Chapter 8
The Cerebellum: A Therapeutic Target in Treating Speech and Language Disorders

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Abbreviations

ASD	Autism spectrum disorders
BOLD	Blood oxygen level dependent
CBI	Cerebellar brain inhibition
cTBS	Continuous theta-burst stimulation
DTI	Diffusion tensor imaging
FC	Functional connectivity
GM	Gray matter
iTBS	Intermittent theta-burst stimulation
MEPs	Motor-evoked potentials
PASAT	Paced auditory serial addition task
PASST	Paced auditory serial subtraction task
PSP	Progressive supranuclear palsy
rs-fMRI	Resting-state functional magnetic resonance imaging
rTMS	Repetitive transcranial magnetic stimulation
SCA	Spinocerebellar ataxia
TBS	Theta-burst stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VWM	Verbal working memory

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8.1 Introduction

Approaches to thinking about the cerebellum have historically been overshadowed by the view that it is a structure mainly involved in motor control and coordination (Manto & Mariën, 2015). However, during the past decades, neuroanatomical, neuroimaging, and clinical studies have substantially modified this traditional view and provided new insights and a body of evidence for cerebellar involvement in a wide range of nonmotor processes, such as cognitive, affective, and social processes (Clausi, Iacobacci, Lupo, et al., 2017; Clausi, Olivito, Lupo, et al., 2019; Lupo, Troisi, Chiricozzi, et al., 2015; Stoodley & Schmahmann, 2010; Tedesco, Chiricozzi, Clausi, et al., 2011). Within the broad range of functions in which the cerebellum is involved, several clinical studies have shown the occurrence of different types of speech and language impairments subsequent to cerebellar damage (Mariën & Borgatti, 2018).

In the first part of the present chapter, we briefly summarize the motor and nonmotor language impairments that have been reported after cerebellar damage in adults and the associated cerebello-cerebral network alterations. Starting from these clinical and neuroimaging data regarding the "linguistic cerebellum," in the second part of the chapter, we provide an overview of the studies that used noninvasive transcranial neuromodulation techniques to further investigate the cerebellar role in speech and language domains. Furthermore, we show the current state of the art and translational potential of the use of cerebellar neuromodulation to improve speech and language functions after cortical and subcortical damage.

8.2 Cerebellar Topographical Organization: An Outline

The neuroanatomical substrate of the cerebellar role in motor, cognitive, and affective processing consists of the proven existence of connections between the cerebellum and the motor, paralimbic, and association cortices (Strick, Dum, & Fiez, 2009). Indeed, the cerebellum receives inputs from the cerebral cortex via cortico-pontine-cerebellar pathways and sends them back to the same cortical areas via cerebello-thalamic-cortical pathways (Schmahmann, 1996). Each cerebellar hemisphere mainly sends information to and receives information from the contralateral cerebral hemisphere.

Neuroanatomical and neurophysiological studies have shown a specific topographical and functional organization of the cerebellar regions as follows: the anterior cerebellar lobe (lobules I–V and extending into medial lobule VI and lobule VIII) is involved in motor functions, the posterior cerebellar lobe (Crus I, Crus II, lobules VI, VIIb, and IX) is involved in cognitive functions, and the posterior vermis is involved in affective functions (Stoodley & Schmahmann, 2010).

Over the years, among the functions in which the cerebellum plays a role, speech and language processes have received high levels of attention. A number of studies have shown cerebellar involvement in both motor and nonmotor aspects of the linguistic domain. These functions have been anatomically localized mainly in the right hemispheric cerebellar regions (Stoodley & Schmahmann, 2009), although bilateral cerebellar involvement has also been described (Mariën, Engelborghs, Fabbro, & De Deyn, 2001; Murdoch & Whelan, 2007).

8.3 Role of the Cerebellum in Speech and Language Impairments: Evidence from Clinical Studies

Evidence for a cerebellar role in the speech and language domains derives predominantly from evaluations of patients with various cerebellar pathologies in which different language problems have been identified (Mariën & Borgatti, 2018). Indeed, according to the most relevant literature, several types of motor and nonmotor language impairments have been reported after cerebellar damage, as outlined in the next sections. When language function is considered a highly complex skill that incorporates different subskills, evidence about specific alterations observed after a cerebellar lesion can lead to new considerations for possible treatments.

8.3.1 Motor Speech Planning

This term refers to an implicit knowledge of the language regularities in motor patterns that are established during speech acquisition (Mooshammer, Goldstein, Nam, et al., 2012). A cerebellar lesion may cause ataxic dysarthria, a speech disorder traditionally ascribed to motor execution impairments and characterized by distorted articulation and prosody. In the last decade, the view of ataxic dysarthria as a mere motor execution problem has changed, and it is now considered to also encompass deficits in motor speech programming (Mariën & Verhoeven, 2007; Spencer & Slocomb, 2007).

8.3.2 Verbal Fluency

Impairments in verbal fluency tasks are commonly reported in patients affected by focal or degenerative cerebellar damage (Leggio, Silveri, Petrosini, & Molinari, 2000; Schweizer, Alexander, Gillingham, et al., 2010; Stoodley & Schmahmann, 2009). Performance differences between semantic and phonological fluency tasks have been described in patients affected by cerebellar lesions with a specific trend for disruption of phonological processing (Leggio et al., 2000). Although there is a general agreement on such impairment in phonological fluency after a cerebellar lesion, less clear is the cerebellar lateralization effect (Leggio et al., 2000; Murdoch & Whelan, 2007).

8.3.3 Grammar Processing

Since the 1990s, a growing number of clinical studies have provided evidence for a possible role of the cerebellum in morphological and syntactic aspects of language processing in terms of deviations from predicted grammar rules such as subject-verb agreement or canonical word order (Mariën, Baillieux, De Smet, et al., 2009; Silveri, Leggio, & Molinari, 1994). Regarding grammatical problems, most of the cases in the literature presented after a right cerebellar lesion (Mariën, Engelborghs, Pickut, & De Deyn, 2000; Silveri et al., 1994). However, left cerebellar hemisphere involvement has also been described (Fabbro, Moretti, & Bava, 2000; Justus, 2004).

8.3.4 Writing

Among language deficits, writing disorders have been frequently reported after cerebellar lesions. Consequent to focal or diffuse cerebellar damage in adults, different studies have described the presence of disorders in the coordination, planning, and execution of writing movements, such as spatial agraphia, apraxic agraphia, micrographia, and neglect dysgraphia (Mariën, De Smet, de Smet, et al., 2013; Silveri, Misciagna, Leggio, & Molinari, 1999), which are not linked to the typical motor impairments due to cerebellar damage. More central processes of writing are also affected by cerebellar lesions (Lupo et al., 2019). These are commonly included in the cluster of graphical buffer deficits (i.e., spelling process, lexical agraphia, deep agraphia, phonological or semantic agraphia) (Haggard, Jenner, & Wing, 1994; Silveri et al., 1999). Although writing problems are mainly described after a right cerebellar lesion, there is no agreement on cerebellar lateralization in this function (Fabbro et al., 2000; Mariën et al., 2009).

8.3.5 Reading

Reading difficulties after cerebellar damage in adults have been reported less often. In the last decade, Moretti, Torre, Antonello, et al. (2002) provided evidence for problems in the reading of letters and words in a population of cerebellar patients with vermal lesions. Furthermore, Mariën et al. (2009) described visual dyslexia in a patient affected by an ischemic infarction in the territory of the right superior cerebellar artery.

8.3.6 Verbal Working Memory

Verbal working memory (VWM) is the ability to temporarily store and manipulate verbal information. Data from studies in adult patients showed that the presence of cerebellar pathology can have a mildly to moderately severe negative impact on VWM (Chiricozzi, Clausi, Molinari, et al., 2008; Hokkanen, Kauranen, Roine, et al., 2006; Ravizza, McCormick, Schlerf, et al., 2006). The shared hypothesis about the cerebellar role in VWM has been that the cerebellum could participate in the articulatory control system and/or the phonological storage system (Chiricozzi et al., 2008; Ravizza et al., 2006) described by Baddeley (2003). Ravizza et al. (2006) suggested that the cerebellum may be involved in creating a memory trace during the first stage of articulatory control when verbal information is translated into a phonological representation. Furthermore, impairment in encoding phonological traces has also been described as a consequence of cerebellar damage (Chiricozzi et al., 2008).

