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Tesi di laurea magistrale

Italian version of the Cerebellar Cognitive Affective Syndrome Scale: Preliminary data collection and analysis.

Cerebellar Cognitive Affective Syndrome Scale – Versione Italiana: raccolta e analisi preliminare dei dati.

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INTRODUCTION

After centuries in which the role of the cerebellum was confined to motor control, it is now well established that its contribution is crucial for a much wider range of mental functions (Argyropoulos et al., 2020). A cerebellar damage results in a plethora of different non-motor symptoms that were classified within the Cerebellar Cognitive Affective/Schmahmann Syndrome (CCAS) (Schmahmann & Sherman, 1998). Such syndrome can be detected through the CCAS scale, a sensitive and practical screening tool originally developed by Hoche and colleagues (2018). To be used for the Italian population, our group first translated and adapted the CCAS scale to the Italian language and then started the collection of normative data. This thesis project aims to describe preliminary results regarding the standardization of this Italian version of the CCAS scale.

In the first chapter, a general background about the cerebellum, the CCAS and the CCAS scale will be presented, divided into three main sections. The first section will deal with general aspects regarding the "intact" cerebellum: after a brief description of the most important aspects of cerebellar anatomy and nomenclature, the historical steps of the investigation about the cerebellar function will be overviewed. Then, the functional localization of motor and non-motor functions within the cerebellar cortex will be described. The second section of the first chapter will contain the major feature of the three syndromes deriving from cerebellar damage: the Cerebellar Motor Syndrome, the Vestibulo-Cerebellar Syndrome and the Cerebellar Cognitive Affective Syndrome. The third section of the first chapter will contain a description of the path towards the validation of the CCAS scale, followed by its recent developments and applications. The second chapter will shift the focus on the current pilot study, describing the sample characteristics, the administration materials and procedures, the data analyses conducted and the results obtained. In the third and last chapter, results will be discussed and major limitations of the study identified. Finally, possible future developments and extensions of the current work will be indicated.

CHAPTER 1 - BACKGROUND: THE CEREBELLUM AND THE CCAS SCALE

1.1. The cerebellum

At the beginning of the present chapter, a brief description of the fundamental knowledge about cerebellar anatomy will be provided. After that, in the second paragraph, a summary of the different nomenclature proposed for the cerebellum and its substructures will be presented. The third section of the chapter will contain an overview of the different theories proposed about the cerebellar function. Hopefully, this overview will be useful to understand how we got to the recent developments and to the actual theoretical framework. The fourth and last part of the chapter will consist of a summary of the current evidence about cerebellar functional localization.

1.1.1. Gross anatomy

The cerebellum is a fundamental part of the vertebrate central nervous system. Although smaller than the encephalon in terms of volume, it contains more than 80% of the total number of neurons of the human brain (Williams & Herrup, 1988). It is located posteriorly to the pons and the medulla oblongata and below the occipital cerebral lobe, in a space called “posterior fossa”. It is separated from the occipital lobe by the tentorium of the cerebellum (Goglia, 2006). Due to its ovoidal shape (Goglia, 2006), it resembles a piece of a cauliflower, splitted in the middle (Tanabe et al., 2018). A sagittal course ledge, the vermis, more pronounced in the inferior surface, separates the two cerebellar hemispheres (Goglia, 2006).

The cerebellum is classically divided into three main lobes: the anterior lobe, the posterior lobe and the flocculonodular lobe (Rahimi Balaei, Ashtari & Bergen, 2017). The so-called primary fissure divides the anterior and posterior (see *Figure 1.1*). Posterior and flocculonodular are separated by the posterior-lateral fissure (Roostaei, Nazeri, Sahraian, & Minagar, 2014).

The lobes are, in turn, composed of ten lobules, shaped like thick lamellae, that appear in a quite constant number, so that from the 18th century they have been systematically named and classified (see section 1.1.2).

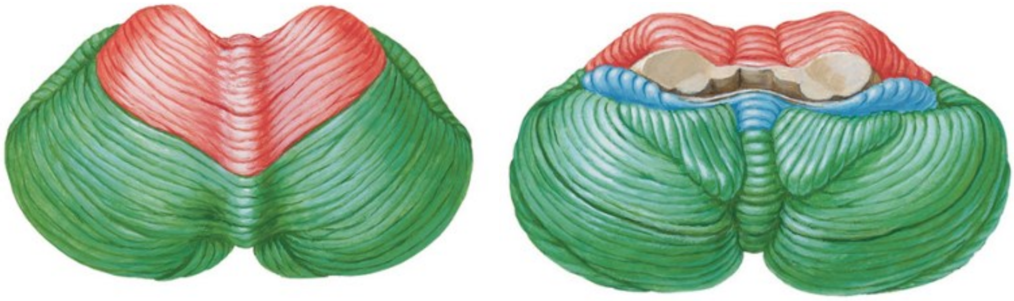


Figure 1.1: *Posterior (on the left) and anterior (on the right) views of the cerebellum, as depicted in Netter's drawing. The cerebellum is divided into three main lobes: anterior (in red), posterior (in green) and flocculonodular (in blue). From www.netterimages.com*

Another functional macroscopic division of the cerebellum is based on the phylogenetic hierarchy of different portions. The phylogenetically oldest part is represented by the vestibulocerebellum (or archicerebellum), that corresponds to the flocculonodular lobe and shows direct reciprocal connections to the vestibular nuclei (Rahimi Balaei, Ashtari & Bergen, 2017). The spinocerebellum is composed of the anterior lobe, the vermis and the paravermal regions (small portions of cortex on either side of the vermis) and is called this way because of its afferent projections from the spinal cord. Finally the largest and newest part is represented by the hemispheres and it is called pontocerebellum (or also cerebrocerebellum or neocerebellum) (Rahimi Balaei, Ashtari & Bergen, 2017). This portion is much larger in human when compared to other mammals and primates (Tanabe et al., 2018).

The cerebellum consists of a gray matter layer (the cortex), surrounding a branched body of white matter, commonly called "arbor vitae" (from the Latin "tree of life") (Roostaei et al., 2014).

Dipped into the white matter are four pairs of cerebellar nuclei. From medial to lateral: fastigial, globose and emboliform (also known as interposed nuclei), and dentate (Rahimi Balaei, Ashtari & Bergen, 2017). Such nuclei of gray matter represent the "gateway" of the cerebellum to other brain structures (Voogd, 2003), because they receive inputs from different parts of the cerebellar cortex and then send efferent projections to the brainstem and the thalamus (Rahimi Balaei, Ashtari & Bergen, 2017).

The cerebellar cortex is visually quite different from the cerebral cortex. Because of its homogeneity and its structure, it is classically described as a “lattice” (Braitenberg & Atwood, 1958). It is approximately 1,5 mm thick (Goglia, 2006) and structured in three layers (Voogd & Glickstein, 1998) (*Figure. 1.2*). The internal layer is called “granular”, being composed of numerous small granular cells. The intermediate layer, instead, is composed of a single line of Purkinje cells and separates the granular layer from the external “molecular layer”, containing the dendritic extensions from the underlying strata (Goglia, 2006).

The cortex is composed of the following four types of neurons: granule cells, Purkinje cells (PCs), stellate/basket cells and Golgi cells (Voogd & Glickstein, 1998). The granule cells represent the vast majority of the cerebellar neurons in terms of numerosity and form the more internal “granular layer” (Apps & Garwicz, 2005). Their excitatory signals are transmitted through the ascending axons that bifurcate in the parallel fibers inside the molecular layer, where they are interconnected with dendritic trees of PCs and with inhibitory interneurons (Voogd & Glickstein, 1998). The PCs owe their name to Jan Evangelista Purkinje, who firstly observed them and described their “flask-like bodies” in 1837, even before the formulation of the neuron doctrine (Glickstein et al., 2009). They present a big cellular body and a dendritic tree with many ramifications that spread within the molecular layer (Goglia, 2006). The axon of the PC arises at the opposite side of the cellular body and, traveling through the cerebellar white matter, reaches the internal cerebellar and brainstem nuclei. It is very important to note that the PCs are the only neural output of the cerebellar cortex and are therefore crucial to return to the brain the processed information (Apps & Garwicz, 2005). Each PC receives excitatory input from about 200,000 parallel fibers (extensions of the granule cells) and from one climbing fiber that arise from the brainstem olivary nuclei (Grangeray et al., in Gruol et al., 2016). The stimulation of parallel or climbing fibers results in different electrical activation of the PCs (respectively simple and complex spikes). The different signals are then integrated within the dendritic tree and action potentials are generated to release GABAergic signals in the deep nuclei, via the PCs axon (Grangeray et al., in Gruol et al., 2016). Other kinds of cerebellar neurons are the basket and stellate cells, that are commonly referred to as molecular layer interneurons (Watanabe in Gruol et al., 2016). They are located within the external molecular layer and provide an inhibitory feed-forward action on the PCs dendrites. Golgi cells also play an inhibitory role but, being located in the granular layer, they represent the only inhibitory input to the granular cells (Dieudonnè in Gruol et al., 2016).

The two main cerebellar afferents are the aforementioned climbing fibers and the mossy fibers. The climbing fibers stem from the contralateral olivary nucleus and target directly the dendritic tree of the PCs (Goglia, 2006). Mossy fibers, instead, target granule cells and therefore stimulate the PCs in a more indirect way (Apps & Grawicz, 2005).

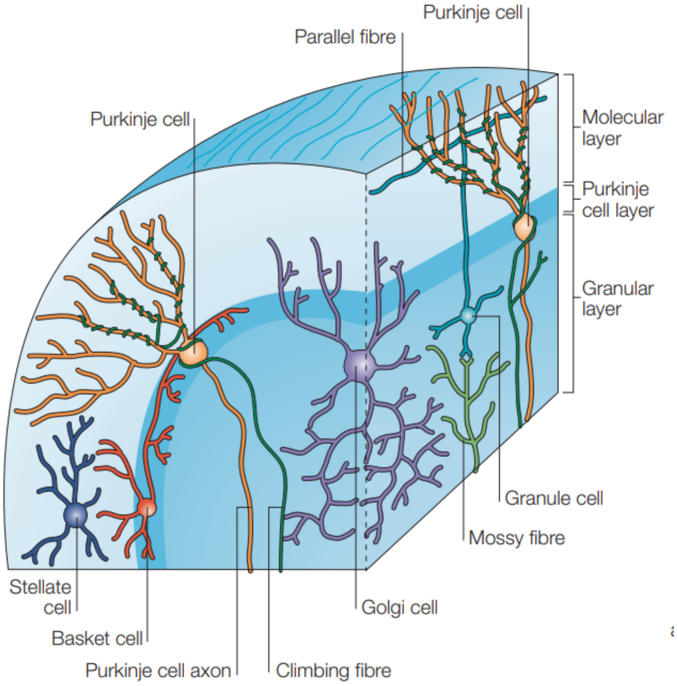


Figure 1.2.: *The structure of the cerebellar cortex. The cortex is composed of three layers: molecular, Purkinje and granular (reported on the right). It is composed of five main types of neurons (on the left): Purkinje cells, granule cells with parallel fibers, Golgi cells and interneurons (stellate cells and basket cells). The main afferents are the climbing and mossy fibers. From Apps & Garwicz (2005).*

Although from a cytoarchitectonic perspective the cerebellum is quite homogeneous, the same cannot be said for what it concerns its connectivity (Schmahmann, Guell, Stoodley & Halko, 2019). In fact, the cerebellum is implied in a heterogeneous pattern of connections with different brain regions, whose anatomical substrate is represented by the three pairs of cerebellar peduncles (Goglia, 2006). In particular, the inferior peduncles are connected to the medulla, the middle peduncles to the pons and the superior peduncles to the midbrain. The latter are the only ones to carry out efferent signals from the cerebellum, directed to thalamic nuclei (Goglia, 2006; Schmahmann in Gruol et al., 2016). In general, since most of the fibers connecting brain and cerebellum cross at pons level, cerebellar hemispheres mainly communicate with contralateral brain hemispheres (Schmahmann in Gruol et al., 2016).

Anatomical connections between brain and cerebellum consist of a two-stage feedforward loop and a two-stage feedback loop (Schmahmann, 2019a) (*Figure 1.3*). The feedforward loop conveys information from the cerebral cortex to the cerebellum via the nuclei of the basis pons (cortico-pontine and ponto-cerebellar projections), whereas the feedback loop brings signals back from the cerebellum to the brain via the thalamus (cerebello-thalamic and thalamo-cortical projections) (Schmahmann, 1996; Schmahmann et al., 2019b).

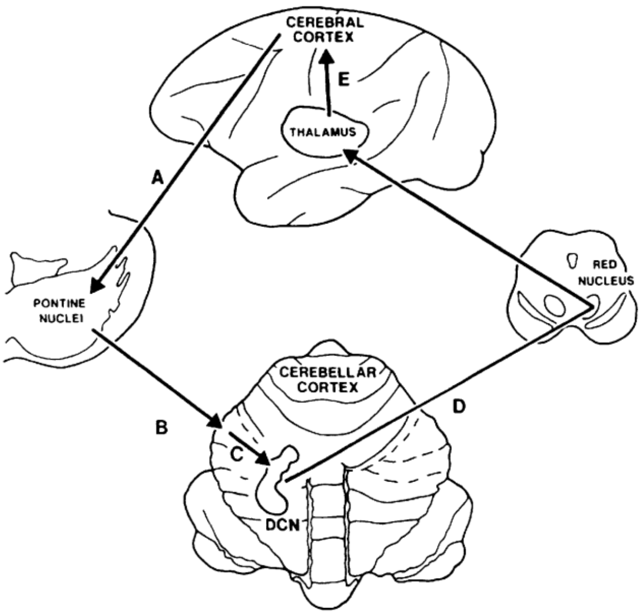


Figure 1.3: *Schematization of the cerebro-cerebellar loop. It is composed of: corticopontine (A), ponto-cerebellar (B), cerebellar corticonuclear (C), cerebello-thalamic (D) and thalamocortical (E) projections. Although the pathway terminates in the same cerebral hemisphere from which it originates, this does not imply a closed-loop system. From Schmahmann, 1996.*

The correspondence between cerebral and cerebellar areas was well-established for what will later be described as “motor cerebellum”, whereas it was investigated in the 90’ by Schmahmann & Pandya in regard to the non-motor sections of the cerebellum (see section 1.2.3). Anterior “motor” cerebellum receives somatotopic information from the spine and medial/dorsal accessory olivary nuclei, but also signals from the motor cortex through the pons (Goglia, 2006, Devita et al., 2021). The posterior cerebellum, instead, receives input from the principal olivary nucleus that in turn doesn't accept any somatotopic input, but is instead connected with a wide range of associative cerebral areas (Devita et al., 2021, Schmahmann et al., 2019b).

1.1.2. Nomenclature

The first accurate anatomical classification of the cerebellum goes back to the Italian surgeon Vincenzo Malacarne (1776), who identified the principal structures (lobe and scissure) and named the lobules according to their anatomical resemblance (Voogd & Marani in Gruol et al., 2016). For this reason the classical nomenclature, that was widely used and adapted thereafter, contains Latin terms as "lingula" (the cat's tongue), "uvula", "tuber" and "pyramis" (Schmahmann et al., 1999). He also identified the paramedian sulcus that separates the vermis from the hemispheres along the entire cerebellar cortex.

The Dutch anatomist Lodewijk Bolk gave a great contribution to the anatomical investigation and classification of the different structures (Bolk, 1906). He concluded that, from a macroscopic point of view, the cerebellum can be conceived as structured in three "folial chains" (a term that he introduced) (Voogd, 2011). A folium is a single structure of white matter, covered with a thin layer of gray matter (Singh, 2020). Such three folial chains (two forming the hemispheres and one the vermis) are contiguous and aligned in the anterior lobe and the lobulus simplex, whereas they take different directions descending in the posterior lobe (Voogd & Marani in Gruol et al., 2016). The lobulus simplex was called this way by Bolk precisely because it lacks a clear distinction between the vermis and the hemisphere (Voogd, 2003). More importantly, he pointed out the anterior-posterior continuity of each one of these folial chains and the independence from one another (Glickstein & Voogd, 1995). In his view, the cerebellum can be overall divided into 4 regions (anterior lobe together with lobulus simplex, posterior vermis, left and right hemispheres), that develop from independent "growth centers" and that present different sizes and features across different mammalians (Glickstein & Voogd, 1995). He confronted the cerebellum of 69 different mammals and proposed its own nomenclature (Glickstein et al., 2009), that, for this reason, is referred to as "comparative" (*Figure. 1.4*).

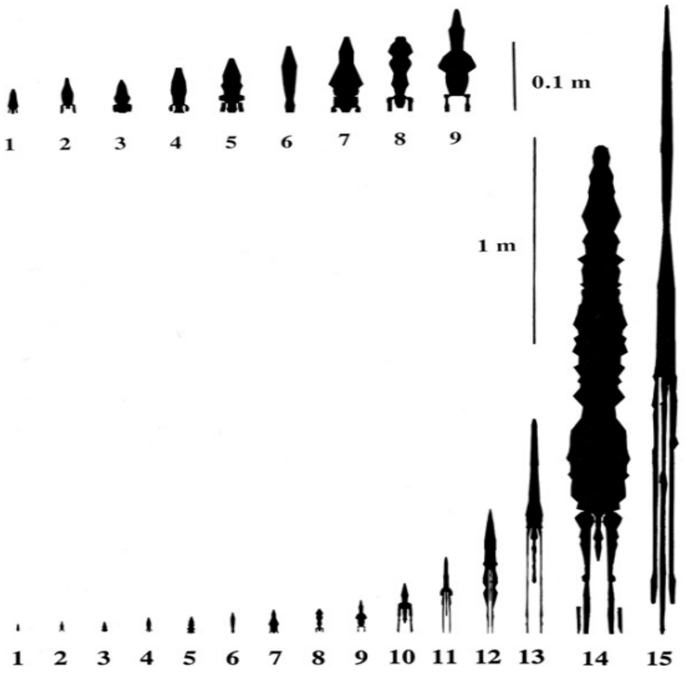
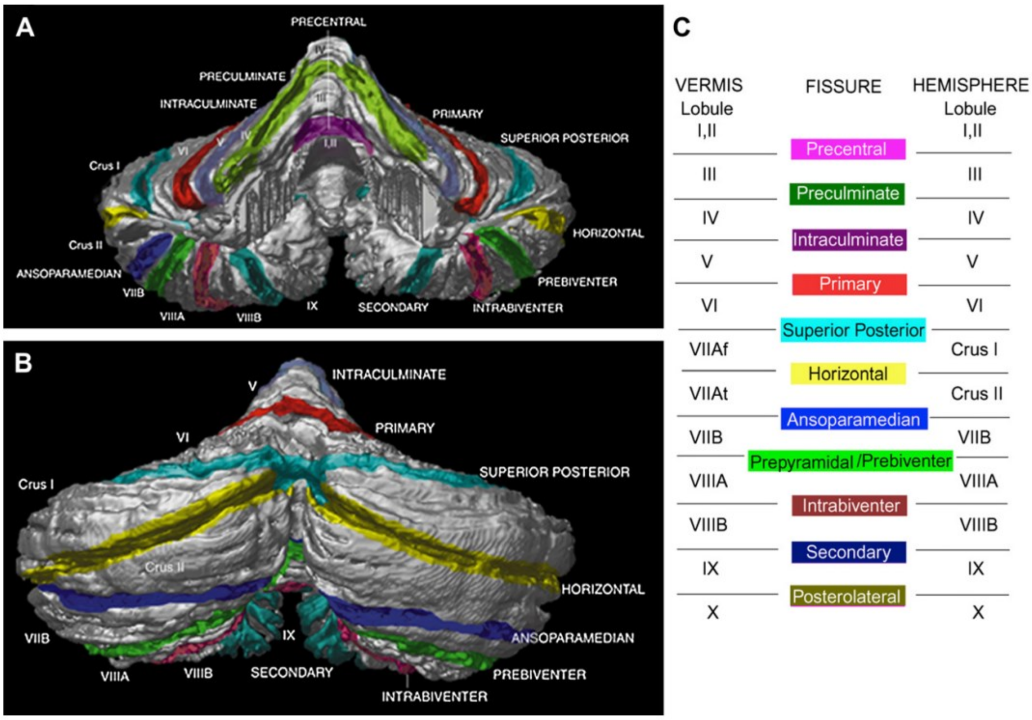


Figure 1.4.: *Size comparison of the cerebellum of different mammals, as if they were "unrolled". Number fourteen corresponds to the human cerebellum. From Glickstein, Strata & Voogd, 2009.*

A complementary conclusion was achieved by Olof Larsell, who emphasized the continuity between the vermal and hemispheric portion of each lobule (Glickstein & Voogd, 1995). In 1948, he also produced a nomenclature through a comparative method. He used the roman numerals I - X to identify the ten folia (when referring to volatile) or lobules (when referring to mammals) (Heines in Gruol et al., 2016). He considered the hemispheric portion of lobules as an extension of the vermal portion and indicated them with the prefix H ("hemispheric portion of") (Heines in Gruol et al., 2016). These choices were made to clarify the current nomenclature, highly variable at the time (Glickstein & Voogd, 1995). Because of its simplicity, Larsell's nomenclature became popular and was used as a standard for some decades (Voogd, 2003).

In more recent times, Schmahmann and colleagues proposed a new revised nomenclature along with the creation of their MRI Atlas of human cerebellum (Schmahmann et al., 1999, 2000). A new atlas was necessary because of the difficulty to precisely localize cerebellar areas in fMRI and PET activation studies, while revised nomenclature was needed because the terminology in use was sometimes contradictory (Schmahmann, 1999). The authors took Larsell's nomenclature as a reference and compared it to previous systems by Malacarne (1776), Bolk (1906) and others. They chose to remove the Latin terminology and to use roman numerals instead (I - X). They also removed the H prefix used by Larsell and added the terminology "vermal area" and "vermis" to the numerals when referring, respectively, to the vermal portion of the anterior or posterior lobes. This choice was made because the vermis is not always distinguishable within the anterior lobe (Schmahmann, 1999). The vermal portion of lobule VIIA was divided into VIIAf and VIIAt (from “folium” and “tuber” in the classical nomenclature), with Crus I and Crus II as hemispheric extensions. The names of fissures were maintained, as they were not cause of confusion. The resulting nomenclature is depicted in *Figure 1.5*.



VERMIS Lobule	FISSURE	HEMISPHERE Lobule
I,II		I,II
	Precentral	
III		III
	Preculminate	
IV		IV
	Intraculminate	
V		V
	Primary	
VI		VI
	Superior Posterior	
VIIAf		Crus I
	Horizontal	
VIIAt		Crus II
	Ansoparamedian	
VIIB		VIIB
	Prepyramidal/Prebiventer	
VIIIA		VIIIA
	Intrabiventer	
VIIIB		VIIIB
	Secondary	
IX		IX
	Posterolateral	
X		X

Figure 1.5.: *MRI reconstruction of the human cerebellum, in its anterior (A) and posterior (B) views. Fissures are reported in different colours. In table (C), the relationship between fissures and vermal/hemispheric portions of lobules is reported. From Schmahmann et al., 2000.*

1.1.3. Brief history of the investigation about cerebellar function

The interest addressed to the study of cerebellum goes back centuries. From antiquity up to the nineteenth century, anatomists focused on its anatomical structure, leaving unsolved questions about its function and the disorders resulting from its damage (Glickstein et al., 2009). An optimal exemplification of this inconsistency is given by Johann Christian Reil, who produced very accurate graphical representations of cerebellar lobules (see *Figure. 1.6*) and, on the other hand, unsatisfactory hypotheses about cerebellar role. In fact, following the recent Volta’s discoveries, he proposed that the alternating layers of white and gray matter of the cerebellar cortex could be seen as a generator of electrical energy (Glickstein et al., 2009). Before the occurring of the animal experimentation carried out by Rolando and Flourens, phrenologists like Gall used to address a sexual related function to the cerebellum (Gall et al.,1838) and relied on this claim to identify potential sexual offenders and to treat nymphomania (Glickstein et al., 2009).

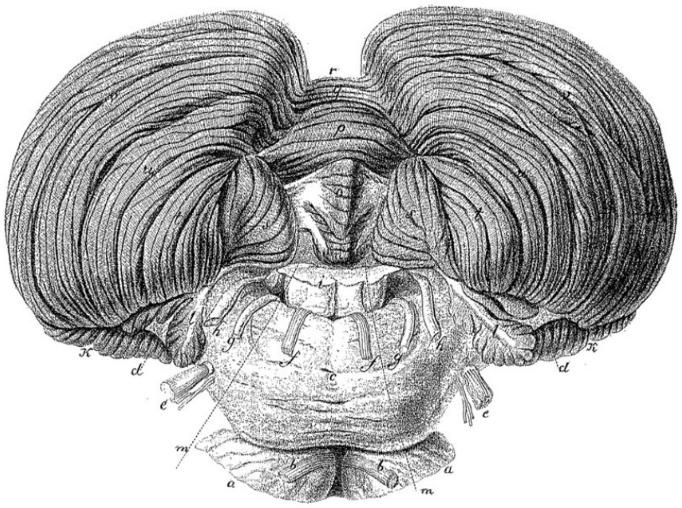


Figure.1.6.: *Reil's illustration of the ventral anterior view of the human cerebellum. From Glickstein, Strata & Voogd, 2009.*

Luigi **Rolando** was the first to identify the presence of motor (and not cognitive or sensory) deficit following cerebellar damage (Rolando, 1809). He thus concluded that the cerebellum was responsible for the initiation of movement. It is to be attributed to Pierre **Flourens** the first observation that cerebellar damage does not lead to paralysis of movement, but to a lack of coordination (Flourens, 1842). His contribution was crucial for the rest of the 19th century and represented the base for the following functional studies, conducted by Luciani, Babinski and Holmes (Glickstein et al., 2009). **Luciani** classified the permanent symptoms of cerebellar damage in three main categories: asthenia (weakness), atonia (lack of tone) and astasia (including tremor, titubation and oscillating movements) (Luciani, 1891). These three aspects were deepened by Gordon **Holmes**, who redefined asthenia as “intention tremor”, and described it as a defect of “the regularity and stability of muscular contractions” (Holmes, 1917). The work of this British neurologist is particularly remarkable because of his accurate description of the different types of movement disorders (hypometria/hypermetria, rebound phenomenon, diadochokinesia, and the aforementioned intention tremor). He was able to conduct such an accurate analysis thanks to the nefarious opportunity offered by World War I, with its numerous cases of focal cerebellar damages from gunshot (Heines in Gruol et al., 2016). His descriptions of the clinical issues related to cerebellar damage are so accurate that they can be considered useful up to these days. The peculiar symptom named "diadochokinesia" or "adiadokinesia" was also studied by Joseph **Babinski**, who focused specifically on this topic in a dedicated work (Babinski, 1902). He defined this cerebellar symptom as "the suspension or decrease of the ability to carry out rapidly successive voluntary movements" (Heines in Gruol et al., 2016), such as the rapid pronation and supination of the forearms. Interestingly, Babinski stated that such a specific function, as other neuropsychological abilities, would have not caught the attention of scientists if it was not for its loss (Glickstein et al., 2009).

