SAPIENZA
UNIVERSITÀ DI ROMA

PhD school in Neuroscience

PhD program in Behavioral Neuroscience

The cerebellar role in Executive Functions:

new insights from behavioral and

structural neuroimaging data.

Academic Year 2016/2017

Candidate: Claudia Iacobacci

Tutor: Prof.ssa Maria Leggio

PhD School in Neuroscience

PhD program in Behavioral Neuroscience

The cerebellar role in Executive Functions:

new insights from behavioral and

structural neuroimaging data.

Academic Year 2016/2017

Candidate: Claudia Iacobacci

Tutor: Prof.ssa Maria Leggio

Contents

CHAPTER I

Cerebellum anatomy and physiology

The term cerebellum literally means "little brain" and it is located dorsally to the brainstem underlying occipital and temporal lobes of the cerebral cortex. Although the cerebellum accounts for approximately 10% of the brain's volume, it contains over 50% of the total number of neurons in the brain.

The cerebellum consists of two major parts (Figure 1a-b). A part is composed of inner white matter and another part of the outer grey matter. The white matter consists in the cerebellar deep nuclei (of cerebellum nuclei). The cerebellar deep nuclei are the sole output structures of the cerebellum. These nuclei are encased by a highly convoluted sheet of tissue called cerebellar cortex, which contains almost all of the neurons in the cerebellum. A cross-section through the cerebellum reveals the intricate pattern of folds and fissures that characterize the cerebellar cortex (Figure 1a).

Like the cerebral cortex, cerebellar gyri are reproducible across individuals and have been identified and named (Larsell, 1934; 1937). Two major fissures running medio-laterally divide the cerebellar cortex into three primary subdivisions. The posterolateral fissure separates the flocculonodular lobe from the corpus cerebelli, and the primary fissure separates the corpus cerebelli into a posterior lobe and an anterior lobe (Figure 1b).
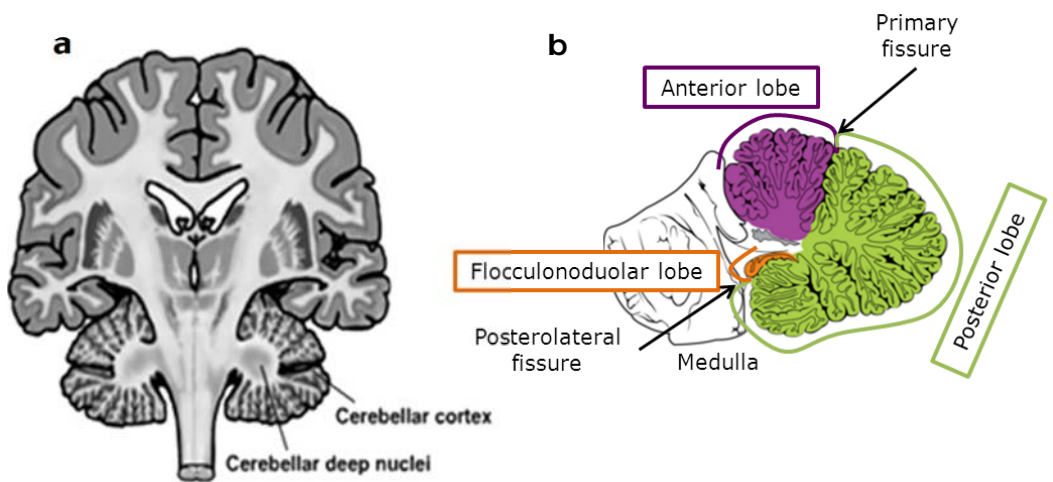
Figure 1. a) Cerebellar deep nuclei and cerebellar cortex in representative brain section. b) Midsagittal cross-section of cerebellum showing the three primary lobes.

The cerebellum is also divided sagittally into three zones that run from medial to lateral (Figure 2). The vermis (from the Latin word for "worm") is located along the midsagittal plane of the cerebellum. Directly lateral to the vermis is the intermediate zone. Finally, the lateral hemispheres are located lateral to the intermediate zone.
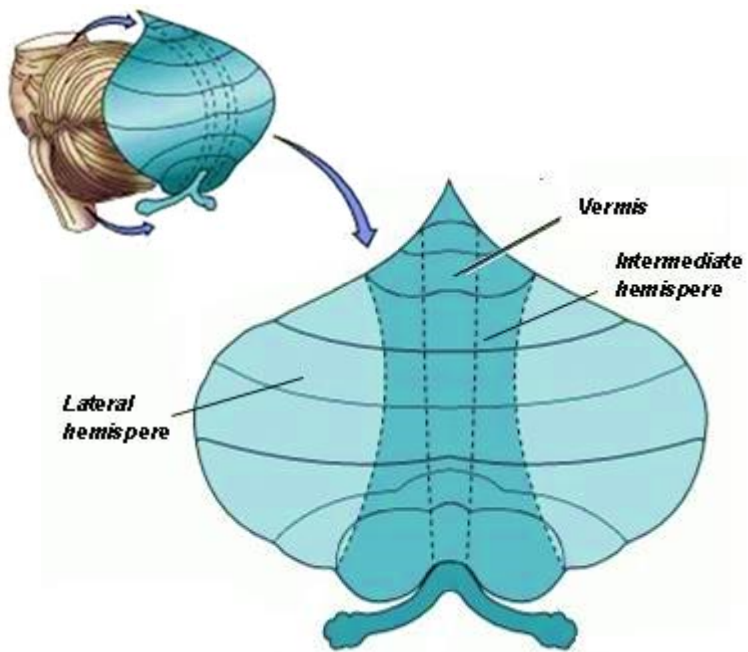
Figure 2. Anatomical subdivision of the cerebellum. Vermis, paravermal zones and intermediate hemispheres are showed.

1.1   Functional subdivisions of the cerebellum

The anatomical subdivisions described above correspond to three major functional subdivisions of the cerebellum (Figure 3).

Vestibulocerebellum. The vestibulocerebellum comprises the flocculonodular lobe and its connections with the lateral vestibular nuclei. Phylogenetically, the vestibulocerebellum is the oldest part of the cerebellum. As its name implies, it is involved in vestibular reflexes (such as the vestibuloocular reflex) and in postural maintenance.

Spinocerebellum. The spinocerebellum comprises the vermis and the intermediate zones of the cerebellar cortex, as well as the fastigial and interposed nuclei. As its name implies, it receives major inputs from the spinocerebellar tract. Its output projects to rubrospinal, vestibulospinal, and reticulospinal tracts. It is involved in the integration of sensory input with motor commands to produce adaptive motor coordination.

Cerebrocerebellum. The cerebrocerebellum is the largest functional subdivision of the human cerebellum, comprising the lateral hemispheres and the dentate nuclei. Its name derives from its extensive connections with the cerebral cortex, via the pontine nuclei (afferents) and the VL thalamus (efferents). It is involved in the planning and timing of movements. In addition, the cerebrocerebellum is involved in the cognitive functions.
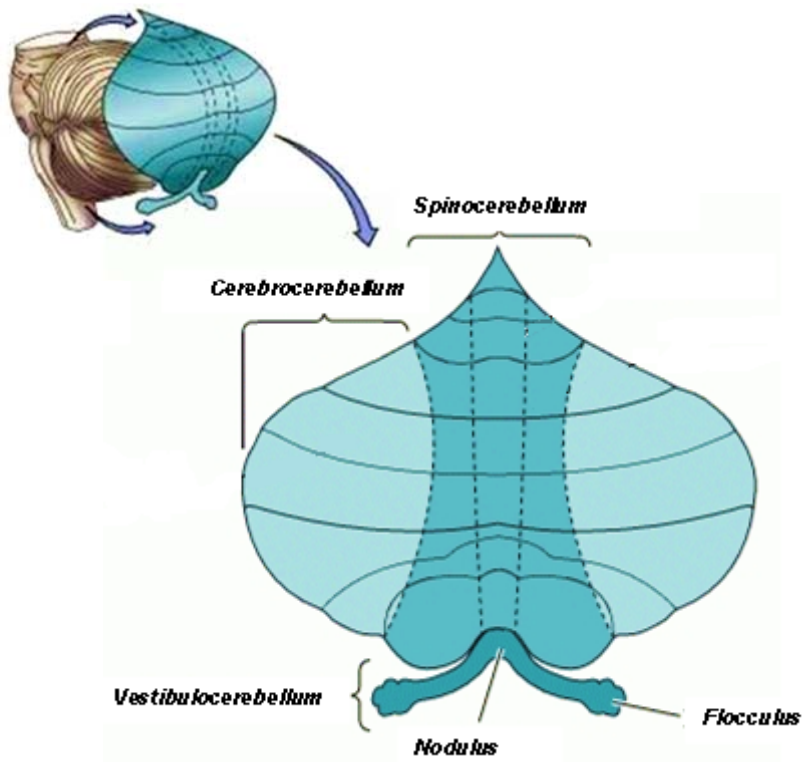
Figure 3. Functional subdivision of the cerebellum. Vermis and paravermal zones (intermediate hemispheres): spinocerebellum; flocculonodular lobe: vestibulocerebellum; lateral cerebellar hemispheres:cerebrocerebellum.

1.2   Basic structure of the cerebellar cortex

Throughout its highly-convoluted extent, the cerebellum can be divided into three cortical layers with the same basic neuronal circuitry everywhere, which involves five main cell types (Figure 4). The most conspicuous of these are the Purkinje cells, which form an orderly monolayer interposed between the granular and molecular layers, extending their planar dendritic trees into the molecular layer above. As these cells are the sole output neurons of the cerebellar cortex they are central to cerebellar cortical information processing. The granular layer below the Purkinje cells derives its name from the small, densely packed granule cells that send their axons into the molecular layer, where they bifurcate to become parallel fibres (Figure 4). These course parallel to the long axis of each folium and as a result they intersect the fan-like dendritic trees of many Purkinje cells. Mossy fibre afferents target granule cells and, therefore, excite the Purkinje cells indirectly through the granule cell–parallel fiber pathway, which causes the Purkinje cells to discharge 'simple spikes' (conventional action potentials). They also contact various types of interneuron in the cerebellar cortex, both directly and indirectly through the parallel fibres.

The other main class of cerebellar afferent is the climbing fibres, which arise exclusively from the inferior olive, a well-defined complex of sub-nuclei in the ventral part of the caudal brain stem

(Armstrong, 1974, 1990; Brodal & Kawamura, 1980). In marked contrast to the indirect influence of mossy fibres, the climbing fibres make direct synaptic contact with Purkinje cells (Figure 4). Moreover, each Purkinje cell receives input from just one climbing fibre, but the contact is so extensive that climbing fibres generate the largest depolarizing event seen in any neuron: a highly characteristic burst of impulses known as a climbing fibres response (Thach, 1967) or complex spike (Hawkes, 1997).
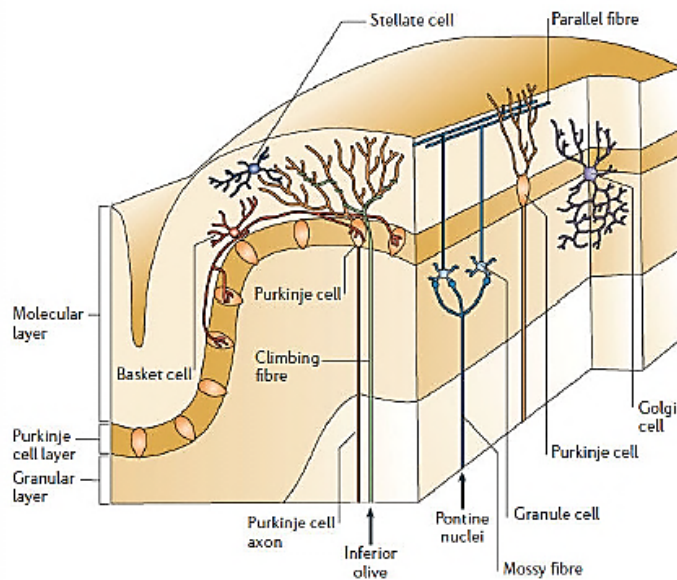
Figure 4. Basic structure of the cerebellar cortex. There are two main afferents to the cerebellar cortex: climbing fibres, which make direct excitatory contact with the Purkinje cells, and mossy fibres, which terminate in the granular layer and make excitatory synaptic contacts mainly with granule cells, but also with Golgi cells. In some cases, the stem axons of climbing and mossy fibres also provide collaterals to the cerebellar nuclei en route to the cerebellar cortex. The ascending axons of the granule cells branch in a T-shaped manner to form the parallel fibres, which, in turn, make excitatory synaptic contacts with Purkinje cells and molecular layer interneurons — that is, stellate cells and basket cells. Typically, parallel fibres extend for several

millimetres along the length of individual cerebellar folia (Brand et al., 1976; Pichitpornchai et al., 1994). With the exception of granule cells, all cerebellar cortical neurons, including the Purkinje cells, make inhibitory synaptic connections with their target neurons.

1.3   Concepts and models of cerebellar function

The importance of the cerebellum in the coordination of movement is undisputed (Babinski, 1899, 1906; Holmes, 1917, 1939; Chambers, 1955a; Dow & Moruzzi, 1958). However, in the last two decades a growing body of evidence indicates that it is also involved in several cognitive processes (Thach, 1967; Schmahmann, 1997). Cerebellar networks show long-term synaptic plasticity (Ekerot & Kano, 1985; Ito, 1989, 2001; Hansel et al., 2001), which indicates that experience-dependent adaptive and learning processes are also a salient feature of cerebellar function (Robinson, 1976; Ito, 1984; Thach, 1998). Such an adaptive capacity is a key feature of many current theories of cerebellar function.

Indeed, modeling has a long tradition in cerebellar studies and models differ in many respects (Houk et al., 1996). Some models address the involvement of the cerebellum in specific reflex behaviours, such as the adaptive regulation of gain in the vestibulo-ocular reflex (Boyden et al., 2004), or the role of the cerebellum in classical conditioning of eye-blink reflexes (Hesslow & Yeo, 2002). More general cerebellar models range from those inspired chiefly by cerebellar cytoarchitecture and the physiological properties of its constituent neurons - historically starting with the timing theory by Braitenberg & Atwood (1958) and the learned pattern recognition theories, (Marr, 1969; Albus, 1971)- to those motivated more

by Control Theory (Kawato & Gomi, 1992; Wolpert & Kawato, 1998). The model presented here builds on a specific tradition that emphasizes the division of the cerebellum into a collection of 'modules' defined by structure–function relationships. These modules are thought to form the basis for information processing performed by the cerebellum (Oscarsson, 1979; Voogd & Bigaré, 1980).

CHAPTER II

The Cerebellum: cognition and emotion

2.1   From motor to cognitive cerebellum

In the last two centuries, the functional interpretation of the cerebellum has undergone many changes. For over 100 years, the cerebellum has been considered to be strictly involved in motor control but in the past two decades, increasing evidences have been showed on non-motor cerebellar functions.

The first experimental studies on the cerebellum highlighted its role in controlling voluntary movement, specifically in the coordination of movement rather than in its genesis. The cerebellar contribution to non-motor functions has not been recognized for a long time and the cognitive and personality changes described in patients affected by cerebellar diseases were considered as an epiphenomenon of concomitant brain diseases.

Phylogenetic study on the evolution of the cerebellum showed that the phylogenetically most recent areas of the cerebellum (lateral portions of the hemispheres) have developed in parallel with the associative areas of the cerebral cortex (Leiner & Dow, 1986). On the basis of these observations Dow (1974) hypothesized that the lateral hemispheres of the cerebellum and the associative cortical areas are functionally interconnected.

However, most of the interest in high cognitive cerebellar functions has stemmed from well-described anatomical evidences of cerebello-cortico-cerebellar connections with non-motor cortical areas including the premotor, prefrontal, and parietal areas.

In 1997, Middleton and Strick proposed that cerebro-cerebellar connectivity is based on discrete "parallel circuits". These parallel loops are organized such that cerebellar regions that receive input from a given cortical area relay output back to the same cerebral area, thus forming parallel segregated circuits. Cortical regions that mediate such organization include the premotor, prefrontal, and parietal areas, which are not only concerned with various aspects of motor functions but also cognitive and emotional domains (Strick et al., 2009; Grimaldi & Manto, 2011). With regard to the cerebellum, cognitive regions have been identified in the posterior lobes (Krienen et al., 2009) while cerebellar vermis is appropriately named "limbic cerebellum".

The suggestion that the cerebellum is involved in cognitive and affective processes is based in part on observations of patients with lesions confined to the cerebellum.

In 1998, Schmahmann and Sherman described the "cerebellar cognitive affective syndrome" (CCAS). The CCAS was described in 20 patients with focal lesions confined to the cerebellum. The CCAS characterized by clinically relevant cognitive and

behavioural dysfunctions including disturbances of EFs, visuospatial disorganizations, difficulty with producing logical sequences, language difficulties and personality changes. The authors prove that cognitive and emotional changes might be even principal manifestations of cerebellar lesions. The authors hypothesized that the CCAS reflects "dysmetria of thought", analogous to "dysmetria of movements" resulting from damage to the anterior lobe of the cerebellum. Their concept of "dysmetria of thought" describes and explains the impairments of higher-order behaviours that result when the distributed neural circuits subserving cognitive operations are deprived of cerebellar modulation. The CCAS supports evidence suggesting that the cerebellum is an important part of a set of distributed neural circuits that subserve higher-order processing.

In 2011, Tedesco and colleagues examined the CCAS with regard to lesion topography in a large group of subjects with cerebellar damage, by analyzing the neuropsychological assessment compared with the lesion. The authors concluded that the locations of lesion provide an understanding of the connectivity between cerebellum and cortical areas involved in each cognitive domain. Of the various cognitive domains, the ability of sequence was the most adversely affected in nearly all subjects, supporting the hypothesis that sequencing is a basic cerebellar operation.

The involvement of the cerebellum in the modulation of cognitive and affective functions is now confirmed by numerous experimental evidences.

In line with studies on lesions, functional magnetic resonance imaging (fMRI) data on healthy subjects have demonstrated cerebellar activation in several cognitive functions such as in emotional behaviour (Stoodley & Schmahmann, 2009).

The cerebellar anatomo-functional connections suggest that the cerebellum is part of different networks of the neocortex-including frontal and parietal regions typically involved in high-order cognitive processing- suggesting its role outside the motor control.

2.2   Cerebellum and language

At the beginning of the twentieth century, it has been suggested that the cerebellum plays a crucial role in motor speech production. However, the cerebellum seems to be involved in linguistic processes not only basically motor. During the past two decades, a variety of higher-order deficits of speech production has been noted in patients with cerebellar lesions, including transient mutism following resection of posterior fossa tumors in children. More recent studies pointed to a cerebellar contribution to central-auditory functions, speech perception and higher-order linguistic processes such as speech timing, phonological aspects of lexical access, and top-down mechanisms of language.

Clinical and experimental evidences showed that different neuroanatomic parts of the cerebellum are critically implicated in a variety of speech and language functions.

Ackermann (1992) has suggested that the cerebellum is important for the creations of a verbal code, highlighting its role in sequencing of verbal stimuli and morphological and syntactic computation of speech.

Agrammatism has been observed in patients with right focal cerebellar lesions. Silveri and colleagues (1994) reported a case of right cerebellar infarction associated with transient expressive agrammatism. The authors hypothesized that the complex morpho-

syntactic operations allow the construction of syntactically correct sentences are represented in the left posterior associative areas. These operations would require a temporal modulation provided by a functional system that could include the contralateral cerebellum.

Leggio and collaborators (1995, 2000) studied patients with focal or degenerative left and right cerebellar lesions and showed that cerebellar damage specifically affects phonological fluency.

Different fMRI studies have shown activation of the right cerebellar hemisphere during linguistic tasks such as verbal fluency (Schlosser et al., 1998), covert verb generation (Papathanassiou et al., 2000), generation of verbs (Frings et al., 2006) confirming that patients with right cerebellar lesions were significantly more impaired than patients with left cerebellar lesions.

In conclusion, experimental evidences showed that different parts of the cerebellum are implicated in a variety of speech and language functions. The neuroanatomical substrate subserving the role of the cerebellum in non-motor language processing is a reciprocal network of crossed cerebro-cerebellar connection between the cerebellum and the supratentorial, limbic and associative cortices. In addition, neuroimaging studies consistently showed a lateralized involvement of the right cerebellar regions in non-motor linguistic processes.

2.3   Cerebellum and visuo-spatial processing

There are consistent reports of altered visuospatial abilities in subjects with cerebellar pathologies; furthermore, experimental evidences indicate the importance of the cerebellar involvement in spatial cognition.

Based on the anatomical connections of the cerebellar hemispheres with the contralateral cerebrum, the right cerebellar hemisphere is thought to be associated with language processing and the left cerebellar hemisphere with visuo-spatial functions.

The function of the cerebellum in spatial navigation has been clearly demonstrated in rats and mice. The studies using rats with surgical hemicerebellar lesion and a Morris Water Maze paradigm showed that cerebellar injury can cause a severe impairment in the ability of using spatial strategies. After the cerebellar lesion, animals showed inefficient exploration strategies with a tendency to swim circulating. They did not completely lose the ability to detect spatial relationships, but this process was possible only after a very prolonged training (Petrosini et al., 1996). In addition, if the lesion was performed after the learning phase, the animals' performance remained unchanged as if they had not undergone any damage (Petrosini et al., 1998; Leggio et al., 1999). Some studies, instead, have suggested that such impairments are linked to the inability to organize and execute complex and effective exploration behaviours

(the procedural component of navigation) rather than to the failure to develop an internal map of the environment (the declarative component of navigation) (Leggio et al., 1999).

In humans, several clinical studies have confirmed the involvement of the cerebellum in spatial abilities. Patients with cerebellar damage showed worse performances than healthy controls, in tasks involving visual-constructional processing (Molinari et al., 2004), in mental rotation tasks (Tagaris et al., 1998), in tasks assessing discrimination and orientation of lines (Molinari et al., 2004). In addition, the performance was worst in patients with left cerebellar lesion than patients with right cerebellar lesion (Molinari et al., 2004).

Stoodley (2012) using fMRI has shown in healthy subjects that the left cerebellar hemisphere appears more active during the execution of tasks related to space navigation (Moffat et al., 2006), confirming a lateralization of visuospatial functions in the left cerebellum.

Tedesco and colleagues (2017) studied how the cerebellum mediates the processing of sequential information in a navigational space and determine whether this involvement is influenced by the modality of the presentation of spatial sequences using 2 types of navigational tasks: the Walking Corsi Test and Magic Carpet, a modified electronic version of first one. The authors hypothesize that

the patients affected by cerebellar lesion performed significantly worse than control one on the electronic version because of a specific deficit in detecting and ordering single independent stimuli as a sequence. Authors concluded that the cerebellum is involved in spatial navigation and in processing sequential information through mechanisms activates from observation. This study suggests that cerebellum plays a specific role in allowing to process sequential information about routes.

In conclusion, experimental, clinical, and fMRI data have clearly demonstrated the involvement of the cerebellum in spatial functions and in processing sequential information through observation.

2.4   Cerebellum and attention

As previously reported, the real revolution in the vision of the cerebellum is derived from the study by Schmahmann and Sherman (1998) who postulated the existence of a CCAS. The deficits have been attributed to the disruption of the neural circuits linking the prefrontal, temporal, posterior parietal and limbic cortices with the cerebellum. Since prefrontal and posterior parietal circuits are supposed to be crucial for attention, their close anatomical connections with the cerebellum indicate a cerebellar relevance for these functions as well.