8.4 Structural and Functional MRI Alterations in the Cerebello-Cerebral Circuitry Related to Speech and Language Deficits

In the context of language deficits related to cerebellar alterations, further support has been provided by structural and functional neuroimaging studies. Starting from the evidence that the cerebellum has a clear topographical organization of functions, linguistic abilities may be selectively affected based on the site of the cerebellar lesion. As proposed by Mariën et al. (2000) and Mariën, Saerens, Nanhoe, et al. (1996), after cerebellar damage, a reduction in excitatory impulses through the cerebello-ponto-thalamo-cortical pathways may result in language disturbances that reflect a remote effect on supratentorial language areas. Consistent with the presence of contralateral projections between the cerebellum and left-lateralized language regions in the cerebral cortex (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; Jansen, Flöel, Randenborgh, et al., 2005), different studies in cerebellar-damaged patients have shown that language deficits (in particular impaired verbal fluency and agrammatism) occur more often after damage of the right posterior cerebellar lobe (Schmahmann & Sherman, 1998; Tedesco et al., 2011). This evidence has been further supported by neuroimaging studies in patients with cerebellar damage using voxel-based lesion-symptom mapping that have shown a link between damage to the right Crus I and verbal fluency deficits (Richter, Gerwig, Aslan, et al., 2007), while damage to right lobules VII through IX was associated with poorer scores on the Boston Naming Test (Stoodley, MacMore, Makris, et al., 2016). As suggested by a whole-brain voxel-based morphometry study (Clausi, Bozzali, Leggio, et al., 2009) in patients affected by isolated cerebellar damage, gray matter (GM) changes may occur in supratentorial regions due to the reduced input via cerebello-cortical pathways and result in the observed functional impairment. Specifically, reduced GM volume in the left superior temporal gyrus has been shown after isolated right cerebellar damage and correlated with verbal fluency deficits in patients (Clausi et al., 2009). It is worth noting that, although most studies have indicated crossed cerebro-cerebellar language lateralization (Méndez Orellana, Visch-Brink, Vernooij, et al., 2015; Starowicz-Filip, Chrobak, Moskała, et al., 2017), clinical and neuroimaging findings have also suggested that the left cerebellar hemisphere contributes to the mediation of language via ipsilateral cerebello-cortical pathways (Murdoch & Whelan, 2007).

From a structural point of view, further support comes from a diffusion tensor imaging (DTI) study that investigated the patterns of microstructural integrity within cerebellar white matter tracts connecting the cerebellum with higher-order cerebral regions, including those relevant to language (Olivito, Lupo, Iacobacci, et al., 2017). In particular, in patients with cerebellar neurodegenerative pathology, specific alterations of diffusion-derived measures within the right superior cerebellar peduncle correlated with verbal and phonological fluency (Olivito et al., 2017). Moreover, cerebellar mutism syndrome has been described in patients with a significant reduction of diffusivity values (i.e., fractional anisotropy) in the superior cerebellar peduncle (McEvoy, Lee, Poliakov, et al., 2016).

Taken together, these observations suggested that altered interactions within specific cerebello-cortical modules may be related to language and speech deficits, both in primary cerebellar pathology and other pathological conditions in which cerebellar damage is reported. In this framework, functional connectivity (FC) studies have provided great insight into the dissection of the complex interactions between the cerebellar and cerebral cortex that may subserve linguistic abilities and have informed our understanding of the cerebello-cerebral functional alterations underlying language and speech dysfunctions. FC refers to synchronous neural activity between anatomically separated brain regions (Biswal, Van Kylen, & Hyde, 1997) and can be analyzed by means of resting-state functional magnetic resonance imaging (rs-fMRI). This approach focuses on spontaneous, low-frequency fluctuations (<0.1 Hz) in the blood oxygen level-dependent (BOLD) signal at rest and allows the detection of synchronous activations between regions that are spatially distinct (Biswal et al., 1997). Over the years, an increasing body of rs-fMRI studies in healthy subjects have revealed the presence of functional intrinsic connectivity networks involving the cerebellum and cerebral cortex regions related to language (Buckner, Krienen, Castellanos, et al., 2011; D'Mello & Stoodley, 2015; O'Reilly, Beckmann, Tomassini, et al., 2010). Connectivity alterations within cerebello-cerebral networks have been specifically linked to language deficits reported in autism spectrum disorders (ASD) (Khan, Nair, Keown, et al., 2015; Verly, Verhoeven, Zink, et al., 2014). By using a seed-based approach, Verly et al. (2014) reported a significant reduction in the FC strength between the right posterior cerebellum (Crus I and Crus II) and cortical language regions, including the left inferior frontal gyrus, dorsolateral prefrontal cortex, left premotor, and supplementary motor area. All these cortical regions are related to different language domains (Alario, 2006; Duffau, 2003), thus suggesting that FC within specific cortico-cerebellar modules might play a crucial role in distinct abnormal language functions in ASD. Further support for these observations has been derived from evidence that FC strength between different cerebello-cortical nodes correlates with distinct expressive and receptive language domains (see Verly et al., 2014 for a review). Overall, the structural and functional observations derived from neuroimaging studies highlight the centrality of the cerebellum in regulating language networks and may provide important therapeutic indications in the context of language deficits, particularly when the increasing interest of cerebellar neuromodulation to treat different motor and cognitive disturbances is considered (D'Mello, Turkeltaub, & Stoodley, 2017; Ferrucci, Bocci, Cortese, et al., 2016; Leow, Marinovic, Riek, & Carroll, 2017).

8.5 Cerebellar Neuro-Stimulation Techniques

As reported in the previous sections, a number of clinical and neuroimaging studies point toward a central role of the cerebellum in regulating speech and language functions. Specifically, the evidence regarding impairments after cerebellar lesions and the activation of specific regions of the cerebellum in speech and language tasks may provide the foundations for developing novel treatments.

The cerebellar anatomical location, right beneath the skull, makes the cerebellum accessible to noninvasive neuro-stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (van Dun, Bodranghien, Manto, & Mariën, 2017), which have been recognized as promising techniques to modulate neuronal activity in both healthy and patient populations (van Dun, Mitoma, & Mario Manto, 2018). Indeed, modeling studies have shown that both TMS and tDCS are capable of inducing electric currents inside the cerebellar cortex (Hardwick, Lesage, & Miall, 2014; Parazzini, Rossi, Ferrucci, et al., 2014). Moreover, if we consider the very high concentration and organized distribution of neurons in the cerebellar cortex, together with the properties of plasticity in the cerebellar microcircuits, these techniques may be very effective when targeting the human cerebellum, with consequent effects on cognitive domains in which the cerebellum plays a role, such as speech and language (van Dun et al., 2017; van Dun, Bodranghien, Mariën, & Manto, 2016).

Before examining the cerebellar neuro-stimulation effects on speech and language abilities, it is useful to briefly describe the main characteristics of TMS and tDCS over the cerebellum.

8.5.1 Cerebellar Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a safe and noninvasive neuro-stimulation technique that allows both activation and modulation of the excitability of neurons depending on the intensity and frequency of the pulses (Sandrini, Umiltà,

& Rusconi, 2011; Walsh & Cowey, 2000). It is administered by using a magnetic coil placed on the scalp to induce weak electric currents in the brain sites beneath the coil. It can be administered as a single pulse (single-pulse TMS) with an excitatory effect or as a series of pulses with different frequencies. Similarly, the effects of repetitive TMS (rTMS) on neuronal activity depend on pulse frequency: high-frequency rTMS (usually 50 Hz) excites and low-frequency rTMS (usually 1 Hz) inhibits neuronal activity (Hallett, 2007). A variation in the rTMS protocol is theta-burst stimulation (TBS), which uses bursts of high-frequency stimulation (3 pulses at 50 Hz) at a 1–5 Hz rhythm. It can be given in a continuous (cTBS, inhibitory) or intermittent (iTBS, excitatory) manner (van Dun et al., 2016, 2018); rTMS is often used in cognitive research to induce a reversible "virtual lesion," as its effects outlast the period of stimulation by some minutes (Walsh & Cowey, 2000).