To summarize, early influential physiologists concluded that the cerebellum function was strictly related to motor control and coordination, and this became the dominant view for almost the next two hundred years (Schmahmann, 2019).

In the second half of the twentieth century, initial evidence of non-motor implications of the cerebellum started to slowly open new windows on the investigation about the cerebellar function.

Snider's work brought fundamental conclusions about the differentiation of areas within the cerebellar cortex and its various lobules. For the first time, he identified tactile, visual and auditory areas of afferent innervation in the cerebellar cortex of the monkey (Snider & Stowell, 1944a), thus rejecting the idea of the undifferentiated cerebellar cortex. The investigation about what the cerebellum does remained still at a preliminary stage. As Snider himself wondered (Snider, 1950): "What does the cerebellum do to the afferent volleys before they become efferent volleys?". At that time, he proposed the hypothesis of the cerebellum as *"the great modulator of neurologic function"*, stating that it was able to influence the action of specific centers by increasing or dampening their electro-physiological activity, through the alteration of their threshold of excitability. Moreover, he was quite firmly convinced that the cerebellar function could not be confined neither to the control of muscular activity, nor to proprioception (Snider, 1950).

Heath later found other evidence about the implication of the cerebellum in the regulation of non-motor functions. Basing on extensive animal studies, he found structural connections between the cortex of the rostral vermis and both hippocampus and septal region (Heath, 1977). In particular, single unit stimulation in this specific cerebellar area was seen to inhibit hippocampal single unit activation and increase, in contrast, the activation of septal single neurons. According to previous studies (Heath, 1974), a coactivation of cerebellum and hippocampus was observed in conjunction with aversive emotions experienced by a single patient. In line with these observations, Heath suggested considering the cerebellum as a *modulator of the emotional brain* (Heath, 1977).

Masao **Ito** addressed the unsolved questions about cerebellar function through a computational model approach. He chose to consider the "corticonuclear microcomplex" (CNMC) as the fundamental functional unit of the cerebellar control models (Ito, 1984). The CNMC is composed of a microzone of the cerebellar cortex, a small group of cerebellar nuclei and a small group of inferior olivary nuclei. Ito nested the CNMC in two different kinds of computational models that could represent the ways in which the cerebellum achieves its goal of movement correction (Ito in Koziol et al., 2014). These two models (Ito, 1993), originally related to voluntary movement control, have different operating mechanisms and different goals. The first one (*Figure 1.7, C*) allows the cerebellum to replace the external feedback loop (efl) provided by sensitive afferents with an internal feedback loop (ifl), provided by CNMC and independent from the peripheral visual information. By means of this dynamic model, humans became able to move accurately without peripheral feedback. The second one, instead, replaces the conscious control of movement, performed by the motor cortex (CX) with a more automatic one, allowing for a non-conscious precise motor control (*Figure 1.7, D*). Thanks to the second inverse dynamic model, the subject develops the ability to move precisely and smoothly without consciously thinking about it (Ito, 1993). These two models depict the ability of the cerebellum to learn dynamics of different movement control, removing the need to correct individual trajectories (Ito in Koziol et al., 2014).

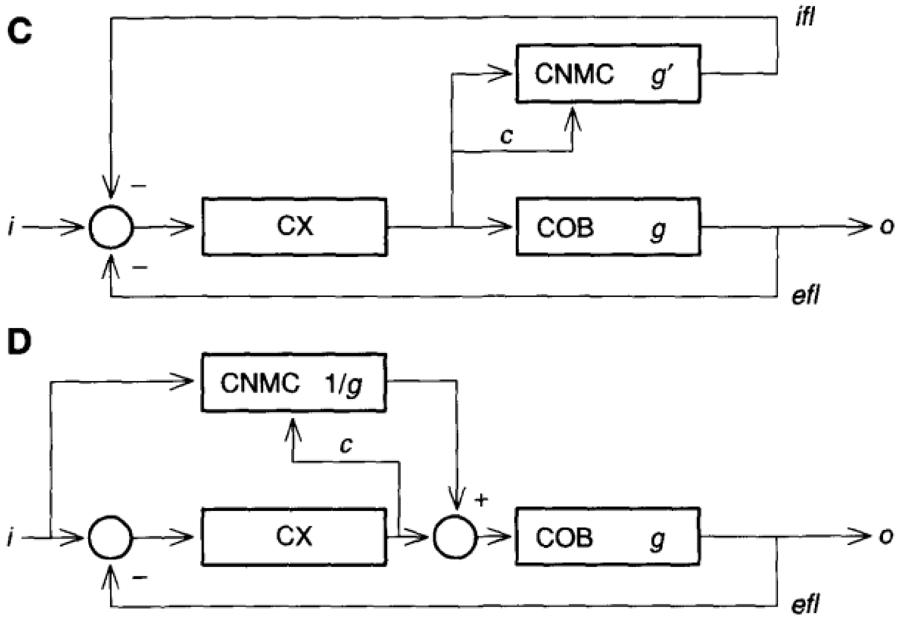


Figure 1.7.: *Models for the control system theory. They include: an input (i), the motor cortex (CX), a controlled object (COB), the corticonuclear microcomplex (CNMC), the climbing fibers (c), internal and external feedback loops (ifl and efl) and an output (o). g and g' represent the motor dynamics. From Ito, 1993.*

To summarize, in Ito's model the cerebellum does not know how to perform the movement but does know how to correct it and is able to automate such corrections. His contribution was greatly influential, and its *control system theory* is today regarded as one of the most solid models of cerebellar functioning and learning (Lisberger, 2021; Sanger, Yamashita, & Kawato, 2020).

Ito also theorized that these computational models could be extended to the control of any kind of mental activity, by replacing the motor cortex (the controller) with different cerebral areas (for example, the prefrontal cortical areas) (Ito in Koziol et al., 2014). He expressed the contribution of the cerebellum in the cognitive domain as the automatization of thought process after repeated exercise (Ito, 1993). From this perspective, the phenomenon of intuition could represent an unconscious mental process made possible by the cerebellar automatization action (Ito in Koziol et al.,2014).

Based on these theorizations, Ito defined the cerebellum as a *“multipurpose learning machine”* (Ito, 1993). Unfortunately, as expressed by the author himself, such a computational approach collided with the impossibility of representing mental processes (such as concepts or ideas) in artificial neural circuits (Ito in Koziol et al., 2014).

In trying to overcome the simplistic view of the cerebellum as responsible for motor control, **Paulin** proposed to conceptualize it as the neural analogue of a *state estimator* (Paulin, 1997) (Paulin in Baumann et al., 2015). A state estimator is responsible for the construction of neural representation of a moving object in space. To do so, it must integrate position in space, velocity and other parameters to create an accurate internal representation of the object. According to such representation, it finally allows for control, perception and imagination of the moving system (Paulin, 1997). This hypothesis is derived from comparative animal studies showing the presence of cerebellum circuitry in all species whose movements are influenced by inertia, that therefore need for an estimation of body future position (Paulin in Bauman et al., 2015). According to this hypothesis, the complication in motor control resulting from a cerebellar damage would be a consequence of a deficit regarding the function of state estimation. This process could also be responsible for a wider range of motor, perceptual and cognitive functions involving the estimation of a dynamic system. Some examples of cognitive functions requiring a state estimator could be: spatial or geometric reasoning in which a dynamic system must be perceived, prediction of objects trajectories and collisions, accurate perception of moving acoustic input in space (Paulin, 1997). This hypothesis is described as, at the same time, more general and specific than the classical motor control idea: more general because it is not restricted to motor control and more specific because it precisely indicates the impaired mechanism in cerebellar damage. According to other authors, however, an important limitation of this theory regards the evidence of cerebellar implication also in acquisition of information related to non-moving objects (Courchesne & Allen, 1997).

Starting from the modularity assumption that each neural system must have a specific computational function, **Ivry** proposed that the cerebellum would be implicated in the programming of temporal patterns and other aspects related to timing of motor and non motor functions. The hypothesis of the *Cerebellar Timing System* (Ivry, 1997) stems from the well-established role of cerebellum in motor coordination, but extends to non motor aspects such as perceptual task (i.e. intervals duration discrimination), sensorimotor learning (i.e. eyeblink conditioning) (Ivry, 1997) or speech perception tasks in which words can be distinguished only through temporal cues (Ivry et al., 2002). The author subsequently proposed a specification for the timing theory, observing that cerebellum appears to have a crucial role in processes that are not continuous but marked by discrete boundaries, as finger tapping or intermittent circle drawing in comparison to continuous circle drawing (Ivry et al., 2002). They further investigated this hypothesis and concluded that cerebellum contributes to what they called "event timing", and not to "emergent timing". The first would be implied when an explicit representation of temporal information is required, whereas the latter would emerge when explicit control of temporal aspects is not mandatory (Ivry et al., 2002), such as in continuous movements. Further evidence in favour of this theory is shown in relation to cerebellar patients. Ataxic patients and cerebellar tumors patients, for example, performed significantly worse than healthy controls in explicit judging and discrimination of time intervals (in terms of milliseconds), but not in the discrimination of pitch (dB) or frequency (Hz) (Salman, 2002). The timing theory could fit very well in the understanding of cerebellar motor deficits, providing a plausible explanation for Diadochokinesia and temporal impairment of agonist/antagonist muscles (see section 1.2.1) (Salman, 2002) (Bares et al., 2019). According to this theory, in controlling event timing, the cerebellum would rely on forward models as a form of prediction. Such predictive function would not be cerebellar-specific, but the predictions about timing would be specifically cerebellar-dependent (Ivry in Baumann et al., 2015).

Bower and other researchers proposed a very unconventional theory, based on previous physiological studies of rat cerebellar cortex (Gao et al.,1996) (Bower,

1997) (Bower in Manto et al., 2012). In their idea, the cerebellum would be implied in motor control only indirectly, whereas it would be directly responsible for the *monitoring and adjusting of sensory data* (Bower, 1997). It could therefore influence the quality of sensory data on which other brain structures (such as basal ganglia or motor cortex) rely (Bower in Manto et al., 2012). This theory implies, among other aspects, that the cerebellum would not have any direct influence neither in motor nor in cognitive functions, but instead would facilitate the brain in carrying out those functions. This is consistent with the findings that cerebellar damage produces an increase in performance variability and in execution time (general slowing), without impairing the general outcome (Bower, 1997). Being more general and wide-ranging, this theory about cerebellar function is thought to be in contrast with other theories that directly link the cerebellum to various motor or cognitive aspects, such as motor control or timing (Bower, 1997). The author stated that theories linking cerebellum with non-motor functions would still be adapting motor-related models to non-motor functions (Bower in Baumann et al., 2015), therefore basing their theorization on wrong premises.

Other researchers have hypothesized a role of the cerebellum in *learning and error detection*. **Thach**, for example, defined the crucial role of the cerebellum in motor learning in terms of linkage between context and correct movement to be performed. Consistently with the widely influential Marr-Albus theory about cerebellar cortex (Marr, 1969; Albus, 1971), he assigned a specific role in this process to each cortical structure. It is the afferent mossy fibers that would detect errors between movements and context, with different firing rates that would in turn modulate the inhibitory strength of parallel fibers on Purkinje Cells (Thach, 1996). After trial-and-error practice, the cerebellum would become able to shape the automatic, more rapid response to perform in relation to certain contexts. Thach extended his theory from motor learning to specific kinds of cognitive learning, related in particular to prefrontal areas and executive functions, reviewing PET and lesions studies (see for example Fiez et al., 1992). He consistently noted that cerebellar lesions reduced, and not abolished, performance, impairing error detection and practice related learning (Thach, 1996). The conclusions reached by Thach are consistent with **Doyon**'s observations about cerebellar implication in *skill learning*. In his review about hemodynamic changes in cerebellar cortex (Doyon, 1997), a cerebellar activation emerged during the acquisition and automatization stages of a skill learning process, whereas a deactivation occurred when the movement or abilities was consolidated. During the latter phase, a concurrent increase of blood level is observed in other cortical and subcortical area (such as supplementary motor area and insular area), suggesting that the cerebellum is solely involved in the acquisition of representation, whereas other structures would contain the storage of such representations (Doyon, 1997).

The *Dysmetria of Thought* (DoT) theory (Schmahmann, 1991, 1998, 2001b, 2004; Schmahmann & Sherman, 1998) represents the theoretical framework proposed by **Schmahmann** and the other authors of the CCAS scale and is therefore of particular importance for the current work. It conceptualizes the cognitive and affective impairments deriving from cerebellar damage (which will be described in detail in sections 1.2.3 and 1.3.1) in analogy with the motor deficits that are classically known to occur after cerebellar lesions. In the same way we observe dysmetria of movements, we also observe dysmetria (hypo or overshoot) or thoughts, in which speed and appropriateness of mental process is impaired (Schmahmann, 1991) (*Figure 1.8*). This theory also aims to explain clinical evidence showing motor and cognitive/affective deficits in relationship to different damage localization. In fact, a dichotomy between cognitive and motor cerebellum was shown in many functional localization studies, with the anterior lobe implicated in motor control, posterior lobe in cognitive modulation, and vermal regions in affective behavioral abnormalities (Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2010). This theory stems from the observation of the homogeneous structure of the cerebellar cortex, paired with anatomical tracing studies showing complex heterogeneity of connectivity with several high order brain areas (Schmahmann, 1996). What the cerebellum does about motor and cognitive control is expressed by the idea of a Universal Cerebellar

Transform (UCT). The UCT describes the function of the cerebellum as a transformation that is constant in nature, but whose outcome differs if applied to different neurological domains, depending on the structural connections with the different cerebral areas. The cerebellum would therefore have a unique regulating function that would be applied both in the motor and in the cognitive domain.

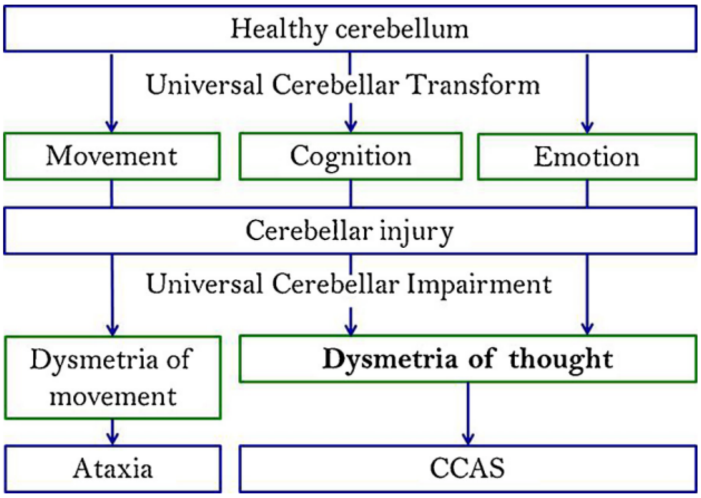


Figure 1.8: *Schematic of the Dysmetria of Thought and Universal Cerebellar Transform theory. From Guell et al., 2015.*

Other examined researchers (such as Ivry or Doyon, for instance) adopted a different approach than that of Schmahmann and colleagues in the quest for the cerebellar function, focusing on the very nature of the cerebellar modulation within the cerebro-cerebellar loops. In other words, on the one hand, Schmahmann focused on the cerebellum role in cognitive process, identifying the specific impaired functions (Schmahmann, 1998), the clinical implications (Schmahmann, 2004, 2020) and trying to provide a functional localization (Stoodley & Schmahmann, 2009, 2010b). On the other hand, another line of research focused specifically on the question of “how the cerebellum acts in relation to cognition?”, arguing that the responses provided by Schmahmann (the DoT theory and the UCT) were to be considered far too vague and metaphoric (Sokolov, Miall & Ivry, 2017). However, these two different approaches are not necessarily incompatible, in that the DoT and UCT theories could be conceived as the general framework for more specific theories about cerebellar functions and should be considered a useful guideline for further investigations.

After investigating the involvement of cerebellum in procedural learning (Molinari, Leggio, Solida, Ciorra, Misciagna, Silveri, & Petrosini, 1997) and visuospatial abilities (Molinari & Leggio, 2007), **Leggio** and **Molinari** proposed the *sequence detection* hypothesis in a series of dedicated works (Molinari & Petrosini, 1997; Leggio, Tedesco, Chiricozzi, Clausi, Orsini, & Molinari, 2008, among the others). They started from the assumptions that: 1) a major role of the brain is to make predictions about the world; 2) one way to make a prediction is to create an internal representation of the action/event; 3) the cerebellum was linked to the ability to predict errors and to generate internal models (see for example Ito, 1984). With such premises, it is clear that the cerebellum could have a crucial role in the "predictive brain" (Leggio & Molinari, 2015). The sequence detection hypothesis is proposed as an explanation to the following question: "how does the cerebellum make these predictions?". According to such hypothesis, the cerebellum role is to detect temporally/spatially regular patterns of event, in relation to motor, perceptual, or cognitive aspects (Leggio & Molinari, 2015). This is supported by three main lines of evidence: 1) damage to cerebellum impairs the ability to recognize sequences without explicit verbal instructions; 2) cerebellar damage affects the correct generation of somatosensory and auditory Mismatch Negativity (MMN) (Molinari & Leggio, 2007) (Leggio & Molinari in Baumann et al., 2015); 3) cerebellar patients were impaired in sequence reconstruction to a greater extent than sequence execution (Molinari et al., 1997), depending on the injury localization (Molinari & Leggio, 2015). These authors also proposed an interesting link between cerebellar damage and schizophrenia and autism, basing on the common perceptual deficits observed (Leggio & Molinari in Baumann et al., 2015).

In a recent work, **Diedrichsen** and colleagues (Diedrichsen, King, Hernandez-Castillo, Sereno, & Ivry, 2019) questioned the very existence of a unique cerebellar function. They argued that the idea of a "universal cerebellar transform" is built on the notion that the cerebellum shows uniformity across its cortex, but this only suggests that the cerebellum is uniform in terms of implementation of its functions and not at a representational level (Diedrichsen et al., 2019). In other words, the cerebellum may be uniform in regard to how it realizes its function (within the neuronal tissue), but it is possible that it is responsible for different computational aspects depending on the task. They base this theory on human fMRI studies, in which a great heterogeneity of cerebellar connectivity with the brain was observed (see King et al., 2019 in the following paragraph). They propose the alternative possibility of *Multiple Functionality*: a single implementation process could subserve multiple computations, resulting in different cerebellar functions in different domains. Among the theories taken into account in the current paragraph, this is the only one that is not compatible with the DoT theory proposed by Schmahmann and colleagues (*Figure 1.9*).

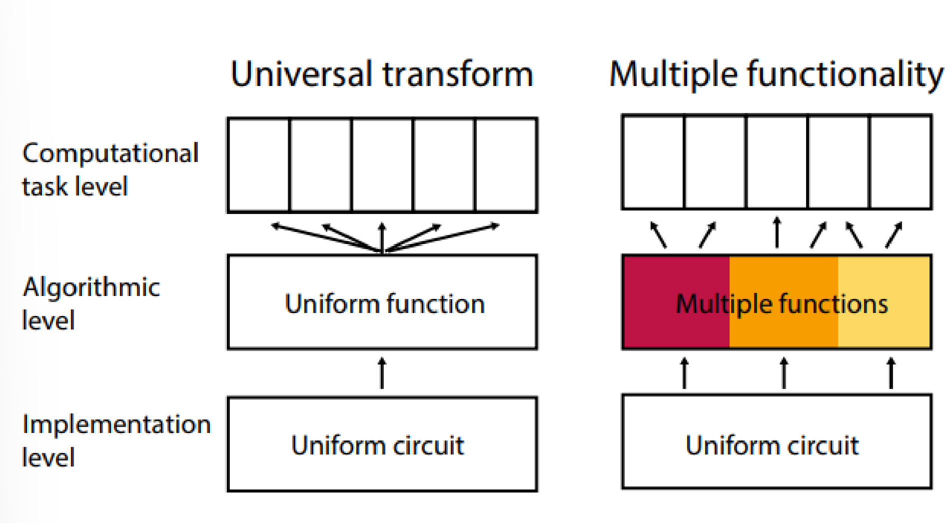


Figure 1.9.: *Schematic of comparison between the Universal Cerebellar Transform and the Multiple Functionality Theory. Such comparison is based on Marr's Three Levels of Analysis (computational level, algorithmic level and implementation level) (Marr, 1982). From Diedrichsen et al., 2019.*

1.1.4. Functional and topographic organization

After their experimentations, both Rolando and Flourens concluded that the cerebellum was solely implicated in motor control and that it was devoid of any functional localization. It was the latter (Fluorens, 1842) who introduced the long-lasting concept of the cerebellum "functioning as a whole" (Snider, 1950). It is noteworthy that this conclusion was widely suggested by the anatomical observations performed by Golgi (1894) and Ramon y Cajal (1909, 1911), who demonstrated that the cerebellar cortex was much more homogeneous than the cerebral cortex (Snider, 1950).

Luciani and Holmes observed that damages to the cerebellar hemispheres produced ipsilateral motor symptoms (Glickstein et al., 2009), whereas damages to the vermis were responsible for impairment of the trunk (Manni & Petrosini, 2004), but they did not have the appropriate means to find evidence of further localization. Holmes wisely wrote: “[...] But although my observations lend no support to the theory of focal localization of function in the cerebellar cortex they cannot be accepted as proof that such localization does not exist.” (Holmes in Glickstein et al., 2009).

Who firstly broke the rule of the “undifferentiated cerebellum" was Bolk (1906), with his pioneering proposal of a somatotopic organization of the cerebellar cortex. He stated that different portions of the cerebellar cortex control different muscle groups, in particular, the anterior lobe and lobulus simplex would be implicated in the movements of head and neck, whereas movements of the arts would be guided by the posterior hemispheres (see *Figure 1.10, a*) (Manni & Petrosini, 2004). The scheme proposed by Bolk was eventually overcome in the 40s, when Adrian (1943) managed to map out afferent and efferent cerebellar connections by means of the evoked potentials technique. He redefined the cerebellar somatotopic representation, with a reversed homunculus, represented entirely within the anterior lobe (see *Figure 1.10, c*) (Manni & Petrosini, 2004). The somatotopic maps were fully developed by Snider & Stowell (1944b) who identified two additional representations in the paramedian lobule bilaterally (see *Figure 1.10, d*) (Manni & Petrosini, 2004).

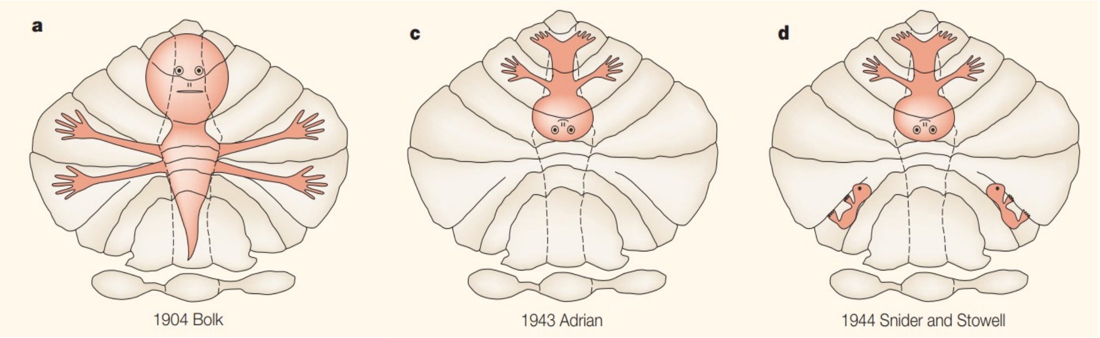


Figure 1.10: *The evolution of cerebellar somatotopic representations: Bolk, 1904 (a), Adrian, 1943 (c), Snider and Stowell, 1944 (d). From Manni & Petrosini, 2004.*

In addition to this, Snider for the first time localized visual and auditory areas within the cerebellar cortex. He also questioned himself about the meaning of the presence of such areas and the implication of the cerebellum in sensory functioning (Snider, 1950).