Akshoomoff and Chourchesne (1994; 1997) have shown the first evidence about a possible role of the cerebellum in attention. They found that patients with damage to the neocerebellum were significantly impaired in the ability to rapidly shift attention between ongoing sequences of auditory and visual stimuli (Akshoomoff & Courchesne, 1992) and in rapidly shifting their attention between visual stimuli that occurred within a single location.

Gottwald and colleagues (2003, 2004) conducted a study that led to find deficits in patients with focal cerebellar lesions in particular aspects of attention. In particular, the authors found deficits in divided attention and working memory attentional tasks (Gottwald et al., 2003). Further analysis revealed that patients with right-sided

lesions were in general more impaired than those with left-sided lesions (Gottwald et al., 2004).

Steinlin and collaborators (2007) studied children affected by posterior fossa malformations; the analyses revealed deficits in attention, processing speed, visuospatial functions and language. In addition, patients with ablation of left cerebellar tumor are more compromised compared to patients with right cerebellar tumor (Steinlin et al., 2003).

Functional imaging studies on attention demonstrated the activation of the cerebellum in attentional tasks.

Allen and colleagues (1997) were the first to emphasize attentional activation of the cerebellum. In a focus attention task they found BOLD responses in posterior parts of the left cerebellar hemisphere, whereas in a motor (manual) control condition responses the activations were localized in more anterior parts. Other studies have reported cerebellar responses for tasks assessing shifts of attention between modalities and paradigms involving spatial shifts of visual attention with emphasis on the lateral hemispheres and/or the posterior vermis.

Studies in non-human primates pointed out that the association areas of the posterior parietal cortex and prefrontal areas, both critical for focused attention, are connected via ventral pontine nuclei to the cerebellum.

Further indications about a link between the cerebellum and attention come from studies describing morphological abnormalities in patients with attention deficit hyperactivity disorder (ADHD). ADHD is known as a disturbance of EFs. Anatomical correlates have been shown in the prefrontal cortex (PFC), in the basal ganglia and in the cerebellum. Studies concerning anatomical features of the cerebellum, as measured by quantitative MRI, have shown smaller posterior inferior vermis (lobules VIII–X) in children with ADHD (Berquin et al., 1998; Castellanos et al., 2001).

Moreover, attentional deficits are described in studies with autistic patients. MRI studies report that autistic children have smaller cerebellar vermal volume as compared to typically developing children (Webb et al., 2009) and postmortem studies in autistic population report microanatomic abnormalities of the cerebellum.

Cerebellar contributions to attention have been suggested from both patient and functional imaging studies. According to these results, the discussion about the cerebellar' contribution to attentional processes is still controversial. It's clear that these studies support the idea of a cerebellar role in different attentional abilities regardless their motor aspects, but it is not clear if there is a functional dominance attributable to left or right cerebellar hemisphere.

2.5 Cerebellum and psychiatric disorders

The CCAS is characterized by impairments in multiple cognitive domains and regulation of affect. This syndrome represents a disruption of the cerebellar contribution to distributed neural circuits linking different regions within the cerebellar posterior lobe with cortical association and limbic areas that subserve higher order perceptual processing, intellectual functions and emotion.

Considering the closing cerebro-cerebellar circuits, the cerebellar vermis is appropriately named "limbic cerebellum" that involves the vermis and fastigial nucleus. An emotional dysregulation occurs when a lesion involves the limbic cerebellum. Posterior lobe lesions were particularly important in the generations of the CCAS and the vermis was consistently involved in patients with pronounced affective presentation.

Levisohn and colleagues (2000) reported affective changes, including irritability, impulsivity, agitation, and apathy in children after cerebellar tumor resection.

Personality change with blunting of affect or disinhibited and inappropriate behaviour was a prominent feature in the cerebellar patients, particularly those with large or bilateral infarcts in the territory of the posterior inferior cerebellar artery and in patient with lesions of the vermis and the paravermian structures. Flattening of affect or disinhibition manifested as overfamiliarity, flamboyant and

impulsive actions, and inappropriate and flippant comments. Behaviour was regressive and childlike, and obsessive-compulsive traits were occasionally observed.

The affective component of the CCAS is grouped according to five major domains that conceptualized the neuropsychiatry of the cerebellum: attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders and social skill set (Schmahmann, 2016).

Studies have also shown that the cerebellum is implicated in many psychiatric disorders including attention deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders (Philips et al., 2015).

Many recent studies have reported a strong association between the structural and functional abnormalities of the cerebellum and psychiatric disorders.

Multiple neuroumaging studies have also showed cerebellar changes in psychiatric disorders (Tomasi et al., 2012; An et al., 2013; Wang et al., 2013). In a PET study, cerebellar hypo-perfusion was evidenced in ADHD patients, involving the more medial part of cerebellar cortices (Di Tommaso et al., 2012).

Many volumetric studies have revealed decrease cerebellar volume along with other brain regions in children with ADHD. The

cerebellar volume reduction is mainly localized in the posterior vermis (Castellanos et al., 2002; Mackie et al., 2007; Ivanov et al., 2014).

Studies that investigated the autism spectrum disorder (ASD) found that in infants the cerebellar damage can predict the occurrence of autism in older age (Limperopoulos et al., 2007). Several studies reported three main cerebellar abnormalities in patients with ASD: diminished Purkinje cells (Tsai et al., 2012; Wang et al., 2014; Skefos et al., 2014), reduced cerebellar volume, and interrupted feedback pathways between cerebellar and cerebral areas (Townsend et al., 2001; Catani et al., 2008; Hanaie et al., 2013). Hypo-perfusion within cerebellar hemispheres was observed in autism (Rumsey & Ernst, 2000).

Neuroimaging studies on schizophrenic patients have found that the cognitive deficits exhibited in some patients are related to cerebellar dysfunction; in particular, it was found abnormal cortico-cerebellar connections (Ueland et al., 2004; Konarsk et al., 2006; Laidi et al., 2015). Structural brain imaging studies have found reduced cerebellar volume in patients affected by schizophrenia, including diminished vermis volume (Levitt et al., 1999; Nopoulos et al., 1999, 2001; Okugawa et al., 2002; Keller et al., 2003). Functional imaging studies in patients with schizophrenia revealed reduced blood flow in the cerebellar cortex and vermis during the

performance of many cognitive tasks such as attention, memory, including both short-term and working memory tasks (Crespo-Facorro et al., 2007), and social inferences (Andreasen et al., 2008).

Reduced cerebellar volume has been reported in several studies and case reports of patients affected by bipolar mood disorder (Jurjus et al., 1994; Brambilla et al., 2002; Monkul et al., 2007; Baldacara et al., 2011). In a population of multiple-episode bipolar disorder patients, the volume of the V3-vermal subregion of the cerebellum was significantly reduced, while the volume of V2-vermal subregion was smaller in multiple-episode patients than first-episode patients (Mills et al., 2005).

Also, in patients with major depressive disorder (MDD) various cerebellar abnormalities have been described (Brambilla et al., 2002). Yucel and collaborator (2013) found a significantly smaller vermis in MDD patients compared to healthy controls.

In the vermal areas of the cerebellum an increase of blood flow has also been linked to symptoms of MDD (Guo et al., 2012, 2013). Acutely depressed patients on various antidepressant medications showed an increased cerebellar activity and blood flow in the vermis when compared to remitting or healthy subjects (Guo et al., 2012, 2013). These findings were positively correlated with the severity of the depressive episodes, severity of cognitive deficits, and resistance to antidepressant medications suggesting that

cerebellar activation patterns could reflect a trait marker for depression.

In addition, a cerebellar impairment has been reported in anxiety disorders and it has been linked to increased arousal present in post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) (Abadie et al., 1999), and social anxiety disorder (SAD). Most studies on anxiety and the cerebellum suggest a hyperactivity of the cerebellum. In a study conducted on healthy subjects performing moderate exercise and complex mental task, increased cerebellar and vermal activity was evidenced in PET scanning (Critchley et al., 2000). Cerebellar hyperactivity correlated positively with increased blood pressure and heart rate, highlighting a possible cerebellar role in the regulation of sympathetic activity, which may explain its role in anxiety disorders.

To conclude, the cerebellum is not only the device of motor coordination but also it has an essential role in the modulation of personality, mood and affect. An evolving body of knowledge has revealed the role of the cerebellum in several psychiatric disorders and personality changes providing further clinical evidences that the cerebellum is an essential node in the distributed neural circuitry subserving higher-order behaviours.

2.6 Functional topography of the cerebellum

The cerebellum is topographically arranged and contributes to a wide range of behaviours. This functional heterogeneity is possible because of the highly organized anatomical connections with the areas engaged in vestibular, sensorimotor, cognitive and emotional processing via cerebro-cerebellar circuits.

A set of large folds are conventionally used to divide the overall structure into ten smaller lobules.

The ten lobules are grouped in the anterior lobe (lobules I through V) and in posterior lobe (lobules VI through IX); the lobule X comprises only the flocculonodular lobe.

Bolk (1906) was the first that hypothesized the existence of a topography in the motor functions of the cerebellum.

Psychological experiments in cats and fMRI studies in humans revealed the presence of sensorimotor homunculi in lobules III-VI and lobule VIII. In contrast, projections from the association areas (prefrontal, posterior parietal, and superior temporal, posterior parahippocampal and cingulate areas) are mainly localized to lobules VI and VII (Kelly & Strick 2003; Stoodley & Schmahmann, 2010).

Using fMRI Stoodley and colleagues (2012) showed the regions active during different tasks consistent with description of the cerebellar homunculi.

Right-handed finger-tapping activated right cerebellar lobules IV-V and VIII, verb generation engaged right cerebellar lobules VI-Crus I and a second cluster in lobules VIIIB-VIIIA. Mental rotation activation peaks were localized to medial left cerebellar lobule VII (Crus II). A 2-back working memory task activated bilateral regions of lobule VI-VII.

The cerebellar functional topography identified in the study of Stoodley and colleagues (2012) reflects the involvement of different cerebro-cerebellar circuits depending on the demands of the task being performed: overt movement activated sensorimotor cortices along with contralateral cerebellar lobules IV-V and VIII, whereas more cognitively demanding task engaged prefrontal and parietal cortices along with cerebellar lobules VI and VII.

In stroke patients, focal lesions also provided insights into cerebellar structure-function relationship. Clinical studies suggested that the cerebellar anterior lobe is principally engaged in motor control, the cerebellar vermis is involved in affective processing and the posterior cerebellum contributes to complex cognitive operations. Also, consistent with the crossed cerebro-cerebellar fiber pathway, linguistic impairments can arise following right cerebellar hemisphere lesions, whereas visuo-spatial difficulties may follow left cerebellar hemisphere damage.

Motor and somatosensory representations show largely overlapping activation pattern, with the major cluster focused in lobule V and the adjacent part of lobule VI and a second cluster in lobule VIII. The motor and somatosensory coordinates are right lateralized.

The strongest activation peaks for the language tasks are lateralized to right lobule VI, Crus I/II and midline lobule VIIAt (Crus II).

Resting state functional connectivity magnetic resonance imaging and task-based functional MRI in humans also supported these structural and functional connectivity patterns.

Anatomical studies showed three major cerebellar connectivity patterns:

1) Peripheral and brainstem vestibular afferents are connected with the flocculonodular lobe, fastigial nucleus, and the oculomotor vermis in lobule VII;

2) Spinal cord and sensorimotor regions of the cerebral cortex are linked with primary sensorimotor areas in the cerebellar anterior lobe (lobules I-V), medial lobule VI and a second representation in the posterior lobe in lobule VIII, together with the related sensorimotor nuclei (globose, emboliform, and dorsal part of the dentate nucleus);

3) The prefrontal, posterior parietal, temporal and cingulate association and paralimbic cortices are reciprocally linked with the posterior cerebellum in lobules VI and VII, and the ventral part of the dentate nucleus.

The cerebellar hemispheres are linked with cerebral association areas, whereas the posterior vermis and fastigial nucleus are interconnected with limbic system structures including hypothalamus, septum and amygdala. The fact that the cerebellum is reciprocally connected to a broad range of limbic structures including the amygdala, hippocampus, and septum, as well as the cerebral cortex including the prefrontal areas, provides a strong neuroanatomical argument in favor of cerebellar involvement in emotion regulation.

Baumann and Mattingley (2012) used fMRI to identify neural activity patterns within the cerebellum in healthy human volunteers as they categorized images that elicited each of the five primary emotions: happiness, anger, disgust, fear and sadness. They advanced the hypothesis that the five emotions evoked spatially distinct patterns of activity in the posterior lobe of the cerebellum. This study has provided the first evidence in healthy humans that distinct subregions of the cerebellum are responsive during the experience of happiness, anger, disgust, fear and sadness. These findings also revealed overlaps between the activation patterns for

selected emotions, indicating the existence of shared neural networks. For instance, the authors detected partial overlap in activations associated with fear and anger (paravermal lobules VI and Crus I), anger and disgust (vermal lobule IX), and happiness and sadness (vermal lobule VIIIA).

These findings provide further support for a cerebellar role in motor, cognitive and emotional tasks and better establish the existence of functional subregions in the cerebellum.

CHAPTER III

The Executive Functions

3.1   Executive Functions models and definitions

Executive Function (EFs) has an umbrella term used for diversity cognitive processes, including planning, working memory, attention, inhibition, self-monitoring, self-regulation, and initiation carried out by the frontal lobes. At the most basic level, EFs are the abilities that enable a person to establish new behavioural patterns and ways of thinking and to introspect upon them.

EFs involve different abilities and cognitive processes that allow selecting and monitoring behaviours to achieve specific goals and cannot be considered as a unitary function (Logan, 1985; Bellebaum & Daum, 2007). EFs generally refer to "higher-level" cognitive functions involved in the control and regulation of "lower-level" cognitive processes and goal-directed, future-oriented behaviour.

There has been a historical linkage of these "higher-level" processes with the frontal lobes although it has been proposed that subcortical structures are involved in EFs by means of specific anatomical connections.

EFs are extremely complex to define and there is lack of consensus about taxonomy of EFs processes.

Phineas Gage (1823-1860) is one of the earliest – and most famous – documented cases of severe frontal brain injury. Thanks to him we know that the frontal lobes are involved not only in cognitive processes but also in behaviour and personality. Gage is the index case of an individual who suffered major personality changes after brain trauma. Gage was an American railroad construction foreman remembered for accident in which a large iron rod was driven completely through his head, destroying much of his brain's left frontal lobe, and for that injury's reported effects on his personality and behaviour over the remaining twelve years of his life.

Several theories have been proposed over the last 25 years to categorize and better understand EFs. By the 1950s, the neuroscientists became more interested in understanding the role of the PFC in behaviour.

Broadbent (1953) described differences between automatic and controlled processes, otherwise referred to as the filter model, and proposed that a filter serves as a buffer that selects information for conscious awareness.

According to Luria (1966) the frontal lobes contain a system which governs the ability of planning and monitoring during new tasks. Luria proposed also that this system is hierarchical in structure and consists of at least three cortical zones built one above the other. The zones are the orbitofrontal, cingulate, and dorsolateral cortex.

According to Luria, whereas the orbitofrontal cortex modulated social control and the cingulate cortex was responsible for the generation of goal-directed behaviour, the neuropsychological functions of the frontal cortex were localized within dorsolateral prefrontal regions.

In 1975 Posner proposed that there is a separate executive branch of the attentional system responsible for focusing attention on selected aspect of the environment.

Logan (1985) supported that EFs may be distinguished in: making choices about alternative strategies for processing environmental stimuli; constructing or instantiating a version of the chosen strategy to enable performance on the task; controlling and coordinating execution of the strategy during real time performance on the task; disabling or disengaging the strategy in response to change goals or changes in task environment that make the current strategy inappropriate.

Norman and Shallice (1986) have argued that EFs operates in a "supervisory" or "executive" capacity over the rest of the cognitive abilities and described situations in which EFs are involved. Their model supports a cognitive system known as the supervisory attentional system (SAS) that plays a part in different processes, such as in novel and non-routine situations, and exerts an executive influence onto automatic schema selection. The SAS would also provide help when conflicting schemas are activated or when the

situation requires responding in a schema-incongruent way. The authors suggested that automatic processes do not require executive control.

Goldman-Rakic (1987) has proposed a neuroanatomical model of the frontal lobe, specifically on the prefrontal cortex (PFC). In this model the PFC is part of a network which includes the parietal and temporal cortices such as the limbic structures and has the role to guide the behaviour.

Baddeley and Hitch (1974, 1994) proposed a similar system as part of their model of Working Memory (WM), arguing there must be a component which he referred to as the "central executive". They proposed that the central executive system actively regulates the distribution of limited attentional resources and coordinates information within verbal and spatial memory buffers. This concept of the central executive system was based on Norman and Shallice's analogous SAS, which is proposed to control cognitive processing when novel tasks are involved, or existing habits must be overridden.

Smith and Jonides (1999) postulated that EFs include: focusing attention on relevant information and processes and inhibiting irrelevant ones ("attention and inhibition"); scheduling processes in complex tasks, which requires the switching of focused attention between tasks ("task management"); planning a sequence

of subtasks to accomplish some goal ("planning"); updating and checking the contents of working memory to determine the next step in a sequential task ("monitoring") and coding representations in working memory for time and place of appearance ("coding").

Diamond (2013) has proposed inhibition, working memory and cognitive flexibility as core aspects of EFs.

Other authors have proposed multifactorial models of EFs. In these studies, factor analysis has been used as a mathematical strategy to analyze the structural correlation of neuropsychological test batteries (Ardila et al., 1994, 1998; Ponton et al., 1994; Ostrosky et al., 1999).

Applying these multifactorial models Miyake and colleagues (2000) studied a normal population and have highlighted three executive processes moderately related to each other, but clearly separable. These EFs are mental set shifting ("Shifting"), information updating and monitoring ("Updating"), and inhibition of reflexive responses ("Inhibition").

Pineda and Merchan (2003) reported an orthogonal structure of five factors in normal healthy young. Factor 1 corresponds to the cognitive activities of organization and flexibility. Factor 2 could be considered sustained attention. Factor 3 could represent speed of inhibitory control. Factor 4 could be considered as visual-motor speed. Factor 5 included verbal fluency.

In the end, multifactorial models assume that EFs are not a single activity, but rather a complex system, formed by different cognitive operations such as anticipation, goal selection, organization, planning, monitoring, shifting, controlling time, speed, and using environmental feedback to modify behaviour (Lezak, 1995; Della Sala et al., 1998).

3.2 Neuroanatomy of Executive Functions

Executive disorders and their association with frontal lobe's lesions have received significant contributions very late in the history of neuropsychology and cognitive neuroscience.

The attention to the frontal lobes is documented from the second half of the nineteenth century, with the description of the famous case of Phineas Gage (Harlow, 1848), and the systematic experimental tests carried out on animals by italian Bianchi (1922).

Bianchi argued that the frontal lobes are the neuroanatomical site for the coordination and integration abilities because the frontal lobes receiving input from numerous motor and sensory areas of the cerebral cortex. Bianchi has identified also the major alterations resulting from frontal lobe injuries. These included defects in attentive control, memory disorders, inability to coordinate the various phases of a goal-oriented process, and emotional regulation disorders with consequent changes in social behaviour, alterations in motivation, and apathetic behaviour (Bianchi, 1922).

Frontal lobe functions have, however, been conceived for a long time as a unified and poorly differentiated control system.

Today we know that the neuroanatomy underlying EFs is complex and involves numerous cortical and subcortical circuits.

Recent advances in cognitive neurosciences show that, whilst the frontal lobes play an important part in EFs, the frontal lobe

contribution is just one part of a wider network on brain involvement. Although EFs are commonly thought as "frontal lobe" functions, the frontal lobes are necessary but not sufficient for intact executive functioning. Today, we know that the terms "frontal lobe behaviour" do not accurately describe the complex, multifaceted behaviours and associated neuroanatomy involved in executive functioning.

The frontal cortex is composed by:

The Dorsolateral prefrontal cortex (DLPFC) which contains heteromodal association cortex and has dense bidirectional connections with most cortical areas and a number of subcortical structures (most predominantly the caudate nucleus). The DLPFC is involved in planning and organization, working memory, maintaining goal - directed behaviours, and self - monitoring for the purpose of modifying behaviours in response to task demands. The posterior aspect of the DLPFC is involved in modulating the allocation of attention to competing stimuli (Petrides & Pandya, 2002).

The Ventrolateral prefrontal cortex which receives motivational and emotional information from the limbic system and highly integrated sensory information from both anterior and posterior association cortices. This allows the binding of sensory information with particular emotional and visceral states for decision making based on the emotional valence and behavioural significance of stimuli (Sakagami & Pan, 2007). The Ventrolateral prefrontal

cortex also appears to play a role in judgment, encoding, and retrieval (Petrides & Pandya, 2002).

The Orbitofrontal cortex is primarily involved in impulse control, inhibition of responses, and regulation of comportment. It also integrates input from sensory systems and more visceral limbic and paralimbic areas to play a role in regulating emotion, reward, and punishment systems which are involved in decision making (Schoenbaum et al., 2006).

The Medial frontal cortex is composed of paralimbic cortex (Kaufer, 2007). The functions of the medial frontal cortex include modulation of attention, arousal, and motivation; disruption of this area is linked to apathy and abulia (Filley, 2000; Kouneiher et al., 2009).

Long-range afferent connections convey higher order sensory information to the frontal cortex, which in turn responds to internal and external stimuli with a flexible and adaptive behaviour.

Recently, a series of parallel frontal-subcortical circuits that link regions of the frontal lobes to subcortical structures have been described. Indeed, all frontal-subcortical circuits originate in the frontal cortex and form loops connecting the striatum (caudate, putamen, and ventral striatum), globus pallidus, thalamus and the cerebellum and returning back to the frontal cortex (Alexander et al.,

1986; Alexander & Crutcher, 1990; Alexander, 1994; Monchi et al.,

2006).

3.3 Fronto-cerebellar circuits

By using viral tracing techniques in nonhuman primates, the identification of multiple, segregated fronto-cerebellar circuits has challenged the traditional view that motor control comprises the complete repertoire of the cerebellum (Leiner et al., 1986; Schmahmann, 1991; Middleton & Strick 1994, 2001; Kelly & Strick, 2003).

Krienen and Buckner (2009) used functional connectivity MRI (fcMRI) in humans to identify 4 topographically distinct cerebellar-frontal circuits that target 1) motor cortex, 2) DLPFC, 3) medial prefrontal cortex, and 4) anterior prefrontal cortex. Direct comparisons of right- and left-seeded frontal regions revealed contralateral lateralization in the cerebellum for each of the segregated circuits. The authors find that the regions of the cerebellum functionally coupled with PFC occupy a significant extent of the cerebellar posterior hemisphere. The cerebellar regions associated with motor cortex areas correspond to lobules IV--VI and VIIIB (Schmahmann et al., 1999, 2000). The DLPFC correlations appear in regions that correspond to Crus I and Crus II of the cerebellum (Schmahmann et al. 1999, 2000).

Habas and colleagues (2009) studied the role of the cerebellum in several non-motor systems by using resting state functional connectivity MRI. They found that the executive networks

consist of a right and a left executive network. These networks entail the PFC, the orbitofrontal cortex, the superior parietal cortex, the angular gyrus, the caudate nucleus and primarily the Crus I and Crus II of the cerebellum with limited extension into lobules VI and VIIB and the rostral hemisphere of lobule IX.

3.4 The Dysexecutive Syndrome

The term "dysexecutive syndrome" was introduced in the 1980s to describe impairments in EFs.

An executive impairment occurs not only after a frontal lobe injury because, as previously said, the frontal lobe is an integral part of distributed network between cortical regions and subcortical regions. All components of these networks are important for task performances, and lesions at any point in the system cause deficits that look like "frontal" damage.