To date, although most TMS studies have been directed at the cerebral cortex, there is growing interest in applying TMS over the cerebellum to investigate the effects of cerebellar stimulation on cognitive functions, including language processing (Grimaldi, Argyropoulos, Boehringer, et al., 2014). It has been proposed that single-pulse TMS over the cerebellum activates Purkinje cells, with increased inhibition of the dentate-thalamo-cortical facilitatory connections that affect the contralateral primary motor and prefrontal cortex (Ugawa & Iwata, 2005). Moreover, different studies on motor and cognitive processes have inferred suppression of the activity of the cerebellar cortex after cTBS (Koch, Mori, Marconi, et al., 2008; Picazio, Oliveri, Koch, et al., 2013).

However, there is no consensus on the effects of rTMS and cTBS of the cerebellum on cerebral cortex function. Indeed, both facilitation and inhibition of motor-evoked potentials (MEPs) have been reported after cerebellar stimulation (van Dun et al., 2017). The situation becomes more complex in cognitive studies, in which behavioral measures are used. In this case, physiological measures of cortical function, i.e., electroencephalogram, should be encouraged, and several methodological issues need to be considered, such as the type of coil, the intensity, and site of stimulation (Tomlinson, Davis, & Bracewell, 2013).

8.5.2 Cerebellar Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that induces site-specific, polarity-dependent modulation of cortical excitability. However, tDCS is not as powerful as TMS in inducing action potentials (Woods, Antal, Bikson, et al., 2016). Two electrodes of different polarities (most frequently used electrode sizes are 25–35 cm^2), the "anode" and the "cathode," are connected to a 9 V battery-driven direct current stimulator and used to deliver a low-intensity constant current of 1–2 mA for 8–25 min. One electrode is placed over the cerebral area of interest and the other electrode over a reference site, which can be on the scalp for bicephalic stimulation (Grimaldi & Manto, 2013) or on a different body part, such as the deltoid muscle, for monocephalic stimulation (Ferrucci, Marceglia, Vergari, et al., 2008). The current flow passes from one electrode to the other and in the opposite direction for anodal versus cathodal tDCS, affecting the sodium and calcium channels and altering resting membrane potentials (Nitsche, Cohen, Wassermann, et al., 2008; Woods et al., 2016).

In general, in healthy subjects, anodal tDCS leads to neuronal membrane depolarization and increases neural excitability, whereas cathodal tDCS leads to neuronal membrane hyperpolarization and decreases neuronal excitability (Bikson, Inoue, Akiyama, et al., 2004). The effects of tDCS can occur both during and after stimulation (e.g., in the motor cortex, the effect can last up to 90 min) (Nitsche & Paulus, 2001) and might result in enhanced or impaired task performance, depending on the stimulated neuronal circuitry (Antal, Nitsche, Kincses, et al., 2004; Rogalewski, Bretenstein, Nitsche, et al., 2004).

In recent years, the cerebellum has been considered an ideal target for tDCS due to its high neuronal concentration and anatomical location. Indeed, as shown in animal studies, the cerebellum is highly susceptible to polarizing currents (Grimaldi, Argyropoulos, Bastian, et al., 2016). Although the unique and complex cytoarchitecture of the cerebellum makes it difficult to predict tDCS outcomes (Rahman, Toshev, & Bikson, 2014), cerebellar tDCS has been increasingly used in both healthy subjects and patients to study the functional connectivity of the cerebellum with other parts of the brain and its effects on motor, cognitive, or affective functions.

The effect of tDCS over the cerebellum in humans has been indirectly investigated by studying its effect on "cerebellar brain inhibition" (CBI) (Galea, Jayaram, Ajagbe, & Celnik, 2009; Ugawa, Uesaka, Terao, et al., 1995), which is the inhibitory action that the cerebellum exerts on the contralateral cerebral cortex by means of inhibitory output from Purkinje cells to the disynaptic dentate-thalamo-cortical facilitatory connections (Oulad Ben Taib & Manto, 2013; Ugawa, Genba-Shimizu, Rothwell, et al., 1994). Specifically, the cerebellar cortex sends efferent fibers to the cerebral cortex through the cerebellar nuclei, on which it exerts inhibitory action. Since the cerebellar nuclei exert excitatory effects on the thalamo-cortical pathway, their inhibition results in reduced dentate-thalamo-cortical facilitation (Schmahmann, Smith, Eichler, & Filley, 2008). Galea et al. (2009), using a conditioning paired-TMS protocol, showed that cerebellar tDCS induces amplitude changes in MEPs elicited from the contralateral primary motor cortex. In particular, they demonstrated that cerebellar cathodal stimulation decreased the ability of TMS to elicit CBI of M1, whereas anodal stimulation had the opposite effects. Although the exact physiological impact of tDCS over the cerebellum is not yet completely understood, it has been proposed that it produces its effects by polarizing Purkinje cells and changing the levels of activity in the deep cerebellar output nuclei, affecting distant plasticity in human cortical areas (Galea et al., 2009). Moreover, cerebellar tDCS might affect the transmembrane polarization resulting in prolonged spiking activity in Golgi inhibitory cerebellar neurons that can explain the long-lasting aftereffects (Grimaldi et al., 2016).

One limitation of cerebellar tDCS is that although modeling studies have demonstrated that the electric field effectively reaches the cerebellum, only the lobules in proximity to the skull, such as the posterior portions of the cerebellum, are accessible

(Ferrucci, Brunoni, Parazzini, et al., 2013; Rahman et al., 2014). Moreover, cerebellar tDCS effects also depend on the electrical field orientation. The position of the reference electrode is thus of critical importance: for example, positioning it on the ipsilateral buccinator muscle or on the shoulder might alter the stimulation effect (Ferrucci, Cortese, & Priori, 2015). Another issue that must be taken into account is that there have been no unambiguous conclusions about the polarity-specific effects of cerebellar tDCS. Indeed, while some studies reported polarity-specific effects (Galea et al., 2009; Pope & Miall, 2015), with anodal cerebellar stimulation increasing and cathodal stimulation decreasing CBI, other studies found no differences between anodal and cathodal cerebellar stimulation (Ferrucci et al., 2008; Hamada, Strigaro, Murase, et al., 2012).

In conclusion, cerebellar tDCS can be considered safe and is not associated with long-lasting negative side effects. However, it is important to carefully consider each stimulation parameter to guarantee the health and safety of subjects undergoing stimulation. In particular, the possible short-term side effects (i.e., itching, tingling, burning, mild intensity pain sensations, sensation of a metallic taste, and redness under the electrode) and subject exclusion criteria (i.e., brain surgery, head trauma, or tumor, metal in the head, implanted medical devices, central nervous system-effective medication, pregnancy, scalp sensitivity) have to be taken into account (Grimaldi et al., 2016).

8.6 Cerebellar Stimulation to Modulate Speech and Language Abilities in Healthy Subjects

The following subsections will be focused on the studies that used TMS and tDCS to investigate the cerebellar role in speech and language domains. We will provide also an overview of the studies that combine these neuromodulation techniques with neuroimaging analyses to investigate the effect of cerebellar stimulation on the cerebral areas involved in speech and language functions.

8.6.1 Cerebellar TMS Effects

Different studies have used TMS to investigate the role of the cerebellum in specific cognitive domains, including speech and language functions (Arasanz, Staines, Roy, et al., 2012; Argyropoulos, Kimiskidis, & Papagiannopoulos, 2011; Tomlinson, Davis, Morgan, & Bracewell, 2014). In particular, to investigate language abilities, tasks assessing working memory, verbal fluency, and lexical decision tasks have been administered before and after different types of cerebellar stimulation. A summary of the studies that investigated the effects of cerebellar TMS on speech and language functions is reported in Table 8.1a.

