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The role of the human cerebellum in linguistic prediction, word generation and verbal working memory: evidence from brain imaging, non-invasive cerebellar stimulation and lesion studies

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ABSTRACT

Lesion studies emphasize the role of the human cerebellum in a variety of cognitive processes. To date, most evidence comes from studies investigating language-related functions, such as verbal short-term/working memory, word generation, or linguistic/semantic predictions. This review summarizes brain imaging, non-invasive cerebellar stimulation and lesion studies in this field. Converging evidence suggests a cerebellar role in error processing and memory encoding although findings are partly contradictory. Future research should focus on common principles of cerebellar processing across different forms of cognitive performance to assess basic principles of cerebellar function.

1. Introduction

1.1. Hypothesis of the cerebellum's role in motor performance

For a long time, the human cerebellum was believed to be exclusively involved in sensorimotor functions (Manzoni, 2005). This association was derived from observations in patients with cerebellar lesions exhibiting ipsilateral errors in coordinating movements such as a- or dysdiadochokinesia, dysmetria, tremor (Bodranghien et al., 2016) as well as balance disorders or ataxia (Tada et al., 2015). In the late 1960's, first studies suggested that the cerebellum may provide sensorimotor error signals arising in the inferior olive/climbing fiber system (Marr, 1969; Albus, 1971; Ito 1982; Gilbert and Thach, 1977; Raymond et al., 1996). These error signals may reflect the difference between the predicted and actual outcome of a movement and constantly update an internal model in response to changes to the inner and outer environment (Miall et al., 1993; Bastian, 2006; Imamizu et al., 2000; Imamizu and Kawato, 2009).

1.2. The cerebellar cognitive affective syndrome

Besides its role in sensorimotor control, the cerebellum supports cognitive and even emotional processing (Petersen et al., 1989; Fiez et al., 1992; Ravizza et al., 2006; Kirschen et al., 2010; Stoodley et al., 2010). Specific cerebellar regions seem to influence related neocortical substrates (Wang et al., 2014). Evidence for these cognitive-emotional functions came from patients with cerebellar damage (Fiez et al., 1992). In 1998, Jeremy Schmahmann and his colleagues at Harvard Medical School defined the so-called cerebellar cognitive affective syndrome which encompasses deficits in executive functioning, spatial cognition, language, affect and intellectual capacities (Manto and Mariën, 2015). Executive dysfunctions span from planning problems to impaired set-shifting, abstract reasoning, and verbal fluency, possibly in combination with perseveration, distractibility and inattention. Other potentially affected cognitive domains are visual–spatial organization and memory. Language impairments include agrammatism or mild anomia (Schmahmann and Sherman, 1998; Levisohn et al., 2000; Schmahmann, 2001, 2010; Wolf et al., 2009).

In adults, such cognitive deficits appear to be more prominent in acute cerebellar lesions, such as in stroke. In later stages they appear well compensated and may be missed by standard neuropsychological tests (Helmuth et al., 1997; Richter et al., 2004; Frank et al., 2008). Alexander and colleagues, for instance, showed that cognitive impairments after focal cerebellar injury in adults are rather mild when tested

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3 months post onset (Alexander et al., 2012). In children, cerebellar cognitive deficits become more obvious and persistent the earlier in life the cerebellar damage occurred (Frank et al., 2008; Timmann and Daum, 2010; Stoodley and Limperopoulos, 2016).

1.3. Motivation and structure of this review

The role of the cerebellum in cognitive processing remains less investigated than its influence on sensorimotor control. The largest body of evidence comes from language processing. Over the last decade, lesion studies, brain imaging and non-invasive cerebellar stimulation techniques accumulated evidence on cerebro-cerebellar projections underpinning language-related functions, such as word generation, linguistic prediction, and working memory. These findings are supported by animal studies that identified cortico-pontine projections from frontal regions, such as Broca's area, that are distributed along medial portions of the pontine nuclei (Brodal, 1978; Wiesendanger et al., 1979; Leichnetz et al., 1984; Schmahmann, 1996; Schmahmann and Pandya, 1997a, 1997b) to project to superior cerebellar areas, such as lobule VI and Crus I (Brodal, 1979, 1982; Glickstein et al., 1994). Connections between parietal cortex and lateral pontine regions (Brodal, 1978; Wiesendanger et al., 1979; Leichnetz et al., 1984; Weber and Yin, 1984; May and Andersen, 1986; Schmahmann and Pandya, 1989, 1991; Schmahmann, 1996; Brodal and Bjaalie, 1997) project to the cerebellar paramedian lobule VIIb (Brodal, 1979, 1982; Glickstein et al., 1994). The strict right-sidedness of fMRI-based cerebellar activations agrees with the well-known cerebro-cerebellar cross-lateralization, which implies that just as the left hemisphere is mainly involved in language processing, the right cerebellum is mainly involved in language based functions (Chen and Desmond, 2005a, 2005b; Friederici, 2011).

In the following, we first introduce methods to study the cognitive cerebellum. Afterwards, we review studies that investigated the role of the cerebellum in language processing. This section is divided into two sub-sections: 1st “The cerebellum and verbal short-term/working memory,” and 2nd “The cerebellum, word generation and linguistic/semantic predictions,” The fourth and last section of this review is called “Conclusion.” This section offers a summary together with possible interpretations as well as our opinion on the current and future research directions.