From a clinical point of view the term of "dysexecutive syndrome" refers to the complex of symptoms that characterize the impairment of EFs including problems in planning, organizing behaviours, disinhibition, perseveration, reduced fluency and initiation (Repovs & Baddeley, 2006; Ardila, 2013).

Actually, according to the different abilities involved in the executive system, diverse types of dissociations have been described in patients with PFC damage (Eslinger & Damasio 1985; Boone, 1999). Taking into account the site of injury an anatomical distinction can be made between dorsal and ventral cortices, which can be considered cognitive and affective, respectively. Further, clinical and experimental researches converged to indicate the fractionation of frontal subprocesses and the initial mapping of these subprocesses linked to discrete frontal regions.

Indeed, patients with PFC damage can be selectively impaired in neuropsychological tests investigating each of the executive processes (Stuss & Benson, 1986).

It is worth noting that executive deficits are not only caused by lesions in the PFC, but also by subcortical lesions (Willingham, 1992; Goel & Grafman, 1995). Indeed, cortico-subcortical circuits which connect the PFC, the basal ganglia and the cerebellum via the thalamus are believed to serve as neuroanatomical substrates of executive processing and play a critical role in EFs (Heyder et al., 2004).

Therefore, dysexecutive symptoms occur in most neurodegenerative diseases and in many other neurologic, psychiatric, and systemic illnesses. In patients with degenerative basal ganglia disorders, such as Parkinson's disease (PD), deficits have been described in problem solving, reasoning, concept formation and complex memory task which require the self-initiated strategic organization of encoding and retrieval. Furthermore, in PD patients an impairment in inhibiting irrelevant stimulus and responses have been evidenced (Pollux & Robertson, 2002). These deficits are generally attributed to dysfunction of the PFC-basal ganglia circuits (Zoppelt & Daum, 2003).

3.5   Cerebellum and Executive Functions

Over the last twenty years several neuroanatomical and functional neuroimaging studies showed the presence of extensive connections between the cerebellum and cortical association areas resulting in a true revolution in the vision of cerebellar functions (Schmahmann & Pandya, 1989; Schmahmann, 1991; Leiner et al., 1991; Ivry, 1997; Tagaris et al., 1998; Harrington & Haaland, 1999; Fink et al., 2004).

As already said, studies on primates have shown the existence of reciprocal connections between the prefrontal cortex and specific areas of the cerebellum (Alexander, Crutcher & DeLong, 1990; Joel & Wiener, 1994; Middleton & Strick, 1997).

The fronto-cerebellar circuit radiates from the CPF dorso-lateral to the cerebellum. The projections of the cerebellum originate from the lateral part of hemispheres and project through the dentate nucleus and the thalamus contralateral to the PFC. The latter is connected to the cerebellum via the pontine nuclei (Schmahmann, 1997; Heyder et al., 2004;).

The cortico-ponto-cerebellar circuit transmits to the cerebellum information not only from the motor and premotor areas, but also from most of the associative cortical areas (Nyby & Jansen, 1951; Brodal, 1978; Wiesendanger et al., 1979; Glickstein et al., 1985; Fries, 1990; Schmahmann & Pandya, 1989, 1991).

Ramnani and colleagues (2006) showed that in humans, cerebellar projections from the prefrontal cortex are more developed when compared with those of non-human primates. They proposed that these connections are rapidly increased during evolution, parallel to prefrontal cortex itself.

Such connections between the cerebellum and the PFC can be considered the possible anatomical-functional substrate which sees the cerebellum also involved in the control of EFs (Daum & Ackermann, 1997; Schmahmann, 1997; Daum et al., 2001; Heyder et al., 2004).

The particular role of the cerebellum in EFs domains has been shown to be modulation rather than generation of executive processes considered to be specific of the cerebral cortex (Dow, 1974; Snider & Maiti, 1976; Heath, 1977).

The concept of cerebellum as incorporated into a distributed cortico-subcortical neural system subserving EFs is based on the observation of existence of numerous connections between the PFC and cerebellum and vice-versa (Middleton & Strick, 1994, 2001; Strick et al., 2009; Alexander et al., 2012).

According to the neuroanatomical and neuroimaging evidences, an increasing number of clinical studies supported the cerebellar involvement in different and specific neuropsychological functions within the executive domain.

Data supporting the hypothesis of a cerebellar role in the modulation of EFs come from studies in which they were used tasks of planning, such as the "Tower of London" and "Tower of Hanoi."

Grafman and colleagues (1992) showed that patients affected by cerebellar atrophy had difficulty to solve problems of the tower of Hanoi task.

Subsequently, Goel and Grafman (1995) found similar impaired performances in patients with cerebellar atrophy and in patients with disorders involving subcortical structures linked to the frontal lobes such as the thalamus and basal ganglia. These executive alterations may be due to difficulty in assembling a sequence of events or actions in a "plan". The cognitive planning can be seen as an analogue of the complex motor procedures, which require a series of movements in order to implement a sequence (Pascual-Leone et al., 1993).

According to Willingham (1992), the frontal cortices program the various steps of an action plan. Therefore, prefrontal cortex injuries could lead to deficits in planning action plans while a damage to subcortical structures, such as the thalamus and basal ganglia, compromise the automated acquisition of the action plan. Damages to the cerebellum, instead, do not guarantee the correct implementation and the correct sequence of the various steps of the plan "programmed" by the frontal cortices (Willingham, 1992).

Several studies have shown that lesions to the cerebellum may cause impairment of planning and problem-solving abilities such as reasoning (Hallett & Grafman, 1997), verbal fluency and other words generation abilities (Appollonio et al., 1993). A lesion of the cerebellum may cause, also, impairment in the organization, the encoding and retrieval of strategies (Bürk et al., 1999, 2003).

Schmahmann and Sherman (1998), describing the CCAS, reporting EFs deficits related to planning, set shifting, abstract reasoning, working memory and verbal fluency. Schmahmann and Sherman (1998) describe the cerebellum as a mediator of these functions which deficits follow a breakdown in fronto-cerebellar connections.

Ravizza and Ivry (2001) observed higher error rates in cerebellar lesioned patients compared to controls in the Wisconsin Card Sorting Test (WCST).

Abel and colleagues (2007) compared EFs in patients affected by PD and in patients affected by degenerative cerebellar diseases in order to differentiate the role of basal ganglia and cerebellum in the executive control. Both groups of patients showed impaired performances in EFs tasks but with a different clinical profile. While the PD group showed a selective increase of non-perseverative errors in the WCST, the cerebellar group showed a high number of

both perseverative and non-perseverative errors together with significant lower performances than PD group in attention tasks.

Cumulative evidence of the cerebellum's involvement in higher cognition processes has led to the development of theories which attempt to understand its precise function.

There are differences between lesions of the PFC and lesions of the cerebellum. The differences are found and identified in the severity of executive deficits: in fact, cerebellar damage determines milder deficits compared to those found in the presence of PFC damage.

The finding of neuropsychological executive deficits in patients affected by cerebellar damage (Schmahmann, 1998; Bellebaum & Daum, 2007) is supposed to be caused by a defect in modulatory activity exerted by the cerebellum on the cognitive functions primarily accounted from the frontal areas (Schmahmann & Pandya, 2004).

Daum and colleagues (2001) have proposed that the PFC may be the structure primarily involved in the generation of specific operations, while the cerebellum serves to optimize and automate the processes necessary to the frontal operations.

Very recently fMRI studies in healthy subjects have demonstrated a direct involvement of specific cerebellar lobuli in EFs.

Keren-Happuch and collaborators (2014) reviewed 88 neuroimaging studies and found that EFs tasks activated Crus 1 bilaterally, left Crus 2 right Lobule VI and midline Lobule VII.

In conclusion, lesions of cerebellum and basal ganglia mimic deficits resulting from cortical lesions but with qualitative differences.

It has been suggested that if the frontal circuit seems involved in initiating, sequencing or inhibiting a series of behaviours or actions, the cerebellar-cortical circuit seems to play a role when these activities need to be optimized, acquired and carried out quickly (Passingham, 1995).
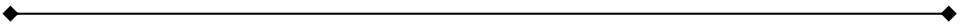
Experimental section

4.1 Introduction

There is a consensus that the lateral prefrontal cortex and basal ganglia together with the cerebellum play a critical role in Executive Functions (EFs) (Heyder et al., 2004) as described in Chapter 3.

The cerebellar involvement in EFs is supported by the existence of specific anatomical connections with the lateral prefrontal cortex (Middleton & Strick, 1994), but remains unclear. We described the fronto-cerebellar circuits in the previous chapters.

As previously said, it has been hypothesized that the role of the cerebellum in motor and non-motor domains is related to an "over-function" that allows an automatic modulation and optimization of behaviour thanks to the specificity of neural sub-circuits within the cerebro-cerebellar system (Schmahmann, 1991, 1996, 2000, 2004; Thach, 1987, 1992; Bloedel, 1997; Schmahmann & Sherman, 1998). Numbers of experimental evidences have suggested that the cerebellum have also a role in modulation and optimization of EFs (Schmahmann & Pandya, 1989; Schmahmann, 1991; Leiner et al., 1991; Ivry, 1997; Schmahmann & Sherman, 1998; Tagaris et al., 1998; Harrington and Haaland, 1999; Karatekin et al., 2000; Ravizza & Giorgi, 2006; Bellebaum & Daum 2007; Riva et al., 2013; Noroozian, 2014; Marien et al., 2015; Mak et al., 2016; Corben et al., 2017; Kansal et al., 2017).

In recent years, several authors described a "dysexecutive syndrome" in cerebellar diseases, hypothesizing that such syndrome could be the primary cause of cognitive deficits and behaviour alterations reported in patients with cerebellar damage (Torrens et al., 2008; Brega et al., 2008).

Actually, before the description in 1998 of the Cerebellar Cognitive Affective Syndrome (CCAS), a syndrome of cognitive deficits was reported by Luria (1964) in a patient with cerebellar tumor called "pseudo-frontal" syndrome. The patient presented with neuropsychological symptoms that at first sight appeared to be consistent with frontal lobe pathology. On further inspection, the author demonstrated a "pseudo-frontal" rather than a "frontal" syndrome, and reported that these symptoms were related not to frontal pathology, but to a cerebellar tumor (Luria, 1964).

Many comparative studies report the existence of deficits within various aspects of EFs in patients with either focal lesions (Gottwald et al., 2004; Starowicz-Filip et al., 2013; Mak et al., 2016) or atrophy (Burk et al., 2001; Suenaga et al., 2008; Ma et al., 2014) of the cerebellum.

An impairment of the EFs was described as one of the main symptoms of the CCAS (Schmahmann & Sherman, 1998).

Gottwald and colleagues (2004) founded deficits in the Semantic and Phonemic Fluency Tests, in the Similarities and Hand

Movements Tests and in the Stroop Color-Word Test in patients with cerebellar focal lesion.

Starowicz-Filip and colleagues (2013) described a patient with an ischemic stroke in the right cerebellar hemisphere, who showed the typical symptoms of a frontal damage. He manifested euphoric mood, disorganized behaviour, lack of criticism and mental plasticity, tendency to shorten the personal distance, alterations in Trail Making Test, Wisconsin Card Sorting Test, Stroop Color-Word Test and Word Fluency Test.

Mak and collaborators (2016) investigated the EFs in 30 patients after cerebellar surgery. The patients showed deficits in the Wisconsin Card Sorting Test, the Stroop Color-Word Test and the Trial Making Test.

An impairment of the EFs was described also in different populations of patients with degenerative disorders of the cerebellum.

Suenaga and colleagues (2008) evaluated cognitive impairment in 18 patients with spinocerebellar ataxia type 6 (SCA6). They founded an impairment in Semantic and Phonemic Verbal Fluency Test. Mild deficits were present also in the Rule Shift Cards Test.

Moreover, neuropsychological studies showed that significant cognitive deficits, especially those affecting frontal lobe related to

the EFs in patients affected by spinocerebellar ataxia type 1 (SCA1) (Burk et al., 2001), spinocerebellar ataxia type 2 (SCA2) (Burk et al., 1999) and spinocerebellar ataxia type 3 (SCA3) (Maruff et al., 1996; Kavai et al., 2004).

Although the research studies reported above clearly showed a cerebellar involvement in executive domain, they have been focused only on single subcomponent of EFs (Suenaga et al., 2008; Starowicz-Filip et al., 2013; Ma et al., 2014; Gottwald et al., 2014) and no systematic study has been yet implemented to characterize the EFs profile in patients affected by a cerebellar pathology.

Aim of the present research project was to draw up a neuropsychological profile of EFs impairment in patients affected by cerebellar pathology and to characterize the cerebellar role in the different EFs sub-components (Miyake et al., 2000). To do that, we used an extensive neuropsychological battery to assess the various aspect of EFs in patients with focal or atrophic cerebellar.

Moreover, advanced neuroimaging techniques were used to analyze the cerebellar damage and to investigate the neuroanatomical substrate of the executive profile of the cerebellar patients.

In the following sections, three studies will be reported.

In the first study, the executive profile of cerebellar patients was deeply investigated using an extensive neuropsychological battery.

In the second study an exploratory factor analysis of the behavioural data was performed in order to characterize the cerebellar involvement in specific sub-components of the EFs.

In the third study the correlation between the behavioural performance and the cerebellar damage was analyzed.

4.2 Study 1: Behavioural investigation of the Executive Functions profile in patients with cerebellar pathology

4.2.1 Rationale

The cerebellum has been proposed to be one of the subcortical structures involved in EFs (Schmahmann & Pandya, 1989; Schmahmann, 1991; Leiner et al., 1991; Ivry, 1997; Schmahmann, 1997; Tagaris et al., 1998; Harrington & Haaland, 1999; Grossi & Trojano, 2005; Bellebaum & Daum, 2007).

Specifically, executive deficits have been described in patients with cerebellar pathology, even if they resulted less severe than those reported in patients with lesions in the frontal lobe (Daum et al., 2001; Schmahmann & Pandya, 2004; Torrens et al., 2008; Brega et al., 2008; Tedesco et al., 2011).

Nevertheless, the cerebellar executive profile in patients affected by cerebellar pathology has never been characterized.

Aim of the present study was to examine the EFs profile in patients affected by degenerative or focal cerebellar damage in order to characterize the dysexecutive syndrome of cerebellar origin.

Patients underwent an extensive EFs neuropsychological battery that also included the "Behavioural Assessment of the Dysexecutive Syndrome" (BADS) (Wilson et al., 1996) to assess the skills involved in everyday life problems associated with the

dysexecutive syndrome (Eslinger and Damasio, 1985; Manes et al.,

2009).

4.2.2 Materials and methods

Participants

Forty-one patients affected by cerebellar pathology (CbT) were recruited from the IRCCS Santa Lucia Foundation rehabilitation hospital (Rome, Italy). Patients were affected by focal (FCb n.18) or degenerative (Ca n.23) cerebellar damage.

None of the patient had a history of neurological or mental illness. All patients underwent a comprehensive neurological examination by an expert neurologist. Motor impairment was quantified by using the International Cooperative Ataxia Rating Scale (ICARS: Trouillas et al., 1997) (Table 2 and 3). The score of ICARS ranges from 0 (the absence of any deficit) to 100 (the presence of all deficits to the highest degree) and evaluates 4 aspects of the symptomatology of ataxia (postural and gait disturbances, kinetic disturbances, speech disorders, and oculomotor disorders) (Trouillas et al., 1997).

According to the inclusion criteria, each patient underwent an MRI examination to exclude the presence of macroscopic extra-cerebellar abnormalities.

All patients did not present any clinical or radiological evidence of extra-cerebellar involvement or increased intracranial pressure at the time of testing.

General intellectual level was assessed by means of "Raven's coloured progressive matrices PM47" (Raven, 1947) and used as inclusion criterion.

An extensive neuropsychological battery was administered by a trained neuropsychologist.

The experimental procedures were approved by the ethical committee of IRCCS Santa Lucia Foundation and of Sapienza, University of Rome (Department of Psychology).

The work has been carried out in accordance with the Declaration of Helsinki. Written consent was obtained from each participant.

A group of 43 healthy subjects (CT) with no history of neurological or psychiatric illness was recruited as control subjects. As demonstrated by the One-way ANOVA, the CbT and the CT groups were well-matched for age ($F(1,82)=.003$; $p=.955$) and education level ($F(1,82)=1.583$; $p=0.211$).

Main demographic characteristics of each group are reported in Table 1.

Group	Patients	M/F	Age	Education	Total ICARS score
CbT	41	20/21	47.59 (11.32)	12.98 (3.30)	25.92 (17.76)
Ca	23	18/5	45.48 (11.68)	13.30 (2.34)	35.04 (17.38)
FCb	18	14/4	50.28 (10.54)	12.56 (4.26)	14.26 (9.75)
CT	43	15/28	47.44 (12.11)	13.91 (3.48)	-

Table 1 - Demographic characteristics of patients and control groups reported as mean and standard deviation (sd).

CbT= total cerebellar patients; Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

Fourteen out of the 18 patients with cerebellar atrophy had a genetic diagnosis (Friedreich ataxia= 1; SCA 1= 1; SCA 2= 6; SCA 8= 1; SCA 15= 2; SCA 28= 1; episodic ataxia= 4) and 5 presented idiopathic cerebellar ataxia (ICA).

The main characteristics of the patients with cerebellar atrophy are reported in Table 2.

Patients	Age	Education	Gender	Etiology	Total ICARS score
CB1	63	13	M	ICA	49
CB2	63	13	F	SCA2	24
CB3	50	13	M	ICA	30
CB4	46	13	F	Friedreich Ataxia	59
CB5	25	13	M	Friedreich Ataxia	78
CB6	41	18	F	SCA2	28
CB7	51	13	M	ICA	44
CB8	52	13	M	SCA8	42
CB9	50	8	F	ICA	68
CB10	38	12	F	SCA2	33
CB11	42	13	F	SCA2	47
CB12	53	11	F	ICA	21
CB13	46	13	F	Episodic Ataxia	9
CB14	58	13	F	Episodic Ataxia	16
CB15	29	11	M	Friedreich Ataxia	25
CB16	24	16	F	SCA1	33
CB17	36	13	F	SCA2	37
CB18	24	11	F	Episodic Ataxia	8
CB19	51	14	F	SCA15	44
CB20	54	18	F	SCA2	27
CB21	56	13	F	SCA15	35
CB22	42	18	F	SCA28	21
CB23	52	13	F	Episodic Ataxia	28

Table 2 - Clinical characteristics and total ICARS scores of the patients with cerebellar atrophy. ICARS= international cooperative ataxia rating scale. ICA= idiopathic cerebellar ataxia. SCA2= spinocerebellar atrophy type 2. SCA 8= spinocerebellar atrophy type 8. SCA 1= spinocerebellar atrophy type 1. SCA 15= spinocerebellar atrophy type 15. SCA 28= spinocerebellar atrophy type 28

The main characteristics of the patients with focal cerebellar damage are reported in Table 3.

The neuroradiological descriptions of the focal cerebellar lesions have been reported in detail in the third experimental study.

Patients	Age	Education	Gender	Diagnosis	Side	Total ICARS score
CB24	30	18	F	Ischemic	R	4.5
CB25	46	8	F	Ischemic	R	21
CB26	57	13	M	Ischemic	R	17.5
CB27	67	5	M	Ischemic	R	34.5
CB28	50	13	M	Ischemic	R	7
CB29	46	13	M	Ischemic	R	16.5
CB30	44	18	M	Ischemic	L	5
CB31	55	18	F	Ischemic	L	8.5
CB32	60	13	M	Ischemic	L	20
CB33	53	8	M	Surgical	L	28
CB34	59	18	M	Ischemic	L	9.5
CB35	38	16	F	Ischemic	L	31.5
CB36	52	13	F	Ischemic	L	3
CB37	36	13	M	Ischemic	L	2
CB38	45	8	M	Ischemic	Bil	9
CB39	72	5	M	Ischemic	Bil	14.26
CB40	49	13	M	Ischemic	Bil	16
CB41	46	13	M	Ischemic	Bil	9

Table 3 - Clinical characteristics and ICARS scores of the cerebellar patients affected by focal cerebellar lesion. ICARS= international cooperative ataxia rating scale. R= cerebellar lesion on the right side; L= cerebellar lesion on the left side; Bil= Bilateral cerebellar lesion.

General Neuropsychological Assessment

A neuropsychological battery was administered by a trained neuropsychologist in order to assess the patients' general cognitive profile.

The following cognitive domains were investigated: intelligence [Raven's coloured progressive matrices PM47 (Raven, 1947)]; verbal comprehension [Token Test (De Renzi & Vignolo, 1962)], verbal memory [forward and backward digit span, prose memory test (Spinnler & Tognoni, 1987)], visuo-spatial abilities and visuo-spatial memory [forward and backward Corsi Test (Corsi, 1972), delayed (DR) recall and copy of Rey-Osterrieth complex figure test (Caffarra et al., 2002)], and attention [Multiple Features Targets Cancellation Task (Marra et al., 2013)].

All tests were administered in the Italian version and the scores obtained were adjusted for age and level of education according to the Italian normative data, when available.

Executive Functions Assessment

Standardized Tests

The EFs have been extensively investigated by using the standardized tests described below.

- Tower of London Test (Krikorian et al., 1994) was used to identify impairments in planning processes involved in generating a plan to accommodate novel demands.

- The verbal fluency test was used to evaluate the ability to generate words fluently in a phonemic format (Phonemic Fluency Test) (Borkowsky et al., 1967; Caltagirone et al., 1995;) or from overlearned concepts (Semantic Fluency Test and Action Verbal fluency test) (Tombaugh et al., 1999; Woods et al., 2005).

- The Stroop Color-Word Test (Caffarra et al., 2002) was used to assess the selective attention and the sensitivity to interference.

- The Wisconsin Card Sorting Test (Heaton, 1993) was used to assess the cognitive flexibility and perseverations, abstract thinking and the ability to set shift.

The executive abilities measured by standardized tests are reported in Table 4.

Executive Functions	Test
Planning and problem solving	Tower of London Test
Generating of unusual strategies based on categorical representations	Phonemic Fluency Test
Spontaneous oral generation of words based on a specified semantic category	Semantic Fluency Test-Animal naming
Ability of verbs production in the absence of external stimuli	Action Verbal Fluency Test
Selective attention and response inhibithion	Stroop Color-Word Test
Cognitive flexibility and perseverations, abstract thinking and the ability to set shift	Wisconsin Card Sorting Test

Table 4 - Executive Functions abilities measured by each test.

Behavioural Assessment of the Dysexecutive Syndrome (BADS)

In addition to the standardized executive tests, the "Behavioural Assessment of the Dysexecutive Syndrome" (BADS) (Wilson et al., 1996) was administered in order to specifically assess the skills and demands involved in everyday life (Wilson et al., 1996). Indeed, recent criticisms on neuropsychological tests for the executive abilities have been focused on the difficulty of interpreting test scores in the light of their importance for patient outcomes (Wilson, 1993; Sbordone, 1996). These criticisms were based on two empirical observations: first, the results of tests which assess a single cognitive function are often unable to predict outcome with robust reliability or validity, while those tests that

assess a range of cognitive functions provide the best estimate of outcome (Tupper & Cicerone, 1990; Girard et al., 1996); second, patients may perform adequately on a battery of tests of cognitive functioning within a structured testing environment, yet exhibit significant impairment in less structured situations (Shallice & Burgess, 1991; Mountain & Snow, 1993; Wilson, 1993; Reitan & Wolfson, 1994). The BADS (Wilson et al., 1996, 1998), was developed in response to these limitations.

BADS consists of 6 subtests. The abilities measured by BADS subtest are reported in Table 5.