A large-scale functional organization was proposed by Schmahmann and colleagues, in various publications over the years (Schmahmann 1991, 1996, 2004) in which they proposed a distinction between motor and cognitive/affective areas within the cerebellar cortex. The idea of a dichotomy between the motor and non-motor cerebellum originally arised from animal and physiological analyses of the input and output cerebellar connectivity (Schmahmann, 2019; Devita et al., 2021) and from clinical evidence about the minimal presence of motor deficits following damages to the posterior cerebellum (Schmahmann, MacMore, & Vangel, 2009) (such clinical proofs included, among the others, the studies by Schmahmann and Sherman (1998) and Levisohn, Cronin - Golomb and Schmahmann (2000), discussed respectively in sections 1.2.3 and 1.3.1). Such suggestion was then corroborated by both resting state and task related fMRI studies (Schmahmann, 2019), resulting in a functional macroscopic subdivision of the cerebellar cortex in motor and cognitive regions, as depicted in *Figure 1.11.*

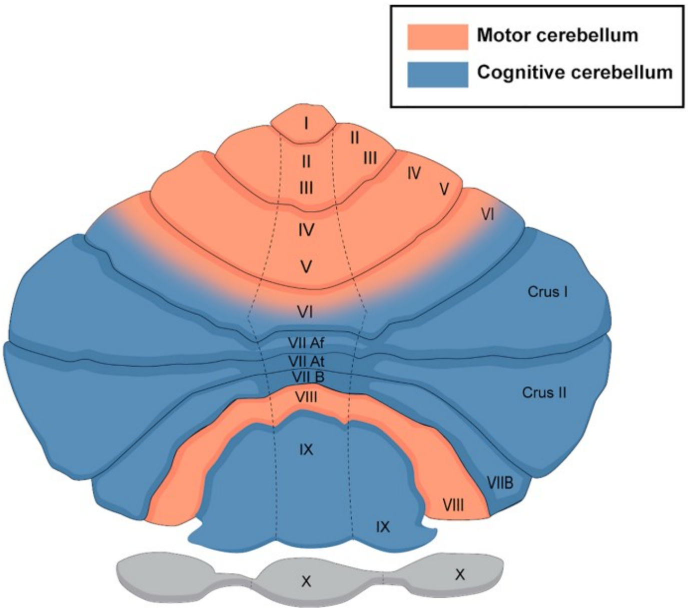


Figure 1.11: *Functional subdivision of the cerebellar cortex. Anterior lobe, part of lobule VI, and lobule VIII represent the "motor cerebellum" (in red), whereas lobule VII, part of*

lobule VI, and lobule IX are proposed as the "cognitive cerebellum" (in blue). As we will see, lobule X is responsible for different aspects than other "motor" areas, but can nonetheless be considered part of the sensorimotor cerebellum. From Devita et al., 2021.

As the cerebellar implication in cognitive and affective regulation was gradually solidified, researchers tried to provide more insights about the precise localization of cognitive functions. Stoodley and Schmahmann tried to better specify the localization of different cognitive functions within the cerebellar cortex through an fMRI meta-analysis (Stoodley & Schmahmann, 2009). By means of the Activation Likelihood Estimation (ALE) method, they localized peaks of functional cerebellar activation during accurately selected motor, cognitive and affective tasks. The results, summarized in *Table 1.1*, support the subdivision of the cerebellum into sensorimotor, cognitive and emotional regions (Stoodley and Schmahmann, 2009). In fact, no activation of the anterior/motor lobe (lobules I - V and VIII) was observed during the tasks implying cognitive/affective functioning.

Sensorimotor tasks	Right lobule V and adjacent part of lobule VI; Right lobule VIII.
Language	Right lobule VI, Crus I/II and lobule VIIAt; Left lobule VI (small).
Verbal Working Memory	Junction of lobule VI and Crus I, bilaterally; Medial lobule VI, bilaterally; Right lobule VIIIA (small).
Spatial processing	Left lobule VI; Right lobule VI (small).
Emotional processing	Left lobule VIIAt; Left lobule VI and Crus I; Right lobule VI.
Executive functions (obtained through comparison analyses)	Left lobule VI; Left lobule VIIB.

Table 1.1: *Summary of the results obtained by Stoodley & Schmahmann, 2009. The areas within the cerebellum which showed activation peaks during specific cognitive/emotional tasks are*

reported. Two regions unique to executive functions were obtained examining the differential activation between tasks implying executive functions and tasks implying other cognitive processes.

The achievement of such evidence was made possible by the previous creation of the already mentioned MRI atlas of the human cerebellum (Schmahmann, 2000), that allowed for a clear and unambiguous identification of activation loci. What was still missing was a fMRI study on a single individual, useful to overcome the difficulties related to the matching of activation sites from different studies, imaging techniques and individuals (Stoodley & Schmahmann, 2009). This lack was filled some years later in two studies by Stoodley, Valera, and Schmahmann (2010b, 2012), in which activation was examined, respectively, in a single healthy subject and in nine healthy individuals. The obtained results supported the subdivision arised in the previous meta-analysis, both for the motor/cognitive dichotomy, the lobule division and the lateralization of different cognitive functions (Schmahmann, 2012).

In the last decade, new evidence regarding functional localization of motor and non-motor functions have been obtained through fMRI studies. This body of evidence was summarized by Guell and Schmahmann (2020), who drew some conclusions about functional localization in the human cerebellum. To do so, functional activation was conceptualized as implying three main kinds of processing: motor processing, attentional/executive processing and default-mode processing (*Figure 1.12, a*).

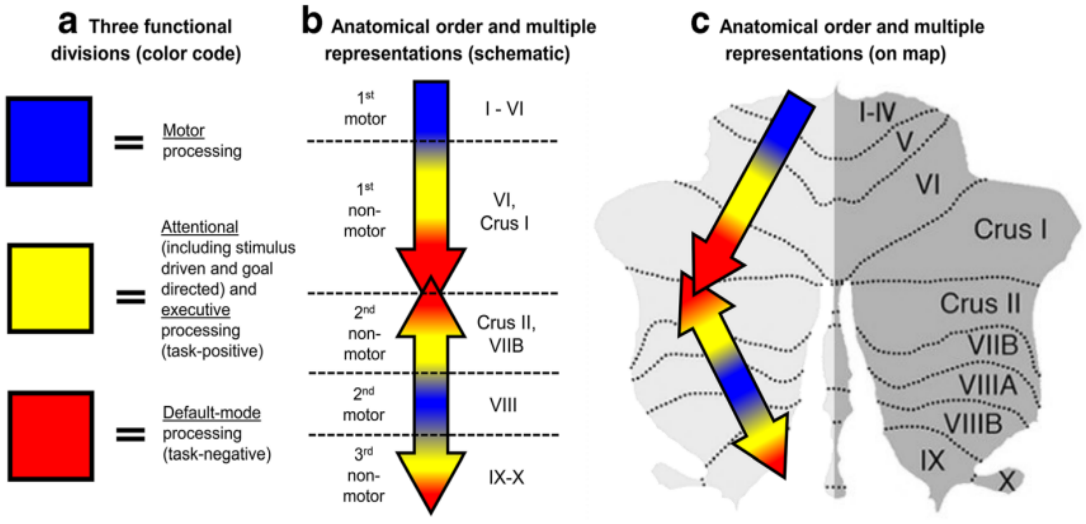


Figure 1.12: *Three colors are used to indicate the three fundamental poles of functional neuroanatomy. The arrows indicate the direction of "propagation" of specific functional ordering, first schematically (b) and then superimposed on the cerebellar cortex (c). From Guell & Schmahmann, 2020.*

Motor processing refers to areas that show pure motor activations (obtained through subtracting method) or functional connectivity with motor cerebral areas. Attentional/executive processing is derived from similar subtracting and connectivity evidence in relation to stimulus-driven attention, goal-oriented attention and executive functioning. This kind of processes imply ventral and dorsal attention networks as well as fronto-parietal areas (Guell & Schmahmann, 2020). Finally, default-mode processing is implied in inattentive states (mind wandering, for example) and is most active at rest, in an inverse correlation with attentional processing (Fox et al., 2015). As depicted in *Figure 1.11 (b)*, these three kinds of functional processes are redundantly present in the cerebellar cortex, in an ordered manner: from motor, to attentional, to default-mode (Guell & Schmahmann, 2020). This regularity results in two motor representations in lobules I-VI and lobule VIII and three non-motor representations in lobules VI-Crus I, lobules VIIB-Crus II and lobules IX-X (*Figure 1.11, c*). Such evidence brought further insights into the investigation of functional cerebellar localization and widened the results previously obtained by Stoodley and Schmahmann (Stoodley & Schmahmann, 2009, 2010a) (Stoodley, Valera & Schmahmann, 2010b, 2012), also integrating cerebellar activation not strictly related to specific motor, cognitive or affective tasks (i.e., default-mode network). This particular aspect is even further reinforcing theorizations of the cerebellum as a widely interconnected component of different cerebro-cerebellar networks, implied in *all kinds* of neural activities.

Recently King, Hernandez-Castillo, Poldrack, Ivry, & Diedrichsen (2019), provided an alternative approach to the cerebellar functional localization, with a strictly task-related analysis conducted in a sample of healthy individuals performing a multi-domain task battery (MDTB) composed of 47 different task conditions. Their result, as depicted in *Figure 1.13,* is a complex parcellation that would comprehensively describe cerebellar functional localization. Interestingly, it emerged that commonly used lobular distinction was not useful in demarcating functional localization, except for a large-scale subdivision into motor and non-motor regions (King et al., 2019). In fact, regions 1, 2 and 3 were active in relation to motor tasks, whereas the remaining regions (from 4 to 10) were more linked with different cognitive processing. This kind of evidence could open the path for new conceptions about localization of cerebellar functions.

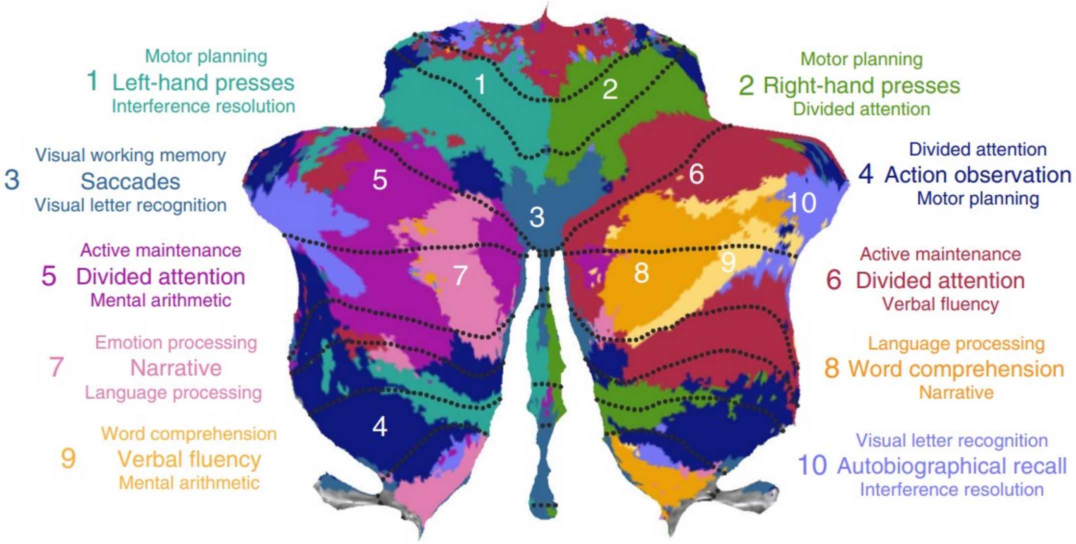


Figure 1.13: *Ten functional regions derived from MDTB parcellation, represented on the unfolded cerebellar cortex. Each area is associated with the three best characterizing features. Font size indicates the weights of each process. From King et al., 2019.*

1.2. The damaged cerebellum

Although attention has historically been posed on the motor aspects, damages to the cerebellum can result in a plethora of different signs and symptoms. Through an increasing body of evidence, we can now state that the cerebellar syndrome is not only characterized by deficit of motor coordination and equilibrium, but also comprehends cognitive, affective and perceptual impairments. In this regard, the classification proposed by Manto & Marien (2015) represents a clarifying framework for the multifaceted cerebellar syndrome and could therefore be useful to better understand the following sections. They proposed to integrate the new Schmahmann's Syndrome (Cerebellar Cognitive Affective Syndrome - CCAS) with the two consolidated Cerebellar Motor Syndrome (CMS) and Cerebellar Vestibular Syndrome (CVS), to form the “*three cornerstones of clinical ataxiology*” (Manto & Marien, 2015). This could represent a precious aid for clinicians to perform complete assessment and consequent treatment of cerebellar deficits, avoiding leaving aside important and often underestimated aspects that could cause relevant functional impairment to the patients in daily life.

1.2.1. The Cerebellar Motor Syndrome

When talking about the Cerebellar Motor Syndrome (CMS), we commonly refer to the occurrence of deficits in three different domains: limbs movement and coordination (limb ataxia), speech mechanics (dysarthria), and gait/postural control (Manto & Marien, 2015). These clinical symptoms have been examined in depth over time and it goes beyond the aim of the present work to examine them in detail. However, an attempt will be made to go through all these different aspects, also providing some hints about the theoretical explanations of the various deficits.

In the general domain of **limb ataxia**, the most frequently observed signs and symptoms can be further classified in three main categories: deficit in reaching objects (i.e., dysmetria), impairment of grasping objects, and difficulties with Rapid Alternating Movements (RAMs) (or Diadochokinesia) (Bodranghien et al., 2016).

Dysmetria is the impairment of a voluntary movement oriented toward a precise goal. The movement can either end or slow down before reaching the goal (and that is the case of hypometria) or overshoot the goal (in the case of hypermetria) (Holmes, 1917). Hypometria is less common in cerebellar patients, and it is therefore less specifically studied (Grimaldi and Manto, 2011). Although hypermetria is not specific to cerebellar disease, its presence strongly suggests an underlying cerebellar damage (Bodranghien & Manto in Bodranghien et al., 2016), especially when associated with other deficits, such as tremor and RAMs impairment (see below). Numerous studies have analysed the main feature of limb dysmetria (Bodranghien & Manto in Bodranghien et al., 2016). The error in reaching the target is modulated by the speed of movement (it is largest when the movement is performed as fast as possible) (Grimaldi, 2021) and increases if a weight is attached to the arm in order to artificially add inertia to the movement (Manto et al., 1994). Therefore, adding a weight to the arm during the evaluation represents a useful precaution to detect hypermetria with more sensitivity. This inertia-sensitivity is thought to reflect an impairment in the coordination of agonist/antagonist muscles during the execution of reaching movements. Among the others, Manto and colleagues (1994) found evidence, through EMG analysis, that cerebellar patients are unable to properly activate antagonist muscles in terms of onset and intensity and therefore cannot adapt to different inertial conditions. This phenomenon is strictly related to the conceptualization of the cerebellum as a crucial player for the creation and storage of internal body dynamics, essential for accurate motor control (Manto, 2009; Bhanpuri et al., 2014).

Impairment in *grasping* objects is another important aspect to consider when evaluating signs and symptoms of CMS, because of the consequent daily life impairment. Such a disorder could be caused by many other signs and symptoms of cerebellar diseases, like dysmetria, tremor or oculomotor deficits (Nowak in Bodranghien et al., 2016). This could be a possible reason why grasping itself is not assessed by the most common clinical ataxia scales. Several studies, conducted by Nowak and colleagues (Nowak et al., 2002; Rost et al., 2005), tried to overcome this issue by evaluating kinetic (related to force) and kinematic (related to timing) aspects of movement with appropriate technological instrumentation. They observed, in particular, that cerebellar damage increases the time needed to obtain a correct grasp and the variability of grasp force (Nowak in Bodranghien et al., 2016). In cerebellar patients, grasp aperture is exaggerated and prolonged time of contact between fingers and object is needed to obtain an acceptable configuration (Nowak, Timmann & Hermsdorfer in Manto et al., 2013). Other observed issues are incorrect coupling of grasp and load force and increased variability related to the presence of tremor (Nowak in Bodranghien et al., 2016). Novak provided an interpretation of grasping deficits in relation to the motor prediction models (Wolpert & Flanagan, 2001), widely used for the theorization of motor cerebellar impairment: he stated that in cerebellar patients the reactive adaptation, relying on external feedback, is preserved, whereas the forward adaptation is impaired, resulting in a correction gap when, for example, inertial forces are added to the movement (Nowak in Bodranghien et al., 2016).

As already mentioned, impairment of *Rapid Alternating Movements* (RAMs) was first observed by Joseph Babinski (Babinski, 1902), through the rapid pronation and supination of the forearm. The term he chose to describe this peculiar deficit, “diadonocinèsie”, was derived from the Greek (“Diadochos” = “Succeeding” and “Kinesis” = “Movement”) (Steiner and Timmann in Bodranghien et al., 2016). The deficit was also observed by Holmes in his pioneering studies and later included in the common cerebellar examinations (Campbell & DeJong, 2005). It is assessed through various tasks, such as asking the patient to imitate screwing in a light bulb (Steiner and Timmann in Bodranghien et al., 2016). Subsequent studies performed on animals or through EMG attributed this peculiar deficit to the delayed cessation of the agonist muscle, that in turn causes a delayed activation of the antagonist (Conrad & Brooks, 1973). For what it concerns its explanation, Thach supported the critical role played by the cerebellum in the coordination of muscle synergies (Thach et al., 1993), in line with the definition previously made by Babinski of “asynergia” as the “inability to combine each element of a movement into a complex motor action” (Babinski, 1899). Moreover, a specific characteristic of the adiadochokinesia is the impairment of the rhythmic and temporal features of movement (Grimaldi in Gruol et al., 2016), originally observed by Wertham, who defined it as “dysrhythmokinesia” (Wertham, 1929). This deficit can be assessed by asking the patient to rhythmically tap a finger on the table and can occur in a context of preserved movement accuracy (Grimaldi in Gruol et al., 2016). Such a feature could be in line with the timing hypothesis, previously described, in which the cerebellum would be implied in regulation of timing aspects of motor and non-motor processes (Ivry, 1996).

No motor coordination deficit can be defined as specific of cerebellar damage (Steiner and Timmann in Bodranghien et al., 2016) but, among all of them, an impairment of RAMs is certainly a very suggestive feature.

Another important aspect implied in MCS is the **control of speech**, whose deterioration was called “ataxic dysarthria” for the first time by Darley, Aronson and Brown (1975). Impairment of speech characteristics and intelligibility was already observed by Holmes, who described the speech of cerebellar patients, with remarkable clinical accuracy, as “[...] usually slow, drawling and monotonous, but at the same time [...] staccato and scanning. This gives it an almost typical “sing-song” character and makes it indistinct and often difficult to understand" (Holmes, 1917). This brief definition is comprehensive of many features that have been accurately analysed in more recent times: articulatory and phonatory disturbances, prosodic deficit, and consequent reduction in intelligibility and naturalness (Kent et al., 2000), (Ackermann, 2013), (Marien & Van Dun in Gruol et al., 2016), (Hilger et al., 2022).

Ataxic dysarthria refers to the motor deficient aspects of speech and language production, consisting in symptoms such as: scanning pattern of speech, impaired articulation of vowels and consonants, and abnormal voice quality (Kent et al., 2000). Besides that, there are specific characteristics of speech that are problematic for cerebellar patients. The most disturbed parameters in a sustained phonation task (prolonged production of vowels) were found to be the fluctuations of fundamental frequency, its standard deviation and the peak amplitude variation (Kent et al., 2000). A syllable alternating motion rate task (syllable AMR, in which the patient is asked to repeat a consonant-vowel syllable as fast as he can for a certain amount of time (Wang et al., 2004)) is optimal in the diagnosis of ataxic dysarthria, because of its independence from high order linguistic capacities. Kent and colleagues observed that the slowness and variability of ataxic patients in syllable AMR was due to the temporal lengthening of both syllable and inter-syllable duration (Kent et al., 2000).

Some researchers attribute this kind of impairment to adiadochokinesia (i.e., the slowing in the production of alternating movements, see above), occurring in a different modality (Ziegler & Wessel, 1994). Ataxic dysarthria was seen to occur also in comorbidity with respiratory insufficiency or “ataxic breathing”, that is most likely caused by compromission or deterioration of the pons and the medulla

(Kent et al., 2000). This additional difficulty consists of irregularity of chest wall movements and can cause a deficit in air supply.

In addition to these specific features of speech, it is crucial to take into account more functional aspects, that are the degree of intelligibility and naturalness of the speech. In contrast to what is observed in different forms of aphasia, intelligibility (the occurred transmission of the communicative message) is not necessarily impaired in cerebellar disease. In a recent study (Hilger et al., 2022), Hilger and colleagues found evidence that both intelligibility and naturalness were significantly different from controls, but naturalness was impaired to a greater extent, and it was therefore a better predictor of the presence of cerebellar disease. It is important to consider this feature of speech production because of its connection to prosody (Cole et al., 2015) and because, if overlooked, clinicians could consider rehabilitation not strictly necessary (Hilger et al., 2022).

In the current paragraph, only the motor related aspects of speech impairment were considered. As it will be later discussed, specific aspects of language production are included in the spectrum of the cognitive deficits resulting from cerebellar damage. This will be dealt with in the section dedicated to the Cerebellar Cognitive Affective Syndrome (1.2.3 and following).

Disorders of **gait and posture** were firstly described in humans by Hammond in 1871, who wrote that the gait of a cerebellar patient was comparable to the gait of a drunken man (Fine, Ionita & Lohr, 2002). Such deficits commonly emerge during the cerebellar neurological examination, in the form of clumsy movements, wide-based gait and swaggering when standing still (Casali and Serrao in Bodranghien et al., 2016). Holmes (1917) observed unsteadiness with danger of falling, especially towards the side of the cerebellar lesion. Moreover, he noted a difficulty to suddenly stop the walking and posture abnormalities ("very striking attitude in standing") that he considered, at least partially, due to a compensatory attempt to maintain equilibrium (Holmes, 1917). Jumping forward to recent times, the clinical evaluation of gait and posture disorders is supported not only by clinical scales, but also by technological methods such as 3D motion capture, pressure-sensitive walkways and inertial sensors (Buckley, Mazzà and McNeill, 2018). Some studies tried to systematically classify gait and posture deficits and to identify the most deficient parameters. Impairments were specifically found in linear walking and in gait initiation, termination and turning (Casali and Serrao in Bodranghien et al., 2016). Buckley and colleagues (2018) conducted a meta-analysis including technological gait analysis studies, to identify the parameters that were better able to distinguish between cerebellar patients and controls. They found that the most prominent features were: decrease in speed and step length and increase in double limb support phase duration, step length variability and stride time variability. This and other studies (see for example Serrao et al., 2012), support the idea that increased gait variability directly reflects cerebellar damage, whereas other features, such as increased step width and reduced step length and gait speed, represent compensatory mechanisms for the general instability (Buckley, Mazzà and McNeill, 2018). EMG studies have highlighted that ataxic patients tend to stiffen both their agonist and antagonist muscle in order to compensate for their instability (Casali and Serrao in Bodranghien et al., 2016).

Deficits of the oculomotor system are commonly deriving from cerebellar damages. They are not separated in the routine bedside evaluation but, in our theoretical framework, fall within the Vestibulo-Cerebellar Syndrome, which will be addressed in the following section.

1.2.2. The Vestibulo-Cerebellar Syndrome

The so-called Vestibular Cerebellum represents the phylogenetically oldest part of the cerebellum and is composed of flocculus and paraflocculus, together with nodulus and uvula (respectively, the vermal portions of lobule IX and X in Schmahmann nomenclature (Schmahmann et al., 1999)) (Kheradmand & Zee, 2011). The Vestibulo-Cerebellar Syndrome results from damage to such areas and to a dorsal portion of the vermis, namely lobules V - VII, also called Oculomotor Vermis (OMV), together with the interconnected posterior portion of the Fastigial Nucleus (Kheradmand & Zee, 2011).

Overall, the VCS implies vertigo, dizziness (Manto & Marien, 2015) and a plethora of oculomotor signs and symptoms, that will be briefly described below.

VCS impairs the ability to smoothly track moving objects through *pursuit* eye movements (Kheradmand, Kim & Zee in Gruol et al., 2016), so that the object is tracked through small saccades instead of a smooth eye movement (Tilikete & Stroop in Bodranghien et al., 2016). *Gaze holding* is also compromised, so that when a patient is asked to maintain fixation on a peripheral side of the visual field, the eyes tend to drift centripetally, resulting in the *gaze - evoked nystagmus* (Kheradmand & Zee, 2011), with slow phase towards the medial axis and fast phase towards periphery. This kind of nystagmus is particularly linked to flocculus-paraflocculus lesions, which interrupts the corrective feedback loop that connects the brainstem integrator of eye movements to this specific cerebellar portion (Beh, Frohman & Frohman, 2017).

The *Vestibulo-Ocular Reflex (VOR)* is produced to compensate for head rotation (rVOR) or translation (tVOR) during gaze fixation (Kheradmand, Kim & Zee in Gruol et al., 2016). The flocculus and paraflocculus are thought to be responsible for rVOR, whereas nodulus and uvula are more likely to produce the tVOR (Beh, Frohman & Frohman, 2017). It is important to note that cerebellar lesions do not abolish VOR completely, but compromise VOR from adapting to change in direction or to variation in target distance (Kheradmand & Zee, 2011).

Down Beat Nystagmus is a common feature deriving from lesions to different parts of the vestibular cerebellum and is characterized by a drifting up slow phase and corrective downward saccades (Kheradmand & Zee, 2011). It can occur in variable velocity and its causes and subserving anatomical structures are still debated. *Periodic Alternating Nystagmus* is instead a horizontal nystagmus that changes its direction every 90-120 seconds (Beh, Frohman & Frohman, 2017). An explanatory hypothesis to this symptom is that vestibular nuclei disinhibition causes the slow phase to occur in conjunction with an intact corrective mechanism, that causes the change in direction (Kheradmand, Kim & Zee in Gruol et al., 2016).

Vestibular Cerebellum also controls *eye vergence* and, for this reason, its damage results in a vertical misalignment of the eyes (Beh, Frohman & Frohman, 2017). If such misalignment occurs in conjunction with ocular torsion and head tilt, the symptom is overall called *ocular tilt reaction* (Beh, Frohman & Frohman, 2017).