Table 8.1 Summary of the studies that investigate the effect of the cerebellar TMS (part A) and tDCS (part B) on speech and language functions

Part A

TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Allen-Walker et al. (2018)	*N* = 19 (9 M, 10 F) Mean age ± s.d.: 24.2 ± 2.1	cTBS 55% of MMO	Lexical decision task (backward associative priming at short SOAs)	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm L or R from inion	Significant increase in backward priming at short SOAs after the stimulation of L CB relative to R CB
Arasanz et al. (2012)	*N* = 27 (9 M, 18 F) Age: range 20–35 years *N* = 14: L stim *N* = 13: R stim	cTBS 80% of AMT	Phonetic and semantic fluency tasks	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm L or R from inion	Lower switching scores in first 15 s of phonemic fluency task after R stimulation Increased number of words produced in phonemic fluency task after R or L stimulation in the late phase of the task No effect on semantic fluency task
Argyropoulos et al. (2011)	*N* = 8 (n.s.) Mean age ± s.d.: 26.9 ± 8.6 years	cTBS 45% of MMO	Lexical decision task with associative (e.g., “gift”-“horse”) or semantic (e.g., “swan”-“chicken”) prime	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	Lateral: 1 cm below, 4.5 cm R from inion Medial: 1 cm below, 1 cm R from inion	Selective increase of associative priming size after medial CB stimulation Selective decrease in accuracy rate after medial CB stimulation in the first session

(continued)

Table 8.1 (continued)

Part A

TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Argyropoulos et al. (2011)	*N* = 24 (n.s.) Mean age ± s.d.: 26.9 ± 8.6 years *N* = 12: lateral stim *N* = 12: medial stim	cTBS 45% of MMO	Lexical decision task with associative (e.g., "gift"-"horse") or semantic (e.g., "swan"-"chicken") prime	3 pulses at 30 Hz every 100 ms (801 pulses) (offline)	Lateral: 1 cm below, 4.5 cm R from inion Medial: 1 cm below, 1 cm R from inion	Impaired learning after medial CB stimulation (lack of decrease in RT for those receiving medial TMS during first experimental session) No effect on priming size
Argyropoulos and Muggleton (2013)	*N* = 50 (n.s.) Mean age ± s.d.: 22.7 ± 5.4 years *N* = 12: R lateral stim *N* = 11: R medial stim *N* = 23: no stim	cTBS 45% of MMO	Lexical decision task with associative (e.g., "chef"-"cooking") or semantic (e.g., "theft"-"stealing") prime	3 pulses at 50 Hz repeated at a 5 Hz rhythm for 40 s (600 pulses) (offline)	Lateral: 10 cm R from inion Medial: 1 cm below, 1 cm R from inion	Selective enhancement of semantic associative noun-to-verb priming after R CB stimulation No effect on semantic categorical priming
Brusa, Ponzo, Mastropasqua, et al. (2014)	*N* = 10 (4 M, 6 F) patients affected by PSP Mean age ± s.d.: 59.3 ± 6.6 years	iTBS 80% of AMT	Clinical rating scale for PSP	2 weeks—10 sessions 2 trains (L and R) of 3 pulses at 50 Hz in 20 trains of 10 bursts with 8 s intervals (600 pulses) (offline)	L and R CB	Improved dysarthria
Desmond, Chen, and Shieh (2005)	*N* = 17 (8 M, 9 F) Mean age ± s.d.: 24.9 ± 6.9 years	Single-pulse TMS 120% of MT	Verbal working memory task	1 pulse immediately after encoding (online)	R superior lobule VI/Crus I	Increased RTs during CB stimulation
Farzan, Wu, Manor, et al. (2013)	*N* = 1 F Patient affected by cerebellar ataxia Age: 62 years	TMS 100% of MMO	Clinical observation	3 weeks—21 sessions 5 pulses with 6-s ISI (offline)	Lateral: 4 cm L or R from inion Medial: over inion	Improvement of speech after CB stimulation

Gilligan and Rafal (2018)	$N = 41$ (20 M, 21 F) Mean age ± s.d.: 23.4 ± 5.5 years	cTBS 80% of MT	Lexical decision task with associative prime	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm R or L of the inion	Decreased priming after L CB stimulation and increased priming after R CB stimulation
Lesage, Morgan, Olson, et al. (2012)	$N = 22$ (n.s.) Mean age = 20.5 years; $N = 21$: vertex; $N = 22$: stim	1 Hz rTMS 55% of MMO	Visual world task	10 min—600 pulses (offline)	1 cm below, 3 cm R of the inion	Increased fixation latencies for predictive condition after R CB stimulation
Oliveri, Bonnì, Turriziani, et al. (2009)	$N = 24$ (n.s.) Age: range 20–35 years	1 Hz rTMS 90% of MT	Spatial-temporal association of linguistic tenses	10 min—600 pulses (offline)	1 cm below, 3 cm L or R of the inion	Selective impairment in RTs to future tense of action verbs after R CB stimulation Selective decrease in accuracy after R and L CB stimulation
Rami, Gironell, Kulisevsky, et al. (2003)	$N = 16$ M Mean age ± s.d.: 26.63 ± 4.57 years	5 Hz rTMS 10% below MT	Verbal working memory (digits forward and backward) Phonetic fluency task	Trains of 10 s with 30 s ISI (online)	2 cm below, 3 cm R of the inion	No effect
Runnqvist, Bonnard, Gauvin, et al. (2016)	$N = 16$ (6 M, 10 F) Mean age ± s.d.: 24 ± 3 years	1 Hz rTMS at 60% of MMO	Speech production task	1 session divided in two parts: (1) 15 min stimulation (900 pulses) followed by the task (2) 15 min stimulation (to the opposite hemisphere) followed by the task	R and L CB (lobules Crus I–II)	Impaired language production after R compared to L CB stimulation

(continued)

Table 8.1 (continued)

Part A						
TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Tomlinson et al. (2014)	*N* = 10 (4 M, 6 F) Age: range 18–35 years	cTBS 80% of AMT	Sternberg task	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses)	1 cm below and 6 cm R or L of the inion	Decreased accuracy on verbal working memory after R CB stimulation
Part B						
tDCS study	*Participants*	*Stimulation*	*Task*	*Number of Sessions*	*Position of the electrodes*	*Effects*
Boehringer, Macher, Dukart, et al. (2013)	*N* = 40 (20 M, 20 F) Mean age ± s.d.: 25 ± 3 years	tDCS (2 mA)	Digit span	1 session (25 min) offline	Cathode: R CB Anode: R buccinators muscle	Reduced forward digit span Blocked the practice-dependent increase in backward digit span
Ferrucci et al. (2008)	*N* = 17 (n.s.) Age: range 19–32 years	tDCS (2 mA)	Sternberg task	1 session (15 min) offline	Anode/cathode: bilateral CB Cathode/anode: R deltoid muscle	Impaired practice-dependent effects after CB stimulation
Macher, Boehringer, Villringer, and Pleger (2013)	*N* = 19 (9 M, 10 F) Mean age ± s.d.: 26 ± 4 years	tDCS (2 mA)	Sternberg task	1 session (25 min) offline	Anode/cathode: R CB Anode/cathode: n.s.	Impaired item recognition after the anodal CB stimulation
Marangolo, Fiori, Caltagirone, et al. (2018)	*N* = 12 (6 M, 6 F) patients with left-brain-damaged affected by chronic aphasia Age: range 48–70 years	tDCS (2 mA)	Verb generation task Verb naming task	5 daily sessions of 20 min for 4 weeks (online)	Cathode/sham: R CB Anode: R deltoid muscle	Improvement in verb generation task at the end of the treatment with the cathodal stimulation