The Rule Shift Cards Test examines the subject's ability to correctly respond to a rule and to shift from one rule to another; investigates persevering tendencies, cognitive flexibility, and subject ability to properly respond to a rule by inhibiting a previously learned approach. This measure uses 21 nonpicture playing cards and it assesses the ability to change from one pattern of responding to another. In the first part of the test, subjects are instructed to answer "Yes" to a red card and "No" to a black card. In the second part, subjects are instructed to respond "Yes" if the card which has just been turned over is the same color as the previous turned card and "No" if the color was different. These rules, typed on a card, are left in full view throughout to reduce memory constraints. Time taken, and number of errors are recorded in both parts.

The Action Program Test was created to provide subjects with a novel, practical task that required the development of a plan of action to solve a problem. The task has five steps to its solution. The subject is presented with a rectangular stand into one end of which is set a large transparent beaker with a removable lid that has a small central hole in it. Into the other end of the stand is set a thin transparent tube at the bottom of which is a small piece of cork. The beaker is two thirds full of water. To the left of the stand is placed a metal rod (roughly L-shaped) which is not long enough to reach the cork, and a small screw top container on its side, with its top unscrewed and lying beside it. Subjects are asked to get the cork out of the tube using any of the objects in front of them but without lifting up the stand, the tube, or the beaker and without touching the lid with their fingers. There is no time limit for this task, but if a subject has not made any attempt at carrying out the next stage after 2 minutes, or is perseverating an inappropriate action, then a prompt is given.

The Key Search Test enables to examine the subject's ability to plan an effective and efficient plan of action and the subject's ability to monitor his/her own performance. In these task subjects are given an A4-sized piece of paper with a 100-mm square in the middle and a small black dot 50 mm below it. The subjects are told to imagine that the square is a large field in which they have lost

their keys. They are asked to draw a line, starting on the black dot, to show where they would walk to search in the field to be sure to find their keys.

Temporal Judgment Test assesses the cognitive estimation's ability. The test contains four short questions about time duration for common events that take from a few seconds (how long does it take to blow up a party balloon?) to several years (how long do most dogs live?). Subjects are asked to make their best guess, related to two things that are usually counted in minutes, one that is usually counted in years, and one in seconds.

In Zoo Map Test subjects are required to show how they would visit a series of designated locations on a map of a zoo. However, when planning the route certain rules must be obeyed. The map and rules have been constructed so that there are only four variations on a route that can be followed in order that none of the rules of the test are infringed. There are two trials: in the first trial, the subject must create a route following the specific rules (high demand), in the second, the subject is simply required to follow a set of written instructions to produce an error-free performance (low demand). Comparing performances between the two trials allows a quantitative evaluation of a subject's spontaneous planning ability when structure is minimal, versus their ability to follow a concrete externally imposed strategy when structure is high.

The Modified Six Elements Test assesses subject's ability to plan, organize, and monitor behaviour. The Modified Six Elements Test is a simplified version of the original Shallice and Burgess (1991) test where the subject is instructed to do three tasks (dictation, arithmetic, and picture naming) each of which is divided into two parts (A and B). The subject must attempt each of the six subtasks within a 10-minute test period, and organize the time (using a stopwatch). They are not allowed to do two parts of the same task consecutively. This test measures the ability to distribute the execution of several tasks in a limited period of time.

Executive Functions	Test
Cognitive flexibility, persevering tendencies, inhibition abilities, rule learning	Rule Shift Cards Test
Planning and problem solving	Action Program Test
Strategy formation and self-monitoring	Key Search Test
Cognitive estimation	Temporal Judgment Test
Spontaneous planning and ability to follow a concrete externally imposed strategy	Zoo Map Test
Planning, organizing, and behaviour monitoring	Modified Six Elements Test

Table 5 - Executive Functions abilities measured by BADS subtest.

Data analysis

In a first step a one-way analysis of variance (ANOVA) was used to compare each variable between total cerebellar patients group (CbT), regardless the etiology, and controls (CT).

In a second step, an analysis of variance (ANOVA) was used to compare each variable between each cerebellar group (Ca and FCb) and controls (CT) in order to better characterize the EFs profile considering the damage type (focal or degenerative). When significant differences were observed, post hoc comparisons were performed using Bonferroni post-hoc test, and P-values were reported.

All statistical analysis were performed using Statistical Package for the Social Sciences (SPSS version 23).

4.2.3 Results

General Neuropsychological assessment

Intellectual level of the cerebellar patients and control group was preserved (Raven'47-adjusted score) (Table 6).

Group	Raven '47
CbT	28,37 (3.85)
Ca	28,46 (3.47)
FCb	28,26 (4.39)
CT	30.41 (2.08)
Cut-off	**18.96**

Table 6 - Mean and standard deviation (sd) at Raven'47 of the cerebellar patients and control group. Cut-off is reported. CbT= total cerebellar patients; Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

The mean scores and standard deviations for each neuropsychological test and for each group (CbT, Ca and FCb) are reported in Table 7.

No of the values were inferior to the cut off levels in all neuropsychological tests.

Group	Verbal Comprehension	Verbal Memory			Visuo-spatial abilities and visuo-spatial memory				Attention
	Token Test-adjusted	Forward Digit Span	Backward Digit Span	Prose Memory Test - adjusted	Forward Corsi Test	Backward Corsi Test	DR Rey-Osterrieth figure - adjusted	Copy Rey-Osterrieth figure-adjusted	MFTC accuracy
CbT	32.50	6.10	4.56	10.34	5.34	4.58	13.86	31.17	0.94
	(2.30)	(1.26)	(1.43)	(3.25)	(1.21)	(1.26)	(6.16)	(3.36)	(0.06)
Ca	32.52	6.00	4.48	9.98	5.24	4.57	12.66	31.22	0.95
	(1.44)	(1.09)	(1.12)	(3.02)	(1.24)	(1.23)	(6.32)	(2.89)	(0.06)
FCb	32.47	6.22	4.67	10.79	5.47	4.59	15.41	31.12	0.94
	(3.13)	(1.48)	(1.78)	(3.40)	(1.19)	(1.33)	(5.76)	(3.97)	(0.06)
Cut-off	32	5	3	4.75	5	3	9.47	28.8	0.869

Table 7 - means and standard deviations (sd) of CbT, Ca and FCb at neuropsychological assessment.

DR Rey Osterrieth figure: delayed recall of Rey-Osterrieth complex figure test; MFTC= Multiple Features Targets Cancellation Test.

CbT = total cerebellar patients; Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion.

Executive Functions Assessment in total cerebellar patients

Standardized Tests

The results obtained from the total group of patients (CbT) and control group (CT) for the EFs standardized tests are summarized in Table 8.

	Tower of London Test	Phonemic Fluency Test	Semantic Fluency Test	Action Verbal Fluency Test
CbT	29.88	30.31*	26.81*	15.07*
	(3.44)	(11.07)	(7.01)	(5.57)
CT	31.02	37.22	30.95	18.09
	(2.50)	(10.34)	(9.24)	(5.13)

	Stroop Color -Word Test		WCST		
	Interference Time	Interference Errors	Total Errors	Perseverative Responses	Perseverative Errors
CbT	24.40	1.43	23.42	13.01*	11.74*
	(13.06)	(2.53)	(17.44)	(11.07)	(9.17)
CT	22.38	0.89	16.69	8.50	7.95
	(8.45)	(1.75)	(15.30)	(8.44)	(6.85)

Table 8 - Performances of CbT, and CT groups. The data are reported as means and standard deviation (sd). CbT= total cerebellar patients; CT= control group.

*p<0.05 significant difference between CbT and CT.

The ANOVA between CbT and CT showed a main group effect. Significant differences resulted in: Phonemic Fluency Test ($F_{(1,82)}$=8.764; p=.004) (Figure 5); Semantic Fluency Test ($F_{(1,82)}$=5.315; p=.024) (Figure 6); Action Verbal Fluency Test ($F_{(1,82)}$=6.689; p=.011) (Figure 7); and in the number of

Perseverative Responses ($F_{(1,82)}=4.441$; $p=.038$) and Perseverative Errors ($F_{(1,82)}=4.640$; $p=.034$) of the Wisconsin Card Sorting Test (Figure 8).
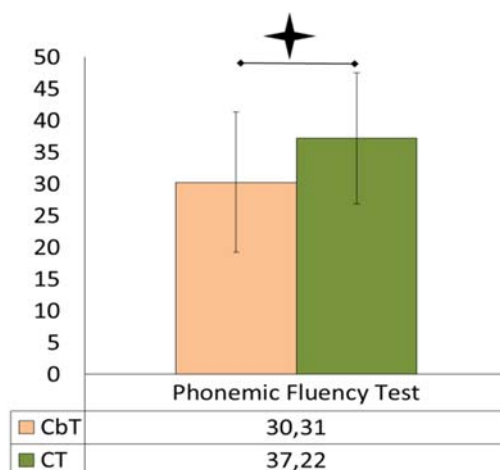

	Phonemic Fluency Test
☐ CbT	30,31
☐ CT	37,22

Figure 5: Phonemic Fluency Test - CbT= total cerebellar patients; CT= control group. *p<0.05 significant difference

	Semantic Fluency Test
☐ CbT	26,81
☐ CT	30,95
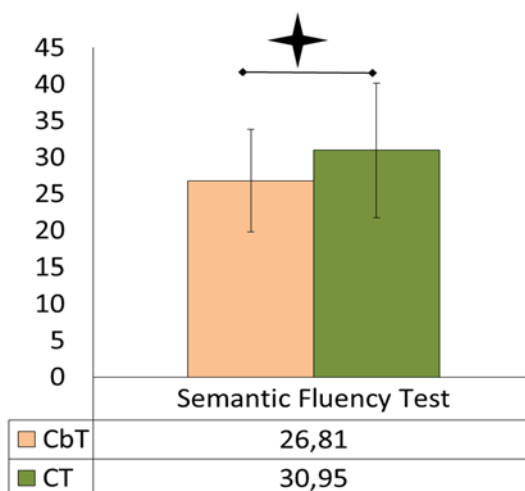
Figure 6: Semantic Fluency Test - CbT= total cerebellar patients; CT= control group. *p<0.05 significant difference
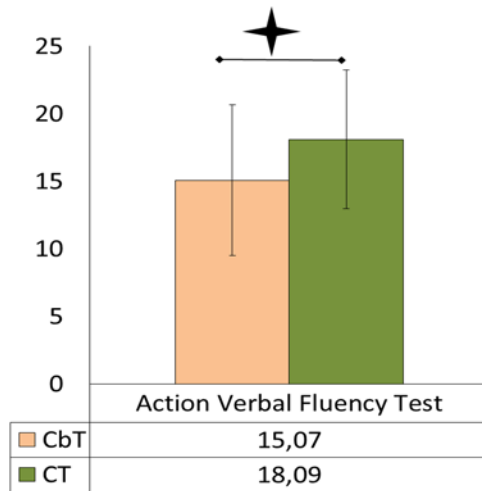
Figure 7: Action Verbal Fluency Test - CbT= total cerebellar patients; CT= control group.

*p<0.05 significant difference

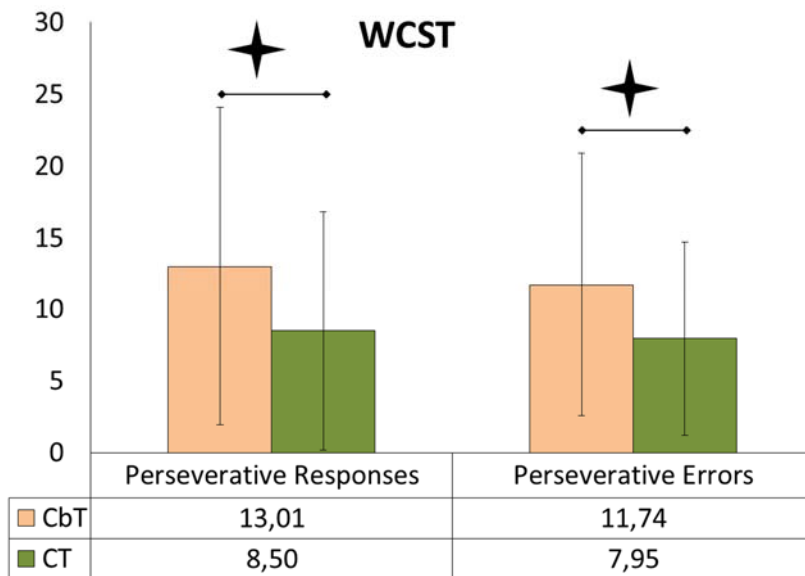**Figure 8: Wisconsin Card Sorting Test (Perseverative Responses; Perseverative Errors)**

- CbT= total cerebellar patients; CT= control group. *p<0.05 significant difference

Performances at "Behavioural Assessment of the Dysexecutive Syndrome" (BADS)

The ANOVA between CbT and CT showed a main group effect. The results obtained from patients (CbT and FCb) and control group for the "Behavioural Assessment of the Dysexecutive Syndrome" are summarized in Table 9.

	Behavioural Assessment of the Dysexecutive Syndrome					
	Rule Shift Cards Test	**Action Program Test**	**Key Search Test**	**Temporal Judgment Test**	**Zoo Map Test**	**Modified Six Elements Test**
CbT	22.85 (4.19)	6.07* (1.94)	8.68 (2.95)	2.59 (1.19)	9.41* (6.34)	4.54* (1.27)
CT	23.98 (3.58)	7.07 (2.20)	8.79 (3.22)	2.74 (0.98)	8.00 (0.00)	5.23 (0.97)

Table 9 - Performances of CbT and CT groups. The data are reported as means and standard deviation (sd). CbT= total cerebellar group; CT= control group.

*p<0.05 significant difference between CbT and CT.

Significant differences between CbT and CT resulted in: Action Program Test ($F_{(1,82)}$=4.780; p=.032) (Figure 9); Zoo Map Test ($F_{(1,82)}$=23.584; p=.000) (Figure 10) and in Modified Six Element Test ($F_{(1,82)}$=.7.874; p=.006) (Figure 11).

No significant differences were found in: Rule Shift Card Test ($F_{(1,82)}$=1.723; p=.193); Key Search Test ($F_{(1,82)}$=.025; p=.874); and in Temporal Judgment Test ($F_{(1,82)}$=.442; p=.508).
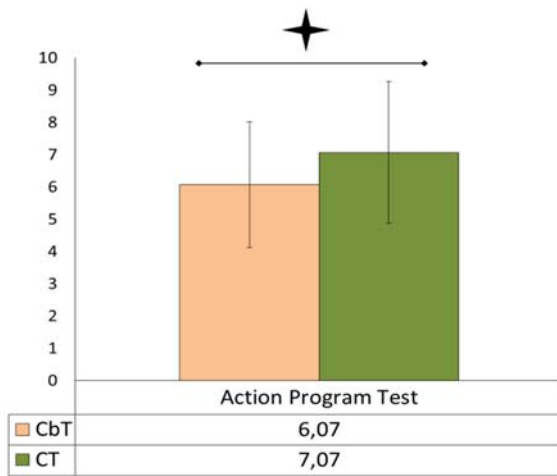
Figure 9: Action Program Test - CbT= total cerebellar group; CT= control group. *p<0.05 significant difference

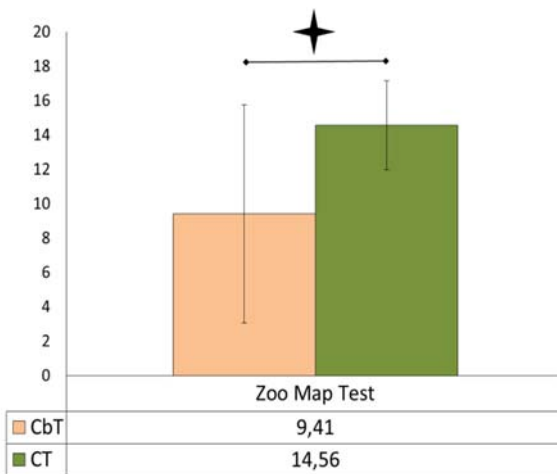
Figure 10: Zoo Map Test Test - CbT= total cerebellar group; CT= control group. *p<0.05 significant difference
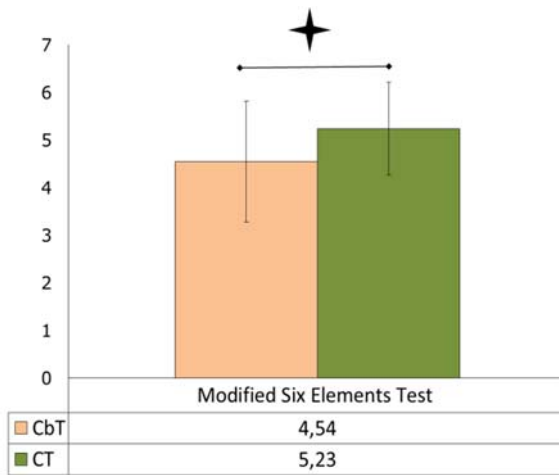
Figure 11: Modified Six Elements Test - CbT= total cerebellar group; CT= control group.

*p<0.05 significant difference

Executive Functions assessment in patients with focal and degenerative cerebellar damage

Standardized Tests

The results obtained from ANOVA between patients (Ca and FCb) and control group for the EFs standardized tests are summarized in Table 10.

The ANOVA between Ca, FCb and CT showed significant differences in: Phonemic Fluency Test ($F_{(2,81)}$=5.386; p=.006) Action Verbal Fluency Test ($F_{(2,81)}$=4.728; p=.011), in the number of Total Errors ($F_{(2,81)}$=3.342; p=.040), Perseverative Responses ($F_{(2,81)}$=4.454; p=.015) and Perseverative Errors ($F_{(2,81)}$=4.385; p=.016) of the Wisconsin Card Sorting Test.

No significant differences were found in Tower of London Test ($F_{(2,81)}$=1.520; p=.225), in the Semantic Fluency Test ($F_{(2,81)}$=2.729; p=.071), in "Stroop Color-Word Test" (Interference Time $F_{(2,81)}$=1.288; p=.282; Interference Errors $F_{(2,81)}$=1.852; p=.163).

A post hoc analysis by means of Bonferroni correction evidenced a different profile between Ca and FCb groups considered separately.

	Tower of London Test	Phonemic Fluency Test	Semantic Fluency Test	Action Verbal Fluency Test
Ca	29.87	28.28**	27.32	16.26
	(3.31)	(10.17)	(6.01)	(5.32)
FCb	29.88	32.91	26.17	13.56*
	(3.71)	(11.90)	(8.25)	(5.66)
CT	31.02	37.22	30.95	18.09
	(2.50)	(10.34)	(9.24)	(5.13)

	Stroop Color-Word Test		WCST		
	Interference Time	Interference Errors	Total Errors	Perseverative Responses	Perseverative Errors
Ca	22.36	0.98	19.52	10.26	9.57
	(7.84)	(1.34)	(14.61)	(8.71)	(7.70)
FCb	27.02	2.01	28.41*	16.53*	14.53*
	(17.57)	(3.48)	(19.82)	(12.90)	(10.32)
CT	22.38	0.89	16.69	8.50	7.95
	(8.45)	(1.75)	(15.30)	(8.44)	(6.85)

Table 10 - Performances of Ca, FCb and CT groups. The data are reported as means and standard deviation (sd). Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

**p<0.05 significant difference between CT and Ca.

*p<0.05 significant difference between CT and FCb.

Ca patients showed significantly lower scores than control subjects in the Phonemic Fluency Test (p=0.005) (Figure 12).

No significant differences between Ca and CT emerged in: Tower of London Test (p=.428); in Semantic Fluency Test (p=.278); in Action Verbal Fluency Test (p=.553); in Stroop Color-Word Test (time effect p=1.000; error effect p=1.000); in the number of Total

Errors (p=1.000), Perseverative Responses (p=1.000) and Perseverative Errors (p=1.000) of the Wisconsin Card Sorting Test.

Figure 12: **Phonemic Fluency Test** - Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

*p<0.05 significant difference

FCb patients showed significantly lower scores than control subjects in the Action Verbal Fluency Test (p=0.009) (Figure 13), in the number of Total Errors (p=0.035), Perseverative Responses (p=0.010) and Perseverative Errors (p=0.011) of the Wisconsin Card Sorting Test (Figure 14).
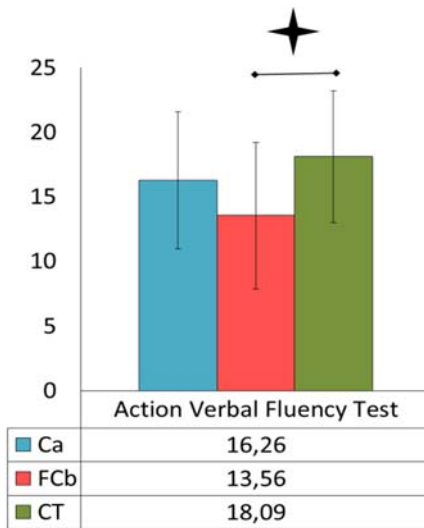
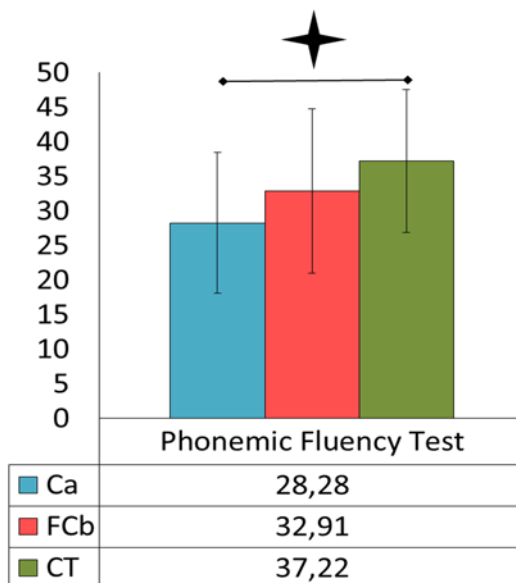**Figure 13**: **Action Verbal Fluency Test** - Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group. *p<0.05 significant difference
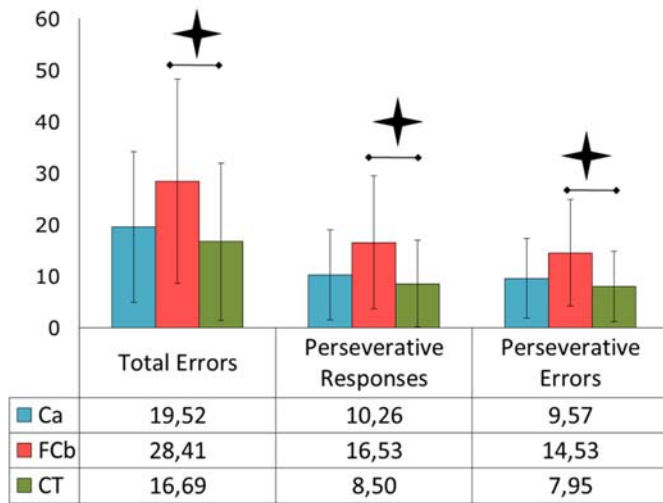
Figure 14: **Wisconsin Card Sorting Test (number of Total Errors**; **Perseverative Responses**; **Perseverative Errors)** - Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group. *p<0.05 significant difference

No significant differences between FCb and CT emerged in: Tower of London Test (p=.545); in Phonemic Fluency Test (p=.457); in Semantic Fluency Test (p=.127) and in Stroop Color-Word Test (Interference Time p=.400; Interference Errors p=.196).

Performances at "Behavioural Assessment of the Dysexecutive Syndrome" (BADS)

The results at the "Behavioural Assessment of the Dysexecutive Syndrome" obtained from patients (Ca, FCb) and control group are summarized in Table 11.