Lastly, control of *saccades* is attributed to Oculomotor Vermis (OMV) and to the posterior Fastigial Nucleus that, if lesioned, produce respectively saccadic hypometria and hypermetria (Kheradmand, Kim & Zee in Gruol et al., 2016). Similarly to what happens in VOR, the cerebellum is not responsible for the production of saccades, but rather for the control of saccades trajectory, latency, accuracy and other dynamic properties (Kheradmand & Zee, 2011). In particular, cerebellum increases the acceleration of the eye movement, monitors its course and ensures that the saccade stops on target (Beh, Frohman & Frohman, 2017). *Square-wave jerks* and *opsoclonus* are two common signs of damage to these portions of the cerebellum and consist of uncontrolled and intrusive saccadic movements (Beh, Frohman & Frohman, 2017).

The overall and widely accepted function of the cerebellum for what it concerns ocular movements, is to correct and smooth oculo-motor movements, in order to maximize the visual analysis of objects. To do so, it is necessary to bring the object of interest to the fovea and to keep it there for the amount of time necessary for the brain to analyse it (Kheradmand & Zee, 2011).

Localization of different subsystems within the Vestibular Cerebellum is difficult, because of multiple overlapping representations, but some preferences are present, such as for saccades to be controlled by VOR and Fastigial Nuclei.

Oculomotor impairments are distinctive cerebellar symptoms and are therefore crucially important for clinical diagnosis and for the study of the cerebellum in general, serving as a “biological marker” (Kheradmand, Kim & Zee in Gruol et al., 2016) of cerebellar disease.

There are three main clinical scales for the assessment of the MCS and VCS, namely ICARS, SARA and BARS scales (Manto & Marien, 2015). The International Cooperating Ataxia Rating Scale (ICARS) (Trouillas et al., 1997) is a complete tool not frequently used in clinical practice because of its length (19 items) (Manto & Marien, 2015). The Scale for Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006) is shorter (8 items) and therefore more practical (Manto & Marien, 2015), but it was criticized because it lacks an assessment of eye movements (Bodranghien et al., 2016). The Brief Ataxia Rating Scale (BARS) (Schmahmann, Gardner, MacMore, & Vangel, 2009) is short (5 items), complete and specially designed for clinical purposes (Bodranghien et al., 2016).

1.2.3. The Cerebellar Cognitive Affective Syndrome

The Cerebellar Cognitive Affective Syndrome (CCAS) was originally defined and characterized by doctors Jeremy Schmahmann and Janet Sherman in the homonymous article, dated 1998 (Schmahmann & Sherman, 1998). This important result, however, was not achieved effortlessly, being preceded by years of anatomical, physiological, and theoretical studies. The first works that must be considered in this sense are those resulting from the collaboration between Schmahmann and Pandya from 1987 to 1998 (see Schmahmann & Pandya, 1997 for a summary). These studies have served to lay the foundation for the CCAS theorization, through the identification of the neuroanatomical substrate of the cerebrocerebellar circuit. These anatomical findings were crucial to give strength to the subsequent clinical and theoretical observations. Such a premise should not be underestimated because, at that time, the cerebellar implication in non-motor functions was a revolutionary idea. It was therefore necessary to determine the existence of the afferent and efferent cerebellar connectivity to give solidity to the finding of cognitive and affective deficits resulting from their disruption.

Two were the main assumptions at the very base of this anatomical investigation (Schmahmann, 1996):

- Cognitive functions are dependent on the structure, so that if there is a cerebellar implication in high order cognitive functioning, one should be able to localize its anatomical substrate.
- Cognitive functions are implemented through “distributed neural circuits”, that in this case comprehend multiple, cortical and subcortical, cerebral and cerebellar areas.

These two notions converge and are confirmed by the numerous evidence of the presence of a **cerebrocerebellar circuit**.

The cerebrocerebellar circuit is composed of a feedforward loop, which is in turn formed by corticopontine and pontocerebellar connections, and a feedback loop, consisting of cortico-nuclear cerebellar connections and cerebello-thalamic and thalamo-cortical pathways (Schmahmann, 1996). The feedforward section is meant to transmit information from brain to cerebellum. The information is then elaborated, adjusted and corrected and then transmitted back to the cerebral cortex. This mechanism was well established for what it concerns motor control, with the widely recognized implication in coordination of movement and equilibrium. On the contrary, the findings regarding anatomical connections from various non-motor areas of the brain cortex to the cerebellum were groundbreaking.

The corticopontine connections within the feedforward pathway were by far the most deeply studied of these aspects, by means of animal tract studies mostly performed on monkeys (Schmahmann in Gruol et al., 2016).

Evidence of vast multiple connectivity between cortical association areas and pons was found, regarding, in particular, posterior parietal areas (superior and inferior parietal lobules), temporal lobe areas (superior temporal gyrus, supratemporal plane and MT area), rostral cingulate areas, parastriate cortices (and parahippocampal gyrus) and anterior insular cortex (Schmahmann, 1996, 1997, 2016). All these structures are implicated in cognitive functions or in emotion regulation, reflecting the variety of deficits observed in cerebellar patients and later classified within the CCAS framework (Schmahmann, 1996, 1998b). These studies reveal that each cortical area is connected with specific portions of the pontine nuclei, forming an articulate pattern of interconnection (Schmahmann, 1996) (see *Figure 1.14*).

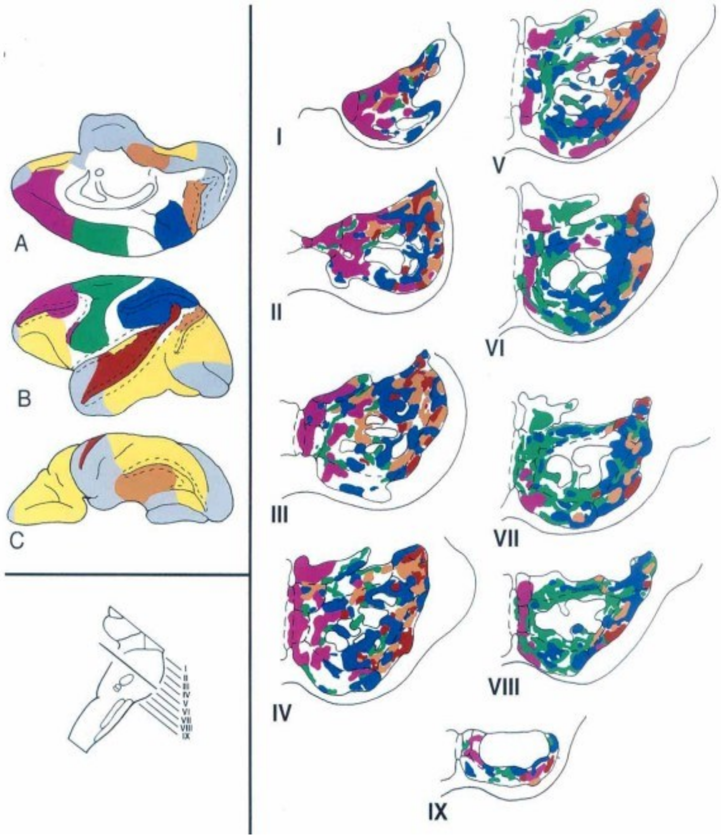


Figure 1.14: *Corticopontine projections of the rhesus monkey. Colors are used to map projections from different associative cortical areas, namely: prefrontal (purple), posterior parietal (blue), temporal (red), and parastriate and parahippocampal (orange). Areas that showed pons projections by other investigators are reported in white. Regions that showed no pons projection in both anterograde and retrograde studies are colored in yellow. Finally, areas that were not connected to the pons according to retrograde studies are indicated in gray. On the upper left of the figure, medial (A), lateral (B) and ventral (C) surfaces of brain hemispheres are reported. On the lower left, the considered pons sections are indicated from I to IX. On the right, the corresponding I-IX rostrocaudal pons views are illustrated. From Schmahmann, 1996.*

Interestingly, no efferent pathways were found coming from the inferotemporal lobe and thus belonging to the ventral visual stream (Schmahmann 1996, 2016). This apparently surprising dichotomy in structural connectivity is consistent with the different kinds of impairment observed in CCAS, that in fact do not concern object recognition (Schmahmann & Sherman, 1998).

In the same period, Leiner, Leiner, & Dow (1986) independently proposed that the cerebellum could play a role in cognition, regarding in particular the “skillful manipulation of ideas”. They based this proposal on phylogenetic and neurophysiological evidence. Specifically, they highlighted the exponential development in humans of the associative cerebral areas and of the neocerebellar cortex, in parallel with the newest ventrolateral portion of the cerebellar dentate nucleus. The loop between cerebellum and such brain regions would subserve the cerebellar role in learning, also applicable to learning of mental functions (Leiner, Leiner, & Dow, 1986).

A theoretical framework for a cerebellar role in cognition and affect regulation was gradually proposed and refined by Schmahmann. In the article entitled, indeed, “An emerging concept” (1991) the author for the first time mentions the DoT theory and the implication of the cerebellar hemisphere in cognitive aspects such as planning, memory, spatial and temporal parameters and learning. Such theorizations were supported by various, but still anecdotal, clinical evidence of non-motor consequence of cerebellar damage. Such findings, regarding for example single case studies of cerebellar agenesis or degenerative cerebellar disease, allowed for limited conclusion because it was not possible to exclude a concurrent cerebral implication (Schmahmann, 1991). However, major neuropsychological evidence was later found in more controlled studies, progressively enriching the clinical background supporting the CCAS. From this point on, the author and his collaborators carried on a work of enlargement of the reported clinical cases of CCAS and of development of the theoretical foundations. The DoT theory was further shaped in the dedicated article of 1998 (Schmahmann, 1998). Here, it is depicted in analogy with the dysmetria of movement, commonly described in the cerebellar motor syndrome. In the same way the cerebellum corrects the fine voluntary motor actions, it also corrects the mental and cognitive actions, by lining up the outcome and the intention of social interactions or mental operations. The cerebellum would therefore act as an “oscillation dampener” (Schmahmann, 1998), bringing back affective and cognitive functioning to a homeostatic baseline. If this tool is removed or damaged, as it happens in cerebellar disease or injury, the mental processes will be unpredictable, the social interaction not adequate to the context demands and the goal in general will be reached by “trial and error”, as it happens in motor cerebellar patients.

The concept of Universal Cerebellar Transform (UCT) was introduced only in 2001, later than the first description of the Cerebellar Cognitive Affective Syndrome in 1998 (Schmahmann, 2001).

As just mentioned, the CCAS was finally theorized in the homonymous article dated 1998 (Schmahmann & Sherman, 1998), in which extensive and longitudinal evaluation of 20 patients with injuries confined to the cerebellum was performed. This aspect represented the missing puzzle piece at the time, because the earlier investigation on clinical single cases was not sufficient for a deep comprehension and classification of CCAS symptoms, especially because the confinement to the cerebellum was not always certain (Schmahmann, 2010).

Patients underwent neurological examination (to assess the presence of Motor and Vestibular Cerebellar Syndrome), bedside mental state testing and in-depth neuropsychological testing, as well as MRI (T1 and T2) and EEG administration. The exclusion and inclusion criteria were a crucial aspect of this study, because, as mentioned before, to take in consideration patients with injury confined to the cerebellum was imperative. The EEG administration was useful to exclude the presence of epileptic issues or general slowing and the neurological examination served to identify possible pathological signs, other than the ones commonly related to the Cerebellar Motor Syndrome.

The bedside clinical evaluation was useful to narrow the field of possible deficit, excluding the presence of deficit related to neglect, agnosia and aphasic syndrome (*Figure 1.15*).

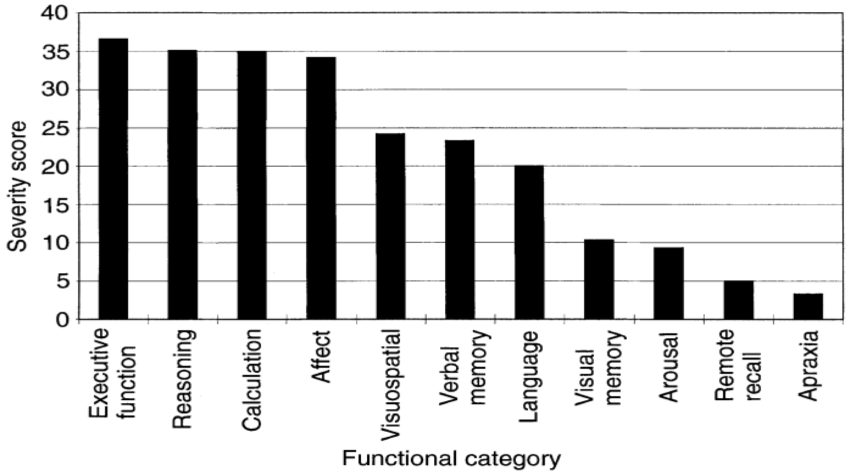


Figure 1.15: *Bar graph describing the results of bedside mental state testing. The assignment of severity scores allowed for a semi-quantitative comparison across*

functional categories and between patients. Major deficits were found in the areas of executive functioning, reasoning, calculation and affect, whereas the less affected domains resulted in visual memory, arousal, remote recall and apraxia. From Schmahmann & Sherman, 1998.

The scores of each patient at neuropsychological testing were transformed into z-scores to confront their performance in different cognitive domains with the available normative data, matched for age and education. The results from the neuropsychological testing were then confronted with what emerged from the bedside clinical evaluation to describe the “core features” of CCAS. The author concluded that the CCAS is characterized by deficit in the following domains:

- Executive functions, related in particular to planning, set shifting, working memory, verbal fluency and abstract reasoning;
- Visuospatial ability, including visuospatial organization and memory;
- Personality changes, in the form of exaggeration or blunting of affects and disinhibition;
- Linguistic difficulties, in particular dysprosody, agrammatism and mild anomia.

Some effective and comprehensive examples of those deficits are reported within the study through single cases (Schmahmann & Sherman, 1998). The 62 years old attorney reported as “Case 3” was unable to reproduce simple arrangements of objects and perseverated multiple times in copying a diagram. His wife also reported changes in personality. At clinical evaluation, his behavior fluctuated between apathy and disinhibition, in the form of hyperfamiliarity. The woman in “Case 1” performed a maze-task at an 8-year-old level and failed at the similarities test. In *Figure 1.16*, her production when asked to draw a clock is reported. “Case 15” was a 20-year-old college student who was unable to generate an alternating list of vegetables and fruits. Her verbal fluency was also diminished (only five cities named in one minute) as well as her visuospatial abilities.

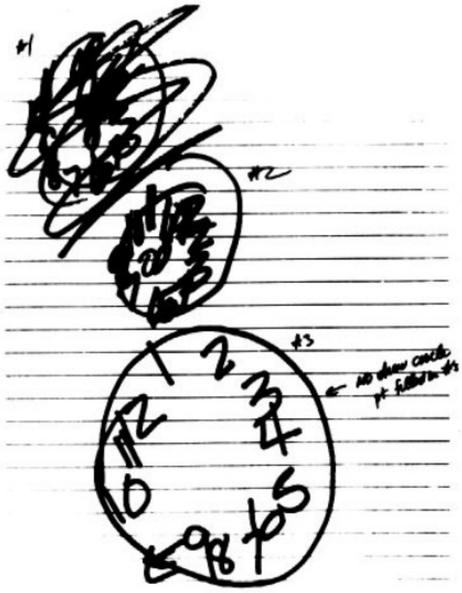


Figure 1.16: *Case 1 was a 22-year-old female college student, with a midline cerebellar tumor that was surgically removed. In the postoperative period, she showed behavioral abnormalities and global cognitive deficits. As depicted in the figure, her illustrations were rudimental and lacking of planification. From Schmahmann & Sherman, 1998*

In a different review article, Schmahmann (1998) reported the case of a patient that is explanatory of the concept of Dysmetria of Thought, as an "overshoot" in cognitive processes (Schmahmann, 1998). When asked to write a sentence and draw a clock, the 28-year-old architect wrote an eight-lines sentence and proceeded to draw a complex figure comprising different clocks and a person next to them (*Figure 1.17*). This peculiar case was reported to exemplify the concept of mismatch between the assignment and the response provided, but also between the context and the produced behavior.

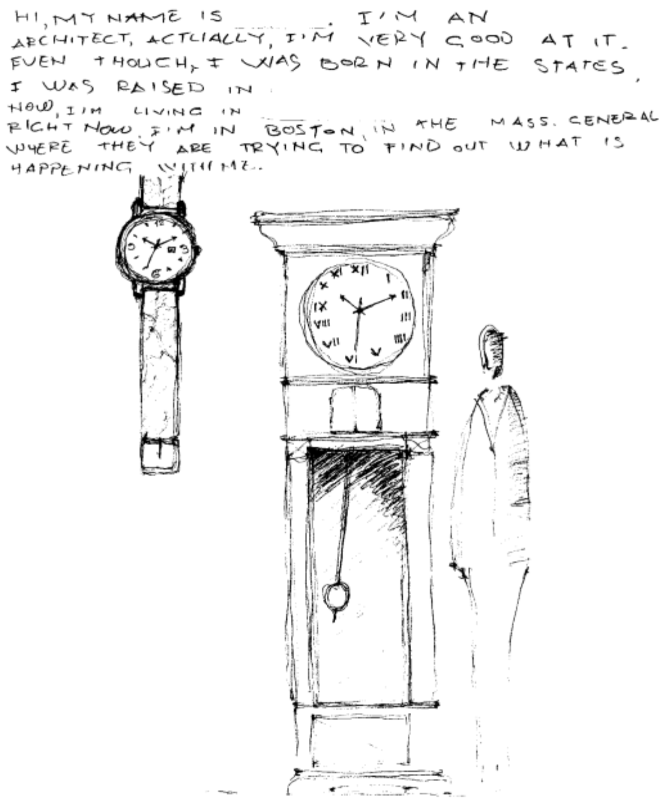

HI, MY NAME IS _______. I'M AN
ARCHITECT, ACTUALLY, I'M VERY GOOD AT IT.
EVEN THOUGH, I WAS BORN IN THE STATES,
I WAS RAISED IN
NOW, I'M LIVING IN _______
RIGHT NOW, I'M IN BOSTON, IN THE MASS. GENERAL
WHERE THEY ARE TRYING TO FIND OUT WHAT IS
HAPPENING WITH ME.

Figure 1.17: *Responses of a patient with cerebellar degeneration when asked to write a sentence and draw a clock. After producing the long text, he first drew the wrist watch, then the grandfather clock and finally the person standing next to it. The whole process, during which he was not interrupted, lasted over twenty minutes. From Schmahmann, 1998.*

Already in the original study (Schmahmann & Sherman, 1998), the authors cautiously proposed a functional localization within the cerebellar cortex. They observed that cognitive and affective disturbances were more pronounced respectively in patients with posterior lobe and vermis lesions, whereas the anterior lobe seemed to be little involved in these kinds of deficits. As we already examined, such internal distinction was later confirmed by functional localization studies (see section 1.1.4).

The clinical and neuropsychological features of CCAS were hence defined. This study was not about the functional role of the cerebellum and so, although strictly linked to the DoT theory proposed by the same author, left the question open for further insights.

1.3. Towards the CCAS scale

In this final section of the chapter, the path towards the creation of the CCAS scale and its clinical uses and applications will be described. Firstly, a brief summary of clinical advancements and theoretical proposals that occurred from the first definition of the CCAS (1998) to the CCAS scale validation (2018) will be provided. In the second part, the main features and characteristics of the original CCAS scale will be analysed. The third section will deal with the clinical applications of the CCAS scale and the recent developments of the investigation about the cerebellar role in cognition, from 2018 to today.

1.3.1. Clinical and theoretical developments

Between 1998 and 2018, the year in which the CCAS scale was finally validated (Hoche et al., 2018), many studies deepened the exploration of the syndrome, through the collection of clinical data in various populations and the development of the theoretical framework. As a complete review would be too long and extensive, some examples of such studies have been selected and described.
Levisohn and colleagues (2000) studied retrospectively the neuropsychological profile of 19 children who underwent cerebellar tumor resection without receiving chemotherapy, which could prove to be a confounding variable. They found

consistent patterns of cognitive deficits, regarding visuospatial abilities, expressive language, verbal memory and digit span. They also found affective regulation impairment that could not be explained as part of the Posterior Fossa Syndrome (Levisohn et al., 2000). Despite some methodological limitations (retrospective analysis, small sample size), this study provided evidence that the cerebellar role in cognition could be important in the development of various cognitive and affective functions.

Rønning and colleagues (2005) investigated the neuropsychological outcomes in young adults that were surgically treated for posterior fossa tumors in childhood. One group (n=12) underwent surgery alone, whereas the other (n=11) was treated with surgery followed by radiotherapy and chemotherapy. They observed a significantly worse outcome, in almost all neuropsychological tests, in patients from the "surgery + chemotherapy" group, compared to the surgery alone group. However, patients belonging to the latter were seen impaired, in comparison with standard norms, in executive function, attention, psychomotor speed, verbal and visual memory. They therefore concluded that cerebellar injury alone could result in cognitive impairment, supporting the existence of the CCAS (Rønning et al., 2005).

When dealing with cerebellar damage occurring in children, other researchers instead preferred to differentiate between the CCAS and the postoperative Cerebellar Mutism Syndrome (or Posterior Fossa Syndrome). Wells and colleagues (2008) observed that, although there is partial overlap between these two syndromes, the CCAS is considered more chronic, occurs predominantly in adults and does not necessarily include the symptom of mutism. Many years later, a consensus was obtained on this issue, abolishing the term "Posterior Fossa Syndrome" and concluding that the postoperative Cerebellar Mutism Syndrome can be accompanied by various disorders, including CCAS (Gudrunardottir et al., 2016) (Schmahmann, 2020).

Wolf, Rapoport & Schweizer (2009) conducted a systematic review to evaluate more deeply the affective symptoms arising from a cerebellar injury and a meta-analysis to investigate the presence of significant difference between cerebellar patients and healthy controls. Five studies comprehended patients with cerebellar disease (spinocerebellar ataxias) and five included patients with cerebellar lesions. The systematic review showed evidence of higher depressive and anxiety scores in cerebellar patients in some of the studies, but not in all of them (Wolf, Rapoport & Schweizer, 2009). Other emotion regulation impairment such as apathy and personality changes were reported in one study. In the light of the promising theoretical framework and the important number of case reports available in literature, the authors concluded that such limited results could be addressed to the important limitations of the studies included in the review, such as inadequate comparison groups and the lack of sufficiently standardized and sensitive measures (Wolf, Rapoport & Schweizer, 2009).

Other forms of affective alterations were explored and, among them, evidence emerged of deficit in social cognition in spinocerebellar ataxia patients (Garrard et al., 2008), pathological laughing and crying in patients with pontocerebellar stroke (Parvizi et al., 2001) and affect dysregulation in other ataxia syndromes (Turkel et al., 2006).

In the years between the theorization of the CCAS and the development of the CCAS scale, numerous case studies were published, in which it was highlighted the presence of cognitive and affective symptoms in *pure* cerebellar patients, i.e., with lesions confined to the cerebellum. Paulus and colleagues (2004), for example, described the case of a 68-year-old man who reported cognitive and behavioral disorders in the acute phase of a cerebellar stroke, that caused a damage to the cerebellar hemispheres and vermis, observable as hyperintense signal at T2-weighted MRI (*Figure 1.18*). No damage was found in the medulla, brain hemispheres or brainstem (Paulus et al., 2004).

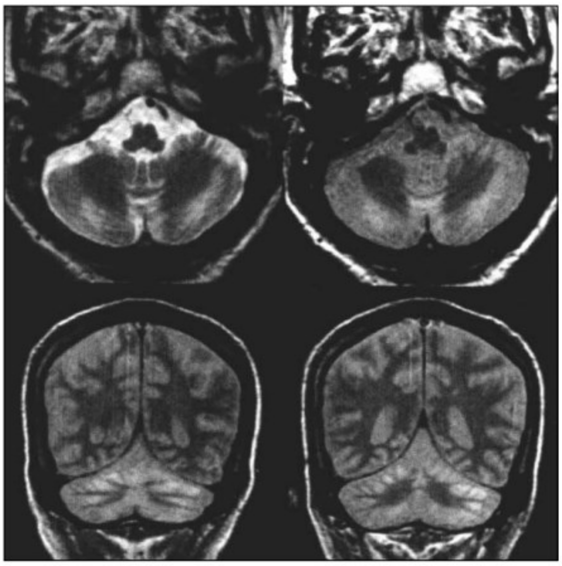


Figure 1.18: *In the higher row, two axial scans show hyperintense signal in the*

posterior cerebellar hemispheric and vermal cortex. In the lower row, coronal scans highlight cerebellar cortical alternation and white matter integrity. From Paulus et al., 2004.

The patient presented typical cerebellar motor symptoms in the acute phase, such as dysmetria, ataxia and dysprosodic language, and behavioral dysregulation in the subacute phase. After 4 months, when he was finally testable, neuropsychological deficits emerged in the domains of executive functioning (reasoning and planning), attention, memory and language. He also presented affective dysregulation and appeared anxious with uncontrollable crying episodes (Paulus et al., 2004).

Marien et al. (2009) examined a 58-year-old man with right superior cerebellar artery infarction and no structural cerebral damages. They observed a set of deficits consistent with the CCAS, in addition to visual dyslexia and surface dysgraphia. Moreover, they found SPECT evidence of cerebro-cerebellar diaschisis, with hypoperfusion of the left medial frontal area (*Figure 1.19*). These findings supported the implication of the cerebellum in contralateral cognitive modulation, relating, in particular, to "frontal" control of linguistic production (Fabbro, 2000), corroborating the regulator role of the cerebellum within the cerebro-cerebellar circuitry.