Miall, Antony, Goldsmith-Sumner, et al. (2016)	N = 73 (17 M, 56 F) Mean age ± s.d.: 19.8 ± 2.7 years N = 26 anodal stim N = 26 cathodal stim N = 20 sham	tDCS (2 mA)	Manual version of the visual word task	1 session (20 min) online	Anode/cathode: R CB Cathode/anode: R shoulder	Decreased response time advantage for the predictable sentence items after the cathodal stimulation
Pope and Miall (2015)	N = 66 (12 M, 54 F) N = 22 (6 M, 14 F) anodal stim Age: mean 21 years N = 22 (2 M, 20 F) cathodal stim Age: mean 20 years N = 22 (4 M, 18 F) sham Age: mean 21 years	tDCS (2 mA)	PASAT/PASST/verb generation task	1 session (20 min) offline	Anode/cathode: R CB Anode/cathode: R deltoid muscle	Improvement in PASST and verb generation task after the cathodal stimulation
Turkeltaub, Swears, D'Mello, and Stoodley (2016)	N = 76 (30 M, 46 F) Mean age ± s.d.: 23.7 ± 6.2 years N = 15 sham N = 30 anodal (15 anterior-medial, 15 right posterolateral) N = 30 cathodal (15 anterior-medial, 15 right posterolateral)	tDCS (2 mA)	Phonemic fluency task	1 session (20 min) offline	Anode/cathode: anterior-medial or R posterolateral CB Anode/cathode: R deltoid muscle	Improved phonemic fluency after anodal R posterolateral CB stimulation

Studies conducted in patients are reported in gray rows

AMT active motor threshold, *CB* cerebellum, *C* conditioning stimulus, *cTBS* continuous theta-burst stimulation, *F* female, *ISI* inter-stimulus interval, *iTBS* intermittent theta-burst stimulation, *L* left, *M* male, *MEP* motor-evoked potential, *MMO* maximum machine output, *MT* motor threshold, *n.s.* not specified, *PASAT* paced auditory serial addition task, *PASST* paced auditory serial subtraction task, *PSP* progressive supranuclear palsy, *R* right, *RT* reaction time, *rTMS* repetitive transcranial magnetic stimulation, *SCA* spinocerebellar ataxia, *SOAs* stimulus onset asynchrony, *stim* stimulation, *tDCS* transcranial direct current stimulation, *TS* target stimulus

The effects of cerebellar TMS on verbal working memory, measured by the Sternberg task, have been reported in two studies, and they demonstrated increased reaction times after single-pulse TMS over the right superior cerebellum (Desmond et al., 2005) and an impairment in accuracy after cTBS over the same site (Tomlinson et al., 2014).

As reported in Sect. 8.3, cerebellar damage may also result in verbal fluency impairments. Arasanz et al. (2012) investigated the impact of cerebellar stimulation on both phonetic and semantic fluency tasks, focusing on the number of category switches, that is, the exhaustion of a phonemic or semantic cluster and the shift to another. They compared two groups of healthy subjects who completed phonemic and semantic fluency tasks before and after cTBS: one group received stimulation over the right cerebellar hemisphere and the other over the left cerebellar hemisphere. The results showed that cTBS over the right posterolateral cerebellum induced lower switching scores during the first 15 s of phonemic fluency performance, with no effect on semantic fluency. These data confirmed previous studies showing that the cerebellum is involved in phonemic but not semantic fluency (Leggio et al., 2000), and these studies probe the effects of cerebellar stimulation on the executive control of word generation.

Another language ability that has been reported as impaired in cerebellar patients and in which the cerebellum seems to play a role is reading ability (see Sect. 8.3), in which lexical aspects are crucial. Since 2011, Argyropoulos and colleagues have used cTBS to investigate the role of the cerebellum in the lexical domain. In particular, in an initial study (Argyropoulos, 2011), cTBS was applied over the right medial and lateral cerebellum to investigate its effect in a lexical decision task by using lexical associative priming. The author found that medial cerebellar stimulation led to a significant enhancement of associative priming when it was based on the co-occurrence of words in idiomatic speech. These results suggest that the cerebellum has a role in predictive aspects of language processing. Moreover, in the same study, the authors found that, when right medial stimulation was administered before (first session) the lateral stimulation (second session), the subjects showed a significant drop in the post-stimulation lexical decision task accuracy. This aspect was further addressed in a subsequent study (Argyropoulos et al., 2011) in which the effects of the right cerebellar cTBS on *practice-induced acceleration of lexical decisions* were investigated. Right medial and right lateral cerebellar sites were stimulated, and a visual lexical decision task was used. The results showed that the practice effects on the lexical decision task were reduced after medial cTBS, suggesting a cerebellar role in acquiring, storing, and/or retrieving associative memories. Moreover, Argyropoulos and Muggleton (2013), using cTBS and a lexical decision task, demonstrated that stimulation of the right lateral cerebellum enhanced noun-to-verb semantic associative priming. These findings were recently reinforced by Gilligan and Rafal's (2018) study. These authors provided evidence that left cerebellar hemisphere cTBS decreased, and right hemisphere stimulation increased, associative word priming in a lexical decision task.

Recently, Allen-Walker and colleagues (2018) showed that cTBS over the left cerebellar hemisphere influenced backward associative priming with short stimulus onset asynchrony (SOA) in a lexical decision task. They found a significant increase in the priming size only for backward related stimuli after the stimulation of the left cerebellar hemisphere and no changes for forward priming. This is in line with a previous fMRI study in which activation of the left cerebellum was found for backward priming at short SOA, together with brain areas involved in lexical processing system (such as the right occipitotemporal network) (Terrien et al., 2013). It has been hypothesized that the presence of automatic and fast feedback loops in the left cerebellum could be involved in the backward priming and seem to be dissociated from forward connections (Allen-Walker et al. 2018).

These results are in line with clinical (Mariën et al., 2001) and neuroimaging (Murdoch & Whelan, 2007) data, indicating the involvement of both cerebellar hemispheres in the language domain. Taking the combined results of these studies in consideration, the right cerebellum is clearly involved in lexical associative computations and the left cerebellum seems to have a selective role in backward priming.

Consistent with the above, Lesage et al. (2012) provided evidence that low-frequency rTMS over the right cerebellum affected predictive processes in a task of sentence comprehension. The results showed that after cerebellar stimulation, participants were significantly slower at predicting the final noun of an auditorily presented sentence. The authors argued that the right cerebellum might contribute to language prediction, providing an efferent copy of internalized speech, due to its connections with cortical language areas such as Broca's area. This idea is in line with language processing theories proposing that the self-monitoring of language production is achieved through internal modeling, in a manner similar to other somatic actions (see Argyropoulos, 2016 for discussion). In this light, Runnqvist et al. (2016) studied the possibility of a causal role of the right posterior cerebellum in self-monitoring of speech errors. They applied low-frequency rTMS over the right or left cerebellar hemisphere (lobules Crus I and II) and used a speech production task. The authors found that language production was impaired after right cerebellar stimulation and interpreted this result as evidence for direct cerebellar involvement in language production *"in terms of internal modeling of upcoming speech through a verbal working memory process used to prevent errors"* (Runnqvist et al., 2016, p. 203).

Finally, Oliveri et al. (2009) investigated the possible involvement of the cerebellum in spatial-temporal interactions in language, linking this aspect with the grammatical aspects in which the cerebellum plays a role. In this study, the subjects were asked to indicate whether a stimulus was past or future tense with right and left response buttons. The participants were faster and more accurate if the left button was associated with the past and the right with the future tense, showing a spatial-temporal association of linguistic tenses. rTMS over both cerebellar hemispheres decreased this enhanced accuracy for identifying future (right) and past (left) tense. In addition, stimulation of the right cerebellum selectively slowed down responses to the future tense of action verbs. The authors interpreted these findings as a demonstration of a cerebellar role in *establishing the grammatical rules for verb conjugation*. They also suggested that the right cerebellum may be important in anticipating future events based on past experiences, in line with the hypothesis that the cerebellum acts as a predictive device across different domains (Leggio & Molinari, 2015; Miall, Weir, Wolpert, & Stein, 1993; Roth, Synofzik, & Lindner, 2013).