	Behavioural Assessment of the Dysexecutive Syndrome					
	Rule Shift Cards Test	Action Program Test	Key Search Test	Temporal Judgment Test	Zoo Map Test	Modified Six Elements Test
Ca	22.87 (4.40)	5.61** (1.90)	8.30 (3.18)	2.74 (1.39)	10.09** (5.31)	4.61 (1.31)
FCb	22.83 (4.16)	6.67 (1.94)	9.17 (2.73)	2.39 (0.92)	8.56* (7.69)	4.44* (1.29)
CT	23.98 (3.58)	7.07 (2.20)	8.79 (3.22)	2.74 (0.98)	14.56 (2.58)	5.23 (0.97)

**Table 11** - Performances of Ca, FCb and CT groups. The data are reported as means and standard deviation (sd). Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

**p<0.05 significant difference between CT and Ca.

*p<0.05 significant difference between CT and FCb.

The ANOVA between Ca, FCb and CT showed significant differences in: Action Program test ($F_{(2,81)}=3.760$; p=.027), Zoo Map Test ($F_{(2,81)}=12.296$; p=.000); and Modified Six Element Test ($F_{(2,81)}=4.004$; p=.022).

No significant differences were found in Rule Shift Card Test ($F_{(2,81)}=.851$; p=.431), in Key Search Test ($F_{(2,81)}=.400$; p=.671) and in Temporal Judgement Test ($F_{(2,81)}=.739$; p=.481).

A post hoc analysis by means of Bonferroni's correction evidenced a different profile between Ca and FCb groups considered separately.

Ca patients showed significantly lower scores than control subjects in the Action Program Test (p=.023) (Figure 15).

	Action Program Test
Ca	5,61
FCb	6,67
CT	7,07

Figure 15: **Action Program Test**- Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

*p<0.05 significant difference

No significant differences between Ca and CT emerged in: Rule Shift Card Test (p=.841); Key Search Test (p=1.000); Temporal Judgment Test (p=1.000) and in the Modified Six Elements Test (p=.112).

FCb patients showed significantly lower scores than control subjects in the Modified Six Elements Test (p=.048) (Figure 16).
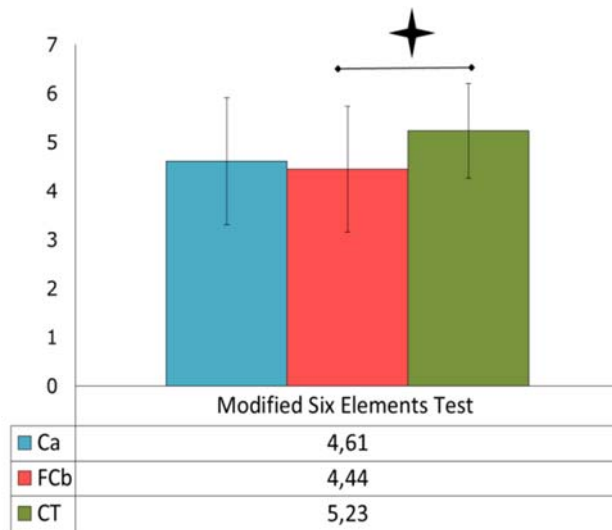
Figure 16: **Modified Sex Elements Test**- Ca=group of patients affected by cerebellar atrophy;

FCb= group of patients affected by focal cerebellar lesion; CT= control group.

*p<0.05 significant difference

No significant differences between FCb and CT emerged in: Rule Shift Card Test (p=.915); Action Program Test (p=1.000); Key Search Test (p=1.000) and in Temporal Judgment Test (p=.752).

The Zoo Map Test is the only test in which both Ca groups and FCb performed significantly worse than control group (p=.002; p=.000) (Figure 17).
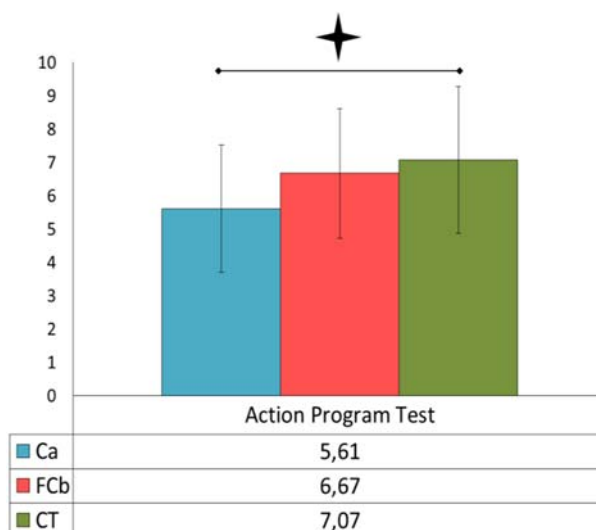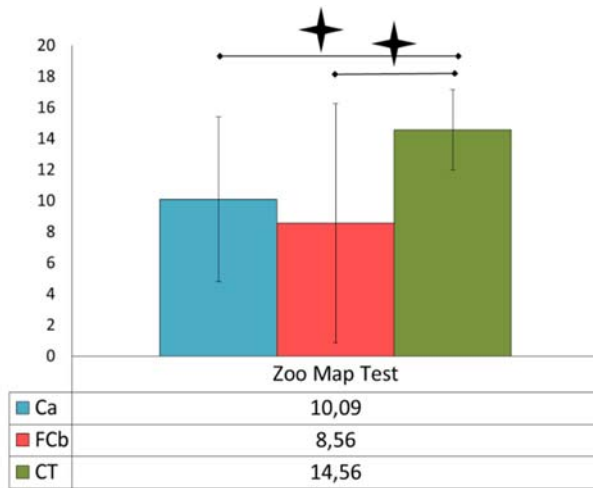
Figure 17: **Zoo Map Test** -Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; CT= control group.

*p<0.05 significant difference

In conclusion, the cerebellar damage in our patient cohort affects only specific tasks and differences in the executive impairments between Ca and FCb have been evidenced.

4.2.4 Conclusion – Study 1

In this first study, we investigated the role of the cerebellum in the EFs, studying different executive aspects in patients with atrophic or focal cerebellar lesions.

For the first time, it has been used an extensive executive battery for the detection of impairments caused by damage of the prefrontal cortex, including "real life" difficulties.

Our results showed that the CbT group was impaired only in specific abilities assessed by executive function tests and not in all tests (Table 12) and that Ca and FCb were significantly impaired in different executive tasks when their performances were analyzed separately (Table 13).

	Executive Functions	Test	
Standardized Tests	Planning and problem solving	Tower of London Test	
	Generating of unusual strategies based on categorical representations	Phonemic Fluency Test	
	Spontaneous oral generation of words based on a specified semantic category	Semantic Fluency Test-Animal naming	
	Ability of verbs production in the absence of external stimuli	Action Verbal Fluency Test	
	Selective attention and response inhibithion	Stroop Color Word Test	Interference Time
			Interference Errors
	Cognitive flexibility and perseverations, abstract thinking and the ability to set shift	Wisconsin Card Sorting Test	Total Errors
			Perseverative Responses
			Perseverative Errors
BADS	Cognitive flexibility, persevering tendencies, inhibition abilities, rule learning.	Rule Shift Cards Test	
	Planning and problem solving	Action Program Test	
	Strategy formation and self-monitoring	Key Search Test	
	Cognitive estimation	Temporal Judgment Test	
	Spontaneous planning and ability to follow a concrete externally imposed strategy.	Zoo Map Test	
	Planning, organizing, and behavior monitoring	Modified Six Elements Test	

Table 12 - The orange rectangles indicate tests in which cerebellar total group perform significantly worse than CT.

Executive Functions	Test	
Standardized Tests		
Planning and problem solving	Tower of London Test	
Generating of unusual strategies based on categorical representations	Phonemic Fluency Task	
Spontaneous oral generation of words based on a specified semantic category	Semantic Fluency Task-Animal naming	
Ability of verbs production in the absence of external stimuli	Action Verbal Fluency Task	
Selective attention and response inhibithion	Stroop Color Word Test	Interference Time
		Interference Errors
Cognitive flexibility and perseverations, abstract thinking and the ability to set shift	Wisconsin Card Sorting Test	Total Errors
		Perseverative Responses
		Perseverative Errors
BADS		
Cognitive flexibility, persevering tendencies, inhibition abilities, rule learning	Rule Shift Cards Test	
Planning and problem solving	Action Program Test	
Strategy formation and self-monitoring	Key Search Task	
Cognitive estimation	Temporal Judgment Test	
Spontaneous planning and ability to follow a concrete externally imposed strategy	Zoo Map Test	
Planning, organizing, and behavior monitoring	Modified Six Elements Test	

Table 13 - The blue rectangles indicate tests in which the group of patients affected by cerebellar atrophy perform significantly worse than CT.

The red rectangles indicated tests in which the group of patients affected by focal cerebellar lesion perform significantly worse than CT.

In particular, Ca patients showed significantly lower scores than control subjects in the Phonemic Fluency Test and in Action Program Test.

To perform a fluency task, the individual, typically will generate words within a subcategory and, when this subcategory is exhausted, he or she will switch to a new one. Switching, involves frontal-lobe processes such as strategic search processes and cognitive flexibility in shifting from one subcategory to another.

Therefore, Phonemic Fluency Test, requires the implementation of unusual strategies to search the words and complete the task. Indeed, it is worth noting that in the Phonemic Fluency Test the words must be retrieved from a phonemic category, which is rarely done in everyday speech production, so that participants must suppress the activation of semantically or associatively related words and must resort to novel retrieval strategies (Luo et al., 2010; Katzev et al., 2013).

Also, the Action Program Test, that assesses the ability to develop a plan of action to solve a novel problem, requires to generate an unusual and new strategy.

FCb patients showed significantly lower scores than control subjects in the Action Verbal Fluency Test, Wisconsin Card Sorting Test and in the Modified Six Elements Test. In these tasks the subject has to mentally coordinate and manipulate the information that may be associated with a verb (Piatt et al., 1999), and to make abstraction and organize the behaviour on the basis of external feedback as the context requires.

Both groups of patients had difficulties in planning a route to solve a problem as showed by the performance obtained in the Zoo Map Test.

In conclusion, considered the different profiles of the cerebellar patients according to the focal or degenerative nature of their cerebellar damage and taking into account the multifactorial models about the EFs (Stuss et al., 1995; Miyake et al., 2000; Fisk & Sharp, 2004), we may hypothesize that a cerebellar damage may affect specific EFs subcomponents.

In the next section we examined the underlying factor structures of previous EFs tests using principal components analysis in order to better characterize the EFs profile in presence of a cerebellar pathology.

4.3 Study 2: An exploratory factor analysis of the executive functioning

4.3.1 Rationale

As reported in the chapter 3, the EFs require the involvement of complex neuronal circuits that include not only the frontal lobe but also other cortical, subcortical and cerebellar regions (Dirnberger et al., 2005; Zgaljardic et al., 2006; Leh et al., 2010).

In the first study we used an extensive neuropsychological battery to assess specific aspects of EFs in patients with focal or degenerative cerebellar damage. Our results demonstrated that the executive profile is different depending on the etiology of the cerebellar damage.

The multifactorial model (Mirsky et al., 1991; Robertson et al., 1996; Miyake et al., 2000; Bondi et al., 2002; Pineda et al., 2003; Vaughan & Giovanello et al., 2010; Rose et al., 2011; Schmidt et al., 2015) assumes that EFs are not a single activity, but a complex system formed by different cognitive operations such as anticipation, goal selection, organization, planning, monitoring, shifting and time control (Lezak, 1995; Della Sala et al., 1998).

Several authors used factor analysis to investigate the structure of EFs and identify the factors underlying EFs (Mirsky et al., 1991; Miyake et al., 2000; Bondi et al., 2002; Pineda et al.,

2003; Vaughan & Giovannello et al., 2010; Rose et al., 2011; Schmidt et al., 2015).

By using the factor analysis in a healthy population Miyake and colleagues (2000) highlighted three executive processes that moderately correlate each another, but that are clearly separable: the mental set shifting ("Shifting"), the information updating and monitoring ("Updating"), and the inhibition of reflexive responses ("Inhibition").

Testa and collaborators (2012) examined the underlying factorial structure of 19 EFs tests in a non-clinical sample. Exploratory factor analysis revealed a model comprising six independent factors: Prospective Working Memory, Set-Shifting and Interference Management, Task Analysis, Response Inhibition, Strategy Generation and Regulation, and Self-Monitoring and Set-Maintenance.

Neuropsychological investigations in populations with frontal lobe damages have significantly contributed to demonstrate the multidimensional and dissociable nature of EFs (Duncan et al, 1997; Burgess et al., 1998; Robbins et al., 1998).

Focusing on the cerebellum, although clinical and neuro-radiological studies have proved its direct involvement in EFs, there are no studies that provide information about its role in specific subcomponent of EFs.

The issue of the present study was to clarify whether the EFs alterations evidenced in the two groups of cerebellar patients (see study 1) were due to a global alteration of the EFs or to latent specific components common to the tests we used in precedent section. To this aim we investigated whether the different tests were grouped according to common executive processes that could explain the different executive profiles detected in the patients affected by focal or degenerative cerebellar damage.

To this purpose a factor analysis was applied on the EFs tests scores obtained by a large heterogeneous population of patients and healthy subjects.

4.3.2 Materials and methods

Participants

Forty-one patients affected by degenerative or focal cerebellar damage (CbT) and 43 healthy subjects (HS) were included in this study and considered as a single group. The subjects are the same enrolled in the study 1. The demographic characteristics of each group have been already reported in Table 1.

Executive tasks

All the tests administered in the first study were included in the factor analysis.

The measures used as dependent variables for each test and the respective mean scores and standard deviations are reported in Table 14.

Instrument	Measure used	Mean	Sd
Standardized Tests			
Tower of London Test	Total correct trials	30,46	3,04
Phonemic Fluency Test	Total number of words	33,85	11,19
Semantic Fluency Test- Animal naming	Total number of words	28,93	8,44
Action Verbal Fluency Test	Total number of words	16,62	5,53
Stroop Color-Word Test	Interference Time	23,37	10,92
	Interference Errors	1,15	2,17
Wisconsin Card Sorting Test (W.C.S.T.)	Total Number of Errors	19,98	16,63
	Perseverative Responses	10,70	10,01
	Perseverative errors	9,80	8,24
BADS			
Rule Shift Cards Test	Total score	23,43	3,94
Action Program Test	Total score	6,58	2,14
Key Search Test	Total raw score	8,74	3,09
Temporal Judgment Test	Total raw score	2,67	1,09
Zoo Map Test	Sum of raw scores in the Zoo Map One and Zoo Map Two	12,05	5,47
Modified Six Elements Test	Total number of subtasks were rules were complied	4,89	1,18

Table 14 - Variable label for each EFs measure selected for the statistical analyses.

Data analysis

In order to examine the cognitive components underlying the performances on the selected executive measures, a principal component analysis (PCA) with Oblimin with Kaiser Normalization (10 iteractions) was used (Floyd & Widaman, 1995).

2-way analysis of variance (ANOVA) was used to compare factorial values between cerebellar patients groups (Ca and FCb) and healthy subjects (HS). Tukey HSD post-hoc test was performed when appropriated (for p<.05).

Data analyses was performed by Statistical Package for Social Sciences (SPSS 23).

4.3.3 Results

Factor analysis of Executive Functions Tests in cerebellar patients and healthy controls

The EFs tasks loaded onto three factors that explained 54.237% of the variance (Table 15). The scree plot indicated a multi-dimensional factor structure (Figure 18).

Total Variance Explained

		Initial Eigenvalues		Rotation Sums of Squared Loadings
Component	Total	% of Variance	Cumulative %	Total
1	4.881	32.543	32.543	3.579
2	1.696	11.307	43.850	3.956
3	1.558	10.387	54.237	1.703
4	1.214	8.091	62.329	
5	1.031	6.876	69.204	
6	.929	6.193	75.397	
7	.804	5.361	80.758	
8	.678	4.520	85.278	
9	.664	4.425	89.703	
10	.534	3.559	93.262	
11	.386	2.574	95.836	
12	.299	1.992	97.828	
13	.256	1.708	99.536	
14	.065	.430	99.966	
15	.005	.034	100.000	

Table 15 - Extraction Method: Principal Component Analysis
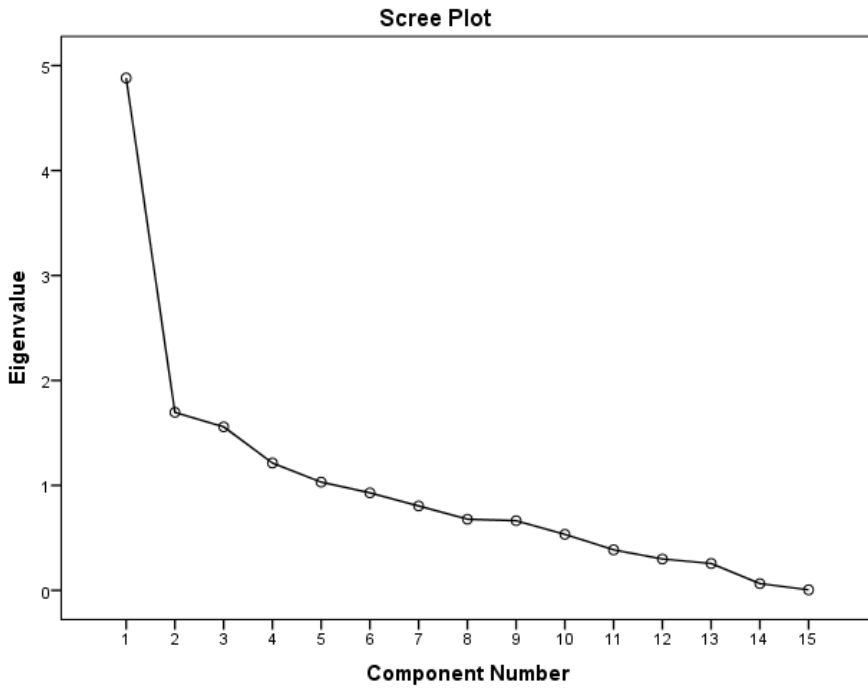
Figure 18: Scree plot — Scree Plot of multidimensional factor structure

In Table 15 the goodness of fit indexes of three factors model has been shown.

Neuropsychological measures	Factor loading		
	Factor 1	Factor 2	Factor 3
Tower of London Test (total trials)	**.342**	-.194	-.183
Phonemic Fluency Test (number of words)	**.718**	.043	-.053
Semantic Fluency Test (number of words)	**.748**	-.010	-.137
Action Verbal Fluency Test (number of words)	**.776**	-.137	.003
Stroop Color-Word Test (Interference Time)	-.207	-.063	**.877**
Stroop Color-Word Test (Interference Errors)	.005	-.069	**.874**
W.C.S.T. (Total Number of Errors)	-.091	**.932**	-.082
W.C.S.T. (Perseverative Responses)	-.079	**.929**	-.047
W.C.S.T. (Perseverative Errors)	-.086	**.948**	-.061
Rule Shift Cards Test	**.451**	-.382	-.042
Action Program Test	**.587**	.077	-.087
Key Search Test	**.359**	-.099	.120
Temporal Judgment Test	-.234	-.25	-.195
Zoo Map Test	**.525**	-.118	.079
Modified Six Elements Test	.058	**-.587**	.008

Table 15 - Rotated component matrix loadings of orthogonally rotated factors extracted by principal factor analysis.

Factor one comprised eight measures: the Tower of London Test, the Phonemic Fluency Test, the Semantic Fluency Test, the Action Verbal Fluency Test, the Rule Shift Cards Test, the Action Program Test, the Key Search Test and the Zoo Map Test. It explained 32.543% of variance in the battery. This factor was thought to reflect "Planning". Indeed, although various cognitive abilities, such as judgment and reasoning, are required to solve the tests belonging to the factor one, this factor can be considered

representative of "Planning" because all the tests require the ability to solve a new problem evaluating different steps before acting, to evaluate information or situations, to break down the problem into key components, to consider various ways of approaching, and to choose the most appropriate way of solving it. All these tasks also include specific rules that must be adhered to.

Factor two comprised four measures: three of them were from the WCST (Total number of errors, Perseverative responses, Perseverative errors) and the other one is the Modified Six Elements Test. It explained 11.307% of the total variance. This factor was thought to reflect "Set Shifting". The tests belonging to the factor two require a good capacity to process, manage and shift between more concurrent stimuli. This factor also needs the ability to modify the behaviour in response to external feedback.

Factor three comprised two measures deriving from the Stroop Color Word Test (Interference Time and Interference Errors). It explained 10.387 % of the total variance. This factor was thought to reflect "Response Inhibition", that is a measure of inhibiting inappropriate responses. The Stroop Color Word Test concerns one's ability to deliberately inhibit dominant or automatic responses when necessary and the ability to deliberately suppress a dominant response in the presence of a nonessential stimuli (Logan et al., 1997).

In conclusion, in the present study the factor analysis of the executive measures revealed a model that comprises three factors. This model is consistent with previous reports on multifactorial models (Mirsky et al., 1991; Pineda et al., 2000; Miyake et al., 2000; Fisk & Sharp, 2004; Vaughan & Giovanello, 2010; Lerner & Lonigan, 2014).

Profile of the cerebellar groups in factors

A 2-way ANOVA was performed to analyze the mean differences between groups of subjects and the dependent variables to understand whether there is was an interaction between groups (groups: subjects with degenerative cerebellar damage (Ca), subjects with focal cerebellar lesion (FCb), and healthy subjects (HS)) and factors (factors: Planning, Set Shifting, and Inhibition) on the executive tests.

There was a main effect of groups x factors interaction ($F_{(4,160)}$=3.753; p=.006).

The post-hoc test (Tukey HSD) showed that in Planning both Ca and FCb groups performed significantly worse than HS (p=.005; p=.049).

In Set Shifting FCb performed significantly worse than HS (p=.009).

In Inhibition no differences between Ca, FCb and HS (p=1.000; p=.208) were reported.

The plot of the mean of "executive factors" values for each combination of groups and factors are reported in Figure 19.
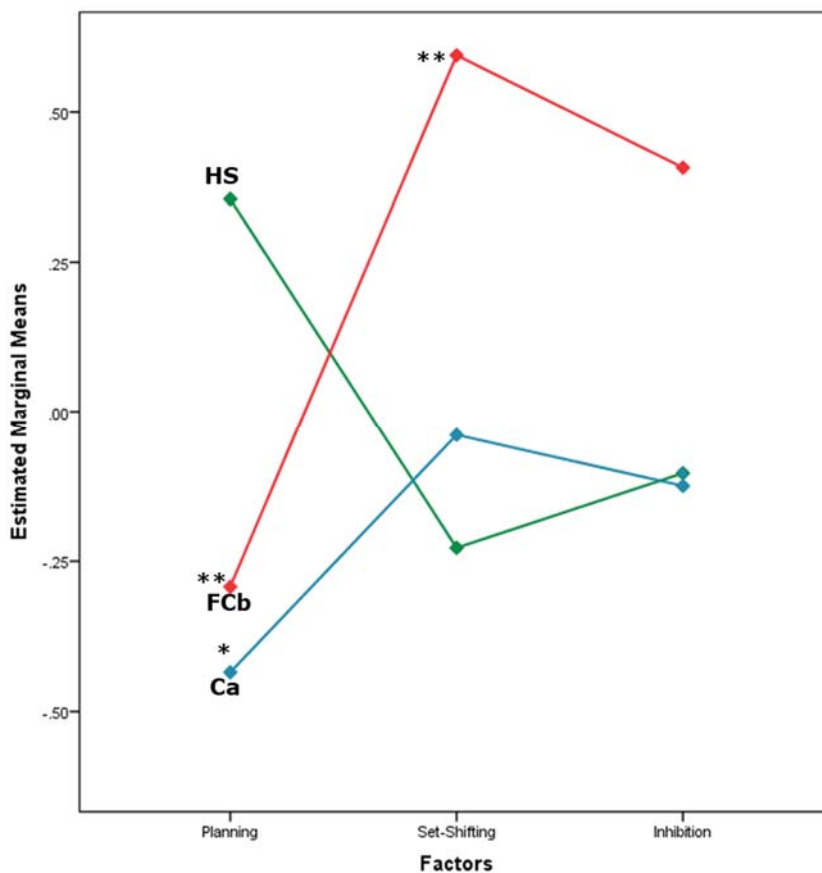

Figure 19: Plot of "executive factors" mean values for each combination of groups and factors. Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; HS= Healthy subjects.

