot for single-trial P3a amplitudes at FCz according to group (patients, controls), feedback valence (positive, negative), and unsigned PE. The PE effect for positive feedback modulated by group and unsigned PE was significant in the control group. Panel B shows the significant interaction between group, learnability (learnable, unlearnable), and unsigned PE. The effect on learnability modulated by group and unsigned PE was significant in controls. Asterisks indicate significant effects. The smoothing around the lines indicates the 95% confidence interval for $N = 46$.

P3b

Feedback-locked grand-average ERPs at electrode Pz according to group (controls, patients), feedback timing (immediate, delayed), feedback valence (positive, negative), and unsigned PE (high, low) are provided in Figure 6. A figure with grand-average ERPs (at Pz) including only feedback timing and valence is provided in the supplement (see Figure S2).

For the single-trial P3b, analysis revealed a significant main effect of feedback timing ($\beta = 2.18$, $t(44.35) = 3.95$, $p < .001$), indicating that the P3b was more pronounced for delayed ($M = 7.30$ μV, $SD = 9.08$ μV) compared to immediate feedback ($M = 5.23$ μV, $SD = 9.08$ μV). In addition, the main effect of feedback valence was significant ($\beta = 0.74$, $t(44.21) = 4.06$, $p < .001$), with higher P3b amplitudes for positive ($M = 6.51$ μV, $SD = 8.59$ μV) compared to negative feedback ($M = 5.93$ μV, $SD = 8.71$ μV). Also, the main effect of the unsigned PE was significant ($\beta = 0.54$, $t(44.89) = 2.47$, $p = .017$), revealing increased P3b amplitudes with higher unsigned PEs. Last, the main effect of learnability was significant ($\beta = -0.34$, $t(26836.04) = -3.21$, $p < .001$), with decreased P3b amplitudes for learnable ($M = 6.03$ μV, $SD = 8.71$ μV) compared to unlearnable trials ($M = 6.49$ μV, $SD = 8.57$ μV).

A four-way interaction between group, feedback timing, feedback valence, and unsigned PE was also significant ($\beta = -3.79$, $t(23933.17) = -2.71$, $p = .007$). To resolve this interaction, we created separate models for patients and controls.