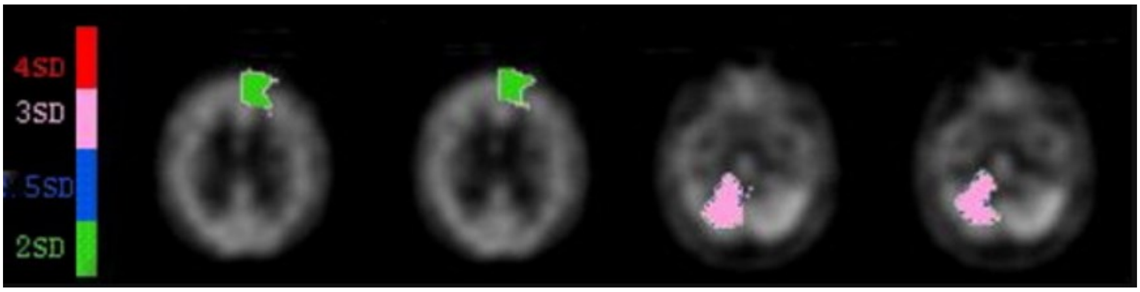


Figure 1.19: *SPECT scan showing coexisting hypoperfusion in the right cerebellar hemisphere and left medial frontal area. The evidence of a crossed cerebellar - cerebral diaschisis in a pure cerebellar patient highlights the functional impact of the lesion on a distant area, due to the lack of excitatory impulses. From Marien et al., 2009.*

Alongside this enrichment of clinical detections of CCAS, the theoretical framework was further expanded and detailed during this period through some publications by Schmahmann (2001a, 2001b, 2004, 2010).

The two works published in 2001 helped to summarize, respectively, the anatomical and clinical findings reached so far. Here, the Universal Cerebellar Transform (UCT) was firstly described and then integrated into the DoT theory (Schmahmann, 2001a, 2001b). The UCT blends well with the DoT, of which it represents a natural evolution and a further clarification. The UCT would be in fact the cerebellar function that could explain the motor *and* cognitive symptoms resulting from a cerebellar lesion.

A new conception of the cerebellum was growing up, as more and more researchers directed their efforts towards the investigation of its non-motor functionality. This was testified by the publication of various Consensus Paper about the cerebellar implication in wide range of mental aspects, such as movement and cognition (Koziol et al., 2014), perception (Baumann et al., 2015), emotion (Adamaszek et al., 2017) and even, more recently, social cognition (Van Overwalle et al., 2020).

1.3.2. CCAS scale: development process and features

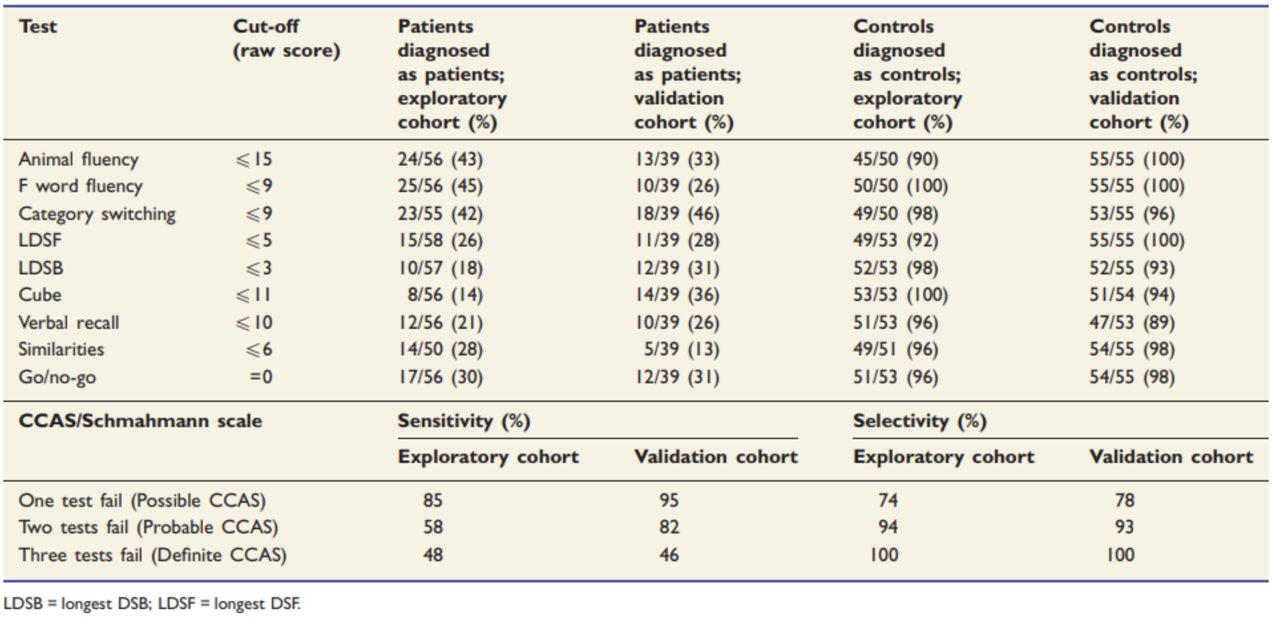
The Cerebellar Cognitive Affective/Schmahmann syndrome scale was finally developed in 2018 by Franziska Hoche and colleagues (Hoche et al., 2018), with the aim of providing a sensitive screening tool that could identify cognitive and affective symptoms attributable to CCAS. Seventy-seven patients (thirty-six with damage confined to the cerebellum) and fifty-eight matched controls were included in the study. All participants underwent comprehensive cognitive and neuropsychiatric evaluation. Patients alone were also administered with standard neurological evaluation and BARS scale (Schmahmann et al., 2009) for assessment of ataxia severity. Cognitive assessment comprehended a wide range of neuropsychological tests and batteries (34 tests, comprising a total of 70 subtests) (Hoche et al., 2018), involving the following cognitive domains: executive function, verbal memory, working memory, linguistic abilities, visuo-spatial abilities and abstract reasoning. Assessment of neuropsychiatric symptoms was performed by means of three instruments, namely the Cerebellar Neuropsychiatric Rating Scale (Daly et al., 2016), that was specifically developed according to previously observed affective and behavioral cerebellar symptomatology, Frontal System Behavior Scale (Grace et al., 1999) and Social and Communication Disorder Checklist (Skuse et al., 1997). All test scores were converted to z-scores to allow for comparison between different test performances. As a first step, each test (8 of them) that failed to show a significant difference (Student's T test) between patients and controls was discarded. Secondly, all tests (13) that didn't show a difference wide enough to derive a diagnostic cut-off were excluded. The remaining ones (49), ranked for mean difference between patients and controls, underwent a further selection, according to the following criteria:

- tests that were too long to be included in a short and practical screening tool and that could not be reduced were excluded;
- tests appropriate for detection of the a priori-defined signs and symptoms of CCAS were selected;
- top-ranked tests that respected the previous two criteria were chosen for the final battery.

The result was a 10-item battery composed of the following tests: Semantic Fluency, Phonemic Fluency, Category Switching, Digit Span Forward, Digit Span Backward, Cube Drawing/Copy, Delayed Verbal Recall, Similarities, Go/No-Go and assessment of neuropsychiatric domains (Affect).

For each subtest, a diagnostic cut-off was derived (defining pass/fail criteria) by evaluating the percentage of patients and controls correctly diagnosed. Each subtest could then be passed or failed according to the specific identified cut-off. The number of failed tests suggested for different levels of diagnosis: one test failed could be interpreted as "Possible CCAS", two tests failed as "Probable CCAS" and three or more tests failed as "Definite CCAS". As expressed by the same authors (Hoche et al., 2018), diagnostic cut-offs were chosen to maximize selectivity (preventing false positive errors) at the expense of sensitivity (increasing the probability of false negatives to occur). Despite such precautions, the derived cut-offs are probably to be considered too severe for the Italian as well as for other populations, as it will be seen in the following sections.

The scale was then validated in a new sample composed by thirty-nine patients and fifty-five healthy controls and showed selectivity/sensitivity values comparable with those of the exploratory cohort (Hoche et al., 2018) (see *Table 1.2* for details).



Test	Cut-off (raw score)	Patients diagnosed as patients; exploratory cohort (%)	Patients diagnosed as patients; validation cohort (%)	Controls diagnosed as controls; exploratory cohort (%)	Controls diagnosed as controls; validation cohort (%)
Animal fluency	⩽15	24/56 (43)	13/39 (33)	45/50 (90)	55/55 (100)
F word fluency	⩽9	25/56 (45)	10/39 (26)	50/50 (100)	55/55 (100)
Category switching	⩽9	23/55 (42)	18/39 (46)	49/50 (98)	53/55 (96)
LDSF	⩽5	15/58 (26)	11/39 (28)	49/53 (92)	55/55 (100)
LDSB	⩽3	10/57 (18)	12/39 (31)	52/53 (98)	52/55 (93)
Cube	⩽11	8/56 (14)	14/39 (36)	53/53 (100)	51/54 (94)
Verbal recall	⩽10	12/56 (21)	10/39 (26)	51/53 (96)	47/53 (89)
Similarities	⩽6	14/50 (28)	5/39 (13)	49/51 (96)	54/55 (98)
Go/no-go	=0	17/56 (30)	12/39 (31)	51/53 (96)	54/55 (98)

CCAS/Schmahmann scale	Sensitivity (%)		Selectivity (%)	
	Exploratory cohort	Validation cohort	Exploratory cohort	Validation cohort
One test fail (Possible CCAS)	85	95	74	78
Two tests fail (Probable CCAS)	58	82	94	93
Three tests fail (Definite CCAS)	48	46	100	100

LDSB = longest DSB; LDSF = longest DSF.

***Table 1.2**: Percentages of patients and controls correctly diagnosed, respectively, in the exploratory and validation cohorts. Below, sensitivity and selectivity values according to possible, probable and definite criteria. From Hoche et al., 2018.*

To corroborate the need for this instrument, both MMSE (Folstein et al., 1975) and MoCA (Nasreddine et al., 2005) batteries were administered to participants. It emerged that cerebellar patients performed significantly worse than controls in MoCA, but fell within range of normality both in MMSE and MoCA. These results underlined the fact that commonly used screening batteries for global mental state assessment are not specific enough to capture cognitive impairment due to cerebellar damage and therefore it was imperative to build a new appropriate diagnostic tool. The CCAS scale resulting from this validation process represents a tool easy and quick to administer, with adequate levels of selectivity and sensitivity (Hoche et al., 2018).

1.3.3. Recent studies

From 2018 to today, further advancements have been made both in experimental findings and theoretical conceptualization of the syndrome.

In a 2019 review, Schmahmann and colleagues (Schmahmann, Guell, Stoodley, & Halko, 2019) talked about a “paradigm shift in cerebellar neuroscience”, implying both the non-motor implication of cerebellum and its role as a node in distributed neural networks. The proposed overall idea is that the cerebellum is implied in all kinds of neural activities and resulting behaviors.

Various studies provided further evidence of the CCAS scale discriminating validity, in particular in relation to specific cerebellar disease. Naeije and colleagues (2020) administered the scale to a sample of Friedreich Ataxia patients to examine the extent of cognitive impairment, whereas Maas, Killaars, van de Warrenburg and Schutter (2021) examined the discriminative ability of the CCAS scale in a sample of spinocerebellar ataxia type 3 (SCA3) patients. Both these studies found that the CCAS scale effectively detects cognitive deficits in such populations and significant correlation with ataxia severity were found. (Naeije et al., 2020; Maas et al., 2021). Chirino-Perez and colleagues (2022) confronted the CCAS scale and MoCA about their discriminative ability in chronic cerebellar stroke patients. They found that CCAS and MoCA were both adequate in discriminating patients and controls, but only CCAS scale deficits were linked with specific cerebellar lesions, localized, in particular, in the posterolateral portions of the cerebellum and therefore supporting the motor-cognitive dichotomy within the cerebellar cortex (Chirino-Perez et al., 2022).

It is noteworthy that many other translation and validation studies were conducted after the CCAS scale creation. Such works were useful to compare the results obtained from the current data collection (see Chapter 3). Specifically, German (Thieme et al., 2020), Dutch (Maas et al., 2021), Brazilian (de Oliveira Scott et al., 2023) and Cuban (Rodriguez-Labrada et al., 2021) validation studies have already been published, whereas several others are currently ongoing, namely Arabic, Bengali, Chinese, French, Korean, Polish, Spanish and Ukrainian (Schmahmann, Vangel, Hoche, Guell & Sherman, 2021).

Beyond the CCAS scale, recent lines of research tried to widen and deepen the conceptualization of the cerebellar role in impairment of cognition, with a focus on specific pathologies.

Some studies focused on the correlation between structural loss of gray matter within the cerebellar cortex and cognitive impairment. Yang and collaborators (2019), through structural MRI, found a relationship between posterior gray matter loss and cognitive deficits in multiple system atrophy (MSA) patients. Similar methods were used by Cocozza and colleagues (2019) in a sample of Friedreich Ataxia patients. A significant correlation was found between Lobule IX volume loss and visuospatial impairment, tested through the Segment Length Discrimination test.

Some authors tried to untangle the complex role of the cerebellum in neurodegenerative disorders, to which it showed to be, depending on the case, vulnerable or resistant (Liang & Carlson, 2020). Devita and colleagues (2021) conducted a review about the structural alterations of the cerebellum in different forms of dementia and their linkage with different cognitive alterations. Their results showed an overlapping of atrophy in Crus I and II of lobule VIIa, together with substantial specificity between different forms of neurocognitive degenerative diseases, i.e., Alzheimer Disease, Progressive non-fluent Aphasia, behavioral variant of Fronto-temporal Dementia and Semantic Dementia (Devita et al., 2021).

Further developments relating to the conceptualization of the cerebellum as a node within brain-cerebellum networks were achieved by means of functional connectivity studies, such those by Habas (2021) and Alahmadi (2023), that investigated the existing functional connections between different cerebellar lobes and between cerebellum and other brain regions involved in distributed neural networks. Functional connectivity was also used by Brady and his group (2019) to study the relationship between schizophrenia negative symptoms and cerebellar cognitive implications. They found that connectivity between dorsolateral prefrontal cortex and midline posterior cerebellum showed the most important correlations with schizophrenia negative symptoms, suggesting a possible role for the disruption of the loops connecting these two areas.

Moreover, by means of transcranial magnetic stimulation (TMS), they proposed a possible causal link between cerebellar ipoactivation and schizophrenia negative symptomatology (Brady et al., 2019).
Finally, some researchers conducted systematic reviews and meta-analysis to make a point of the available evidence in these issues. Ahmadian, van Baarsen, van Zandvoort and Robe (2019) conducted a meta-analysis to better understand the dimension of cognitive deficits due to isolated cerebellar injury. Their findings supported the presence of executive, processing speed, memory, visuo-spatial and language deficits, but failed to find significant impairment of attention (Digit Span test) and neuropsychiatric components. Vlasova, Panikratova and Pechenkova (2022) conducted a meta-analysis more specifically focused on language impairment due to cerebellar damage, to better understand the specific cerebellar role in language and possible further localization of language-related functions. They found that the cerebellum was implicated in different aspects of language, such as semantic access and prosody, and concluded that it provided a “multiform functional contribution” to brain linguistic processing (Vlasova et al., 2022).

Overall, it is possible to state that all recent studies adapted to the current shifted paradigm (Schmahmann et al., 2019) directing their efforts towards a better understanding, characterizing and developing of the cerebellar role in cognition.

CHAPTER 2 - DATA COLLECTION AND ANALYSIS

The aim of the present study is the standardization of the Italian version of the CCAS scale, by means of the administration of the scale on a wide sample of Italian healthy participants. Other goals of the study are to provide, if needed, corrections for demographic variables, new provisional cut-offs and equivalent scores for each subtest of the scale. In conjunction with the CCAS scale, the Cognitive Reserve Index questionnaire (Nucci et al., 2012) and the Coloured Raven Progressive Matrix (Raven, 1981) were administered in order to, respectively, investigate possible connections with the CCAS scores and to exclude major intellectual impairments.

2.1. Subjects

The present project is part of an observational multicentric study carried out thanks to the collaboration between various universities, neurological centers and medical departments across Italy. The participating centers are reported below (in brackets the responsibles for each center): University of Padua (Dr. Maria Devita, Dr. Alessandra Coin, Dr. Adele Ravelli); Sapienza University of Rome (Prof. Maria Leggio, Dr. Giusy Olivito, Dr. Libera Siciliano); University of Bergamo (Prof. Zaira Cattaneo, Dr. Maria Arioli); University of Pavia (Dr. Chiara Ferrari); I.R.C.C.S. Fondazione Santa Lucia (Prof. Maria Leggio, Dr. Giusy Olivito, Dr. Libera Siciliano); Brain Connectivity Center C.Mondino (Prof. Zaira Cattaneo); I.R.C.C.S. Neurological Institute Carlo Besta (Dr. Cateria Mariotti, Dr. Anna Castaldo, Dr. Lorenzo Nanetti). The investigation was carried out on a sample of participants recruited from different regions of Italy. Part of the data collection was administered to participants from different districts of the aforementioned cities: Padua (Veneto), Bergamo, Milan and Pavia (Lombardy) and Rome (Lazio). The remainder of the data were collected in other Italian regions, such as Piedmont, Sardinia and Sicily (see *Figure 2.1*). Thanks to the multicentric nature of the study, the total sample of 257 participants can be considered heterogeneous in regard to the participants origin as well as to other demographic characteristics.

Figure 2.1: *Distribution of participants across different Italian regions. Pinned in red: areas where participating centers are located (i.e., Milan, Pavia, Bergamo, Padua and Rome). Pinned in yellow: other areas where participants were recruited (i.e., Turin, Nuoro and Palermo).*

All subjects participated in the study on a voluntary basis, without receiving any reward. All participants signed the informed consent module at the beginning of the meeting and were aware that they could withdraw from the testing at any time. The current study was approved with protocol number 5080 by the Ethical Committee of the School of Psychology (area 17), University of Padua, in accordance with the Declaration of Helsinki.

The following data description and analysis will refer to the data available at the current state of the data collection, meaning that the obtained results could change upon study completion.

The sample was composed of 257 healthy Italian subjects, of which 155 women (60,31%) and 102 men (39,69%). Mean age of the sample was 40,90 years (SD

= 18,94), ranging from 18 to 95 years old. Mean education was 15,92 years (SD = 4,03), ranging from 5 (elementary license) to 27 (multiple PhD degrees) years of education, referring to the Italian school system. Median values for age and education were respectively 32 years and 16 years. All participants were administered with the Cognitive Reserve Index Questionnaire (CRIq) in its digital form (Nucci et al., 2012). Mean CRIq total value was 105,74 (SD = 16,45), ranging from 78 to 166. Median CRIq value was 100. Demographic distribution of the sample is illustrated in *Table 2.1*.

	Age (years)															
	18 - 24		25 - 29		30 - 34		35 - 39		40 - 44		45 - 49		50 - 54		55 - 59	
Education (years)	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0 - 5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6 - 8	-	-	-	-	-	-	-	-	-	-	-	-	1	4	2	-
9 - 13	2	3	8	3	-	-	-	2	2	-	1	-	3	5	3	5
13.5 - 16	10	26	4	5	3	2	1	1	1	2	-	-	1	6	-	4
> 16	8	10	13	19	5	13	3	1	3	2	3	5	3	7	2	7
Total	20	39	25	27	8	15	4	4	6	4	4	5	8	22	7	16

	Age (years)														
	60 - 64		65 - 69		70 - 74		75 - 79		80 - 84		85 - 89		90 - 95		Total
Education (years)	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
0 - 5	-	-	-	-	1	-	-	-	1	1	1	-	-	-	4
6 - 8	-	-	-	2	-	-	-	1	-	1	2	1	-	-	14
9 - 13	6	-	2	3	1	-	-	2	-	1	1	1	-	-	54
13.5 - 16	-	-	-	2	-	1	-	1	-	-	-	-	-	1	71
> 16	1	2	-	3	2	-	1	-	1	-	-	-	-	-	114
Total	7	2	2	10	4	1	1	4	2	3	4	2	0	1	257

Table 2.1: *Demographic distribution of the sample. Participants from 18 to 59 years of age are reported in the upper table, whereas participants 60 - 95 are depicted below. The Total column in the lower table refers to all subjects (from 18 to 95), depending on the specific level of education.*

2.1.1. Inclusion and exclusion criteria

Participants were included in the study only if they were 18 years old or older, Italian native speakers and able to give their consent to participate.

Exclusion criteria were the following: current or past neurological or psychiatric history (with a diagnosis made by a specialist); sensory deficits or health conditions that could interfere with tests administration; current or past drugs/alcohol abuse; chemo/radiotherapy (ongoing or concluded by less than a year); severe insomnia (due for example to obstructive sleep apnea); drugs assumptions (such as antidepressants) for psychiatric diseases.

To exclude the presence of such conditions, each administration was preceded by a brief collection of anamnestic information about the relevant clinical condition of the participant. A semi-structured interview was crafted to evaluate the following specific aspects:

- Visual and auditory deficits;
- Relevant health conditions and relative drug assumptions;
- Past episodes of stroke;
- Past episodes of Traumatic Brain Injury (TBI);
- Current or past epileptic disorders or seizures;
- Past or current neurological, psychiatric and psychological disorders and treatments;
- Genetic predisposition towards neurologic or psychiatric/psychological disorders (family history);
- Current or past drugs and alcohol abuse;
- Sleep impairment.

Every information was documented in the participant’s anamnestic module.

Family history of neurological, psychiatric or neurological disorders did not represent an exclusion criterion, but was still recorded because of its possible future usefulness for further exploratory analysis about such topics.

All participants were administered with the Raven Coloured Progressive Matrix test (Raven, 1981) and those who performed at ES = 0 at were also excluded, because such level of performance is suggestive of impaired general intellectual functioning and reasoning (Carlesimo et al., 1996).

A total of eleven participants were excluded from the study according to the exclusion criteria. Two subjects held diagnosis of Generalized Anxiety Disorder, one of Panic Attack Disorder and one of Major Depressive Disorder. Two were excluded because of past neurological damages (cerebral haemorrhages and stroke) and three because of past TBI. Lastly, one participant was excluded because of ongoing carcinoma treatment with Letrozole.

2.2. Materials and procedures

The one - on - one meetings were mostly conducted at the participants' domicile to make it as convenient as possible for the people to participate in the study. Whether this was not possible, regardless of the specific place, the setting had to be quiet and free of distracting elements.

Each administration was preceded by an explanation of the experimental procedure, the compilation of the informed consent module and the anamnestic interview.

The tests administration was comprehensive of CCAS scale - Italian version A, Raven Coloured Progressive Matrix (RCPM) (Raven, 1981) and Cognitive Reserve Index Questionnaire (CRIq) (Nucci et al., 2012), presented in a randomized order to avoid confounding effects.

The four available different Italian versions of the CCAS scale (versions A, B, C and D) were translated before the beginning of the data collection, thanks to the work of Prof. Maria Leggio and her colleagues of "La Sapienza" University of Rome.

The CCAS scale - Italian version A consists of 10 subtests, described below.

1 - Semantic Fluency (range not defined *a priori*), in which the subject is asked to name as many words as possible belonging to a certain semantic category ("animals" in version A) in one minute of time. He is assigned with one point for each word correctly produced.

2 - Phonemic Fluency (range not defined *a priori*), in which the subject is asked to name as many words as possible that start with a certain letter ("F" in version A) in one minute of time. As in Semantic Fluency, he is assigned with one point for each word correctly produced.

3 - Category Switching (range not defined *a priori*), in which the subjects have to autonomously alternate words belonging to two semantic categories

(“vegetables” and “jobs” in version A) and say as many words as possible in one minute of time. One point is assigned for each “shift” correctly completed.

4 - Verbal Delayed Recall (range 0 - 15), composed of two distinct phases. The registration phase, in which a series of five unrelated words is read to the subjects, who must repeat them immediately. Up to four attempts are given to the subject in this phase of registration, without any score being assigned. After the administration of subtests 5, 6 and 7 (when about 5-6 minutes have passed), the subject is asked to repeat the five words in any order. If unable to repeat one or more of them, he is helped with a semantic cue and then with multiple choice alternatives. He is assigned with 3 points for each word reported without any help, 2 points for each word reported with a semantic cue and 1 point for each word reported with multiple choices.

5 - Digit Span Forward (DSF) (range 0 - 8), in which the subject must repeat series of numbers in the same order in which he hears them from the examiner. He is assigned with a score equal to the length of the series correctly reported.

6 - Digit Span Backward (DSB) (range 0 - 6), in which the subject must repeat series of numbers in the reverse order to that proposed by the examiner. As in DSF, he is assigned with a score equal to the length of the series correctly reported.

7 - Cube Drawing/Copy (range 0 - 15), in which the subject is asked to draw a three-dimensional cube (or alternatively a “transparent box with six faces”, to clarify the concept of three-dimensionality). If all twelve lines are present and the cube is three-dimensional, fifteen points are assigned. If not, the subject is asked to reproduce the cube by copying it. One point is assigned for each line correctly reported, up to twelve. One point is removed for each line missing or in excess. One point is removed if the cube is not three-dimensional. For how this subtest is structured, it is not possible to obtain a score of 13 or 14.

8 - Similarities (range 0 - 8), in which the subject has to express what two objects or words have in common. An example trial is given and then four couples of words are verbally presented to the subject. Two points are assigned for each correct/conceptual answer, one point for each partially correct/concrete answer and zero points for each answer in which there is no categorization attempt.

9 - Go/No-Go (range 0 - 2), in which the subject is asked firstly to put both his hands on the table and then to raise a finger and put it down again whenever the examiner taps on the table. Moreover, he must stay still whenever the examiner taps on the table twice. The examiner performs a series of tapping and then two points are assigned for no error, one point for one error and zero point for two or more errors.