*significant difference between HS and Ca.

**significant difference between HS and FCb.

4.3.4 Conclusion – Study 2

The goal of the second study was to better understand the structure of executive tasks administered in the study 1, analyzing whether they were grouped according to a common executive process. We used a factor analysis to identify the latent structure underlying the performances observed in the cerebellar patients.

The factor analysis confirmed the existence of different subcomponent of EFs that account for the performances resulted impaired in our population samples.

In particular, three dissociable components were found: - Planning, - Set Shifting, and - Inhibition.

The factors we found in our population samples are similar to the factors reported by several authors in literature (Pineda et al., 2000; Miyake et al., 2000; Fisk & Sharp, 2004; Weintraub et al., 2005; Brandt et al., 2009; Vaughan & Giovanello, 2010; Rose et al., 2011).

The factor "Planning" was proposed by Weintraub (2005) and Brandt and colleagues (2009). The authors advanced that this factor comprised tests requiring strategy formation and application as well as tests requiring creativity and novelty.

The factor Set Shifting, and the factor Inhibition can be considered comparable to those proposed by several authors (Pineda

et al., 2000; Miyake et al., 2000; Fisk & Sharp, 2004; Vaughan & Giovanello, 2010; Rose et al., 2011).

Our results demonstrated that the patients affected by cerebellar degenerative disorders and the patients affected by cerebellar focal lesions are impaired in tasks belonging to factor one and two. However, they differ from each other regarding the executive subcomponents that result affect.

Indeed, the patients with cerebellar degenerative disorders are impaired only in Planning, while the patients with focal cerebellar lesions are impaired both in Planning and Set Shifting.

Taking into account these findings we thus examined in detail the relationship between the EFs subcomponents and their relationship with the brain structural alterations.

It could be hypothesized that on one hand the two groups of patients affected by a different cerebellar damage have an involvement of the same lobules that explain the common impairment in "Planning"; on the other hand, they selectively and differ so that only the patients with cerebellar focal lesions are also impaired in Set Shifting.

In the next section we used Voxel-Based morphometry (VBM) to determine the degree and the pattern of pathological microstructural changes of the cerebellar gray matter in patients with degenerative or focal cerebellar damage.

4.4 Study 3 - Gray matter reduction and lobule alterations associated with executive dysfunction: an MRI study

4.4.1 Rationale

In the precedent section the executive data have been analyzed using the Factor Analysis that identified three distinct executive factors namely "Planning", "Set-shifting" and "Inhibition", thus confirming the existence of multifactorial model of EFs (Mirsky et al.,1991; Robertson et al.,1996; Boone et al., 1998; Miyake et al., 2000; Bondi et al., 2002; Pineda et al., 2003; Giovanello et al., 2010; Rose et al., 2011; Schmidt et al.,2016).

The results also showed that patients with degenerative disorders and patients affected by focal lesion of the cerebellum differ from each other regarding the executive subcomponents involved.

Indeed, the patients with degenerative disorders of the cerebellum were uniquely impaired in "Planning" factor while the patients with cerebellar focal lesion were impaired in "Planning" and "Set Shifting". Overall, these findings suggest that the cerebellum plays a role in executive processes and that different patterns of cerebellar structural alteration may lead to impairment in selective executive subcomponents.

However, the mechanisms through which the cerebellum subserve higher order functions, still remain largely debated and to

be clarified. Consistent with the discovery of distinct cerebellar functional modules segregated in parallel cerebello-cortical loops (Strick et al., 1993; Middleton & Strick, 1994, 1996; Schmahmann & Pandya, 1997), several studies addressed the importance of the topography of cerebellar damage in cognition (Tavano et al., 2007; Stoodley & Schmahmann, 2010).

More recently, the introduction of advanced neuroimaging techniques, have provided a great insight into understanding the relation between structure and function in the brain in vivo, thus proving particularly useful in the case of cerebellum. Among these techniques, Voxel Based Morphometry (VBM) is a method of brain image analysis that essentially allows the detection of local changes in the composition of brain tissues (grey or white matter) which may be correlated with behavioural performance (Ashburner & Friston, 2000).

Aim of the third study was to investigate the neuroanatomical correlates of the patients' executive impairment by using advanced neuroimaging techniques.

In order to assess the relationship between cerebellar damage and executive deficits, in the next section it has been characterized, in vivo, the extent of cerebellar damage and the pattern of cerebellar alterations has been to correlate with the patients' executive performances. VBM has been used to localize and

quantify the cerebellar GM loss in patients with neurodegenerative disorders, while a detailed assessment of the macroscopic cerebellar lesions, in terms of extension and location, has been performed in patients with focal lesions

This allowed to map the topographic organization of EFs within distinct cerebellar subregions and better clarify the cerebellar role in executive processing. We hypothesized that, in presence of a cerebellar pathology, different profiles of EFs alterations are related to the extension and specific site of the cerebellar damage.

4.4.2 Materials and methods

Participants

Twenty-seven patients with cerebellar pathology (CbT) were recruited from the IRCCS Santa Lucia Foundation rehabilitation hospital (Rome, Italy). Patients were affected by cerebellar neurodegenerative disease of different etiology (Ca n.16) or unilateral focal (FCb n.11) damage of the left (n=6) or right (n=5) side (Table 16).

Group	Patient	Gender (M/F)	Age	Education
CbT	27	10/17	44.82 (9.90)	13.59 (3.08)
Ca	16	2/14	43.69 (10.61)	13.50 (2.80)
FCb	11	8/3	46.45 (9.02)	13.73 (3.58)
HS	25	6/19	53.88 (5.99)	

Table 16-Demographic characteristics of patients reported as mean and standard deviation (sd). CbT= total cerebellar patients; Ca=group of patients affected by cerebellar atrophy; FCb= group of patients affected by focal cerebellar lesion; HS= Healthy Subjects.

According to the inclusion criteria, the absence of any additional brain abnormality was further investigated by an expert neuro-radiologist and performed by visual inspection of conventional MRI scans acquired as part of this research study.

Main clinical and demographic characteristics of Ca and FCb are reported in Table 17 and 18, respectively.

All patients underwent a comprehensive neurological examination and motor deficit was assessed using a quantitative ataxia scaling method (International Cooperative Ataxia Rating Scale, ICARS, Trouillas et al., 1997), whose global score ranges from 0 (absence of any motor deficit) to 100 (presence of motor deficits at the highest degree).

A group of 25 healthy subjects (HS) with no history of neurological or psychiatric illness was also recruited as control group.

This research study was approved by the Ethics Committee of Santa Lucia Foundation, according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from each subject.

Patients	Age	Education	Gender	Etiology
CB1	46	13	F	Friedreich Ataxia
CB2	41	18	F	SCA2
CB3	51	13	M	ICA
CB4	50	8	F	ICA
CB5	42	13	F	SCA2
CB6	53	11	F	ICA
CB7	46	13	F	Episodic Ataxia
CB8	58	13	F	Episodic Ataxia
CB9	29	11	M	Friedreich Ataxia
CB10	24	16	F	SCA1
CB11	36	13	F	SCA2
CB12	24	11	F	Episodic Ataxia
CB13	51	14	F	SCA15
CB14	54	18	F	SCA2
CB15	42	18	F	SCA28
CB16	52	13	F	Episodic Ataxia

Table 17 - Clinical characteristics of the patients with cerebellar atrophy. ICA= idiopathic cerebellar ataxia. SCA2= spinocerebellar atrophy type 2. SCA 8= spinocerebellar atrophy type 8. SCA 1= spinocerebellar atrophy type 1. SCA 15= spinocerebellar atrophy type 15. SCA 28= spinocerebellar atrophy type 28

Patients	Age	Education	Gender	Diagnosis	Side
CB24	30	18	M	Ischemic	R
CB25	46	8	F	Ischemic	R
CB26	57	13	M	Ischemic	R
CB27	50	13	M	Ischemic	R
CB28	46	13	M	Ischemic	R
CB29	44	18	M	Ischemic	L
CB30	53	8	M	Surgical	L
CB31	59	18	M	Ischemic	L
CB32	38	16	F	Ischemic	L
CB33	52	13	F	Ischemic	L
CB34	36	13	M	Ischemic	L

Table 18- Clinical characteristics of the cerebellar patients affected by focal cerebellar lesion. R= cerebellar lesion on the right side; L= cerebellar lesion on the left side.

MRI acquisition protocol

All subjects underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany) that included the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); 2) fast-FLAIR (TR = 8170 ms, 204TE =96 ms, TI=2100 ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256 × 224 × 176, in-plane FOV = 250 × 250 mm2, slice thickness=1 mm). TSE and fast-FLAIR scans of patients were reviewed by an expert neuro-radiologist in order to characterize the brain anatomy and exclude the presence of macroscopic abnormalities in extracerebellar structures. For the HS, the same scans were also inspected in order

to exclude any pathological conditions and ensure that they met the inclusion criteria.

Image processing

The cerebellum was pre-processed individually using the Spatially Unbiased Infratentorial Template (SUIT) toolbox (Driedrichsen et al., 2009) implemented in Statistical Parametric Mapping [Wellcome Department of Imaging Neuroscience; SPM-8 (http://www.fil.ion.ucl.ac.uk/spm/). The procedure involved: cropping and isolating the cerebellum from the T1 anatomical images; normalizing each cropped image into SUIT space; reslicing the probabilistic cerebellar atlas into individual subject space using the deformation parameters from normalization. Finally, the images were smoothed using a 8-mm FWHM Gaussian kernel.

Quantification of cerebellar gray matter changes in patients with neurodegenerative disorders

Voxel based morphometry (VBM) was used to identify differences between Ca patients and HS in regional cerebellar volume and statistical analyses were performed on grey matter (GM) maps entered into a voxel-wise two-sample t-test analysis for assessing between group differences in regional GM cerebellar volumes. Age and sex were set as variables of no interest. Results were considered

significant at p values <0.05 after FWE cluster-level correction (clusters formed with p<0.001 at uncorrected level).

Lesions characterization in focal cerebellar patients

For each FCb patient, a detailed assessment of the macroscopic cerebellar damage, including lesion volume and localization, was performed.

Each lesion was manually outlined on normalized T1 anatomical images using the FSL view image viewer from the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl/) and anatomically localized with reference to the SUIT atlas (Diedrichsen et al., 2009).

The involvement of specific cerebellar structures (lobules, vermis, nuclei) was then evaluated.

4.4.3 Results

Results of the VBM in patients with degenerative cerebellar damage.

The VBM analysis demonstrated a cluster of significantly lower GM volume (cluster size:43754 voxels) in the Ca patients compared to HS. In addition to the general atrophy as detected by conventional MRI visual inspection, the following cerebellar regions demonstrated a significantly smaller local volume: the lobules I-IV and V-VI in the anterior lobe and the lobule VIIIa, posterior vermis (lobule IX), lobule IX and X (Figure 20).

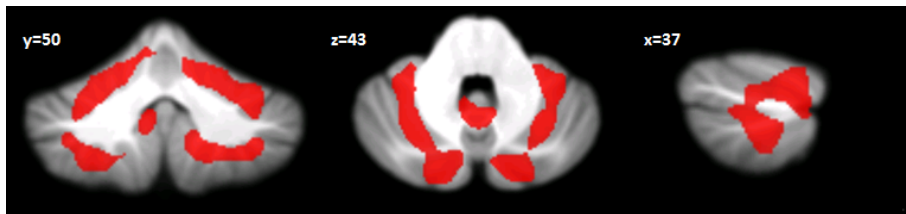All these regions were symmetrically distributed within the cerebellum.

Figure 20: significant pattern of cerebellar atrophy (in red).

Results of lesions characterization in focal cerebellar patients

The anatomical distribution of tissue damage in terms of cerebellar structures involved by each lesion is reported in Table19.

ID	Side	PICA	AICA	SCA	DCN	ANT	POST	Hem	Vermis	Peduncles
CB24	R	X					X	X		
CB25	R			X	X	X	X	X		X
CB26	R			X		X	X	X	X	X
CB27	R			X		X		X		
CB28	R	X			X		X	X		X
CB29	L			X		X		X		X
CB30	L			X		X	X	X	X	X
CB31	L		X	X	X	X	X	X		X
CB32	L			X	X	X		X		X
CB33	L									X
CB34	L	X	X	X		X	X	X		

Table 19- Lesion characteristics of the patients affected by focal cerebellar lesions. PICA= posterior inferior cerebellar artery. R= cerebellar lesion on the right side; L= cerebellar lesion on the left side; PICA=posterior inferior cerebellar artery; AICA= anterior inferior cerebellar artery; SCA= superior cerebellar artery; DCN= deep cerebellar nuclei; ANT= anterior cerebellar lobe; POST= posterior cerebellar lobe; Hem= cerebellar hemisphere.

FCb showed a pattern of lesions involving the lobules I-IV and V-VI in the anterior lobe, the lobule VI, the lobule VIIa (Crus I and Crus II) and VIIb. In FCb the dentate nucleus is involved (in green). The overlap of the lesions in dentate nucleus is reported in cyan (Figure 17).
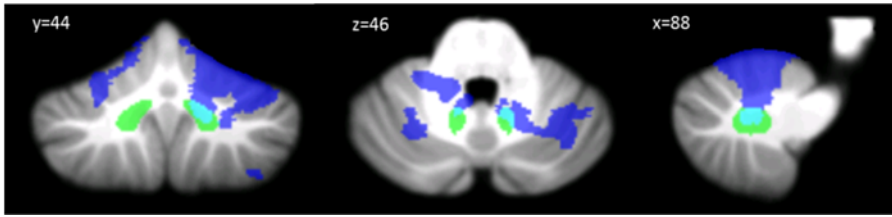
Figure 17: pattern of lesions of the focal cerebellar patients (in blue). Dentate nucleus lesion is in green. Overlap in dentate nucleus is in cyan.

Overlap of the cerebellar damage

In addition, we examined within cerebellum the subregions in which cerebellar damage overlap among between the two groups.

The overlap between the focal cerebellar lesions of FCb patients and the rate of atrophy of Ca patients is shown in Figure 18. The overlap is shown in the lobules I-IV and V-VI.
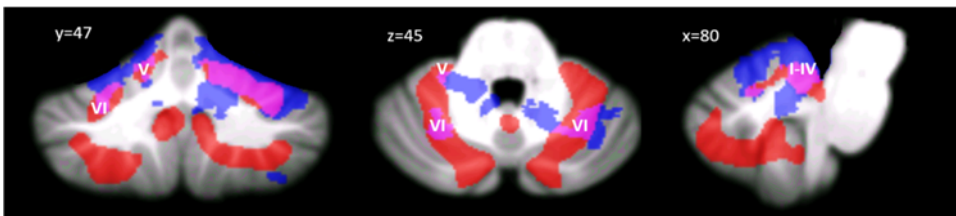

Figure 18: Overlap of cerebellar damages (in pink) among groups.

4.4.4 Conclusion – Study 3

Aim of the study 3 was to investigate, in a cohort of patients with cerebellar neurodegenerative disorder or focal lesions, the specific pattern of cerebellar damage and its relationship with the patients' executive impairment.

The present findings suggest the cerebellum to be part of the neural network subserving EFs and distinct cerebellar subregions to support different EFs subcomponents.

To summarize, neuropsychological assessment showed that both Ca and FCb were impaired in "Planning" executive tasks, while a selective impairment in performing "Set Shifting" tasks was only found in FCb group. When looking at cerebellar structural alterations, we found a selective involvement of distinct cerebellar subregions among the two groups with an overlap of the cerebellar damage localized in the lobules I-IV and V-VI.

In our interpretation, the fact that both groups of patients were impaired in Planning tasks may be explained by this common pattern of structural alterations. The lobule VI of the cerebellum is part of the most phylogenetically recent part of the cerebellum (Kelly and Strick 2009), and shows connections with associative regions in the cerebral cortex, including prefrontal regions. Functional connectivity data also supported these evidences showing that lobule VI largely correlates with anterior prefrontal cortex (Krienen and

Buckner, 2009) and contributes to the executive control network (Habas et al., 2009). Additionally, cerebellar lobules VI, together with medial prefrontal cortex, has been found to be uniquely active during planning of goal-directed aimed movements (Boyd et al., 2009). On the other hand, although the involvement of anterior motor cerebellar lobules (I-V) seem to be counter-intuitive, we speculate that this datum could be related to the fact that performing Planning tasks engages significant motor components (Kansal et al., 2017).

Interestingly, lesion assessment of FCb patients showed that the cerebellar damage selectively extended to lobule VIIa (Crus I and Crus II) and VIIb, known to have the strongest prefrontal connectivity, and dentate nucleus, the main cerebellar output channel to cerebral associative areas. Consistently, we found that many executive processes were involved in FCb group, compared to Ca, also affecting Set Shifting ability. This suggest that, according to the cerebellar functional topography, the anatomical distribution of the cerebellar damage is important in determining the specific pattern of functional alteration.

Set Shifting is the ability to adapt to changing environments by permitting shifts from one mental state (cognitive set), directed toward a particular reaction tendency, to another, thus suggesting

an high attentional and working memory engagement (Orellana & Slachevsky, 2008).

Functional connectivity data indicate that lobule VII participates in 3 functional sub-networks including dorso-lateral prefrontal, inferior parietal and lateral temporal areas (Buckner et al., 2011), strictly related to attentional processes. Additionally, lobule VII has been shown to be strongly activated by working memory and executive function tasks (Stoodley & Schmahmann, 2009).

The importance of deep cerebellar nuclei in cognition has been demonstrated by anatomical (Strick et al., 2009) and functional MRI data (Habas, 2010). The deep cerebellar nuclei facilitate the cerebello-thalamo-cortical projections and the cerebellar cortex, thus being an important element of the cerebellar microcomplexes.

Interestingly, our findings may further support the functional significance of the deep cerebellar nuclei when evaluating cognitive impairments showing that the executive performances tends to be worse in the presence of deep cerebellar nuclei damage, as previously proposed by Tedesco and colleagues (2011).

Overall, these data further emphasize that the site of the cerebellar lesion is a key factor in outcome.

CHAPTER V

———————————————————————————

General Discussion

Cerebellar damage has long been linked to an exclusive alteration in motor domain (Babinski, 1899, 1906; Holmes, 1917, 1939; Chambers, 1955a; Dow & Moruzzi, 1958). Nevertheless, in the 19th century, a number of clinical, anatomical, neuropsychological and functional observations suggested that the cerebellum is involved in cognitive processes (Schmahmann & Sherman, 1998).

However, the issue about the cerebellar contribution to executive processes is still controversial and it is difficult to draw unitary conclusions.

There are several evidences of altered EFs (including mental flexibility, scheduling capacities, verbal working memory and verbal fluency) in cerebellar patients (Schmahmann & Sherman, 1998). Lack of mental flexibility (perseveration of gesture or while drawing, inhibition difficulties, etc.) has been reported in these patients, together with impaired planning and decreased attentional abilities (Gottwald et al., 2004).

These impairments could be a consequence of an alteration in the connection between the cerebellum and the prefrontal cortex (PCF).

Some studies reported different performances in EFs tasks between patients affected by cerebellar damage and patients with lesions of the frontal lobe (Casini & Ivry, 1999; De Oliveira Cardoso et al., 2014). In particular, Casini and Ivry (1999), suggested that the alterations in temporal perceptual tasks can be related to the attention demands in frontal patients and to a more specific timing problem in cerebellar patients.

De Oliveira Cardoso and colleagues (2014) investigated the differences in decision making between patients with cerebellar and frontal strokes using the Iowa Gambling Task (IGT). The authors demonstrated that the cerebellar patients display less severe impairments in decision making than the frontal patients but, anyway, they are less preserved than healthy subjects.

These data suggest that while the frontal lobes may be the most important brain structures for the EFs, the cerebellum might also play an active role in this cognitive domain.

To better understand the characteristics of the EFs performances in cerebellar population we investigated in detail the EFs using an extensive neuropsychological battery. Subsequently, we used an exploratory factor analysis of the behavioral data to characterize the cerebellar involvement in specific sub-components of the EFs and to identify the cognitive constructs that underlie the performances in patients with focal or atrophic damage. Finally, we

investigate the neuroanatomical correlates of the patients' executive impairments by using advanced neuroimaging techniques.

The analysis on the behavioral data demonstrated that the cerebellar patients were impaired only in specific EFs tasks.

In particular, the factor analysis evidenced that the executive variables were grouped in three components: - Planning, -Set Shifting, and –Inhibition.

Taking into account these factors both the patients affected by degenerative damage and those affected by focal cerebellar lesion showed a selective impairment in test assessing the ability to develop a plan of action in novelty situations (Planning), but only the patients with focal lesion showed a selective impairment in tests that require to organize the behavior on the basis of an external feedback (Set Shifting).

The impairment in planning ability is in line with the theory that the cerebellum is necessary to generate an internal representation of actions (Ito, 2008).

According to this concept, the cerebellum forms (through a learning process) an internal model that reproduces either the dynamics of a body part formed and adjusted as a movement is repeated. Schmahmann (2010) suggested that the cerebellum regulates the speed, consistency and appropriateness of cognitive processes, based on an analogy between the control of the

movement of body parts and the manipulation of mental representations associated with an implicit information processing.

Therefore, planning ability requires to that the cerebellum to creates a copy of an operative model thanks to the feedback and feedforward connections with the PFC. This ability is damaged in both patient groups of our population sample.

Moreover, we founded that the patients affected by cerebellar focal lesion are also impaired in set shifting tasks. In set shifting tasks it is required the ability to integrate predictions about the consequences of an action in the internal representations and to update the internal models in order to adapt them to the different situations. This allows to shift from a cognitive set to another (Orellana & Slachevsky, 2008).

The ability to generate, modify and adjust an internal operative model represents the cerebellar specificity in the predictive brain (Koziol et al., 2014).

According to the VBM results, the patterns of behavioural alterations in the two patient populations could be explained by the localization of cerebellar damage. Interestingly, both patients' groups showed an alteration in the anterior portion of the cerebellum (lobule I-V) and in the lobule VI, that is in the most phylogenetically recent part of the cerebellum (lobule VI) and in regions involved in motor coordination. The involvement of these lobules may subtend

the planning impairment (Manto et al., 2012). Indeed, the lobule VI, together with medial prefrontal cortex, has been found to be uniquely active during planning of goal-directed aimed movements (Boyd et al., 2009).

Moreover, lesion characterization showed that, differently from the patients with cerebellar degeneration, in the patients with focal cerebellar damage also have an involvement of lobule VIIa (Crus I and Crus II) and VIIb and dentate nucleus. Accordingly, the patients affected by focal damage showed a more diffuse executive impairment than the patients affected by degenerative damage, also affecting Set Shifting ability. This suggests that, according to the cerebellar functional topography, the anatomical distribution of the cerebellar damage is important in determining the specific pattern of functional alterations (Stoodley et al., 2012).