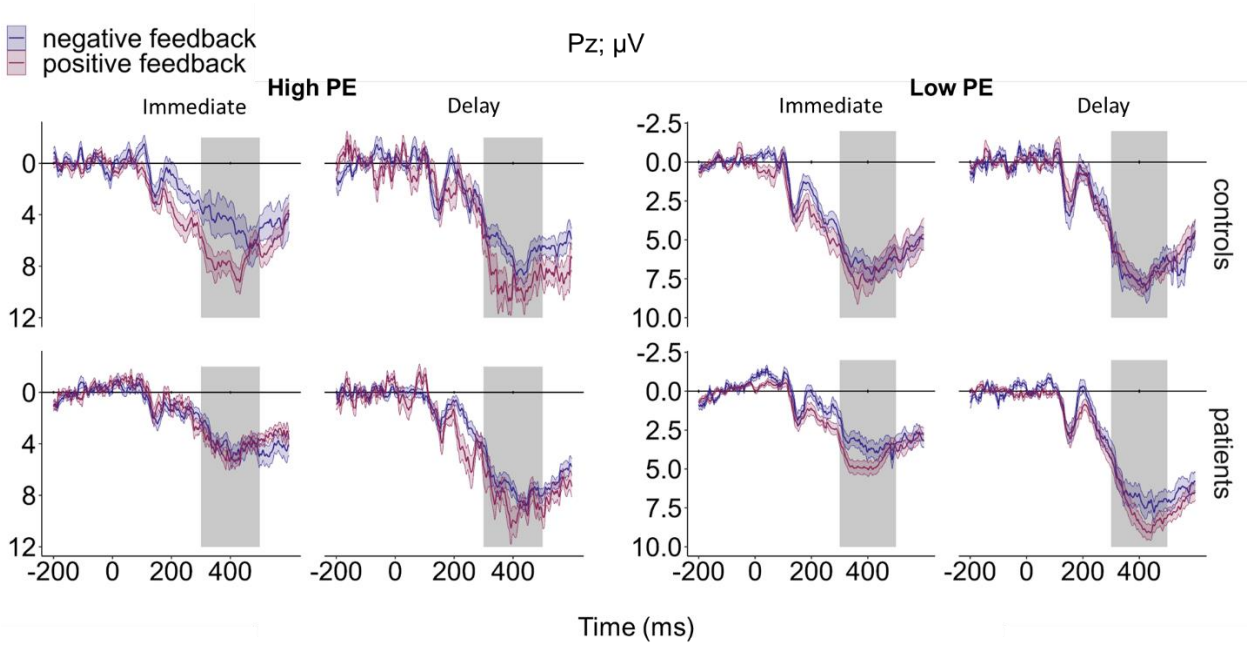

Figure 6. Feedback-locked grand-average ERPs at electrode Pz according to group (patients, controls), feedback timing (immediate, delayed), feedback valence (positive, negative) and unsigned PE categorized into high unsigned PE (> 0.5) and low unsigned PE (≤ 0.5). The gray rectangle indicates the time window for the P3b (300 – 500 ms).

For patients, the main effects of feedback timing (β = 3.00, $t(20.06) = 4.89$, $p < .001$) and feedback valence (β = 0.74, $t(19.45) = 3.39$, $p = .003$) were significant. P3b amplitudes were more positive for delayed feedback ($M = 7.21$ µV, $SD = 8.49$ µV) compared to immediate feedback ($M = 4.18$ µV, $SD = 7.44$ µV). Additionally, the P3b was more positive for positive feedback ($M = 6.09$ µV, $SD = 8.05$ µV) compared to negative feedback ($M = 5.20$ µV, $SD = 8.20$ µV). All other main and interaction effects for this model were non-significant (all p-values ≥ .050).

For controls, a main effect of unsigned PE was significant (β = 0.70, $t(3307.36) = 3.12$, $p = .002$ with higher P3b amplitudes for higher unsigned PE. In addition, a three-way interaction between feedback timing, feedback valence, and unsigned PE was significant (β = 2.42, $t(13684.19) = 2.55$, $p = .011$, see Figure 7 for the interaction plot). Simple slope analysis moderated by feedback timing and feedback valence revealed a significant effect on the unsigned PE for positive, delayed feedback (β = 2.36, $SE = 0.44$, $t = 5.43$, $p < .001$). The P3b amplitude was more positive, i.e. increased, for higher unsigned PEs when feedback was positive and delayed. In addition, a significant negative effect on the unsigned PE for negative, delayed feedback was present (β = -0.97, $SE = 0.49$, $t = -2.01$, $p = .045$). For negative, delayed feedback, P3b amplitudes decreased with higher unsigned PEs. A positive effect on the unsigned PE for positive, immediate feedback was also significant (β = 1.18, $SE = 0.44$, $t = 2.65$, $p = .008$), indicating more positive P3b amplitudes for higher unsigned PEs. The effect for negative, immediate feedback was nonsignificant ($p = .595$). The full

results tables for the main model on the P3b (see Table S6) and subordinate group-specific models (see Table S7 for patients and S8 for the controls) are provided in the supplemental material.

Figure 7. Interaction plots for the single-trial P3b at electrode Pz. The categorical factors are feedback timing (immediate, delay), feedback valence (positive, negative), and the continuous factor unsigned PE. Panel A: the effects for positive immediate and positive and negative delayed feedback in the control group were significant. Asterisks indicate significant effects. The smoothing around the lines indicates the 95% confidence interval for $n = 46$.

Voxel-based morphometry (VBM)

The analysis of GMV in patients ($n = 18$) and controls ($n = 24$) revealed significant volume reduction in patients in widely distributed cerebellar clusters (see Figure 8A and Table S10/ S11 in the supplement for the whole-brain and Figure 8B for the cerebellar results uncorrected and in Figure 8C the FWE corrected and Table 3 for the peak coordinates of the largest cluster after FWE correction in SUIT-space). Note that there were no extracerebellar clusters with significant volume reduction in patients relative to controls.

Cerebellar VBM revealed the most pronounced GMV reduction (here shown for cluster size > 500 voxel) in right Crus I (1452 voxel), right Crus II (1401 voxel), left Crus II (872 voxel), right I-IV (828 voxel), right IX (742 voxel), left I-IV (706 voxel), left Crus I (677 voxel) and left IX (563 voxel, see Table S9 in the supplement for a complete list of clusters and Table S10 for the list of uncorrected clusters).