In this complex set of findings, when we look at cerebellar speech and language functions, in most of the studies, the right lateral cerebellum (lobule VIIa/Crus I) appears to be the preferred target for the TMS. This region has been implicated in a range of language tasks by both lesion and imaging studies (Mariën et al., 2001). However, starting from these studies, specific conclusions are difficult to draw. Indeed, in some experiments, low-frequency rTMS or cTBS led to enhanced performance (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), whereas in others, there was a disruptive effect (Argyropoulos et al., 2011; Desmond et al., 2005; Lesage et al., 2012; Oliveri et al., 2009; Tomlinson et al., 2014). These findings may be due to the excitatory and inhibitory connections that the cerebellum has with different cerebral areas; thus, the stimulation effects may depend on the targeted pathways and on their contribution to the studied task. Therefore, a number of variables must be taken into account to design therapeutic protocols, and the few negative results reported in the literature need to be examined. In one relatively early study, Rami et al. (2003) did not find any effect of online high-frequency rTMS over the right cerebellar hemisphere in phonetic fluency and episodic memory tasks. These results could be due to differences in the timing or types of TMS protocols.

8.6.2 Cerebellar tDCS Effects

A novel line of research is also represented by the study of cerebellar tDCS effects on cognitive functions (Ferrucci & Priori, 2014). In the present section, we will focus on the studies in which the effect of cerebellar tDCS on speech and language abilities was investigated to understand the potential use of this technique as a treatment intervention. A summary of the studies that investigated the effects of cerebellar tDCS on speech and language functions is reported in Table 8.1b.

Studies have primarily focused on the effects on verbal working memory task performance (i.e., Sternberg task) (Ferrucci et al., 2008; Macher et al., 2013). In particular, Ferrucci et al. (2008) found that both anodal and cathodal cerebellar stimulation impaired practice-dependent improvements, significantly affecting the reaction times, but with no effect on task accuracy.

In 2013, Boehringer et al. (2013) found that cathodal tDCS over the right cerebellum decreased forward digit span task performance and blocked the practice-dependent increase in verbal working memory for backward digit spans, with no effect on word reading, finger tapping, and visually cued sensorimotor tasks. These findings are in line with those that demonstrated an impairment of the practice-induced facilitation in word-generation tasks after cerebellar damage (Fiez, Petersen, Cheney, et al., 1992; Gebhart, Petersen, & Thach, 2002). In the same year, in contrast with the absence of an effect on accuracy reported by Ferrucci et al. (2008), Macher et al. (2013) reported a positive effect of right anodal cerebellar stimulation on the recognition of items of medium difficulty in the Sternberg task, with no effect on the items of easy or hard difficulty level. These results seem to indicate that task complexity might influence the effects of cerebellar tDCS and explain the absence of a significant effect of cerebellar stimulation on accuracy in the study by Ferrucci et al. (2008), in which intermixed Sternberg stimuli of three difficulty levels were used. A task-difficulty influence on cerebellar tDCS findings has also been demonstrated by Pope and Miall (2015). In this study, the authors reported an effect of tDCS over the right cerebellum on the difficult paced auditory serial subtraction task (PASST), but not on the easier paced auditory serial addition task (PASAT). In particular, the authors observed an improvement of the performance and a reduction in verbal response latency on the PASST selectively after cathodal stimulation. The authors suggested that cerebellar stimulation affects distinct levels of executive demand and memory load, hypothesizing that when cognitive load is high, cathodal depression of the right cerebellar cortex may release cognitive resources by disinhibiting the left prefrontal cortex and enhancing performance (Pope & Miall, 2015). Moreover, in the same study, the authors found a facilitatory effect of cathodal tDCS over the right cerebellum on the rate and consistency of subjects' verbal responses in a verb generation task. They explained these facilitatory effects as a result of disinhibition of the left prefrontal cerebral cortex. Indeed, the inhibitory effect of the cathodal tDCS on the cerebellar cortex releases the cerebellar nuclei, thus resulting in enhanced activity in the projections to cerebral areas (Pope & Miall, 2015). These results are in line with the enhanced lexical associative priming observed after the cerebellar cTBS that has an inhibitory effect on the cerebral cortex as well (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). In a more recent study, Turkeltaub et al. (2016) demonstrated that anodal tDCS over the right posterolateral cerebellum significantly improved phonemic fluency (the same trend was found for cathodal stimulation).

As shown in studies that investigated the cerebellum's role in language abilities by using cerebellar TMS (reported in Sect. 8.6.1) and in line with recent hypotheses (Argyropoulos, 2016; Miall et al., 2016; Moberget & Ivry, 2016), the cerebellum might support predictive and learning mechanisms involved in linguistic processing (Lesage et al., 2012), as it does on motor control, to optimize the behavior. In this framework, Miall et al. (2016) investigated the polarity-specific effects of cerebellar tDCS on linguistic prediction, hypothesizing that cathodal polarity should impair and anodal polarity should facilitate linguistic prediction. Their experimental design also tested whether tDCS modulated associative learning in a manual variation of the visual world paradigm used by Lesage et al. (2012). Consistent with the previous TMS study by Lesage et al. (2012), the authors found that cathodal stimulation decreased and anodal stimulation enhanced the response time advantage for the predictable sentence items, without changing performance for the nonpredictable ones. These results are consistent with a role for the right posterolateral cerebellum beyond motor aspects of language and suggest that internal models of linguistic stimuli in the cerebellum might also support semantic prediction, due to the cerebellar functional connectivity with cerebral cortical language networks.

As evidenced by the studies reported above, there have been inconsistent reports on whether anodal or cathodal tDCS over the cerebellum improves or disrupts language processing. Thus, additional studies are needed to clarify the polarity-specific effects of the cerebellar tDCS on cognitive processing.

8.6.3 Cerebellar TMS/tDCS Effects on Cerebro-Cerebellar Networks

As shown in Sect. 8.4, neuroimaging studies clearly demonstrated that the cerebellum is a component of distributed language networks (Buckner et al., 2011; O'Reilly et al., 2010), but the functional relationship between the cerebellum and cerebral areas involved in language processing remains to be further elucidated. A novel approach to this issue has been recently employed, by combining brain stimulation and neuroimaging techniques to precisely investigate how magnetic or electrical stimulation over the cerebellum may affect this structure, the rest of the brain, as well as the interaction between them. A summary of the studies that combine cerebellar TMS or tDCS with neuroimaging analyses to investigate the effect of cerebellar stimulation on the cerebral areas involved in speech and language functions is reported in Table 8.2.

Interestingly, some studies have shown that the application of TMS and tDCS over the cerebellar cortex might determine changes in the activity not only of cerebellar output (Das, Spoor, Sibindi, et al., 2017; Oulad Ben Taib & Manto, 2013) but also of the cortical areas targeted by the cerebellar projections (Cho et al., 2012; Macher et al., 2014).

In a combined rTMS and positron emission tomography study, Cho et al. (2012) observed increased glucose metabolism in cognition- and language-related areas, such as the left superior temporal gyrus (Wernicke's area) and left inferior frontal gyrus (Broca's area), when 1 Hz rTMS was applied over the left cerebellum. Taking into account the data showing co-activation of Broca's area and the cerebellum during language-related tasks (Honey, Bullmore, & Sharma, 2000; Majerus, Laureys, Collette, et al., 2003; Paulesu, Frith, & Frackowiak, 1993), the authors hypothesized that rTMS works as a cerebellar "virtual lesion" and compensatory neuronal activity can occur in other brain areas to maintain the functional state. It has to be underlined that this result is to be seen in the context of the ongoing debate about the role of left and right cerebellar hemispheres in linguistic abilities (Gebhart et al., 2002). Indeed, although cerebellar language-related deficits have been observed more often after lesions of the right lateral cerebellum (Baillieux, De Smet, Dobbeleir, et al., 2009; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004), and some studies have demonstrated activation of the right cerebellar hemisphere during language tasks (Hubrich-Ungureanu et al., 2002; Jansen et al., 2005), both clinical and neuroimaging studies have provided evidence for a role of the left cerebellar hemisphere in the language domain (Gebhart et al., 2002).