10 - Affect (range 0 - 6), that include six items describing possible cerebellar neuropsychiatric symptoms and changes in mood, affect or behaviors. The examiner subtracts one point from the total of six for each one of them that is directly observed or reported by family/caregivers.

The CCAS scale is designed to address four cognitive domains (Schmahmann & Sherman, 1998), namely executive functioning, linguistic functioning, visuospatial abilities and affect/behavior.

Executive functions imply many different aspects that are covered by different CCAS scale subtests, such as working memory (FDS and BDS), switching ability (Category Switching), abstract reasoning (Similarities), inhibition (Go/No-Go) and retrieval of semantic and phonemic knowledge (Semantic and Phonemic Fluency) (Hoche et al., 2018). Linguistic functioning is heavily implied in Semantic and Phonemic Fluency, which require intact verbal production other than executive functions. Visuospatial ability, assessed through the Cube Drawing/Copy subtest, was seen to be impaired in cerebellar patients just for what it concerns 3D figures, whereas it was intact for 2D figures drawing or copy (Schmahmann & Sherman, 1998). The cube must be produced initially from verbal instructions, because cerebellar patients proved to be mostly impaired in the self-directing process of drawing than in visually guided copy (Guell et al., 2015).

Verbal Recall subtest taps the domains of retrieval of previously learned information and associative learning, which are related to frontal-executive functions rather than encoding processing. In fact, the inability to recall words spontaneously should be addressed to the presence of CCAS, whereas the inability to recall words with multiple choice alternatives is suggestive of a cerebral implication (Hoche et al., 2018).

Lastly, Affect subtest allows to detect difficulties relating to emotional lability, attentional dyscontrol, autism and psychotic spectrum signs and symptoms, apathy and lack of social skills (Hoche et al., 2018).

Cognitive Reserve Index Questionnaire (CRIq) (Nucci et al., 2012) was administered in his digital online version (https://www.cognitivereserveindex.org/NewEdition/index.html). Its aim is to quantify the amount of Cognitive Reserve that a person has built up during his lifetime through formal education, working activity and leisure time activities (Nucci et al., 2012). The questionnaire consists of a semi-structured interview composed of an initial demographic investigation and twenty questions about the aforementioned three main aspects of life history.

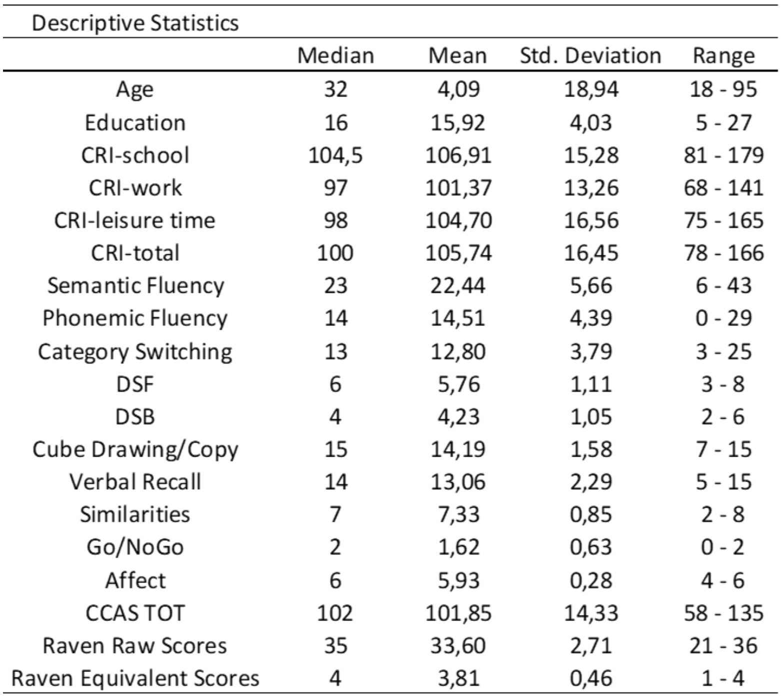
The Raven Coloured Progressive Matrix Test (Raven, 1981) is composed of three sets of twelve boards each. A board consists of a rectangular coloured geometrical figure with a missing portion inside. The participant must choose the alternative that better completes the original figure from six different options, by pointing at it or by saying the corresponding number (from 1 to 6). The boards within each set are ordered by increasing level of difficulty. The test is conceived to examine the ability to deduce logical or visual regularity and relations between visuospatial elements (Carlesimo et al., 1996), as a feature of fluid intelligence. In the present study its aim was to exclude participants with relevant general intellective deficit.

A subgroup of participants from the whole sample attended the CCAS scale administration in the presence of two experimenters, who assigned scores independently to evaluate inter-rater reliability of the scale.

A further subgroup of participants underwent the CCAS scale administration a second time after a period of about a month, to investigate test-retest reliability. Half of them were retested with CCAS scale - version A to address reliability of the scale, whereas the other half with version B, to evaluate whether the two versions could be considered equivalent.

2.3. Data Analysis

After performing the **descriptive analysis** of the sample (see *Table 2.2* for details), **normality** of the distributions was evaluated through the examination of skewness and kurtosis (Kim, 2013). According to the widespread rule of thumb, an unacceptable departure from normality would be present with absolute values of skewness > 2 and kurtosis > 7 (West, Finch, & Curran, 1995). The method proposed by Kim is more precise because it keeps into consideration the numerosity of the sample. Normality was therefore assessed firstly by visual inspection of the distribution plots (histograms and Q-Q plots) and subsequently, according to this method, by calculating z scores for skewness (z = skewness/standard error of skewness) and kurtosis (z = kurtosis/standard error of kurtosis). For a sample numerosity between 50 and 300, substantial departure from normality is suggested for absolute z values > 3,29 (Kim, 2013).



Descriptive Statistics

	Median	Mean	Std. Deviation	Range
Age	32	4,09	18,94	18 - 95
Education	16	15,92	4,03	5 - 27
CRI-school	104,5	106,91	15,28	81 - 179
CRI-work	97	101,37	13,26	68 - 141
CRI-leisure time	98	104,70	16,56	75 - 165
CRI-total	100	105,74	16,45	78 - 166
Semantic Fluency	23	22,44	5,66	6 - 43
Phonemic Fluency	14	14,51	4,39	0 - 29
Category Switching	13	12,80	3,79	3 - 25
DSF	6	5,76	1,11	3 - 8
DSB	4	4,23	1,05	2 - 6
Cube Drawing/Copy	15	14,19	1,58	7 - 15
Verbal Recall	14	13,06	2,29	5 - 15
Similarities	7	7,33	0,85	2 - 8
Go/NoGo	2	1,62	0,63	0 - 2
Affect	6	5,93	0,28	4 - 6
CCAS TOT	102	101,85	14,33	58 - 135
Raven Raw Scores	35	33,60	2,71	21 - 36
Raven Equivalent Scores	4	3,81	0,46	1 - 4

Table 2.2: *Descriptive statistics.*

Correlations between demographic variables, CRIq scores and single subtests scores were then investigated. Pearson's correlation coefficient was calculated for all variables and Spearman's correlation coefficient was calculated in addition for variables that resulted non-normally distributed.

Independent sample **T-tests** (Student) were performed to evaluate significant sex differences in the sample in relation to each considered variable (age, education, CRIq scores and single CCAS scale subtest).

To assess the influence of demographic variables on participants' scores, **multiple linear regressions** were performed, each one with a specific subtest as dependent variable and age, education and sex as independent variables. Regression analysis was performed for those subtests that showed significant correlations with demographic variables (i.e., age, education and gender), in order to provide a correction factor to apply to each subject score in each subtest. Predictors were entered simultaneously within the model. It was not of interest to evaluate their influence on the CCAS total score, because such score is obtained by the raw sum of the single subtest scores and it is meant to add performance details that could be useful for longitudinal investigation, but doesn't give information about the presence of CCAS (Hoche et al., 2018).

By means of the correction factors obtained in this way, an adjustment grid was built to correct scores for age and education values.

Once all scores were adjusted, the **Equivalent Scores** method (ES method) (Capitani & Laiacona, 1997, 2017; Aiello & Depaoli, 2022) was applied to provide for new provisional cutoffs for the Italian population. The ES method is a non-parametric methodology that allows to standardize regression-adjusted values into a 5 point scale. This method to provide cut-offs was chosen because of its well established validity (Bianchi, 2013) and because some of the subtest scores were non-normally distributed and therefore was not possible to apply parametric methods (Mondini, Mapelli, & Arcara, 2016).

The outer and inner Tolerance Limits (oTL and iTL) are defined as the threshold under which lie, respectively, "at most" the 5% of the normal population and "at least" 5% of the normal population, with 95% confidence (Capitani & Laiacona, 2017). All values that fall equal or lower than the oTL can be considered not normal and all values equal or above the iTL can be considered normal. Between the oTL and the iTL there is a “grey zone”, in which no conclusion can be made without a considerable error. The new provisional cut-offs were represented by the values immediately above the oTL, so that it was sure that error was kept below 5% (Aiello & Depaoli, 2022).

The 4 ES were hence defined as follows: 0 = values equals or below the outer Tolerance Limit (oTL); 4 = values above the median; 1, 2, 3 = obtained dividing into three equivalent parts the distribution between levels 0 and 4 (Capitani & Laiacona, 2017). The observations corresponding to each ES were identified through the applet provided by Aiello and Depaoli (Aiello & Depaoli, 2022).

The new provisional cut-offs were then compared with the cut-offs proposed in the original work (Hoche et al., 2018) and the percentage of false positives that the latter would have provided if applied to the Italian population data was calculated.

Finally, the internal reliability of the scale was assessed through **internal consistency analysis** (Cronbach’s alpha) (Cronbach, 1951).

It was not possible to calculate test-retest reliability and inter-rater reliability because the amount of data collected in these modalities up to this point was too small. Preliminary observations about test - retest and inter - rater administration will be discussed qualitatively in Chapter 3.

2.4. Results

For what it concerns **normality assessment**, the distribution of education values could be considered normal, whereas the distribution of age values was significantly asymmetric on the left side, with a z-value of 4,80, as we can see in *Figure 2.2*. This result was expected because, at the current state of the data collection, the participants between 18 and 40 years of age are overrepresented, as they account for about 55% of the sample. To note that the mean age of the participants was 40,90 (SD = 18,94), but the median value was lower (32 years of age). Education, on the other hand, could be considered normally distributed, although around a quite high mean value. For what it concerns the distribution of subtest scores, no departure from normality was observed in Semantic Fluency, Phonemic Fluency, Category Switching, DSF and DSB. This result was expected for fluency tests, that don't have a maximum score, and it moreover indicates that no ceiling effect was observed in the span tests, although a maximum score was present (8 for the DSF and 6 for the DSB). Normal distribution was not expected for the remaining subtest (i.e., Cube Drawing/Copy, Verbal Recall, Similarities, Go/No-Go and Affect) in which a ceiling effect was found to be present to various degrees (see *Figure 2.3*).

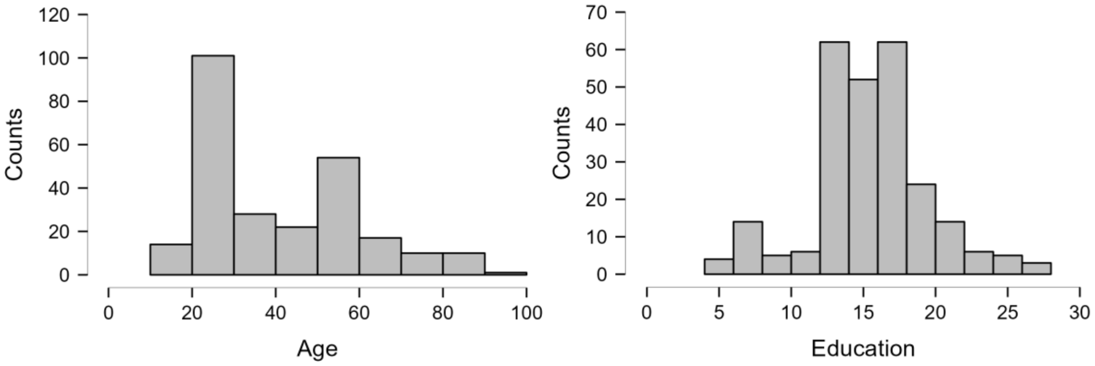


Figure 2.2: *Distributions of age ed education values. Age distribution showed asymmetry on the left side, because of the high percentage of participants under 40 years of age, whereas education could be considered normally distributed, even if around a high mean value (15,92 years; SD = 4,03).*

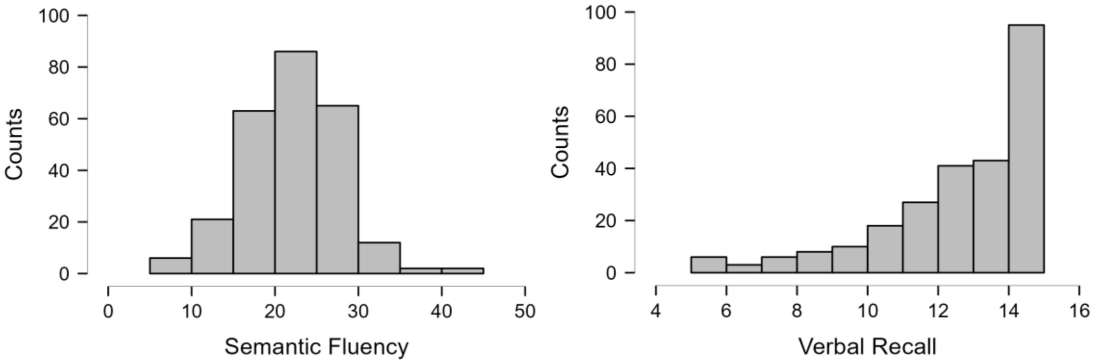


Figure 2.3: *Illustrative examples of normal (Semantic Fluency, on the left) and not normal (Verbal Recall, on the right) distributions of scores. Verbal Recall distribution, whose maximum score was 15, showed a large ceiling effect.*

Significant **correlations** were found between various subtests of CCAS scale and other demographic variables, as shown in *Table 2.3*.

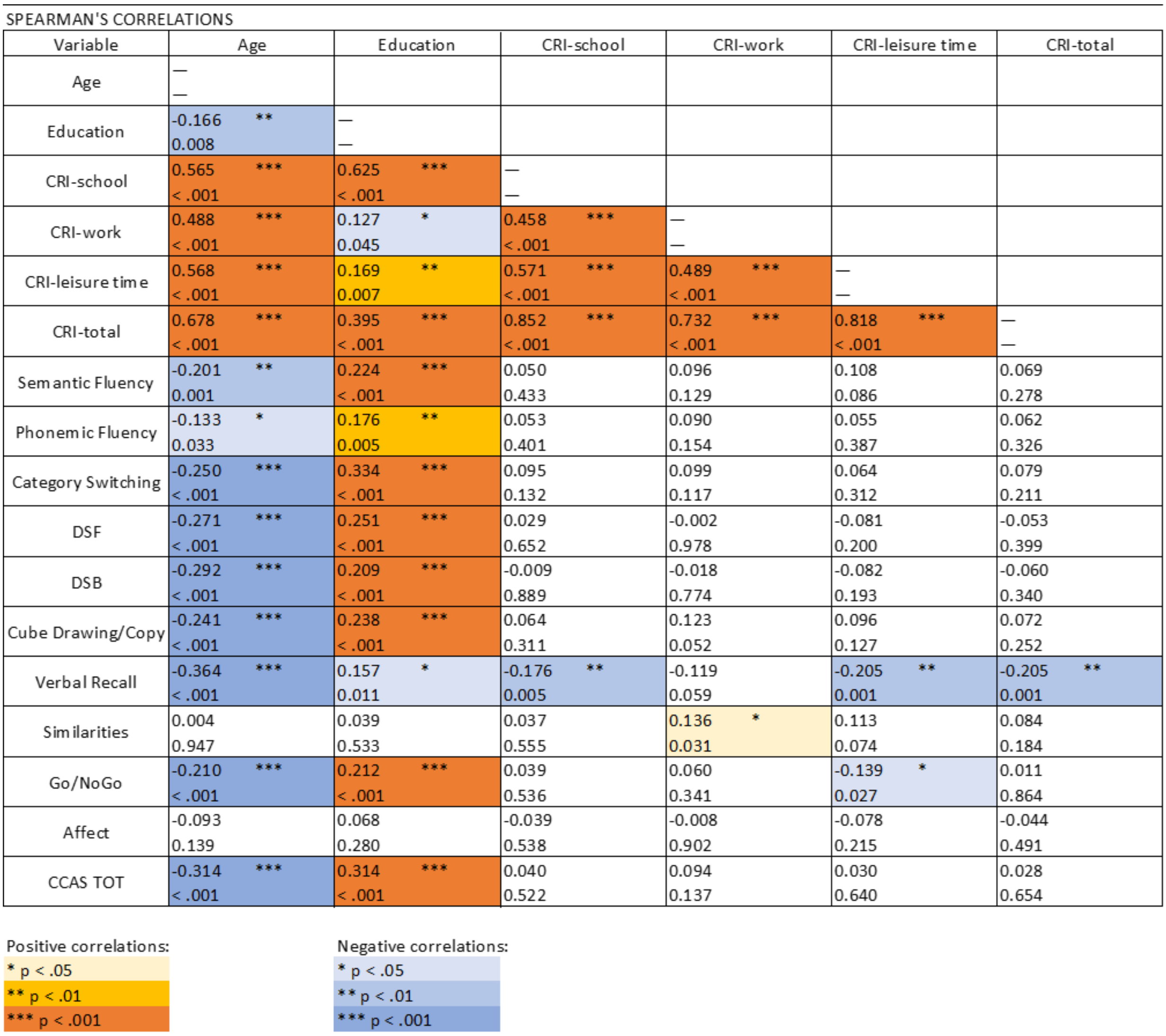
As expected, age showed a significant negative correlation (Pearson's r = -0,314; p<0,001) with education level, indicating that younger participants tended to be more schooled than older ones. Regarding the subtests of the scale, age also significantly correlated with Semantic Fluency (r = -0,236; p<0,001), Phonemic Fluency (r = -0,206; p<0,001), Category Switching (r = -0,332; p<0,001), DSF (r = -0,282; p<0,001), DSB (r = -0,298; p<0,001), Cube Drawing/Copy (r = -0,314; p<0,001), Verbal Recall (r = -0,383; p<0,001) and Go/No-Go (r = -0,290; p<0,001), but not with Similarities and Affect. Moreover, age showed significant correlation with the total score of the CCAS scale (r = -0,403; p<0,001). To confirm these results when it comes to non-normal distribution, Spearman's r was also calculated. According to this index the strength of the correlation was confirmed, although slightly lowered, for Cube Drawing/Copy (r = -0,241; p<0,001), Verbal Recall (r = -0,364; p<0,001), Go/No-Go (r = -0,210; p<0,001). Still no correlations were found with Similarities and Affect.

Also the education level resulted to be linked with different scale subtests. In fact, it showed significant positive correlations with Semantic Fluency (r = 0,244; p<0,001), Phonemic Fluency (r = 0,223; p<0,001), Category Switching (r = 0,321; p<0,001), DSF (r = 0,284; p<0,001), DSB (r = 0,224; p<0,001), Cube Drawing/Copy (r = 0,346; p<0,001) and Go/No-Go (r = 0,207; p<0,001), but not with Verbal Recall and Affect. Education level was found to be positively correlated with CCAS total score (r = 0,353; p<0,001). A small and less significant correlation was found with the Similarities subtest (r = 0,140, p<0,05), which was not confirmed by the Spearman index. The latter corroborated the positive correlation of education with Cube Drawing/Copy (r = 0,238; p<0,001) and Go/No-Go (r = 0,212; p<0,001), and also the absence of correlation with Affect. A small positive correlation emerged with Verbal Recall (r = 0,157, p<0,05), less significant than the others.

Unexpectedly, CRIq score showed very few correlations with the CCAS total and subtests scores. The only subtest that resulted to be significantly correlated with CRIq measures was Verbal Recall, that showed negative correlation with CRI-education (r = -0,176, p<0,01), CRI-leisure time (r = -0,205, p<0,01) and CRI-total score (r = - 0,205, p<0,01) (Spearman's correlation index was used in this case because the distributions of CRIq scores substantially departed from normality).

PEARSON'S CORRELATIONS

Variable	Age	Education	CRI-school	CRI-work	CRI-leisure time	CRI-total
Age	— —					
Education	-0.314 *** < .001	— —				
CRI-school	0.438 *** < .001	0.649 *** < .001	— —			
CRI-work	0.416 *** < .001	0.206 ** 0.001	0.496 *** < .001	— —		
CRI-leisure time	0.553 *** < .001	0.135 * 0.032	0.548 *** < .001	0.533 *** < .001	— —	
CRI-total	0.570 *** < .001	0.402 *** < .001	0.829 *** < .001	0.794 *** < .001	0.853 *** < .001	— —
Semantic Fluency	-0.236 *** < .001	0.244 *** < .001	0.048 0.449	0.129 * 0.041	0.096 0.128	0.104 0.101
Phonemic Fluency	-0.206 *** < .001	0.223 *** < .001	0.026 0.685	0.088 0.161	-0.028 0.659	0.031 0.628
Category Switching	-0.332 *** < .001	0.321 *** < .001	0.047 0.462	0.088 0.162	-0.011 0.865	0.041 0.515
DSF	-0.282 *** < .001	0.284 *** < .001	0.035 0.584	0.021 0.734	-0.096 0.127	-0.023 0.714
DSB	-0.298 *** < .001	0.224 *** < .001	0.005 0.937	0.022 0.732	-0.093 0.143	-0.032 0.617
Cube Drawing/Copy	-0.314 *** < .001	0.346 *** < .001	0.099 0.117	0.154 * 0.014	0.068 0.283	0.126 * 0.046
Verbal Recall	-0.383 *** < .001	0.056 0.373	-0.266 *** < .001	-0.166 ** 0.008	-0.227 *** < .001	-0.269 *** < .001
Similarities	-0.101 0.107	0.140 * 0.025	0.017 0.787	0.114 0.071	0.060 0.339	0.074 0.240
Go/NoGo	-0.290 *** < .001	0.207 *** < .001	0.030 0.638	0.055 0.388	-0.171 ** 0.007	-0.044 0.492
Affect	-0.049 0.431	0.027 0.672	-0.023 0.721	0.010 0.878	-0.084 0.185	-0.043 0.496
CCAS TOT	-0.403 *** < .001	0.353 *** < .001	0.012 0.850	0.104 0.100	-0.022 0.723	0.029 0.646



SPEARMAN'S CORRELATIONS

Variable	Age	Education	CRI-school	CRI-work	CRI-leisure time	CRI-total
Age	— —					
Education	-0.166 ** 0.008	— —				
CRI-school	0.565 *** < .001	0.625 *** < .001	— —			
CRI-work	0.488 *** < .001	0.127 * 0.045	0.458 *** < .001	— —		
CRI-leisure time	0.568 *** < .001	0.169 ** 0.007	0.571 *** < .001	0.489 *** < .001	— —	
CRI-total	0.678 *** < .001	0.395 *** < .001	0.852 *** < .001	0.732 *** < .001	0.818 *** < .001	— —
Semantic Fluency	-0.201 ** 0.001	0.224 *** < .001	0.050 0.433	0.096 0.129	0.108 0.086	0.069 0.278
Phonemic Fluency	-0.133 * 0.033	0.176 ** 0.005	0.053 0.401	0.090 0.154	0.055 0.387	0.062 0.326
Category Switching	-0.250 *** < .001	0.334 *** < .001	0.095 0.132	0.099 0.117	0.064 0.312	0.079 0.211
DSF	-0.271 *** < .001	0.251 *** < .001	0.029 0.652	-0.002 0.978	-0.081 0.200	-0.053 0.399
DSB	-0.292 *** < .001	0.209 *** < .001	-0.009 0.889	-0.018 0.774	-0.082 0.193	-0.060 0.340
Cube Drawing/Copy	-0.241 *** < .001	0.238 *** < .001	0.064 0.311	0.123 0.052	0.096 0.127	0.072 0.252
Verbal Recall	-0.364 *** < .001	0.157 * 0.011	-0.176 ** 0.005	-0.119 0.059	-0.205 ** 0.001	-0.205 ** 0.001
Similarities	0.004 0.947	0.039 0.533	0.037 0.555	0.136 * 0.031	0.113 0.074	0.084 0.184
Go/NoGo	-0.210 *** < .001	0.212 *** < .001	0.039 0.536	0.060 0.341	-0.139 * 0.027	0.011 0.864
Affect	-0.093 0.139	0.068 0.280	-0.039 0.538	-0.008 0.902	-0.078 0.215	-0.044 0.491
CCAS TOT	-0.314 *** < .001	0.314 *** < .001	0.040 0.522	0.094 0.137	0.030 0.640	0.028 0.654

Positive correlations:
* p < .05
** p < .01
*** p < .001

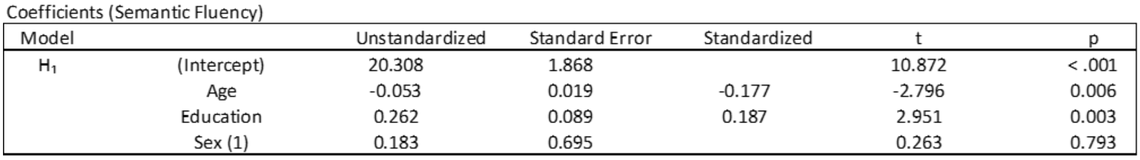
Negative correlations:
* p < .05
** p < .01
*** p < .001

Table 2.3: *Pearson's and Spearman's correlations. Pearson/Spearman's Index are reported together with level of significance (p). As described in the legend, different colors were used to visually represent different levels of significance. Significant positive correlations are reported in shades of red, negative in shades of blue.*

To identify sex differences within the sample, **Independent Samples T-Test** were performed. Age and education didn't show any significant difference between male and female participants, as well as CRIq scores. No significant gender difference emerged in any subtest, except for Category Switching: t (255) = -2,740, p = 0,007, d = -0,343, with females performing significantly better than males (mean score 12,01 ± 3,73 for males and 13,32 ± 3,75 for females). After removing three outliers the difference and its significance level were unchanged.