Table 3. Summary of the six local maxima from the largest cluster of the between subject contrast control > patient

location	side	X	Y	Z	peak *p*-value	peak *t*-value
VI	right	29	-38	-35	$p < .001$	11.43
VIIb	right	35	-43	-44	$p < .001$	10.13
Crus I	left	-39	-67	-36	$p < .001$	10.00
Crus II	left	-8	-80	-39	$p < .001$	9.80
I-IV	right	11	-44	-25	$p < .001$	9.52
IX	right	10	-50	-46	$p < .001$	9.46

Note. Covariates of no interest were TIV and age. The cluster size was 11869 voxels. Results were FWE-corrected for $p < 0.05$. Complete list of significant regions can be found in the supplement Table S9.

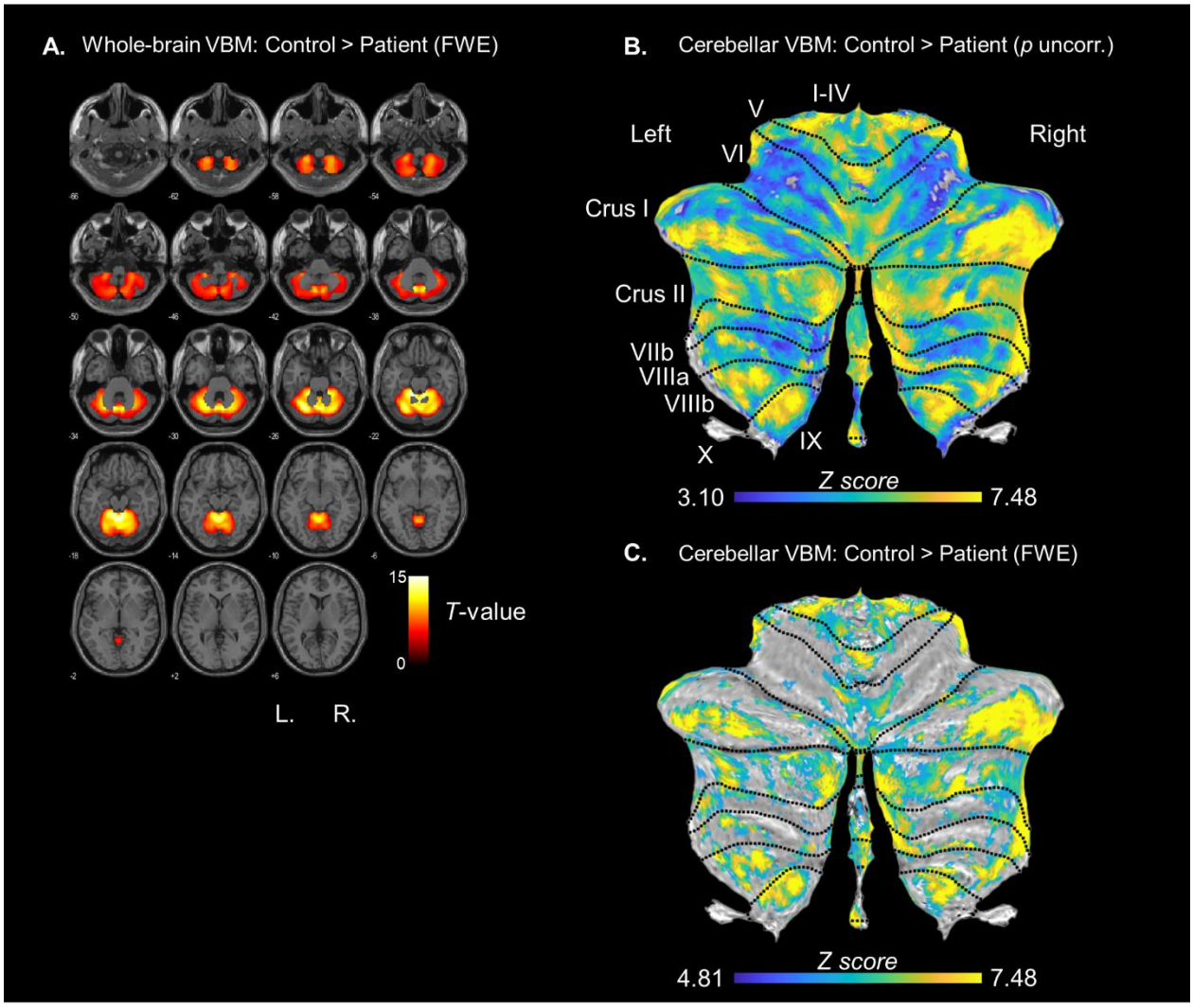

Figure 8. Panel A: Whole-brain GMV reduction in patients compared to controls. Panel B: Cerebellar GMV reduction in patients relative to controls (SUIT space) for uncorrected ($p < .001$) and in panel C after FWE-correction (for $p < 0.05$) projected on the cerebellar flatmap (75). TIV and age were used as covariates of no interest. The color bars indicate the range of *T*-values for whole brain and z scores for the cerebellar flatmaps.