2. Methods to study the cognitive cerebellum

2.1. Brain imaging and cerebellar lesions

Despite agreements between cerebellar anatomy in primates and cerebellar function in the human brain, the causal relationship between distinct cerebellar sub-regions and their contribution to cognitive processing remains largely unexplored. Cross-sectional functional magnetic resonance imaging (fMRI) only yields correlative evidence. Corresponding cerebellar activity may not necessarily index cognitive processing, but also contaminations such as task-related motor demands. Cerebellar damage, on the other hand, rarely occurs in isolation. Hence, lesion studies alone are often insufficient to address the causal cerebellar role in cognitive processing (Glickstein and Doron, 2008; Glickstein, 2006). Non-invasive cerebellar stimulation in healthy subjects may circumvent the inconsistencies observed in patient studies, but available studies revealed partly conflicting findings. In the following, we first introduce non-invasive cerebellar stimulation techniques before we summarize studies investigating the linguistic cerebellum using non-invasive cerebellar stimulation, brain imaging, or lesion studies.

2.2. Non-invasive brain stimulation to modulate cerebellar excitability

The two most widely-used non-invasive cerebellar stimulation techniques are transcranial magnetic stimulation (TMS) and transcranial direct/alternating current stimulation (tDCS/tACS). Evidence for their effectiveness was accumulated by studies that used these techniques to stimulate the primary motor cortex. Induced effects can be directly measured by peripheral electromyography of the muscle whose cortical representation was stimulated. Non-invasive brain/cerebellar stimulation in combination with cognitive tasks does not offer such clear read-out. Interpretations are solely based on evaluating stimulation-induced effects on cognitive performance.

During cerebellar TMS, the stimulating coil that consists of a magnetic field generator is placed over either the right or left cerebellar hemisphere. The magnetic field elicited by the coil produces small electric currents in the brain region underneath the coil via electromagnetic induction. The double-cone and batwing coils designed to stimulate deeper tissue can effectively stimulate cerebellar targets. The double-cone coil was found to be most effective (Hardwick et al., 2014).

Applied to the primary motor cortex, low frequency rTMS (e.g., 1 Hz) appears to produce a transient reduction in cortical excitability without a substantial effect on cortical inhibition. High frequency rTMS ($\geq$ 5 Hz) appears to produce a persistent reduction in cortical inhibition (Fitzgerald et al., 2006). More recent TMS protocols favor higher frequencies of 50 Hz and more. Theta-burst TMS (50 Hz, TBS) protocols that can be applied continuously (cTBS) or intermittently (iTBS) may be used to induce inhibitory or faciliatory effects, respectively (e.g., Di Lazzaro et al., 2005). Cerebellar TMS studies in combination with cognitive tasks do not follow the well-reproduced dichotomy of effects in the primary motor cortex. To date, they provide an inconsistent picture of how off-line (i.e., before the task) or on-line (i.e., during the task) TMS applied with either inhibitory or faciliatory protocols influences linguistic performance. The advantage of cerebellar TMS, as compared to tDCS/tACS, is that it allows stimulation with higher spatial accuracy. The disadvantage is that it provokes muscle contractions underneath the coil. This limits its applicability to more inferior parts of the cerebellum due to awkward or even painful neck muscle contractions. Another problem are the tingling sensations on the skull that occur with each stimulation. These side-effects complicate the applicability of a valid sham or placebo stimulation. Modern placebo coils mimic the sounds and the tingling sensations on the skull through stimulating electrodes that do not stimulate the brain (Mennemeier et al., 2009).

There are several cerebellar TMS studies that investigated the influence of TMS on cognitive functions (Arasanz et al., 2012) and cerebellar connectivity (Rastogi et al., 2017). Cerebellar cTBS applied to one hemisphere was shown to reduce cerebellar excitability (Bologna et al., 2016) and modulate the cerebellar output to contralateral interconnected cortical areas such as the motor cortex (Koch et al., 2008), the posterior parietal cortex (Casula et al., 2016) or the default network (Halko et al., 2014). Rastogi and colleagues (2017) investigated immediate effects of cTBS applied to lateral parts of the cerebellum on the strength of functional connectivity between cerebellar, cortical motor and cognitive regions. CTBS significantly weakened functional connectivity with frontal and parietal cognitive regions, while connectivity with motor regions remained unaltered. These results suggest an influence of cTBS on cognitive performance (Rastogi et al., 2017).

TDCS allows the passing of a direct current through the brain via two surface electrodes (anode and cathode) fixed on the participant's head. This means that this method uses two large electrodes (i.e., ~25 cm^2), hence limiting its spatial resolution (Woods et al., 2016). TDCS has become feasible as a non-invasive brain stimulation method to study motor cortex function since it allows for modification of the excitability of neurons in vivo in a polarity-specific manner (Stagg and Nitsche, 2011). Anodal tDCS of the primary motor cortex reduces intracortical inhibition and enhances facilitation after tDCS but not during tDCS. Cathodal tDCS reduces facilitation during, and additionally increases inhibition after its administration. Like TMS, tDCS thus offers the opportunity to investigate the behavioral consequences