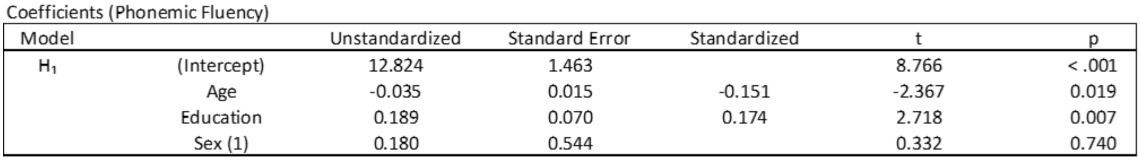
According to correlations results, eight out of ten subtests (Similarities and Affect were excluded from this process) were entered into **multiple linear regression models**. Semantic Fluency, Phonemic Fluency, Category Switching, DSF, DSB, Cube Drawing/Copy and Go/No-Go were significantly predicted both by age and education, but not by sex. Verbal Recall was better predicted by age alone. Category Switching, consistently with the result of the T-test (see above), was better predicted by all three demographic variables.

Even though the amount of variance explained by these factors was relatively small (with R^2 ranging from 0,071 to 0,168), p value was consistently <0,05 and acceptable correction adjustment was obtained. Detailed results of multiple regression analysis are reported in *Table 2.4*.



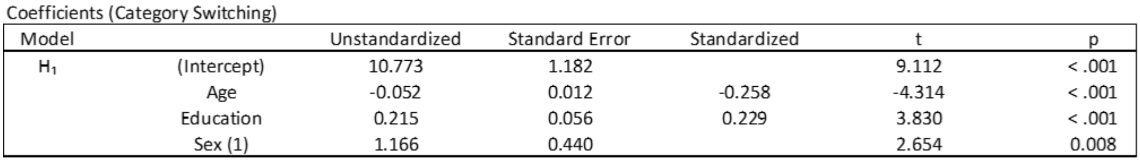
Coefficients (Semantic Fluency)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	20.308	1.868		10.872	< .001
	Age	-0.053	0.019	-0.177	-2.796	0.006
	Education	0.262	0.089	0.187	2.951	0.003
	Sex (1)	0.183	0.695		0.263	0.793



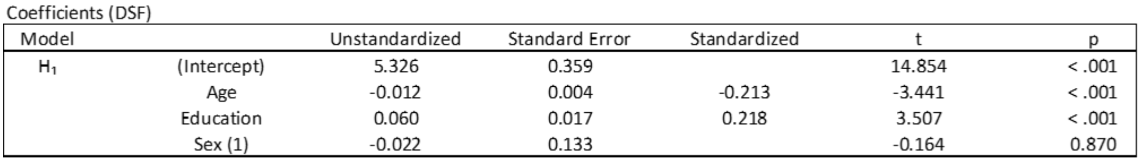
Coefficients (Phonemic Fluency)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	12.824	1.463		8.766	< .001
	Age	-0.035	0.015	-0.151	-2.367	0.019
	Education	0.189	0.070	0.174	2.718	0.007
	Sex (1)	0.180	0.544		0.332	0.740



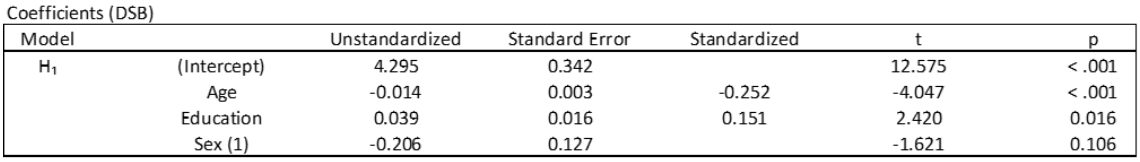
Coefficients (Category Switching)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	10.773	1.182		9.112	< .001
	Age	-0.052	0.012	-0.258	-4.314	< .001
	Education	0.215	0.056	0.229	3.830	< .001
	Sex (1)	1.166	0.440		2.654	0.008



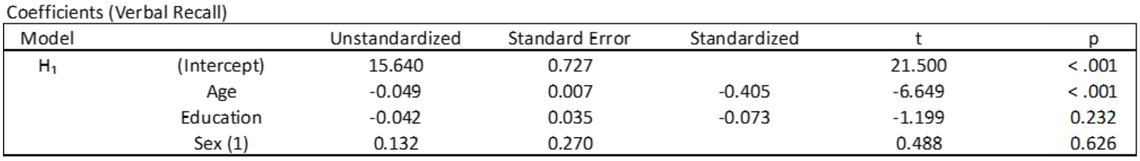
Coefficients (DSF)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	5.326	0.359		14.854	< .001
	Age	-0.012	0.004	-0.213	-3.441	< .001
	Education	0.060	0.017	0.218	3.507	< .001
	Sex (1)	-0.022	0.133		-0.164	0.870



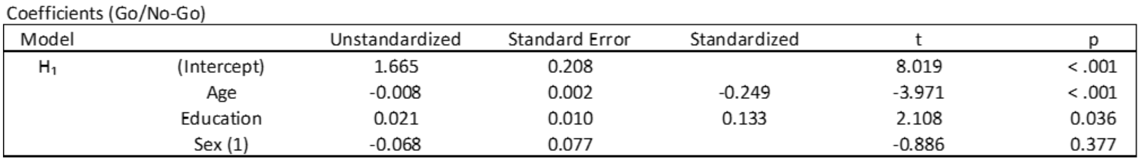
Coefficients (DSB)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	4.295	0.342		12.575	< .001
	Age	-0.014	0.003	-0.252	-4.047	< .001
	Education	0.039	0.016	0.151	2.420	0.016
	Sex (1)	-0.206	0.127		-1.621	0.106



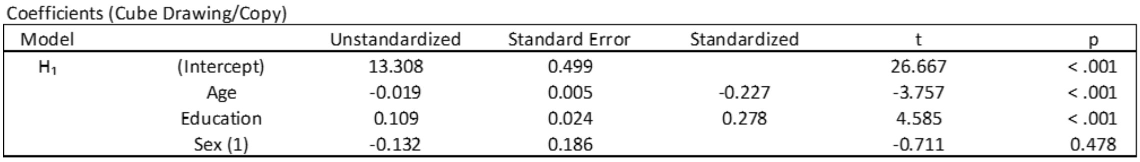
Coefficients (Verbal Recall)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	15.640	0.727		21.500	< .001
	Age	-0.049	0.007	-0.405	-6.649	< .001
	Education	-0.042	0.035	-0.073	-1.199	0.232
	Sex (1)	0.132	0.270		0.488	0.626



Coefficients (Go/No-Go)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	1.665	0.208		8.019	< .001
	Age	-0.008	0.002	-0.249	-3.971	< .001
	Education	0.021	0.010	0.133	2.108	0.036
	Sex (1)	-0.068	0.077		-0.886	0.377



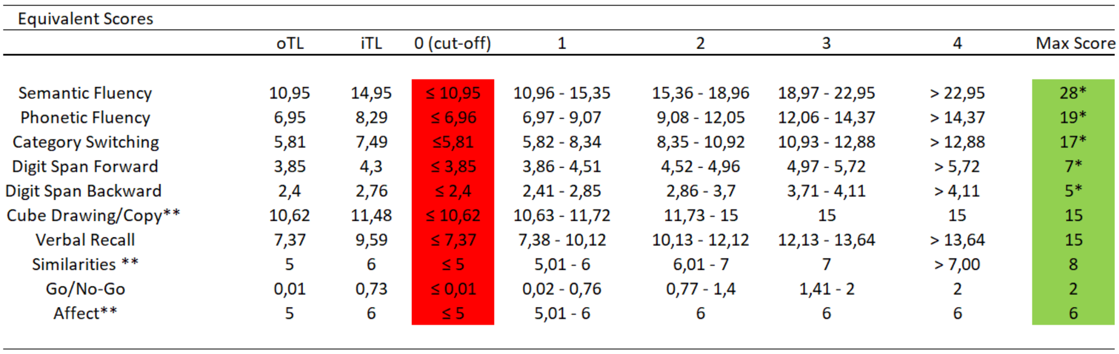
Coefficients (Cube Drawing/Copy)

Model		Unstandardized	Standard Error	Standardized	t	p
H_1	(Intercept)	13.308	0.499		26.667	< .001
	Age	-0.019	0.005	-0.227	-3.757	< .001
	Education	0.109	0.024	0.278	4.585	< .001
	Sex (1)	-0.132	0.186		-0.711	0.478

Table 2.4: *Multiple regression analysis coefficients. Regression analysis was performed for eight out of ten subtests that showed significant correlations with age, sex and/or education. In the table, coefficients of all three variables are reported for completeness of the results. Only factors with $p<0.05$ were included in the regression model.*

By means of regression equations, all scores were adjusted to account for the influence of demographic variables and a **correction grid** was derived. The grid was built to cover age levels ranging from 20 to 100 years (with intervals of 10 years) and education levels ranging from 5 to 25 years (with intervals of 3 years). It is important to note that this grid, reported in the Appendix, is just preliminary, but it possibly resembles the final result of the complete data collection.

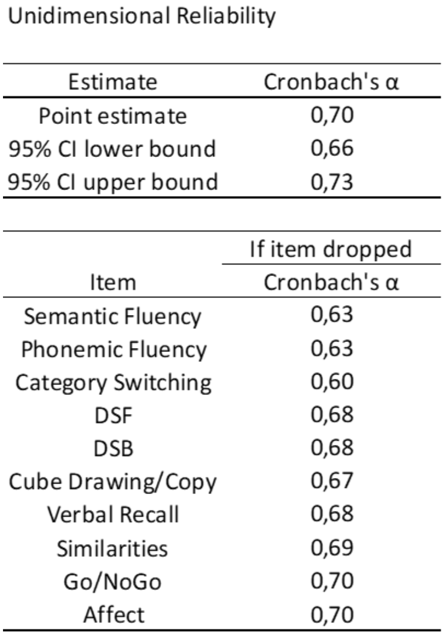
Equivalent Scores were calculated and the level of performance corresponding to ES = 0, 1, 2, 3 and 4 was derived for each subtest. According to what was done in the original study, the maximum score for each task was calculated. A maximum value for each item is useful to avoid distortion of the CCAS total score that, as mentioned before, is obtained as the sum of single subtest scores. For Semantic Fluency, Phonemic Fluency, Category Switching, DSF and DSB the upper limit was set at 1 standard deviation above the mean. For the other tasks, maximum score corresponded with a perfect score (Hoche et al., 2018). ES scores, new corresponding cut-offs and maximum scores are all reported in *Table 2.5*. It must be noted that for Cube Drawing/Copy and Similarities it was not possible to build a complete five-point scale, because of the huge ceiling effect that, not surprisingly, emerged in these specific tasks (see *Table 2.5* for details). Moreover, it was not very informative to obtain ES scores about Affect because of the very low variability (high ceiling effect) and also considering the observative and qualitative nature of this specific component.



Equivalent Scores								
	oTL	iTL	0 (cut-off)	1	2	3	4	Max Score
Semantic Fluency	10,95	14,95	≤ 10,95	10,96 - 15,35	15,36 - 18,96	18,97 - 22,95	> 22,95	28*
Phonetic Fluency	6,95	8,29	≤ 6,96	6,97 - 9,07	9,08 - 12,05	12,06 - 14,37	> 14,37	19*
Category Switching	5,81	7,49	≤5,81	5,82 - 8,34	8,35 - 10,92	10,93 - 12,88	> 12,88	17*
Digit Span Forward	3,85	4,3	≤ 3,85	3,86 - 4,51	4,52 - 4,96	4,97 - 5,72	> 5,72	7*
Digit Span Backward	2,4	2,76	≤ 2,4	2,41 - 2,85	2,86 - 3,7	3,71 - 4,11	> 4,11	5*
Cube Drawing/Copy**	10,62	11,48	≤ 10,62	10,63 - 11,72	11,73 - 15	15	15	15
Verbal Recall	7,37	9,59	≤ 7,37	7,38 - 10,12	10,13 - 12,12	12,13 - 13,64	> 13,64	15
Similarities **	5	6	≤ 5	5,01 - 6	6,01 - 7	7	> 7,00	8
Go/No-Go	0,01	0,73	≤ 0,01	0,02 - 0,76	0,77 - 1,4	1,41 - 2	2	2
Affect**	5	6	≤ 5	5,01 - 6	6	6	6	6

Table 2.5: *Equivalent Scores for CCAS scale subtests. New provisional cut-offs and maximum values for the Italian population are marked, respectively, in red and green. Flagged top scores (*) were obtained as mean + SD, according to the original work, whereas the remaining top scores correspond to the perfect scores for each subtest. For flagged subtests (**) it was not possible to derive all different ES levels because of the large ceiling effect and low variability of scores.*

Internal reliability of the scale, evaluated by means of Cronbach's Alpha (Cronbach, 1951), was 0,695, indicating a modest/good internal consistency. This value falls at middle way between the value of the original work (0,59; Hoche et al., 2018) and of other validation studies (0,74 of the Cuban study and 0,75 of the Brazilian validation) (Rodriguez-Labrada et al., 2021, de Oliveira Scott et al., 2023). In *Table 2.6* internal reliability values if a specific item was dropped from the scale are also reported.



Unidimensional Reliability

Estimate	Cronbach's α
Point estimate	0,70
95% CI lower bound	0,66
95% CI upper bound	0,73

	If item dropped
Item	Cronbach's α
Semantic Fluency	0,63
Phonemic Fluency	0,63
Category Switching	0,60
DSF	0,68
DSB	0,68
Cube Drawing/Copy	0,67
Verbal Recall	0,68
Similarities	0,69
Go/NoGo	0,70
Affect	0,70

Table 2.6: *Unidimensional reliability analysis. Internal consistency was addressed through Cronbach's Alpha (upper table). The lower table shows how Cronbach's Alpha would change if specific items were removed from the scale.*

CHAPTER 3 - DISCUSSION AND CONCLUSION

3.1. Discussion

The present work represents a preliminary step in the Italian CCAS scale standardization process. Data from a heterogeneous sample of two hundred and fifty-seven Italian healthy participants were collected and analysed, resulting in a significant association with age and education levels and new provisional adapted cut-offs. The great amount of data and their heterogeneity likely represent a strong point of the current study compared to the other cultural adaptation of the scale.

Correlations analysis showed convincing results, which will be briefly discussed. As expected, a negative correlation emerged between age and education, coherently with the upward trend in educational level of the new generations. Age influenced performance in all subtests except for Similarities and Affect. Education was able to predict scores of all subtests except for Similarities, Affect and Verbal Recall. In the healthy control group of the original validation of the scale by Hoche and colleagues (2018), no significant correlations were found between test scores and demographic variables, with the exception of age and Verbal Recall (r = -0,438, one tailed P-value <0,001). This mismatch with the original work can be addressed by the differences in sampling method. In fact, Hoche and colleagues only included participants under 65 years of age, to avoid confounding effects due to possible hidden neurocognitive disorder in the older population (Schmahmann et al., 2021). This could have led to a greater uniformity of performances, “masking” any age/education related differences.

Back to the present study, a result that, at first sight, could be considered surprising is that CRIq scores proved to be scarcely linked with subtests scores. Significant negative correlations were found only between Verbal Recall and CRI-education, CRI-leisure time and CRI-total score. Better analysing this result, it could be attributed to the characteristics of the sample. CRIq score, as it is conceived, can only grow with age and is, in fact, strongly related to this variable (for example, CRI-total and Age show a Pearson’s r = 0,570, p<0,001). Among all the CCAS scale subtests, Verbal Recall is the only one that shows strong correlation with age and no correlation with education. This specific characteristic could account for its correlation with CRIq scores, that is in fact negatively characterized (i.e., high CRIq levels correspond to low scores in Verbal Recall). All other subtests are related both to age and education: these two variables could then “compensate” each other and abolish correlations with CRIq scores. Despite these results, we should not conclude that CRIq score is not a useful predictor of scores at neuropsychological testing. Various studies demonstrated that CRIq has more predictive power than raw demographic variables (i.e., age, education and gender) and therefore provides a more accurate method to adjust scores (see for example: Mondini et al., 2022; Montemurro et al., 2022). As mentioned above, the current sample has relatively low mean age (40,90, SD = 18,94) and even lower median age (32). It emerges therefore that CRIq is more effective in predicting test scores in older samples, in which the Cognitive Reserve is already a consolidated value for each individual and is hence a more informative index.

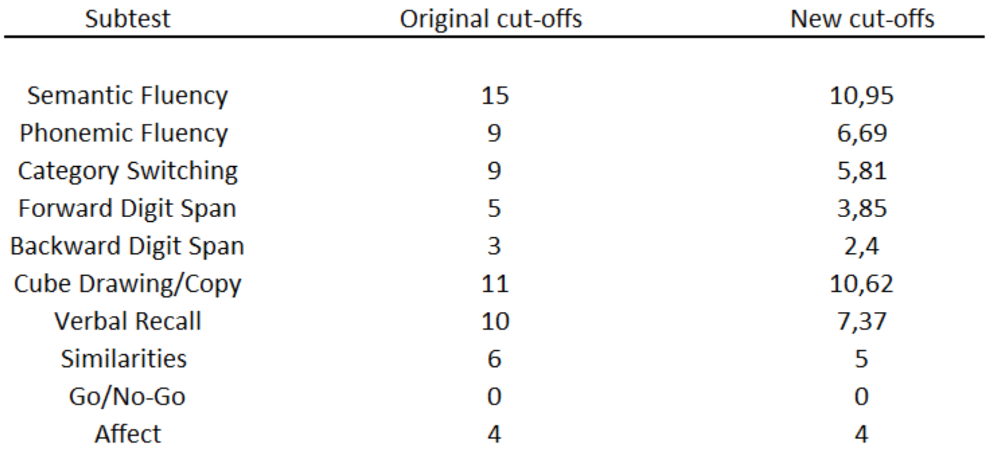
Significant gender differences only emerged in the Category Switching subtest, with women performing better than men. This result is consistent with previous studies reporting that women tend to switch more frequently between different categories than men in verbal fluency tasks (Weiss et al., 2006; Lanting, Haugrud, & Crossley, 2009). This tendency could reflect the advantage observed in the Category Switching test, even though evidence about this topic have often proved to be inconsistent (Sokołowski, Tyburski, E., Sołtys, & Karabanowicz, 2020).

Overall, demographic variables were able to predict relatively small amounts of variance in many subtests, but with high significance levels, so that it appeared useful to correct scores for such variables. Correction for demographic variables was often necessary in large and wide-range standardization samples: see for example MoCA (Santangelo et al., 2015) and FAB (Aiello et al., 2022) Italian validations studies.

The correction grid that was derived from this adjustment contains corrective factors that are minimal in some cases, in particular when the participant falls near the mean age and education values (40,90 and 15,92 respectively), but that can become not negligible for subjects which are far from mean values.

The choice to rely on the Equivalent Scores method to provide for new cut-offs values was made both for practical and theoretical reasons. Since the current data collection just included healthy participants and not cerebellar patients, it was neither possible to utilize sensitivity/selectivity values, as was done in the original study (Hoche et al., 2018) and in the German validation study (Thieme et al., 2020), nor the area under the receptor operating characteristic (ROC) curve (AUC), as was done in Dutch (Maas et al., 2021), Brazilian (de Oliveira Scott et al., 2023) and Cuban (Rodriguez-Labrada et al., 2021) validation studies. Beyond that, the ES method was chosen because it represents one the most solid and widely used non-parametric methods to derive diagnostic cut-offs (Mondini, Mapelli, & Arcara, 2016). ES method was used, for example, in the aforementioned MoCA and FAB validation studies, but also in the standardization of the Raven Matrices test (Carlesimo et al., 1996).

At the current point of data collection and examination, the cut-offs provided in the original study seem to be too severe for the Italian population. If they were applied to the current sample, 30,74% of participants would result in “possible CCAS” (1 subscale failed), 16,73% in “probable CCAS” (2 subscale failed) and 19,84% in “definite CCAS” (3 or more subtest failed). Therefore, if applied to a sample of cerebellar patients and matched healthy controls, these values would probably provide a very good sensitivity level, but unacceptably low selectivity. It is important to mention that it is not the first time that, in a validation study for the Italian population, diagnostic cut-offs had to be lowered, relative to the original values. Again, in MoCA validation study, Santangelo and colleagues found a cut-off value for MoCA total score quite lower than the one provided in the original study (Santangelo et al., 2015). Bosco and colleagues (2017) found that the optimal cut-off for MoCA total score in Italian patients with probable Alzheimer Disease was lower than those reported for other countries' populations. It goes beyond the goals of the present work to provide a satisfactory explanation for this phenomenon. In *Table 3.1* the new cut-offs are compared to the ones of the original study.



Subtest	Original cut-offs	New cut-offs
Semantic Fluency	15	10,95
Phonemic Fluency	9	6,69
Category Switching	9	5,81
Forward Digit Span	5	3,85
Backward Digit Span	3	2,4
Cube Drawing/Copy	11	10,62
Verbal Recall	10	7,37
Similarities	6	5
Go/No-Go	0	0
Affect	4	4

Table 3.1: *Comparison of provisional cut-offs derived from the present study and original cut-offs. New values are, in most cases, markedly lower than the original ones.*

The present results are consistent with those obtained in the Brazilian Portuguese validation study, in which several cut-off values had to be modified (lowered in most cases) to adapt to cultural characteristics of the sample (de Oliveira-Scott et al., 2023). Also in the German validation study, significantly lower levels of selectivity were found using original cut-offs values (Thieme et al., 2021). The latter research group has obtained another result coherent with the present work, i.e., significant correlations between test scores and age and education values. In particular, they reported a significant age-related decline of CCAS scores in healthy controls and a significant lower performance, both in patients and controls, in participants with lower education levels (Thieme et al., 2021). These results did not emerge in the original study (Hoche et al., 2018) and they addressed this issue to the low age and high education levels of the original sample (Thieme et al., 2021). Schmahmann, Vangel, Hoche, Guell, and Sherman (2021) agreed that these findings could be attributed to the characteristics of the sample, but provided an alternative interpretation: these results would not imply that the cut-offs are not valid for old and low-educated participants, but rather that, in such population, neurocognitive incipient impairment is not easy to exclude. They also suggested that the CCAS scale could represent a “better mousetrap” than what initially planned (Schmahmann et al., 2021): a tool useful to detect cerebellar deficits, but also early cognitive impairment in individuals over 65 years of age. The results of the current work support the need for demographic corrections and do not preclude any of these interpretations, in that it is entirely possible that the age-related decline could also represent early prediction for neurocognitive decline in older individuals. Considering that the German study recruited just 25 healthy controls over 65 and the current sample only contained 34 people above 65 years of age, further investigations are needed to understand whether the CCAS scale is a useful tool to detect incipient neurocognitive disorders.

Inter-rater and test-retest data collections were too few to derive quantitative analyses about reliability. From a qualitative point of view, very few variations in scores emerged between raters in the inter-rater administrations, suggesting possible high reliability levels. For what it concerns test-retest, various participants tested through CCAS scale Version B, spontaneously reported greater subjective difficulty in Semantic Fluency (“clothes”) and Category Switching (“fruits” and “cities”) than in Version A. Such aspects must be kept into account for what it concerns equivalence between different versions of the scale.

3.2. Limitations

Some limitations of the current work have already been suggested in previous sections. Young participants accounted for a large percentage of the sample, resulting in an overrepresentation of the under-40 population and a left asymmetric distribution of age values. Also, the education level of the sample, despite being normally distributed, was quite high overall, with an average of 15,92 years of formal education, corresponding to a bachelor degree in the Italian schooling system.

Moreover, inter-rater and test-retest administrations were too few to derive informative results. In particular four inter-raters and eleven test-retests were performed, with the test-retest being administered alternatively through CCAS scale Version A (5 of them) and through CCAS scale Version B (6).

Another current limitation of the study, in comparison with the other CCAS scale translation and validation works considered in the current section, is represented by the fact that the Italian scale has not been administered to patients with cerebellar disease. This limitation did not prevent deriving normative data for the Italian population but did not allow to compare selectivity and sensitivity, in order to calculate adjusted cut-offs. Such methodological difference could also affect comparison between the result of the current study and those of other research groups. Moreover, as currently structured, the present study does not provide supporting evidence about the cerebellar role in cognition and affect regulation. As extensively described in Chapter 1, the implication of the cerebellum in cognitive and affective functioning is well established but, nevertheless, further evidence is always useful to better understand the precise extent of its role and to explore its implication in specific patient populations.

3.3. Future directions

The goal of our group is to achieve a total sample of 500 Italian healthy participants, to further increase the statistical power of the deriving results.

To effectively complete the data collection, it will be crucial to pay particular attention to the participant recruitment criteria, in order to fill the gaps within the distribution, thus obtaining a better heterogeneity of the sample.

It would be important to keep open the possibility of eventual adjustment of the CCAS scale, keeping in account present and future accumulating evidence of clinical applications. In the meta-analysis performed by Ahmadian and colleagues (2019), for example, no difference overall was found between the performance of patients and controls in the Forward Digit Span. Also in the current data collection, FDS emerged as one of the subtests that more often fell below the originally provided cut-off value. This and other future evidence should be kept into account for a more precise shaping of the CCAS scale and of the CCAS itself.