Multiple regression analysis revealed that volume reduction in bilateral Crus I (left = 266, right = 103) and Crus II (left = 620, right = 249 voxel) was associated with more positive (i.e., blunted) FRN amplitudes (here shown for cluster size > 100 voxel, see Figure 9 and Table S12 for all clusters in the supplement).

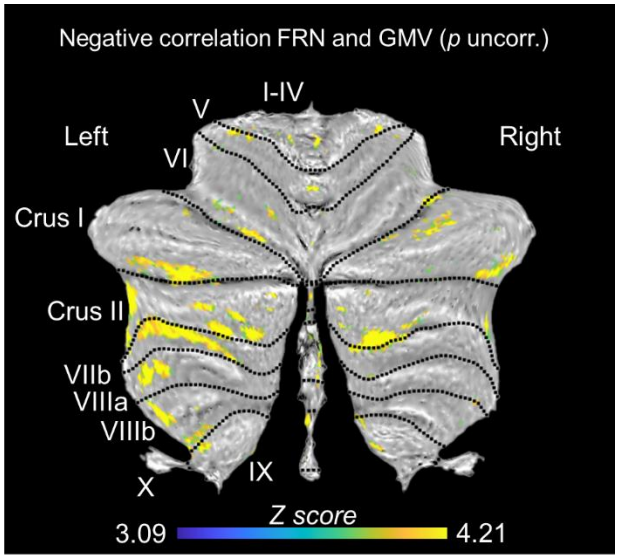

Figure 9. Clusters in which cerebellar GMV loss in patients relative to controls was linked to blunting of the FRN (aggregated across all single trials). The biggest cluster was present in left Crus II. TIV and age were used as covariates of no interest. The color bar indicates the range of z-scores. All identified clusters were uncorrected $p < .001$.

Discussion

The goal of the present study was to investigate feedback-based learning and RL-PE processing in patients with pure cerebellar degeneration.

To this end, EEG was recorded while participants completed a probabilistic feedback-based learning task in two sessions with different feedback timings, i.e. immediate feedback (delay = 500 ms) or delayed feedback (delay = 6500 ms). FRN, P3a, and P3b in the feedback-locked ERP were analyzed in relation to the PE for each individual trial. VBM was conducted on the whole-brain data and in a separate analysis for the cerebellum to characterize GMV volume loss in patients relative to controls, and to potentially link specific cerebellar regions to group differences in task performance and/or EEG measures reflecting RL-PE processing.

Analysis of the behavioral data revealed that accuracy increased with task progression, indicating that learning took place gradually. Importantly, we did not find the hypothesized group differences, nor differential effects of feedback timing in patients. Likewise, Huvermann et al. (20) did not find behavioral differences in choice accuracy between patients with cerebellar stroke and healthy controls in a similar learning task. The present behavioral findings thus appear to suggest that the cerebellum is not differentially involved in learning from immediate and delayed feedback.

Regarding behavioral flexibility, the present results revealed increased choice switching after incorrect choices and after negative feedback, as expected. Choice switching was higher for correct choices during immediate compared to delayed feedback across groups. Given that accuracy was generally increased for delayed feedback (see above), this finding may hint at decreased uncertainty when feedback was delayed. Interestingly, we found only subtle group differences in choice switching that related to task progression:

While in controls, decreased choice switching for delayed relative to immediate feedback was found in later task stages, such an effect was absent in patients, indicating that choice switching was not modulated by the learning progress. This could hint at decreased behavioral flexibility in patients as has been reported in patients with cerebellar damage for rule- and reversal learning tasks (see 40 for a review).