To conclude, the patients affected by degenerative and focal damage show specific impairments in executive tasks, that are related to the neuroanatomical alterations of specific cerebellar regions. In the present study it has been advanced the hypothesis that, in presence of a cerebellar pathology, different profiles of EFs alterations depend on the localization of cerebellar damage.

All in all, the present data support the idea of the existence of a "dysexecutive cerebellar syndrome" different from the "dysexecutive syndrome" caused by frontal damage. The

"dysexecutive cerebellar syndrome" is characterized by impairments in specific EFs tasks according to the cerebellar damage localization.

This aspect has to be kept in mind when it is set up a rehabilitation program and indicates that in presence of a cerebellar lesion an executive evaluation is needed.

Limitations to this study are largely related to the sampling size. Population was composed by heterogeneous participants affected by different degenerative pathology and different focal site of lesion.

Future researches are needed is warranted in discovering if clear patterns emerge from on a larger population of participants and on specific sub-populations of cerebellar patients investigating in order to investigate the anatomical correlations between EFs performances and specific lobules as well as specific cerebello-cortical and cerebello-cortical networks.

Bibliography

Abadie, P., Baron, J.C., Bisserbe, J.C., Boulenger, J.P., Rioux, P., Travère, J.M., Barrè, L., Petit-Taboué, M.C. & Zarifian, E. 1992 Central benzodiazepine receptors in human brain: estimation of regional Bmax and Kd values with positron emission tomography. Eur. J. Pharmacol., 213, 107–115.

Abel C., Stein G., Arakaki T., Mancuso M., Nano G., Garretto N., et al. (2007). Evaluación de la aptitud en la toma de decisiones en pacientes con daño subcortical degenerativo de gânglios basales y cerebelo: enfermedad de Parkinson, enfermedad de Huntington y enfermedad cerebelosa degenerativa pura. Rev. Neurol. Argent. 32, 20–34

Ackermann H, Ziegler W. Cerebellar dysarthria--a review of the literature Fortschr Neurol Psychiatr. 1992 Jan;60(1):28-40.

Akshoomoff NA, Courchesne E, Townsend J. Attention coordination and anticipatory control. In J. D. Schmahmann (Ed.) International review of neurobiology on the cerebellum and cognition 1997 (Vol. 41, pp. 575–599). San Diego: Academic Press

Akshoomoff NA, Courchesne E. A new role for the cerebellum in cognitive operations. Behav Neurosci. 1992 Oct;106(5):731-8.

Akshoomoff NA, Courchesne E. ERP Evidence for a Shifting Attention Deficit in Patients with Damage to the Cerebellum. J Cogn Neurosci 1994; 6(4):388-99.

Albus, J S (1971) A theory of cerebellar function. Math Biosci, 10, 25–61.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience, 9, 357-381.

Alexander GE., Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 1990;13:266–271.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Progress In Brain Research, 85, 119-146.

Alexander GE. Basal ganglia-thalamocortical circuits: their role in control of movements. J Clin Neurophysiol. 1994;11:420–431.

Alexander GE, Bergfield KL, Chen K, Reiman EM, Hanson KD, Lin L, Bandy D, Caselli RJ, Moeller JR.Gray matter network associated with risk for Alzheimer's disease in young to middle-aged adults. Neurobiol Aging. 2012 Dec;33(12):2723-32.

Allen G., Buxton R.B., Wong E.C., Courchesne E. Attentional activation of the cerebellum independent of motor involvement. Science 1997; 275:1940-1943.

An L, Cao QJ, Sui MQ, Sun L, Zou QH, Zang YF, et al. Local synchronization and amplitude of the fluctuation of spontaneous brain activity in attention-deficit/hyperactivity disorder: a resting-state fMRI study. Neurosci Bull (2013) 29(5):603–13

Andreasen, N. C., & Pierson, R. (2008). The Role of the Cerebellum in Schizophrenia. Biological Psychiatry, 64(2), 81–88.

Appollonio, I. M., Grafman, J., Schwartz, V., & Massaquoi, S. (1993). Memory in patients with cerebellar degeneration. Neurology, 43(8), 1536-1544.

Ardila A, Rosselli M, Bateman JR.Factorial structure of cognitive activity using a neuropsychological test battery.Behav Neurol. 1994;7(2):49-58.

Ardila A, Galeano LM, Rosselli M.Toward a model of neuropsychological activity.Neuropsychol Rev. 1998 Dec;8(4):171-90.

Ardila A.Development of metacognitive and emotional executive functions in children. Appl Neuropsychol Child. 2013;2(2):82-7.

Armstrong DM, (1974) Functional significance of connections of the inferior olive. Physiol Rev, 54:358-417

Armstrong DM, (1990) Topographical localisation in the projections from the inferior olive to the paravermal cortex of the anterior lobe and paramedian lobule in the cerebellum of the cat A brief review. Arch Ital Biol 128:183-207.

Ashburner J, Friston KJ.Voxel-based morphometry--the methods. Neuroimage. 2000 Jun;11(6 Pt 1):805-21.

Babinski J (1899) De l'asynergie cerebelleuse. Rev Neurol 7:806–816.

Babinski J (1906) Asynergie et inertie cerebelleuses. Rev Neurol 14:685–686.

Baddeley, A. D., & Hitch, G. (1974). Working memory. In G.H. Bower (Ed.), The psychology of learning and motivation: Advances in research and theory (Vol. 8, pp. 47–89). New York: Academic Press.

Baddeley, A. D., & Hitch, G. J. (1994). Developments in the concept of working memory. Neuropsychology, 8(4), 485-493.

Baumann O, Mattingley JB. Functional topography of primary emotion processing in the human cerebellum. Neuroimage. 2012 Jul 16;61(4):805-11.

Bellebaum C, Daum I. Cerebellar involvement in executive control. Cerebellum. 2007;6(3):184-92.

Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain BA, Rapoport JL, Castellanos FX. Cerebellum in attention-deficit hyperactivity disorder. Neurology, 1998, 50, 1087–1093.

Bianchi, l. (1922) The Mechanism of the Brain and the Function of the Frontal Lobes. Edinburgh: Livingstone.

Bloedel J. R. "Functional heterogeneity with structural homogeneity: How does the cerebellum operate?" Behavioral and Brain Sciences. 1992. 15, 666-678.

Bolk, L. Das cerebellum der saugetiere. Fischer; Jena: 1906.

Bondi MW, Serody AB, Chan AS, et al. Cognitive and neuropathologic correlates of Stroop Color-Word Test performance in Alzheimer's disease. Neuropsychology. 2002;16:335–343.

Boone, K. B. (1999). Neuropsychological assessment of executive functions: Impact of age, education, gender, intellectual level, and vascular status on executive test scores. In B. L. Miller & J. L. Cummings (Eds.), The science and practice of neuropsychology series. The human frontal lobes: Functions and disorders (pp. 247-260). New York: Guilford Press.

Borkowski John G., Benton Arthur L., Spreen Otfried, Word fluency and brain damage, In Neuropsychologia, Volume 5, Issue 2, 1967, Pages 135-140.

Boyd LA, Vidoni ED, Siengsukon CF, Wessel BD.Manipulating time-to-plan alters patterns of brain activation during the Fitts' task. Exp Brain Res. 2009 Apr;194(4):527-39.

Boyden ES, Katch, A and Raymond, JL (2004) Cerebellum-dependent learning: the role of multiple plasticity mechanisms. Annu Rev Neurosci 27:581-609.

Braitenberg, V and Atwood, R P Morphological observations on the cerebellar cortex. J Comp Neurol 1958; 109:1–33.
Brambilla P, Barale F, Caverzasi E, Soares JC. Anatomical MRI findings in mood and anxiety disorders. Epidemiol Psichiatr Soc (2002) 11(2):88–99.

Brand S, Dahl A-L and Mugnaini E (1976) The length of the parallel fibres in the cat cerebellar cortex. An experimental light and electron microscopic study. Brain Res 26:39–58.

Brandt, J., Aretouli, E., Neijstrom, E., Samek, J., Manning, K., Albert, M. S., & Bandeen-Roche, K. (2009). Selectivity of executive function deficits in mild cognitive impairment. Neuropsychology, 23(5), 607–618.

Brega AG, Goodrich G, Bennett RE, Hessl D, Engle K, Leehey MA, Bounds LS, Paulich MJ, Hagerman RJ, Hagerman PJ, Cogswell JB, Tassone F, Reynolds A, Kooken R, Kenny M, Grigsby J The primary cognitive deficit among males with fragile X-associated tremor/ataxia syndrome (FXTAS) is a dysexecutive syndrome..J Clin Exp Neuropsychol. 2008 Nov;30(8):853-69.

Broadbent, D. E. (1953). Noise, paced performance and vigilance tasks. British Journal of Psychology, 44(4), 295-303.

Brodal, P. (1978). The corticopontine projection in the rhesus monkey. Origin and principles of organization. Brain : a journal of neurology, 101(2), 251-283.

Brodal A, Kawamura K. Olivocerebellar projection: a review. Adv Anat Embryol Cell Biol. 1980;64:IVIII, 1-140.

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., & Yeo, B. T. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. Journal of Neurophysiology, 106(5), 2322–2345.

Burgess PW, Alderman N, Evans J, Emslie H, Wilson BA.The ecological validity of tests of executive function. J Int Neuropsychol Soc. 1998 Nov;4(6):547-58

Burgess, P. W. (2003). Assessment of executive function. In P. Halligan, U. Kischka & J. C. Marshall (Eds.), Handbook of Clinical Neuropsychology (pp. 302-321): Oxford: Oxford University Press

Bürk K, Globas C, Bösch S, Gräber S, Abele M, Brice A, Dichgans J, Daum I, Klockgether T. Cognitive deficits in spinocerebellar ataxia 2. Brain. 1999 Apr;122 (Pt 4):769-77.

Bürk, K., Globas, C., Bösch, S., Gräber, S., Abele, M., Brice, A., et al. (1999). Cognitive deficits in spinocerebellar ataxia 2. Brain, 122(4), 769-777.

Bürk K, Bösch S, Globas C, Zühlke C, Daum I, Klockgether T, Dichgans Executive dysfunction in spinocerebellar ataxia type 1. J.Eur Neurol. 2001;46(1):43-8.

Bürk, K., Globas, C., Bosch, S., Klockgether, T., Zuhlke, C., Daum, I., et al. (2003). Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. J Neurol, 250(2), 207-211.

Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A.Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci. 2002 Mar;22(6):443-7.

Caffarra Paolo, Vezzadini Giuliana, Dieci Francesca, Zonato Fabrizio, Venneri Annalena A short version of the Stroop test : Normative data in an Italian population sample. 2002, Nuova Rivista di Neurologia 12 (4) 111-115

Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, Vaituzius C, Blumenthal JD, Nelson J, Bastain TM, Zijdenbos A, Evans AC, Rapoport JL. Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactvity disorder." Archives of General Psychiatry 2001, 58, 289–295.

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL.Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA. 2002 Oct 9;288(14):1740-8.

Catani M, Jones DK, Daly E, Embiricos N, Deeley Q, Pugliese L, Curran S, Robertson D, Murphy DG.Altered cerebellar feedback projections in Asperger syndrome. Neuroimage. 2008 Jul 15;41(4):1184-91.

Catherine J. Stoodley and Jeremy D. Schmahmann Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing Cortex. 2010 ; 46(7): 831–844.

Chambers WW and Sprague, JM (1955a) Functional localization in the cerebellum II: somatotopic organization in cortex and nuclei. Arch Neurol Psychiatry 74:653–680.

Corben LA, Klopper F, Stagnitti M, Georgiou-Karistianis N, Bradshaw JL, Rance G, Delatycki MB.Measuring Inhibition and Cognitive Flexibility in Friedreich Ataxia. Cerebellum. 2017 Aug;16(4):757-763.
Corsi, P.M. (1972). Human memory and the medial temporal region of the brain (Ph.D.). McGill University.

Crespo-Facorro, B., Barbadillo, L., Pelayo-Terán, J. M., & Rodríguez-Sánchez, J. M. (2007). Neuropsychological functioning and brain structure in schizophrenia. International Review of Psychiatry, 19(4), 325-336.

Critchley HD, Daly EM, Phillips M, Brammer M, Bullmore E, Williams SC, et al. Explicit and implicit neural mechanisms for processing of social information from facial expressions. A functional magnetic resonance imaging study. Hum Brain Mapp 2000; 9: 93–105.

Daum I., Snitz B.E., Ackerman H. "Neuropsychological deficits in cerebellar syndromes". International Review of Psychiatry. 2001; 13(4), 268-275.

Daum, I., & Ackermann, H. (1997). Neuropsychological abnormalities in cerebellar syndromes--fact or fiction? Int Rev Neurobiol, 41, 455-471.

Daum, I., Snitz, B. E., & Ackermann, H. (2001). Neuropsychological deficits in cerebellar syndromes. Int Rev Psychiatry, 13(4), 268-275.

De Oliveira Cardoso C., Damiani Branco L., Cotrena C., Kristensen C.H., Di Giorge Schneider Bakos D. and Fonseca R. P. The impact of frontal and cerebellar lesions on decision making: evidence from the Iowa Gambling Task Front. Neurosci., 2014

De renzi e, vignolo la.The token test: A sensitive test to detect receptive disturbances in aphasics. Brain. 1962 Dec;85:665-78.

Della Sala S, Gray C, Spinnler H, Trivelli C. Frontal lobe functioning in man: the riddle revisited. Arch Clin Neuropsychol. 1998 Nov;13(8):663-82.

Di Tommaso MC.A comparative study of bipolar disorder and attention deficit hyperactivity disorder through the measurement of regional cerebral blood flow. J Biol Regul Homeost Agents. 2012 Jan-Mar;26(1):1-6.

Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68.

Diedrichsen J., Balster J.H., Flavell J., Cussans E., Ramnani N. (2009). A probabilistic MR atlas of the human cerebellum. Neuroimage.

Dirnberger G, Frith CD, Jahanshahi M (2005): Executive dysfunction in Parkinson's disease is associated with altered pallidalfrontal processing. Neuroimage 25:588–599.

Donna L. Gruol, Noriyuki Koibuchi, Mario Manto, Marco Molinari, Jeremy D. Schmahmann, Ying Shen.Essentials of Cerebellum and Cerebellar Disorders: A Primer For Graduate Students Springer, 22 nov 2016 - 656 pag

Dow R.S., "Some novel concepts of cerebellar physiology" Mt. Sinai J. Med. (NY), 41:103-119, 1974

Dow RS and Moruzzi G (1958) The Physiology and Pathology of the Cerebellum (Minnesota Univ Press, Minneapolis)

Dow, R. S. (1974). Some novel concepts of cerebellar physiology. Mt Sinai J Med, 41(1), 103-119.

Duncan J, Johnson R, Swales M, Freer C. Frontal lobe deficits after head injury: Unity and diversity of function. Cognitive Neuropsychology. 1997;14(5):713–741.

Ekerot, C.F. and Kano, M (1985) Long-term depression of parallel fibre synapses following stimulation of climbing fibres. Brain Res 342:357–360.
Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology, 35(12), 1731-1741.

Filley, C. M. (2000). Clinical neurology and executive dysfunction. In Seminars in Speech and Language (Vol. 21, No. 02, pp. 0095-0108). Copyright© 2000 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.:+ 1 (212) 584-4663.

Fink, G. R., Marshall, J. C., Weiss, P. H., Shah, N. J., Toni, I., Halligan, P. W., et al. (2000). 'Where' depends on 'what': a differential functional anatomy for position discrimination in one- versus two-dimensions. Neuropsychologia, 38(13), 1741-1748.

Fisk JE, Sharp CA.Age-related impairment in executive functioning: updating, inhibition, shifting, and access. J Clin Exp Neuropsychol. 2004 Oct;26(7):874-90.

Floyd, F. J., & Widaman, K. F. (1995). Factor analysis in the development and refinement of clinical assessment instruments. Psychological Assessment, 7, 286-299.

Fries, W. (1990). Pontine projection from striate and prestriate visual cortex in the macaque monkey: an anterograde study. Vis Neurosci, 4(3), 205-216.

Frings M, Maschke M, Gerwig M, Diener HC, Timmann D.Acquisition of simple auditory and visual sequences in cerebellar patients. Cerebellum. 2006;5(3):206-11.

Glickstein, M., May, J. G., 3rd, & Mercier, B. E. (1985). Corticopontine projection in the macaque: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. J Comp Neurol, 235(3), 343-359.

Goel, V., & Grafman, J. (1995). Are the frontal lobes implicated in "planning" functions? Interpreting data from the Tower of Hanoi. Neuropsychologia, 33(5), 623-642.

Goldman-Rakic PS.Development of cortical circuitry and cognitive function. Child Dev. 1987 Jun;58(3):601-22.

Gottwald B, Mihajlovic Z, Wilde B, Mehdorn HM. Does the cerebellum contribute to specific aspects of attention? Neuropsychologia 2003, 41(11):1452-60.

Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM. "Evidence for distinct cognitive deficits after focal cerebellar lesions". J Neurol Neurosurg Psychiatry. 2004; 75(11):1524-31.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., & Hallett, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. Neurology, 42(8), 1493-1496.

Grimaldi G, Manto M. Topography of cerebellar deficits in humans. Cerebellum 2012 Jun;11(2):336-51.

Grossi D. e Trojano L. Neuropsicologia dei lobi frontali. Sindromi disesecutive e disturbi del comportamento. Bologna, Il Mulino. 2005.

Guo WB, Liu F, Xue ZM, Xu XJ, Wu RR, Ma CQ, et al. Alterations of the amplitude of low-frequency fluctuations in treatment-resistant and treatment-response depression: a resting-state fMRI study. Prog Neuropsychopharmacol Biol Psychiatry 2012b;37: 153–60

Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C, Chen H, Zhao J. Abnormal resting-state cerebellar–cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression Prog Neuropsychopharmacol Biol Psychiatry. 2013 Jul 1;44:51-7

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD. Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci. 2009 Jul 1;29(26):8586-94.

Habas PA, Kim K, Corbett-Detig JM, Rousseau F, Glenn OA, Barkovich AJ, Studholme C. A spatiotemporal atlas of MR intensity, tissue probability and shape of the fetal brain with application to segmentation. Neuroimage. 2010 Nov 1;53(2):460-70.

Hallett, M., & Grafman, J. (1997). Executive function and motor skill learning. Int Rev Neurobiol, 41, 297-323.

Hanaie R, Mohri I, Kagitani-Shimono K, Tachibana M, Azuma J, Matsuzaki J, Watanabe Y, Fujita N, Taniike M. Altered microstructural connectivity of the superior cerebellar peduncle is related to motor dysfunction in children with autistic spectrum disorders. Cerebellum. 2013 Oct;12(5):645-56.

Hansel C, Linden D J and D'Angelo E (2001) Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. Nature Neurosci 4:467–475.

Hardoy MC, Carta MG, Hardoy MJ, Cabras PL. WCST-Wisconsin Card Sorting Test. Firenze, Italy: Giunti O.S.; 2000.

Harlow, J.M. (1848) Passage of an Iron Rod Through the Head, Boston Med. Surg. J. 39: 389–393.

Harrington DL, Haaland KY. "Neural underpinnings of temporal processing: a review of focal lesion, pharmacological, and functional imaging research". Rev Neurosci. 1999, 10(2), 91-116.

Hawkes R (1997) An anatomical model of cerebellar modules. Prog Brain Res 114:39–52.

Heath, R. G. (1977). Modulation of emotion with a brain pacemaker: Treatment for intractable psychiatric illness. Journal of Nervous and Mental Disease, 165(5), 300-317.

Heaton, R. K. (1981). A Manual for the Wisconsin Card Sorting Test: Western Psycological Services.

Hesslow, G and Yeo, C H (2002) in A Neuroscientist's Guide to Classical Conditioning (ed Moore, J W) (Springer, New York, Berlin, Heidelberg) 86–146.

Heyder K, Suchan B, Daum I. Cortico-subcortical contributions to executive control. Acta Psychol (Amst). 2004 Feb-Mar;115(2-3):271-89. Review.

Holmes G (1917) The symptoms of acute cerebellar injuries due to gunshot injuries. Brain 40: 461–535.

Holmes G (1939) The cerebellum of man. Brain 62:1–30.

Houk JC, Buckingham JT and Barto AG. Models of the cerebellum and motor learning Behav. Brain Sci 1966; 19:368–383.

Ito M, (1984) The cerebellum and neural control. (Raven, New York).

Ito M (1989) Long-term depression. Annu Rev Neurosci 12:85–102.

Ito M (2001) Cerebellar long-term depression: characterization, signal transduction, and functional roles. Physiol Rev 81:1143–1195.

Ito M. Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci. 2008 Apr;9(4):304-13.

Ivanov I, Murrough JW, Bansal R, Hao X, Peterson BS. Cerebellar Morphology and the Effects of Stimulant Medications in Youths with Attention Deficit-Hyperactivity Disorder. Neuropsychopharmacology. 2014;39(3):718-726.

Ivry, R. (1997). Cerebellar timing systems. Int Rev Neurobiol, 41, 555-573.

Joel, D., & Weiner, I. (1994). The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. Neuroscience, 63(2), 363-379.

Jurjus GJ, Weiss KM, Jaskiw GE. Schizophrenia-like psychosis and cerebellar degeneration. Schizophr Res. 1994 May;12(2):183-4.

Kansal K, Yang Z, Fishman AM, Sair HI, Ying SH, Jedynak BM, Prince JL, Onyike CU Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration..Brain. 2017 Mar 1;140(3):707-720.

Karatekin C., Lazareff J.A., Asarnow R.F. "Relevance of the cerebellar hemispheres for executive functions". Pediatr Neurol. 2000. Feb;22(2):106-12.

Keren-Happuch, Shen-Hsing Annabel Chen, Moon-Ho Ringo Ho, and John E. Desmond A Meta-analysis of Cerebellar Contributions to Higher Cognition from PET and fMRI studies Hum Brain Mapp. 2014 Feb; 35(2): 593–615.

Katzev M., Tüscher O., Hennig J., Weiller C., Kaller C. P. (2013). Revisiting the functional specialization of left inferior frontal gyrus in phonological and semantic fluency: the crucial role of task demands and individual ability. J. Neurosci. 33, 7837–784

Kaufer The dorsolateral and cingulate cortex. In The Human Frontal Lobes: Functions and Disorders. 2007 a cura di Bruce L. Miller,Jeffrey L. Cummings 44-58

Kawai Y, Takeda A, Abe Y, Washimi Y, Tanaka F, Sobue G Cognitive impairments in Machado-Joseph disease. Arch Neurol. 2004 Nov;61(11):1757-60.

Kawato M and Gomi HA (1992) computational model of four regions of the cerebellum based on feedback-error learning. Biol Cybern 68: 95–103.

Keller, A., Castellanos, F. X., Vaituzis, A. C., Jeffries, N. O., Giedd, J. N., & Rapoport, J. L. (2003). Progressive loss of cerebellar volume in childhood-onset schizophrenia. American Journal of Psychiatry, 160(1), 128-133.
Kelly, R. M., & Strick, P. L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci, 23(23), 8432-8444.

Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? J Psychiatry Neurosci. 2005;30:178–186.

Kouneiher, F., Charron, S., & Koechlin, E. (2009). Motivation and cognitive control in the human prefrontal cortex. Nature neuroscience, 12(7), 939-945.

Krienen F.M. and Buckner R.L. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 2009; 19(10): 2485-97.

Krikorian R, Bartok J, Gay N.Tower of London procedure: a standard method and developmental data. J Clin Exp Neuropsychol. 1994 Dec;16(6):840-50.