An interesting development of the study could be represented by the inclusion of patients with various cerebellar disease, from which to derive selectivity and sensitivity values of the scale. Until now, to the best of the author's knowledge, no other study has performed an administration of CCAS scales on a large sample of healthy controls. The present work includes a large body of data that could be confronted with those from patients matched for age and education, providing for very statistically solid results. Moreover, no other CCAS study has included the administration of the Cognitive Reserve Index questionnaire, that could represent a better predictor than demographic variables in a more balanced sample, as discussed in section 3.1. Beyond that, such data would be useful to further investigate whether and how the Cognitive Reserve interacts both with the presence of neurodegenerative cerebellar diseases and of cerebellar focal injuries, as recently done by Siciliano and colleagues (Siciliano, Olivito, Urbini, Silveri and Leggio, 2023).

The inclusion of cerebellar patients could also potentially provide an answer to the question raised by Schmahmann and colleagues in their response to Thieme and collaborators (2021), i.e. if the CCAS scale could be useful to detect neurocognitive deficits earlier than other widely used screening tools. To verify this suggestion, a longitudinal study should be conducted, in which, over a period of time of approximately two years, a large sample of participants older than 65 years of age would be periodically tested with both the CCAS scale and another commonly used screening instrument (MoCA). In this way, it could be possible to evaluate if the CCAS scale has the ability to early predict the subsequent development of cognitive impairment, objectified by means of the MoCA performance. It could also emerge a greater rate of decline in CCAS scores than MoCA scores that, if associated with other markers of neurodegeneration, would equally point to the CCAS scale as an earlier indicator. If the CCAS proved to be an effective predictor of subsequent cognitive decline, two different interpretations could be provided: 1) that the CCAS scale is indeed a “better mousetrap” (Schmahmann et al., 2021), able to early identify neurocognitive impairment; 2) even more intriguingly, that cognitive/affective cerebellar impairment represents an early marker of dementia onset, suggesting a role of the CCAS as a very initial sign of neurodegeneration (Devita et al., 2021).

3.4. Conclusions

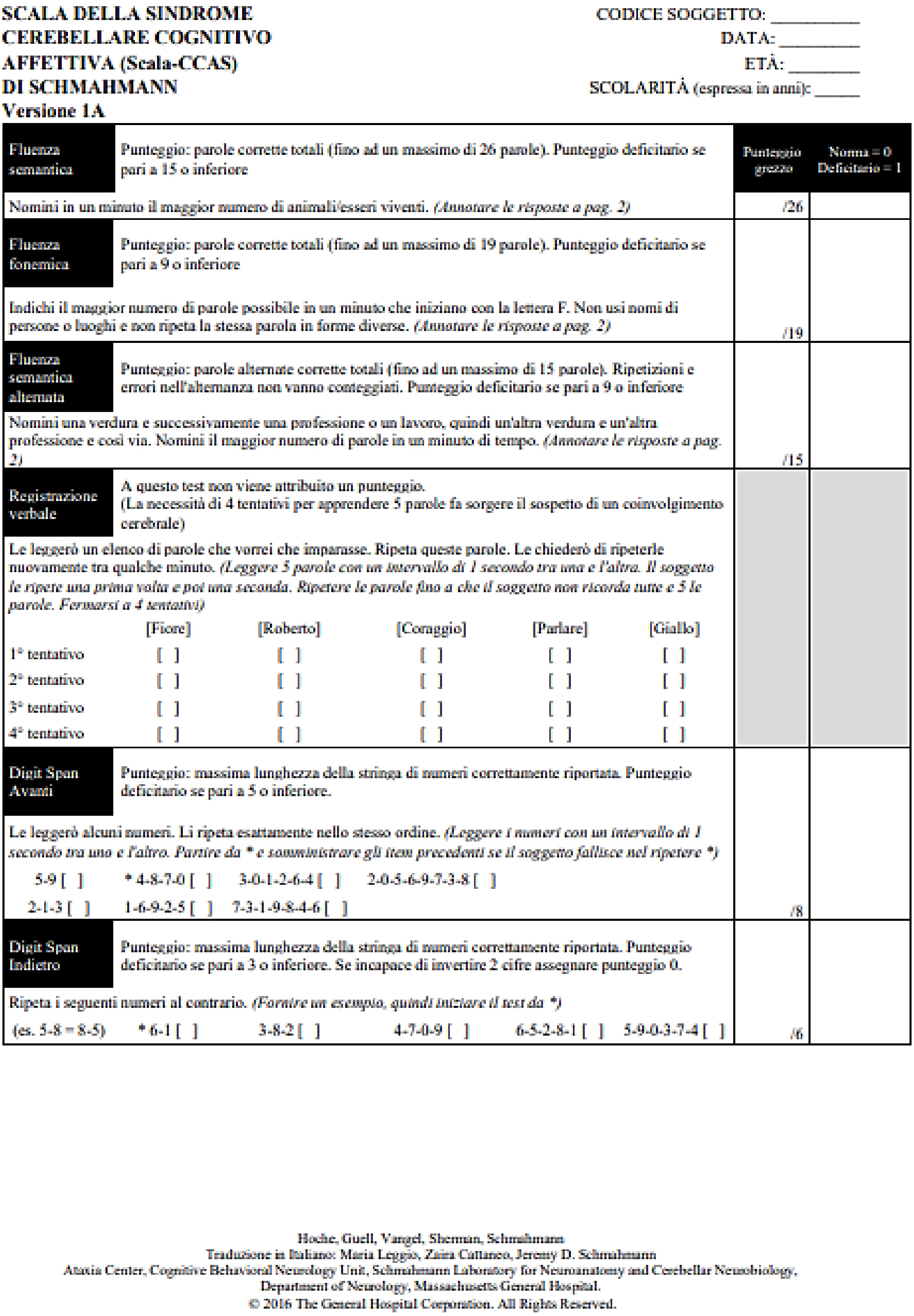
In the current work, the initial background comprehended general notions about the cerebellum and the different syndromes deriving from its damage, in accordance with the framework of the “three cornerstones of clinical ataxiology”

(Manto & Marien, 2015). The role of cerebellum in cognition is currently consolidated, and nowadays researchers are proposing new ideas and unexplored hypotheses that are progressively widening our understanding of its functions and topography.

Thanks to the multicentric nature of the study, a wide and heterogeneous sample of healthy participants has been recruited to provide CCAS scale normative data for the Italian population. The provisional results reported in the current work support the need for age/education scores adjustment for eight out of ten subtests of the scale. Sex-adapted corrections were necessary for a single subtest (Category switching). New possible cut-offs were provided for eight out of ten subtests, which in all cases showed to be lower than the original ones. The scale showed modest/good internal consistency (Cronbach's alpha = 0,695). In the prosecution of the data collection, particular attention should be paid to the accurate completion of demographic distribution. The inclusion in the study of patients suffering from different kinds of cerebellar disease and injury could provide the opportunities to further investigate the potentiality of the CCAS scale and the implication of the cerebellum in different forms of cognitive impairment, such as cognitive degeneration.

APPENDIX

Sub-test	Education	Age								
		20	30	40	50	60	70	80	90	100
Semantic Fluency	5	1,26	1,78	2,30	2,82	3,34	3,86	4,38	4,90	5,42
	8	0,62	1,14	1,66	2,18	2,70	3,22	3,74	4,26	4,78
	11	-0,03	0,49	1,01	1,53	2,05	2,57	3,09	3,61	4,13
	13	-0,46	0,06	0,58	1,10	1,62	2,14	2,66	3,18	3,70
	16	-1,10	-0,58	-0,06	0,46	0,98	1,50	2,02	2,54	3,06
	18	-1,53	-1,01	-0,49	0,03	0,55	1,07	1,59	2,11	2,63
	21	-2,18	-1,66	-1,14	-0,62	-0,10	0,42	0,94	1,46	1,98
	25	-3,04	-2,52	-2,00	-1,48	-0,96	-0,44	0,08	0,60	1,12
Phonetic Fluency	5	1,33	1,68	2,03	2,38	2,73	3,08	3,43	3,78	4,13
	8	0,77	1,12	1,47	1,82	2,17	2,52	2,87	3,22	3,57
	11	0,20	0,55	0,90	1,25	1,60	1,95	2,30	2,65	3,00
	13	-0,18	0,17	0,52	0,87	1,22	1,57	1,92	2,27	2,62
	16	-0,75	-0,40	-0,05	0,30	0,65	1,00	1,35	1,70	2,05
	18	-1,12	-0,77	-0,42	-0,07	0,28	0,63	0,98	1,33	1,68
	21	-1,69	-1,34	-0,99	-0,64	-0,29	0,06	0,41	0,76	1,11
	25	-2,45	-2,10	-1,75	-1,40	-1,05	-0,70	-0,35	0,00	0,35
Category Switching (males)	5	1,96	2,48	3,00	3,52	4,04	4,56	5,08	5,60	6,12
	8	1,32	1,84	2,36	2,88	3,40	3,92	4,44	4,96	5,48
	11	0,67	1,19	1,71	2,23	2,75	3,27	3,79	4,31	4,83
	13	0,24	0,76	1,28	1,80	2,32	2,84	3,36	3,88	4,40
	16	-0,40	0,12	0,64	1,16	1,68	2,20	2,72	3,24	3,76
	18	-0,83	-0,31	0,21	0,73	1,25	1,77	2,29	2,81	3,33
	21	-1,48	-0,96	-0,44	0,08	0,60	1,12	1,64	2,16	2,68
	25	-2,34	-1,82	-1,30	-0,78	-0,26	0,26	0,78	1,30	1,82
Category Switching (females)	5	0,80	1,32	1,84	2,36	2,88	3,40	3,92	4,44	4,96
	8	0,15	0,67	1,19	1,71	2,23	2,75	3,27	3,79	4,31
	11	-0,49	0,03	0,55	1,07	1,59	2,11	2,63	3,15	3,67
	13	-0,92	-0,40	0,12	0,64	1,16	1,68	2,20	2,72	3,24
	16	-1,57	-1,05	-0,53	-0,01	0,51	1,03	1,55	2,07	2,59
	18	-2,00	-1,48	-0,96	-0,44	0,08	0,60	1,12	1,64	2,16
	21	-2,64	-2,12	-1,60	-1,08	-0,56	-0,04	0,48	1,00	1,52
	25	-3,50	-2,98	-2,46	-1,94	-1,42	-0,90	-0,38	0,14	0,66
Digit Span	5	0,40	0,52	0,64	0,76	0,88	1,00	1,12	1,24	1,36
	8	0,22	0,34	0,46	0,58	0,70	0,82	0,94	1,06	1,18
	11	0,04	0,16	0,28	0,40	0,52	0,64	0,76	0,88	1,00
	13	-0,08	0,04	0,16	0,28	0,40	0,52	0,64	0,76	0,88
	16	-0,26	-0,14	-0,02	0,10	0,22	0,34	0,46	0,58	0,70
	18	-0,38	-0,26	-0,14	-0,02	0,10	0,22	0,34	0,46	0,58
	21	-0,56	-0,44	-0,32	-0,20	-0,08	0,04	0,16	0,28	0,40
	25	-0,80	-0,68	-0,56	-0,44	-0,32	-0,20	-0,08	0,04	0,16
Backward Digit Span	5	0,13	0,27	0,41	0,55	0,69	0,83	0,97	1,11	1,25
	8	0,02	0,16	0,30	0,44	0,58	0,72	0,86	1,00	1,14
	11	-0,10	0,04	0,18	0,32	0,46	0,60	0,74	0,88	1,02
	13	-0,18	-0,04	0,10	0,24	0,38	0,52	0,66	0,80	0,94
	16	-0,30	-0,16	-0,02	0,12	0,26	0,40	0,54	0,68	0,82
	18	-0,37	-0,23	-0,09	0,05	0,19	0,33	0,47	0,61	0,75
	21	-0,49	-0,35	-0,21	-0,07	0,07	0,21	0,35	0,49	0,63
	25	-0,65	-0,51	-0,37	-0,23	-0,09	0,05	0,19	0,33	0,47
Cube Drawing/Copy	5	0,79	0,98	1,17	1,36	1,55	1,74	1,93	2,12	2,31
	8	0,47	0,66	0,85	1,04	1,23	1,42	1,61	1,80	1,99
	11	0,14	0,33	0,52	0,71	0,90	1,09	1,28	1,47	1,66
	13	-0,08	0,11	0,30	0,49	0,68	0,87	1,06	1,25	1,44
	16	-0,41	-0,22	-0,03	0,16	0,35	0,54	0,73	0,92	1,11
	18	-0,62	-0,43	-0,24	-0,05	0,14	0,33	0,52	0,71	0,90
	21	-0,95	-0,76	-0,57	-0,38	-0,19	-0,00	0,19	0,38	0,57
	25	-1,39	-1,20	-1,01	-0,82	-0,63	-0,44	-0,25	-0,06	0,13
Verbal Recall		-1,02	-0,53	-0,04	0,45	0,94	1,43	1,92	2,41	2,90



SCALA DELLA SINDROME
CEREBELLARE COGNITIVO
AFFETTIVA (Scala-CCAS)
DI SCHMAHMANN
Versione 1A

CODICE SOGGETTO: __________
DATA: _________
ETÀ: ________
SCOLARITÀ (espressa in anni): ______

Fluenza semantica	Punteggio: parole corrette totali (fino ad un massimo di 26 parole). Punteggio deficitario se pari a 15 o inferiore	**Punteggio grezzo**	**Norma = 0 Deficitario = 1**
Nomini in un minuto il maggior numero di animali/esseri viventi. *(Annotare le risposte a pag. 2)*		/26	
Fluenza fonemica	Punteggio: parole corrette totali (fino ad un massimo di 19 parole). Punteggio deficitario se pari a 9 o inferiore		
Indichi il maggior numero di parole possibile in un minuto che iniziano con la lettera F. Non usi nomi di persone o luoghi e non ripeta la stessa parola in forme diverse. *(Annotare le risposte a pag. 2)*		/19	
Fluenza semantica alternata	Punteggio: parole alternate corrette totali (fino ad un massimo di 15 parole). Ripetizioni e errori nell'alternanza non vanno conteggiati. Punteggio deficitario se pari a 9 o inferiore		
Nomini una verdura e successivamente una professione o un lavoro, quindi un'altra verdura e un'altra professione e così via. Nomini il maggior numero di parole in un minuto di tempo. *(Annotare le risposte a pag. 2)*		/15	
Registrazione verbale	A questo test non viene attribuito un punteggio. (La necessità di 4 tentativi per apprendere 5 parole fa sorgere il sospetto di un coinvolgimento cerebrale)	▨	▨
Le leggerò un elenco di parole che vorrei che imparasse. Ripeta queste parole. Le chiederò di ripeterle nuovamente tra qualche minuto. *(Leggere 5 parole con un intervallo di 1 secondo tra una e l'altra. Il soggetto le ripete una prima volta e poi una seconda. Ripetere le parole fino a che il soggetto non ricorda tutte e 5 le parole. Fermarsi a 4 tentativi)* [Fiore] [Roberto] [Coraggio] [Parlare] [Giallo] 1° tentativo [ ] [ ] [ ] [ ] [ ] 2° tentativo [ ] [ ] [ ] [ ] [ ] 3° tentativo [ ] [ ] [ ] [ ] [ ] 4° tentativo [ ] [ ] [ ] [ ] [ ]		▨	▨
Digit Span Avanti	Punteggio: massima lunghezza della stringa di numeri correttamente riportata. Punteggio deficitario se pari a 5 o inferiore.		
Le leggerò alcuni numeri. Li ripeta esattamente nello stesso ordine. *(Leggere i numeri con un intervallo di 1 secondo tra uno e l'altro. Partire da * e somministrare gli item precedenti se il soggetto fallisce nel ripetere *)* 5-9 [ ] * 4-8-7-0 [ ] 3-0-1-2-6-4 [ ] 2-0-5-6-9-7-3-8 [ ] 2-1-3 [ ] 1-6-9-2-5 [ ] 7-3-1-9-8-4-6 [ ]		/8	
Digit Span Indietro	Punteggio: massima lunghezza della stringa di numeri correttamente riportata. Punteggio deficitario se pari a 3 o inferiore. Se incapace di invertire 2 cifre assegnare punteggio 0.		
Ripeta i seguenti numeri al contrario. *(Fornire un esempio, quindi iniziare il test da *)* (es. 5-8 = 8-5) * 6-1 [ ] 3-8-2 [ ] 4-7-0-9 [ ] 6-5-2-8-1 [ ] 5-9-0-3-7-4 [ ]		/6	

Hoche, Guell, Vangel, Sherman, Schmahmann
Traduzione in Italiano: Maria Leggio, Zaira Cattaneo, Jeremy D. Schmahmann
Ataxia Center, Cognitive Behavioral Neurology Unit, Schmahmann Laboratory for Neuroanatomy and Cerebellar Neurobiology,
Department of Neurology, Massachusetts General Hospital.

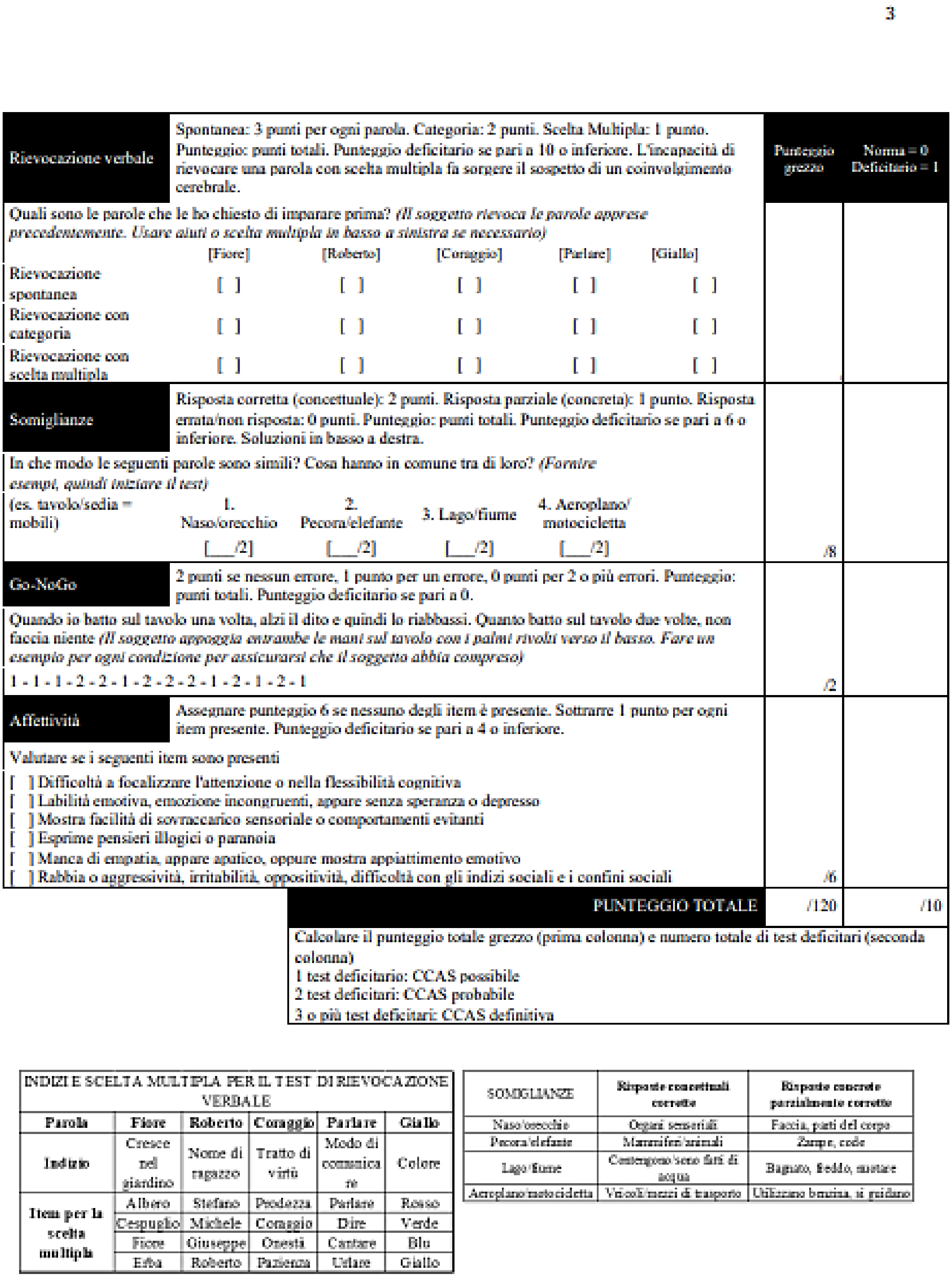
Cubo (Disegno)	Punteggio: 15 punti se sono presenti le 12 linee e il disegno è tridimensionale. Se non sono presenti le 12 linee oppure il disegno non è tridimensionale, somministrare "Cubo (Copia)"		
Si prega di disegnare un cubo – una scatola a sei lati, trasparente. *(Usare lo spazio in basso a sinistra)*			
Cubo (Copia)	Punteggio: 12 punti, uno per ogni linea. Togliere un punto se non è tridimensionale, un punto per ogni linea non disegnata, un punto per ogni linea aggiuntiva >12. Punteggio deficitario se pari a 11 o inferiore.		
Copi il cubo mostrato a pagina 2. *(Non valutata la precisione)*		/15	

Fluenza semantica

Fluenza fonemica

Fluenza semantica alternata

Disegnare il cubo qui



3

Rievocazione verbale	Spontanea: 3 punti per ogni parola. Categoria: 2 punti. Scelta Multipla: 1 punto. Punteggio: punti totali. Punteggio deficitario se pari a 10 o inferiore. L'incapacità di rievocare una parola con scelta multipla fa sorgere il sospetto di un coinvolgimento cerebrale.	**Punteggio grezzo**	**Norma = 0 Deficitario = 1**

Quali sono le parole che le ho chiesto di imparare prima? *(Il soggetto rievoca le parole apprese precedentemente. Usare aiuti o scelta multipla in basso a sinistra se necessario)*

	[Fiore]	[Roberto]	[Coraggio]	[Parlare]	[Giallo]
Rievocazione spontanea	[ ]	[ ]	[ ]	[ ]	[ ]
Rievocazione con categoria	[ ]	[ ]	[ ]	[ ]	[ ]
Rievocazione con scelta multipla	[ ]	[ ]	[ ]	[ ]	[ ]

Somiglianze	Risposta corretta (concettuale): 2 punti. Risposta parziale (concreta): 1 punto. Risposta errata/non risposta: 0 punti. Punteggio: punti totali. Punteggio deficitario se pari a 6 o inferiore. Soluzioni in basso a destra.		

In che modo le seguenti parole sono simili? Cosa hanno in comune tra di loro? *(Fornire esempi, quindi iniziare il test)*

(es. tavolo/sedia = mobili)	1. Naso/orecchio	2. Pecora/elefante	3. Lago/fiume	4. Aeroplano/ motocicletta	
	[___/2]	[___/2]	[___/2]	[___/2]	/8

Go-NoGo	2 punti se nessun errore, 1 punto per un errore, 0 punti per 2 o più errori. Punteggio: punti totali. Punteggio deficitario se pari a 0.		

Quando io batto sul tavolo una volta, alzi il dito e quindi lo riabbassi. Quanto batto sul tavolo due volte, non faccia niente *(Il soggetto appoggia entrambe le mani sul tavolo con i palmi rivolti verso il basso. Fare un esempio per ogni condizione per assicurarsi che il soggetto abbia compreso)*

1 - 1 - 1 - 2 - 2 - 1 - 2 - 2 - 2 - 1 - 2 - 1 - 2 - 1 /2

Affettività	Assegnare punteggio 6 se nessuno degli item è presente. Sottrarre 1 punto per ogni item presente. Punteggio deficitario se pari a 4 o inferiore.		

Valutare se i seguenti item sono presenti

[ ] Difficoltà a focalizzare l'attenzione o nella flessibilità cognitiva
[ ] Labilità emotiva, emozione incongruenti, appare senza speranza o depresso
[ ] Mostra facilità di sovraccarico sensoriale o comportamenti evitanti
[ ] Esprime pensieri illogici o paranoia
[ ] Manca di empatia, appare apatico, oppure mostra appiattimento emotivo
[ ] Rabbia o aggressività, irritabilità, oppositività, difficoltà con gli indizi sociali e i confini sociali /6

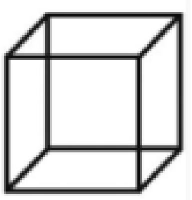
PUNTEGGIO TOTALE	/120	/10

Calcolare il punteggio totale grezzo (prima colonna) e numero totale di test deficitari (seconda colonna)
1 test deficitario: CCAS possibile
2 test deficitari: CCAS probabile
3 o più test deficitari: CCAS definitiva

INDIZI E SCELTA MULTIPLA PER IL TEST DI RIEVOCAZIONE VERBALE					
Parola	**Fiore**	**Roberto**	**Coraggio**	**Parlare**	**Giallo**
Indizio	Cresce nel giardino	Nome di ragazzo	Tratto di virtù	Modo di comunicare	Colore
Item per la scelta multipla	Albero	Stefano	Prodezza	Parlare	Rosso
	Cespuglio	Michele	Coraggio	Dire	Verde
	Fiore	Giuseppe	Onestà	Cantare	Blu
	Erba	Roberto	Pazienza	Urlare	Giallo

SOMIGLIANZE	**Risposte concettuali corrette**	**Risposte concrete parzialmente corrette**
Naso/orecchie	Organi sensoriali	Faccia, parti del corpo
Pecora/elefante	Mammiferi/animali	Zampe, code
Lago/fiume	Contengono/sono fatti di acqua	Bagnato, freddo, nuotare
Aeroplano/motocicletta	Veicoli/mezzi di trasporto	Utilizzano benzina, si guidano

4



Copiare il cubo qui

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SITOGRAFIA

1. Figure 1.1, derived from: https://www.netterimages.com/cerebellum-unlabeled-general-anatomy-frank-h-netter-2291.html