For the FRN, as expected, amplitudes were more negative for negative compared to positive feedback (e.g., 26–28). In addition, the unsigned PE was reflected in the FRN, with more negative amplitudes for more unexpected feedback (i.e., higher unsigned PE; e.g., 35,58). However, unexpectedly, the FRN was also more negative for patients compared to controls. A previous study using a similar learning task found no differences in the FRN between cerebellar lesion patients and controls, and no differences in healthy young participants for cerebellar transcranial magnetic stimulation (TMS) compared to vertex TMS (20). In addition, we found the expected more negative FRN for delayed compared to immediate feedback which is in line with previous results for the FRN scored peak-to-peak in the original waveforms (relative to the preceding P2) as opposed to in the difference signal (42). Crucially, further FRN analysis revealed interesting group differences: Coding of the unsigned PE in the FRN was present in controls and not in patients, albeit only for positive feedback. This finding in controls is consistent with recent reports of modulation of the FRN by positive PEs (31,76), indicating that coding of high PEs (i.e., unexpected feedback) in the FRN was more pronounced for positive compared to negative feedback. The absence of PE coding in the FRN in patients in both timing conditions could be indicative of an overall deficit in PE coding. Patients revealed an overall higher and more negative FRN than controls which could be explained by increased unexpectedness independent of the PE during the task. Evidence for impaired coding of surprise, which can also be interpreted as deficit in PE coding, was found in cerebellar stroke (10), but in this study, PEs were not modelled at single-trial level. However, Huvermann et al. (20) did model RL-PEs and found a similar pattern for the FRN, with completely absent RL-PE coding in cerebellar stroke patients compared to controls. Interestingly, they also observed a lack of RL-PE coding in healthy subjects who received cerebellar TMS. Together with the present findings, these results point to an association of cerebellar dysfunction with deficits in coding of RL-PEs. Also, a very recent meta-analysis on PE processes in humans discovered an association between unsigned PEs with cerebellar activation, among other regions (77). For the signed PE, cerebellar effects were not found.

Analysis of the P3a revealed only in controls a specific effect for unsigned PE and positive feedback, with a more pronounced P3a with higher unsigned PE, which is again in line with recent findings on the P300 showing an exclusive effect of positive PE coding for immediate feedback (31,76). Importantly, the P3a has been linked to attentional reorienting and suggested to encode expectancy (35,58) which could explain the positive PE effects as a surprise response in controls for immediate feedback. Similar to the FRN, no significant coding of the unsigned PE in the P3a was observed in patients. Besides the FRN which was

identified to reflect a non-binary signed RL-PE, the P3 was found to represent an unsigned PE in healthy subjects (38). Also, they identified a more central scalp distribution of the P3 similar to the P3a when analyzing the magnitude of the RL-PE solely by positive feedback. A more posterior distribution was identified when taking positive and negative feedback together into the analysis reflecting the P3b. We did not find an effect of feedback timing for the P3a which is in accordance with findings by Höltje and Mecklinger (78).

Interestingly, modulation of the P3b by feedback valence, feedback timing, and unsigned PE differed between patients and controls. This is particularly relevant because the P3b has been implicated in updating of context-related information (34), and directly in PE processing (79). Stewardson and Sambrook (80) demonstrated calculating great grand-averages across multiple studies that a parietal scalp deflection related to reward PE processing was stronger than an earlier frontal effect, underlining the significance of the P3b for processing of PEs. In line with this, the unsigned PE was coded in the P3b controls in the present study, with more positive amplitudes for higher PEs. Likewise, a modulation of the PE by positive, immediate feedback was present, with increased P3b amplitudes when the PE was high. Moreover, differential patterns emerged for positive and negative delayed feedback: Amplitudes were more positive for higher positive PEs but decreased with higher negative PEs. For positive immediate feedback, amplitudes were also more positive for higher unsigned PEs. Crucially, coding of the unsigned PE in the P3b was completely absent in patients. Together with largely absent PE coding in patients also in FRN and P3a, this result appears to indicate a rather global alteration of feedback-related ERPs in cerebellar degeneration. Interestingly, patients did show a generally more positive P3b for delayed feedback, which might be driven by the functional role of the P3b for updating contextual information. Höltje and Mecklinger (78) found a more pronounced P3b for immediate compared to delayed feedback in healthy subjects and linked this observation to increased action value updating when feedback was presented immediately. Our control group did not reveal a main effect of feedback timing, but we observed the opposite pattern in patients, with a decreased P3b for immediate feedback. In our point of view, it is conceivable that context updating is more demanding for longer delay duration due to higher working memory demand.