Laidi C, d'Albis MA, Wessa M, Linke J, Phillips ML, Delavest M, et al. Cerebellar volume in schizophrenia and bipolar I disorder with and without psychotic features. Acta Psychiatr Scand (2015) 131(3):223–33.

Larsell O. Morphogenesis and evolution of the cerebellum. Arch neurpsych. 1934;31(2):373–395.

Larsell O. (1937) The cerebellum. A review and interpretation. Arch Neurol Psychiatric (Chicago) 38:580-607.

Leggio M, Solida A, Silveri M, Gainotti G, Molinari M. Verbal fluency impairment in patients with cerebellar lesions. Society for Neuroscience Abstracts. 1995;21:917.

Leggio MG, Silveri MC, Petrosini L, Molinari M. Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. J Neurol Neurosurg Psychiatry 2000; 69(1):102-6.

Leiner HC, Leiner AL, Dow RS. Does the cerebellum contribute to mental skills? Behav Neurosci. 1986 Aug;100(4):443-54.

Leiner HC, Leiner AL, Dow RS. The human cerebro-cerebellar system: its comptuting, cognitive and language skills. Behav. Brain Res. 1991; 44: 113-128.

Lerner MD, Lonigan CJ.Executive Function Among Preschool Children: Unitary Versus Distinct Abilities. J Psychopathol Behav Assess. 2014 Dec;36(4):626-639.

Levisohn L, Cronin-Golomb A, Schmahmann JD.Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain. 2000 May;123 (Pt 5):1041-50.

Levitt, Jennifer G., Rebecca Blanton, Linda Capetillo-Cunliffe, Donald Guthrie, Arthur Toga and James T. McCracken: Cerebellar Vermis Lobules VIII-X in Autism. Prog Neuropsychopharmacol Biol Psychiatry. 1999 May;23(4):625-33.

Lezak, M. (1995). Neuropsychological assessment (3rd ed.). New York: Oxford University Press.

Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, Avery L, Stewart J, Soul JS, Ringer SA, Volpe JJ, duPlessis AJ. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics. 2007 Sep;120(3):584-93.

Logan G.D Executive control of thought and action Acta Psychologica 60 (1985) 193-210 North-Holland 193

Logan GD, Schachar RJ, Tannock R. Impulsivity and inhibitory control. Psychological Science. 1997;8:60–64.

Luo L., Luk G., Bialystok E. (2010). Effect of language proficiency and executive control on verbal fluency performance in bilinguals. Cognition 114, 29–41

Lurija, A. R. (1966). Higher cortical functions in man. London: Tavistock.

Mackie S, Shaw P, Lenroot R, Pierson R, Greenstein DK, Nugent TF, Sharp WS, Giedd JN, Rapoport JL (2007). Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. American Journal of Psychiatry 164, 647–655

Mak M, Tyburski E, Madany Ł, Sokołowski A, Samochowiec A Executive Function Deficits in Patients after Cerebellar Neurosurgery..J Int Neuropsychol Soc. 2016 Jan;22(1):47-57.

Manes F., Villamil A. R., Ameriso S., Roca M., Torralva T. (2009). "Real life" executive deficits in patients with focal vascular lesions affecting the cerebellum. J. Neurol. Sci.

Manto M, Bower JM, Conforto AB, Delgado-García JM, da Guarda SN, Gerwig M, Habas C, Hagura N, Ivry RB, Mariën P, Molinari M, Naito E, Nowak DA, Oulad Ben Taib N, Pelisson D, Tesche CD, Tilikete C, Timmann D. Consensus paper: roles of the cerebellum in motor control--the diversity of ideas on cerebellar involvement in movement. Cerebellum. 2012 Jun;11(2):457-87.

Mariën P., Ackermann H., Adamaszek M., & Barwood C.H.S., Beaton A., Desmond J., De Witte E., Fawcett A.J, Hertrich I., Küper M., Leggio M., Marvel C., Molinari M., Murdoch B.E., Nicolson R.I., Schmahmann J.D., Stoodley C.J., Thürling M., Timmann D., Wouters Ziegler E., W. Consensus Paper: Language and the Cerebellum: an Ongoing Enigma. Cerebellum. 2014; 13:386–410.

Marr D. A theory of cerebellar cortex. J Physiol (Lond) 1969; 202:437–470.

Marra, C., Gainotti, G., Scaricamazza, E. et al. The Multiple Features Target Cancellation (MFTC): an attentional visual conjunction search test. Normative values for the Italian population Neurol Sci (2013) 34: 173.

Maruff P, Tyler P, Burt T, Currie B, Burns C, Currie Cognitive deficits in Machado-Joseph disease. J.Ann Neurol. 1996 Sep;40(3):421-7.

Middleton F.A. e Strick P.L. "Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function". Science. 1994; 266: 458-461.

Middleton FA, Strick PL (1997) New concepts about the organization of basal ganglia output. Adv Neurol 74:57–68.

Middleton, F. A., & Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. J Neurosci, 21(2), 700-712.

Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. Am J Psychiatry (2005) 162(8):1530–2

Mirsky A., Anthony B., Duncan C., Ahearn M., Kellam S. Analysis of the elements of attention: A neuropsychological approach Neuropsychology Review, 2 (1991), pp. 109-145

Miyake A, Friedman NP, Rettinger DA, Shah P, Hegarty M. How are visuospatial working memory, executive functioning, and spatial abilities related? A latent variable analysis. Journal of Experimental Psychology: General. 2001;130:621–640.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. Cognitive psychology, 41(1), 49-100.

Molinari M., Petrosini L., Misciagna S., Leggio M.G. Visuospatial abilities in cerebellar disorders. J Neurol Neurosurg Psychiatry 2004; 75: 235-240.

Monchi, Oury, Ji Hyun Ko, and Antonio P. Strafella. "Striatal Dopamine Release during Performance of Executive Functions: A [11C] Raclopride PET Study." NeuroImage 33.3 (2006): 907–912.

Monkul ES, Hatch JP, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, et al. MRI study of the cerebellum in young bipolar patients. Prog Neuropsychopharmacol Biol Psychiatry (2008) 32(3):613–9

Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC.An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. Biol Psychiatry. 1999 Sep 1;46(5):703-11.

Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC.An MRI study of midbrain morphology in patients with schizophrenia: relationship to psychosis, neuroleptics, and cerebellar neural circuitry. Biol Psychiatry. 2001 Jan 1;49(1):13-9

Norman, D., & Shallice, T. (1986). Attention to action: willed and automatic control of behavior. In R. Davidson, R. Schwartz & D. Shapiro (Eds.), Consciousness and Self-Regulation: Advances in Research and Theory IV: Plenum Press.

Noroozian M. The role of the cerebellum in cognition: beyond coordination in the central nervous system. Neurol Clin. 2014 Nov;32(4):1081-104.

Nyby O, Jansen J (1951) An experimental investigation of the corticopontine projection in Macaca mulatta. Skrifter utgitt av det Norske Vedenskapsakademie; Mat Naturv Klasse 3:1– 47

Okugawa G, Sedvall G, Nordström M, et al. Selective reduction of the posterior superior vermis in men with chronic schizophrenia. Schizophr Res. 2002;55:61–67.

Orellana, G., & Slachevsky, A. (2013). Executive Functioning in Schizophrenia. Frontiers in Psychiatry, 4, 35.

Oscarsson O (1979) Functional units of the cerebellum — sagittal zones and microzones. Trends Neurosci 2:143–145.

Ostrosky-Solís, F., Ardila, A., & Rosselli, M. (1999). NEUROPSI: A brief neuropsychological test battery in Spanish with norms by age and educational level. Journal of the International Neuropsychological Society, 5, 413–433

Papathanassiou D, Etard O, Mellet E, Zago L, Mazoyer B, Tzourio-Mazoyer N.A common language network for comprehension and production: a contribution to the definition of language epicenters with PET. Neuroimage. 2000 Apr;11(4):347-57.

Pascual-Leone, A., Grafman, J., Clark, K., & Stewart, M. (1993). Procedural learning in Parkinson's disease and cerebellar degeneration. Annals of Neurology, 34(4), 594-602.

Passingham R.E, Jueptner M., Frith C.,. Brooks D.J, & Frackowiak, R. S. J. (1995). An analysis of motor learning. Human Brain Mapping, 3(S1), 410.

Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci. 2002 Jul;16(2):291-310.

Petrosini L, Leggio MG, Molinari M. The cerebellum in the spatial problem solving: a co-star or a guest star? Progress in Neurobiology 1998, 56, 191-210.

Petrosini L., Molinari M., Dell'Anna M.E. Cerebellar contribution to spatial event processing: Morris Water Maze and T-Maze. The European Journal of Neurosciences 1996; 8(9): 1882-96.

Phillips JR, Hewedi DH, Eissa AM, Moustafa AA. The Cerebellum and Psychiatric Disorders. Frontiers in Public Health. 2015; 3:66.

Pichitpornchai C, Rawson JA, Rees S. Morphology of parallel fibres in the cerebellar cortex of the rat: an experimental light and electron microscopic study with biocytin. J Comp Neurol 1994; 342:206–220.

Pineda D.A. & Merchan V. Executive function in young colombian adults International Journal of Neuroscience Vol. 113 , Iss. 3, 397-410, 2003

Pollux PM, Robertson C. Reduced task-set inertia in Parkinson's disease. J Clin Exp Neuropsychol. 2002 Dec;24(8):1046-56.

Ponton, M. O., Satz, P. & Herrera, L. (1994) Factor analysis of a neuropsychological screening battery for hispanics (NeSBHIS). XVII European Meeting International Neuropsychology Society, Angers, Francia.

Posner, M. I., & Snyder, C. R. R. (1975). Attention and Cognitive Control. In R. L. Solso (Ed.), Information Processing and Cognition (pp. 55-85). Hillsdale, NJ: Erlbaum.

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. Nat Rev Neurosci, 7(7), 511-522.

Ramnani, N., Behrens, T. E., Johansen-Berg, H., Richter, M. C., Pinsk, M. A., Andersson, J. L., et al. (2006). The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from Macaque monkeys and humans. Cereb Cortex, 16(6), 811-818.

Raven, J. C. Progressive Matrices (1947) Sets A. Ab. B; Board and Book Form . London: Lewis, 1947.

Raven, J. C. Progressive Matrices (1947): Sets I and II . London: Lewis, 1947.

Ravizza SM, Ivry RB. Comparison of the basal ganglia and cerebellum in shifting attention. J Cogn Neurosci. 2001 Apr 1;13(3):285-97.

Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA Cerebellar damage produces selective deficits in verbal working memory. Brain. 2006 Feb;129 (Pt 2):306-20.

Repovs G, Baddeley A. The multi-component model of working memory: explorations in experimental cognitive psychology. Neuroscience. 2006 Apr 28;139(1):5-21.

Ríos, M., Periáñez, J. A., & Muñoz-Céspedes, J. M. (2004). Attentional control and slowness of information processing after severe traumatic brain injury. Brain Injury, 18, 257-272.

Riva D, Cazzaniga F, Esposito S, Bulgheroni S Executive functions and cerebellar development in children. Appl Neuropsychol Child. 2013;2(2):97-103.

Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, Rabbitt PM.A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J Int Neuropsychol Soc. 1998 Sep;4(5):474-90.

Robertson I. H. (1996). Goal Management Training: A Clinical Manual. Cambridge: PsyConsult

Robinson, DA (1976) Adaptive gain control of vestibule-ocular reflex by the cerebellum J Neurophysiol, 39:954–969.

Rose S. A., Feldman J. F., Jankowski J. J. (2011). Modeling a cascade of effects: the role of speed and executive functioning in preterm/full-term differences in academic achievement. Dev. Sci. 14, 1161–1175

Rumsey, J. M. and Ernst, M. (2000), Functional neuroimaging of autistic disorders. Ment. Retard. Dev. Disabil. Res. Rev., 6: 171–179.

Sakagami M, Pan X.Functional role of the ventrolateral prefrontal cortex in decision making. Curr Opin Neurobiol. 2007 Apr;17(2):228-33.

Sandra E Leh, Michael Petrides and Antonio P Strafella The Neural Circuitry of Executive Functions in Healthy Subjects and Parkinson's Disease. Neuropsychopharmacology (2010) 35, 70–85

Sbordone R.J., C.J. Long (Eds.), Ecological validity of neuropsychological testing, GR Press/St. Lucie Press, Delray Beach, FL (1996), pp. 15-41

Schlosser R, Hutchinson M, Joseffer S, Rusinek H, Saarimaki A, Stevenson J, Dewey SL, Brodie JD. Functional magnetic resonance imaging of human brain activity in a verbal fluency task. Journal of Neurology, Neurosurgery and Psychiatry. 1998;64:492–498.

Schmahmann J.D. e Pandya D.N. "Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey" The Journal of Comparative Neurology. 1989; 289(1):53-73.

Schmahmann J.D. "An emerging concept: the cerebellar contribution to highter function". Archives of Neurology. 1991. 48: 1178-1187.

Schmahmann, J. D., & Pandya, D. N. (1991). Projections to the basis pontis from the superior temporal sulcus and superior temporal region in the rhesus monkey. The Journal Of Comparative Neurology, 308(2), 224-248.

Schmahmann J.D."From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing." Human Brain Mapping. 1996; 4(3):174-98

Schmahmann JD, Pandya DN. The cerebrocerebellar system. Int Rev Neurobiol 1997; 4:31-60.

Schmahmann, JD (1997) The Cerebellum and Cognition (Academic, San Diego).

Schmahmann J.D. e Sherman J.C. "The cerebellar cognitive affective syndrome". Brain. 1998; 121: 561-579.

Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, et al. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. Neuroimage. 1999 Sep;10(3 Pt 1):233-60.

Schmahmann J.D. "The role of the cerebellum in affect and psychosis". Journal of Neurolinguistics. 2000; 13: 189-214.

Schmahmann JD, Dojon J, Toga AW, Petrides M, Evans CA. MRI atlas of the human cerebellum. San Diego: Academic Press; 2000.

Schmahmann J.D. "Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome." Journal of Neuropsychiatry and Clinical Neuroscience. 2004; 16(3):367-78.

Schmahmann JD. The role of the cerebellum in Cognition and Emotion: Personal Reflections Since 1982 on the Dysmetria of Thought Hypothesis, and Its Historical Evolution from Theory to Therapy. Neuropsychology 2010; 20(3), 236-260.

Schmidt M., Jager K., Egger F., Roebers C. M., Conzelmann A. (2015). Cognitively engaging chronic physical activity, but not aerobic exercise, affects executive functions in primary school children: a group-randomized controlled trial. J. Sport Exerc. Psychol. 37, 575–591.

Schoenbaum, Geoffrey, Matthew R. Roesch, and Thomas A. Stalnaker. "Orbitofrontal Cortex, Decision-Making and Drug Addiction." Trends in neurosciences 29.2 (2006): 116–124. PMC. Web. 24 Oct. 2017.

Silveri MC, Leggio MG, Molinari M.The cerebellum contributes to linguistic production: a case of agrammatic speech following a right cerebellar lesion. Neurology. 1994 Nov;44(11):2047-50.

Skefos J., Cummings C., Enzer K., Holiday J., Weed K., Levy E., et al. . (2014). Regional alterations in purkinje cell density in patients with autism. PLoS One.

Smith EE, Jonides J.Storage and executive processes in the frontal lobes. Science. 1999 Mar 12;283(5408):1657-61.

Snider RS, Maiti A.Cerebellar contributions to the Papez circuit. J Neurosci Res. 1976;2(2):133-46.
Spinnler H, Tognoni G (1987) Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 8[Suppl]:1–120

Steinlin M, Imfeld S, Zulauf P, Boltshauser E, Lövblad KO, Ridolfi Lüthy A, Perrig W, Kaufmann F.Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain. 2003 Sep;126(Pt 9):1998-2008.

Steinlin M. The cerebellum in cognitive processes: supporting studies in children. Cerebellum. 2007;6(3):237-41.

Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. Neuroimage 2009; 44 (2): 489-501.

Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. NeuroImage, 59(2), 1560–1570.

Strick P.L., Dum R.P., Fiez J.A. Cerebellum and Nonmotor Function. Annu. Rev. Neurosci 2009; 32: 413-434.

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. Psychological Bulletin, 95(1), 3-28.

Stuss DT, Alexander MP, Shallice T, Picton TW, Binns MA, Macdonald R, Borowiec A, Katz DI.Multiple frontal systems controlling response speed Neuropsychologia, 43 (2005), pp. 396-417

Suenaga M, Kawai Y, Watanabe H, Atsuta N, Ito M, Tanaka F, Katsuno M, Fukatsu H, Naganawa S, Sobue G Cognitive impairment in spinocerebellar ataxia type 6..J Neurol Neurosurg Psychiatry. 2008 May;79(5):496-9.

Tagaris G. A., Richter W., Kim S.-G., Pellizer G., Andersen P., Ugurbil K., et al. "Functional magnetic resonance imaging of mental rotation and memory scanning: A multidimensional scaling analysis of brain activation patterns". Brain Research Reviews, 1998: 26(2-3), 106-112.

Tagaris GA, Richter W, Kim SG, Pellizzer G, Andersen P, Ugurbil K, Georgopoulos AP. Functional magnetic resonance imaging of mental rotation and memory scanning: a multidimensional scaling analysis of brain activation patterns. Brain Res Brain Res Rev. 1998, 26(2-3), 106-12.

Tavano A, Grasso R, Gagliardi C, Triulzi F, Bresolin N, Fabbro F, Borgatti R.Disorders of cognitive and affective development in cerebellar malformations. Brain. 2007 Oct;130(Pt 10):2646-60.

Tedesco AM, Chiricozzi FR, Clausi S, Lupo M, Molinari M, Leggio MG (2011) The cerebellar cognitive profile. Brain 134:3672-86.

Tedesco AM, Bianchini F, Piccardi L, Clausi S, Berthoz A, Molinari M, Guariglia C, Leggio M. Does the cerebellum contribute to human navigation by processing sequential information? Neuropsychology. 2017 Jul;31(5):564-574.

Testa R, Bennett P, Ponsford J.Factor analysis of nineteen executive function tests in a healthy adult population. Arch Clin Neuropsychol. 2012 Mar;27(2):213-24
Thach WT. Somatosensory receptive fields of single units in cat cerebellar cortex. J Neurophysiol 1967; 30:675-696.

Thach WT. Cerebellar inputs to motor cortex. Ciba Found Symp. 1987;132:201-20. Review.

Thach W.T., Goodki H.P., Keating J.G. "The cerebellum and adaptive coordination of movement". Annu. Neurosci., 1992; 15: 403-442.

Thach WT. A role for the cerebellum in learning movement coordination. Neurobiol Learn Mem 1998; 70:177–188.

Tom N Tombaugh, Jean Kozak, Laura Rees, Normative Data Stratified by Age and Education for Two Measures of Verbal Fluency: FAS and Animal Naming, In Archives of Clinical Neuropsychology, Volume 14, Issue 2, 1999, Pages 167-177

Tomasi D, Volkow ND. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. Biol Psychiatry (2012) 71(5):443–50

Torrens L, Burns E, Stone J, Graham C, Wright H, Summers D, Sellar R, Porteous M, Warner J, Zeman A.Spinocerebellar ataxia type 8 in Scotland: frequency, neurological,

neuropsychological and neuropsychiatric findings. Acta Neurol Scand. 2008 Jan;117(1):41-8.

Townsend J, Westerfield M, Leaver E, Makeig S, Jung T, Pierce K, Courchesne E. Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks. Brain Res Cogn Brain Res. 2001 Mar;11(1):127-45

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R. D., Subramony, S. H., Wessel, K., et al. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci, 145(2), 205-211.

Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM et al (2012). Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. Nature 488: 647–651.

Tupper David E., Cicerone Keith D. The Neuropsychology of Everyday Life: Assessment and Basic Competencies – 1990

Ueland T, Oie M, Inge Landro N, Rund BR. Cognitive functioning in adolescents with schizophrenia spectrum disorders. Psychiatry Res (2004) 126(3):229–39.

Vaughan L, Giovanello K. Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. Psychol Aging. 2010 Jun;25(2):343-55

Voogd, J. & Bigaré, F. (1980). Topographical distribution of olivary and cortico nuclear fibers in the cerebellum: A review. In The Inferior Olivary Nucleus: Anatomy and Physiology, ed. Courville, J., de Montigny, C. & Lamarre, Y., pp. 207–234. Raven Press, New York

Wang SS, Kloth AD, Badura A (2014). The cerebellum, sensitive periods, and autism. Neuron 83: 518–532

Wang X, Jiao Y, Tang T, Wang H, Lu Z. Altered regional homogeneity patterns in adults with attention-deficit hyperactivity disorder. Eur J Radiol (2013) 82(9):1552–7.

Webb SJ, Sparks BF, Friedman SD, Shaw DW, Giedd J, Dawson G, Dager SR. Cerebellar vermal volumes and behavioral correlates in children with autism spectrum disorder. Psychiatry Res. 2009 Apr 30;172(1):61-7.

Weintraub S, Morhardt DJ 2005. Treatment, education and resources for non-Alzheimer dementia: One size does not fit all. Alzheimer's Care Q July/September: 201–214

Wiesendanger, R., Wiesendanger, M., & Ru¨egg, D. G. (1979). An anatomical investigation of the corticopontine projection in the primate (Macaca fascicularis and Saimiri sciureus)—II. The projection from frontal and parietal association areas. Neuroscience, 4(6), 747-765.

Willingham, D. B. (1992). Systems of motor skill. In L. R. Squire & N. Butters (Eds.), Neuropsychology of memory (2nd ed.). (pp. 166-178). New York, NY US: Guilford Press.

Wilson B.A. Ecological validity of neuropsychological assessment: Do neuropsychological indexes predict performance in everyday activities? Applied and Preventative Psychology, 2 (1993), pp. 209-215

Wilson B.A., Alderman N., Burgess P., Emslie H., Evans J. "Behavioural Assessment of the Dysexecutive Syndrome" 1996 Bury St. Edmunds, Suffolk: Thames Valley Test Company

Wilson B.A., J.J. Evans, H. Emslie, N. Alderman, P. Burgess The development of an ecologically valid test for assessing patients with a dysexecutive syndrome Neuropsychological Rehabilitation, 8 (3) (1998), pp. 213-228

Wilson, B. A. (1996). BADS: Behavioural Assessment of the Dysexecutive Syndrome: Manual: Harcourt Assessment.

Wolpert, D M and Kawato, M (1998) Multiple paired forward and inverse models for motor control. Neural Net 11:1317–1329.

Wolpert, D M, Miall, R C and Kawato, (1998) M Internal models in the cerebellum. Trends Cogn Sci 2:338–347.

Woods, s., Scott, j., Sires, d., Grant, i., Heaton, r., Tröster, a., & Group, t. (2005). Action (verb) fluency: Test–retest reliability, normative standards, and construct validity. Journal of the International Neuropsychological Society, 11(4), 408-415.

Yucel K, Nazarov A, Taylor VH, Macdonald K, Hall GB, Macqueen GM. Cerebellar vermis volume in major depressive disorder. Brain Struct Funct. 2013 Jul;218(4):851-8.

Zgaljardic, d. J., borod, j. C., foldi, n. S., mattis, p. J., gordon, m. F., feigin, a., & eidelberg, d. (2006). An Examination of Executive Dysfunction Associated with Frontostriatal Circuitry in Parkinson's Disease. Journal of Clinical and Experimental Neuropsychology, 28(7), 1127–1144.

Zoppelt, D., & Daum, I. (2003). Exekutive und mnestische Funktionen. In H.-O. Karnath & P. Thier (Eds.), Neuropsychologie (pp. 541–550). Berlin: Springer.