Table 8.2 Summary of studies that combine cerebellar TMS or tDCS with neuroimaging analyses to investigate the cerebellar role in speech and language domains

Study	Participants	Type of stimulation	Measuring method	Task	Timing of neuroimaging signal	Location of the stimulation	Activations
Brusa et al. (2014)	10 (4 M, 6 F) PSP Mean age ± s.d.: 59.3 ± 6.6 years	iTBS 80% of AMT 2 weeks—10 sessions 2 trains (L and R) of 3 pulses at 50 Hz in 20 trains of 10 bursts with 8 s intervals, 600 pulses (offline)	rs-fMRI	No task	Before and after the iTBS sessions	L and R CB	Increased activation of the caudate nuclei Alleviated dysarthria
Cho, Yoon, Bang, et al. (2012)	N = 12 (6 M, 6 F) Mean age ± s.d.: 23.7 ± 2.6 years	1 Hz rTMS (900 pulses) 90% of MT Active or sham offline	PET	No task	Within 5 min after stimulation (10 min scans)	L CB	Increased glucose metabolism in cognition and language-related areas (e.g., left superior temporal gyrus, left inferior frontal gyrus, after CB stimulation
D'Mello et al. (2017)	N = 35 (12 M, 23 F) Mean age ± s.d.: 23.7 ± 2.7 years N = 15 sham stim N = 20 anodal stim	tDCS (1.5 mA) 1 session (20 min) offline	Task-based and rs-fMRI	Sentence completion task	Before and after tDCS	Anode: R CB Cathode: R clavicle	Increased activation in R Crus I/II during semantic prediction after anodal stimulation Enhanced FC between nodes of the predictive reading/ language network and regions involved in second language learning and syntactic and semantic processing, after anodal stimulation

(continued)

Table 8.2 (continued)

Study	Participants	Type of stimulation	Measuring method	Task	Timing of neuroimaging signal	Location of the stimulation	Activations
Macher, Boehringer, Villringer, and Pleger (2014)	*N* = 16 (8 M, 8 F) Mean age ± s.d.: 26 ± 3.4 years	tDCS (2 mA) 1 session (25 min) offline	Task-based fMRI	Sternberg task	After tDCS	Anode/cathode: R CB Anode/cathode: R buccinators muscle	Reduced item recognition capacity and attenuated neural signal from the R CB (lobule VIIb), during the late encoding phase, after anodal stimulation Affected task-associated FC between R CB lobule (VIIb) and the posterior parietal cortex, after anodal stimulation
Turkeltaub et al. (2016)	*N* = 76 (30 M, 46 F) Mean age ± s.d.: 23.7 ± 6.2 years *N* = 15 sham *N* = 30 anodal (15 anterior-medial, 15 R posterolateral) *N* = 30 cathodal (15 anterior-medial, 15 R posterolateral)	tDCS (2 mA) 1 session (20 min) offline	rs-fMRI	Phonemic fluency task	Before and after tDCS	Anode/cathode: anterior-medial or R posterolateral CB Anode/cathode: R deltoid muscle	Improved phonemic fluency after anodal R posterolateral CB stimulation Increased FC between the R posterolateral CB and frontoparietal cognitive networks

CB cerebellum, *F* female, *FC* functional connectivity, *fMRI* functional magnetic resonance imaging, *ISI* inter-stimulus interval, *iTBS* intermittent theta-burst stimulation, *L* left, *M* male, *MT* motor threshold, *PET* positron emission tomography, *PSP* progressive supranuclear palsy, *R* right, *rs-fMRI* resting state fMRI, *rTMS* repetitive transcranial magnetic stimulation, *tDC* transcranial direct current stimulation

Brusa et al. (2014) administered daily iTBS sessions over the cerebellum for 2 weeks in patients with progressive supranuclear palsy (PSP). The CBI measure (to investigate the interaction between the cerebellum and M1), rs-fMRI and a clinical rating scale were involved both pre- and post-iTBS. The authors observed an increase in CBI and alleviation of dysarthria. Moreover, the rs-fMRI showed an increased BOLD signal in the caudate nuclei, suggesting an enhanced functional connectivity between the cerebellar hemispheres, caudate nuclei, and cortex.

Furthermore, combining right cerebellar tDCS with fMRI in healthy adults, Macher et al. (2014) found an impaired digit recognition performance in a modified Sternberg task after anodal cerebellar stimulation. They also found attenuated hemodynamic signal in the right lobule VIIb and decreased FC between this lobule and the posterior parietal cortex during the late encoding phase. However, in a more recent study, Turkeltaub et al. (2016) demonstrated that anodal tDCS over the right posterolateral cerebellum modulated rs-fMRI FC in language networks, increased the FC between the cerebellum and language and speech motor regions, and improved verbal fluency.

In a subsequent study combining tDCS over the right posterolateral cerebellum and fMRI, D'Mello et al. (2017) showed that anodal tDCS increased activation in right Crus I/II during semantic prediction and enhanced resting-state FC between hubs of the reading/language networks. Interestingly, they observed that cerebellar tDCS did not broadly increase activation throughout the brain; indeed, the effects of tDCS were focal to language-associated regions of the cerebellum and cerebral cortex. This is consistent with the previous study by Turkeltaub et al. (2016) showing that cerebellar tDCS over the posterolateral cerebellum altered FC in cerebro-cerebellar association networks without affecting somato-motor networks.

All in all, these studies further confirm that the cerebellum has functional links to the cerebral areas involved in specific aspects of language processing and that electric or magnetic stimulation applied over the cerebellum affects these cerebello-cerebral networks.

8.7 Cerebellar Stimulation to Modulate Speech and Language Abilities in Patients

In recent literature, studies have applied TMS or tDCS over specific cerebral areas, such as the left dorsolateral prefrontal cortex or posterior perisylvian area in patients presenting with language deficits to investigate the effect of neuromodulation on specific language tasks, often obtaining therapeutically promising improvements in linguistic performance (Monti, Ferrucci, Fumagalli, et al., 2013).

Regarding the cerebellum, initial studies reported an improvement in ataxic gait after 21 days of rTMS over the cerebellum in patients with spinocerebellar ataxia (SCA) (Shiga, Tsuda, Itoyama, et al., 2002; Shimizu, Tsuda, Shiga, et al., 1999). Farzan et al. (2013) applied the same protocol on a patient affected by idiopathic late-onset cerebellar atrophy. The patient presented with scanning speech dysarthria, a type of ataxic dysarthria in which spoken words are broken up into separate syllables, often separated by a noticeable pause, and spoken with varying force. During the training sessions, the patient was required to complete one trial of normal walking and one trial of motor-cognitive dual tasking during which they had to name items found in a supermarket while walking. Interestingly, when cerebellar stimulation was applied, the authors found not only an improvement in limb coordination and gait but also in speech, as characterized by a louder and clearer voice. Moreover, the patient named more items in the dual-task condition.

The authors linked this finding to a reduction in CBI due to transient depletion of cerebellar cortical neuro-mediatory mechanisms responsible for suppression of the dentate nucleus consequent to the inhibitory effect of low-frequency stimulation over the cerebellar cortex. Farzan et al. (2013) argued that the low-frequency TMS might exert its therapeutic efficacy by reducing the cerebellar cortical inhibitory control over the dentate nucleus, thereby potentiating the residual activity of the dentate nucleus, resulting in a facilitatory effect on both motor and nonmotor cerebral areas. This hypothesis is in line with studies that described modifications in prefrontal cortical activity and language functions after cerebellar stimulation in healthy subjects (see Sect. 8.6.3). The case study described by Farzan et al. (2013) provides important evidence about the efficacy of cerebellar stimulation as a therapeutic approach in cerebellar degenerative ataxia. These findings have been reinforced by the study of Brusa et al. (2014), in which alleviation of dysarthria was observed in PSP patients after 2 weeks of daily iTBS sessions over the cerebellum.