Whole-brain VBM results showed significant GMV reduction in patients compared to controls spanning wide regions of the cerebellum. Importantly, whole-brain VBM revealed no extra-cerebellar differences between patients and controls. Cerebellar VBM using SUIT showed the strongest GMV reduction in bilateral Crus I/ II and other posterolateral regions of the cerebellum. The cerebellar regions Crus I and II have been linked to cognitive functions in the past (81,82), and according to the functional atlas by King et al. (45) and Van Overwalle et al. (83), Crus II is particularly implicated in cognitive functions such as action observation. GMV reduction particularly in bilateral Crus I/ II was associated with more positive FRN amplitudes. At first glance, this finding is surprising, as the observation of generally more negative FRN

amplitudes in patients compared to controls suggested that the direction of the correlation would be the opposite. However, we assumed that the FRN would be blunted with increasing GMV reduction, as previously shown for the response-locked ERP component ERN (error-related negativity: 84,85) in a similar sample of patients with cerebellar degeneration (17), and also in line with recent findings in healthy subjects when cerebellar function was disrupted due to single-pulse TMS applied to the posterolateral cerebellum (86). Both, the FRN and ERN originate from the ACC (32,87) and are closely linked to RL-PE processing (23). Thus, the present findings suggest that the cerebellum influences the ACC, and that cerebellar GMV reduction ultimately affects reinforcement learning.

Limitations

The present study was designed to characterize the cerebellum's role in reinforcement learning and coding of RL-PEs by investigating patients with different ataxia disorders characterized by progressive cerebellar degeneration. Including patients with etiologically different diseases might have led to increased (unexplained) variance in our results that was particularly problematic for the VBM. However, we used a homogeneity analysis to exclude participants with extreme cerebellar GMV reduction to cope with strong variance differences. Also, the discrepancy between the group effect in the FRN for the MLM and the negative correlation in the VBM could have been the result of the aggregated data points for the FRN in the GLM. While MLMs model each individual trial for each participant, the GLM models only the aggregated values of the FRN for each participant. Hence, individual variability is lost with the GLM. In addition, we did not see the expected differences in the CCAS between patients and controls (see Table 2). However, recent research has questioned the interpretation of the CCAS to identify cognitive alterations in patients with cerebellar diseases (88). On the one hand, based on the CCAS findings, general cognitive performance in the present sample appears to have been similar for patients and controls, possibly explaining the lack of group differences in accuracy in the feedback learning task. On the other hand, the task may not have been sensitive enough to find accuracy differences. General learning performance in the present study was comparable to previous studies (e.g., accuracy in the acquisition stage ranged between 50 % and 80 % in Thoma et al. (9), and Rustemeier et al. (10)). Of note, we did not include reversal learning which was shown to be altered in patients with cerebellar lesions (9). Thus, our task design unfortunately does not allow for insights in this direction beyond the behavioral findings on choice switching.

Conclusion

In conclusion, the present results revealed altered RL-PE processing in probabilistic feedback-based learning in patients with pure cerebellar degeneration. Integrating findings on the feedback-locked ERP components FRN, P3a, and P3b, we find consistent results showing absence of PE coding in patients. Whole-brain and cerebellar VBM results showed global cerebellar degeneration in patients compared to

controls, and multiple regression revealed that reduced GMV in bilateral Crus I/ II was associated with a blunting of the FRN. The present results did not provide evidence for differential involvement of the cerebellum in reinforcement learning as a function of feedback timing. Nevertheless, the present results underline the cerebellum's role in reinforcement learning, and here specifically in coding of PEs. More research is needed to fully elucidate the mechanisms of cerebellar contributions to PE processing as well as contextual factors that may modulate these processes using task-based fMRI, particularly to disentangle the (cerebro-cerebellar) networks underlying reinforcement learning in healthy and diseased cerebellum.

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Author contribution

JP, DT, and MM devised the project idea. AB, DH, EB, CB, DT, MM, and JP planned the study. AB programmed the task. DH created the single-trial ERP analysis pipeline. AB preprocessed and analyzed the data. DT, MM, and JP supervised the project. AB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Data and Code availability statement

The study protocol was defined prior to the experiment and preregistered on OSF. The preregistration, data, and code are openly available through OSF at https://osf.io/fgw8h/

Competing Interests: none

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