Recently, cerebellar tDCS has also been used in clinical populations to investigate its potential application as a therapeutic tool in the language domain. Characteristically, Marangolo et al. (2018) investigated the effect of cerebellar tDCS coupled with language treatment in improving performance in a verb generation task in subjects with aphasia by using a randomized, crossover, double-blind design. Each participant received cerebellar tDCS in four experimental conditions (right and left cathodal or sham stimulation), run in five consecutive daily sessions over 4 weeks. tDCS was administered during a verb naming task or a verb generation task. Significant improvements were found only in the verb generation task following the cathodal stimulation conditions. The authors hypothesized that cerebellar tDCS is a viable tool for recovery from aphasia, particularly when the language task also demands the activation of nonlinguistic strategies, as in the case of the verb generation task, which requires executive and memory components.

The studies above provided evidence that cerebellar neuromodulation has the potential to become a treatment tool for speech and language disorders, not only for patients affected by cerebellar pathology but also for other patient populations, such as SCA, PSP, and subjects affected by aphasia.

8.8 Conclusions and Future Directions

Cerebellar involvement in speech and language domains has been largely demonstrated by clinical and neuroimaging studies. These data have been reinforced by the application of neuromodulation techniques, such as TMS and tDCS, which hold a significant advantage over correlational fMRI methods and clinical studies because of the capacity to demonstrate the causal relationship between cerebellar functioning and language abilities (Arasanz et al., 2012; Pope & Miall, 2015). Thus, as described in the present chapter, in recent years, the cerebellum has become an interesting target for these novel and highly promising techniques. Although, to date, these noninvasive tools have been mainly employed in a research context, cerebellar stimulation represents not only an interesting tool to study the role of the cerebellum in language processing but also a therapeutic approach that could be exploited for speech and language disorders (Grimaldi et al., 2016). In the literature, a number of studies have demonstrated a behavioral facilitatory effect of tDCS over different brain areas (Vallar & Bolognini, 2011), in motor and perception tasks (Antal et al., 2004; Fregni, Boggio, Nitsche, et al., 2005), and in working memory and language-related tasks (Fertonani, Rosini, Cotelli, et al., 2010; Fregni et al., 2005). These findings highlight the potential of neuromodulation as a therapeutic intervention in psychiatric and neurological conditions (i.e., depression and stroke) (Flöel, 2014; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). Regarding the speech and language domains, despite some discrepancies in the findings as described in the previous sections, it is clear that both TMS and tDCS over the cerebellum can modulate speech and language functions and also produce improvements in specific abilities (Argyropoulos, 2011; Argyropoulos et al., 2011; Turkeltaub et al., 2016). In this light, very recent studies using cerebellar transcranial stimulation in clinical populations have reported improvements in dysarthria in PSP patients and verb generation in patients with aphasia (Bradnam, Graetz, McDonnell, et al., 2015; Brusa et al., 2014; Marangolo et al., 2018). Considering the cerebellar role in learning and skill acquisition through the error-based adaptation of internal models that enable fluent, optimized performance (Ito, 2008), cerebellar neuromodulation may enhance language abilities, with potential positive effects on aphasia recovery. Indeed, pairing cerebellar tDCS with speech-language therapy might enhance the learning of compensatory strategies and relearning of language mechanisms during aphasia rehabilitation.

In fact, targeting the cerebellum might represent a novel way to modulate the excitability of not only the cerebellum but also remote cortical regions and their functions. Indeed, as evidenced in Sect. 8.6.3, both cerebellar TMS and tDCS are capable of modulating cerebello-cerebral FC, affecting the connectivity between the cerebellum and language networks (D'Mello et al., 2017; Macher et al., 2014; Turkeltaub et al., 2016). Providing sufficient reinforcement of this enhanced network connectivity through multiple sessions of cerebellar stimulation could contribute to long-lasting effects on the reorganization of residual language networks after stroke. However, due to the high variability in the impact of cerebellar TMS and tDCS on the cortico-cerebellar pathways, studies with more stringent methodological standards (larger sample size, sham-controlled designs) are needed to understand the effects of different experimental protocols (Nordmann, Azorina, Langguth, & Schecklmann, 2015). This information could be crucial to efficiently implement cerebellar TMS and tDCS in therapeutic settings.

In comparison with cortical neuromodulation, cerebellar neuromodulation might have some additional practical advantages as a treatment approach for specific pathological conditions (Turkeltaub et al., 2016), and future potential applications should be considered. For example, in patients with aphasia consequent to a cerebral cortical stroke with encephalomalacia at the lesion site, cerebellar stimulation might represent a useful choice. Indeed, encephalomalacia makes direct perilesional cerebral cortical stimulation difficult (Baker, Rorden, & Fridriksson, 2010; Dmochowski, Datta, Huang, et al., 2013). Targeting the right hemispheric language homologs could be an alternative, but encephalomalacia in the left hemisphere may result in unpredictable patterns of current flow when stimulation is delivered over the right hemisphere (Anglade, Thiel, & Ansaldo, 2014; Gainotti, 2015). As an alternative approach, in the case of right posterolateral cerebellar stimulation, this site is distant enough from the cerebral cortical stroke sites associated with aphasia, and it is unlikely that the electrical current flow would be affected by encephalomalacia, especially when the reference electrode is placed off the head. Furthermore, considering the emerging literature about the possible role of connectivity alterations within cerebello-cerebral networks in language deficits reported in ASD subjects (Khan et al., 2015; Verly et al., 2014) (as described in Sect. 8.4), the neuromodulation of cerebellar activity might represent a potential tool to intervene in autism language disorders.

Before concluding, it is important to warn that prior to using the cerebellar TMS and tDCS as potential treatment techniques in speech and language disorders, both researchers and clinicians have to take into account the working mechanisms and the advantages/disadvantages of each technique. Indeed, while TMS is capable of inducing action potentials by acting on axons and monosynaptic or polysynaptic pathways resulting in genuine neuronal firing, tDCS cannot excite neurons and is mostly used to modulate neuronal excitability. Nevertheless, in many cases, the aftereffects of the two techniques are very similar, probably due to shared electrical characteristics of cerebellar neuronal populations (Grimaldi et al., 2016).

As a therapeutic tool, cerebellar tDCS seems to have some advantages over TMS. The device to administer TMS is sophisticated and costly, while the tDCS device is simple to use and less expensive. In addition, since the device is small and easily portable, no specific room is required for the administration of tDCS, making it easy to combine tDCS with other speech therapies (Priori, Hallett, & Rothwell, 2009). Other practical advantages of cerebellar tDCS over TMS regard the possibilities of implementing sham-controlled and double-blind studies (Hummel, Celnik, Giraux, et al., 2005). Indeed, placebo stimulation, often named "sham" stimulation, is more reliable in tDCS than in TMS, particularly with respect to the extent of the physiological artifacts that cerebellar TMS can generate (Merabet & Pascual-Leone, 2008).

Furthermore, during TMS, the copper wire windings within the coil tense and often produce a brief “click” exceeding 120 dB (Pascual-Leone, Cohen, Shotland, et al., 1992). This noise might represent a potential confound in behavioral performance, especially in speech perception and auditory sentence comprehension tasks. Moreover, because the suboccipital muscles of the neck attach to the skull close to the cerebellum, the magnetic field generated by the electrical current running through the coil can activate local sensory nerves or muscles with an unpleasant effect or induce a startle reaction affecting reaction-time measures (Hummel et al., 2005; Merabet & Pascual-Leone, 2008; Paulus, 2003). These aspects might also compromise the sham condition. In contrast, during tDCS, no sounds are produced, and only mild transient tingling sensations with no twitches may occur during the first few seconds (Ferrucci et al., 2015). One limitation of tDCS is its spatial resolution, which is markedly lower than that of TMS (Jahanshahi & Rothwell, 2000). In this light, the more focal effect of TMS might allow the stimulation of particular cerebellar regions specifically involved in language subcomponents.

In conclusion, cerebellar neuromodulation has enormous potential as a treatment tool in speech and language disorders, not only for patients affected by cerebellar pathology but also for other patient populations. Future placebo-controlled trials in patients with specific diagnoses would permit the identification of individuals who can benefit the most from this therapeutic approach. Furthermore, neuroimaging studies should be implemented to precisely identify the mechanisms of cerebellar TMS and tDCS to guarantee more efficacious personalized treatment protocols.

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