The cerebellar topography of attention sub-components in Spinocerebellar Ataxia Type 2

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Abstract

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disease characterized by a progressive cerebellar syndrome and multiple-domain cognitive impairments. The cerebellum is known to contribute to distinct functional networks related to higher-level functions. The aims of the present study were to investigate the different sub-components of attention and to analyse possible correlations between attention deficits and specific cerebellar regions in SCA2 patients.

To this purpose, 11 SCA2 patients underwent an exhaustive attention battery that evaluated several attention sub-components. The SCA2 group performed below the normal range in tasks assessing selective attention, divided attention, and sustained attention, obtaining negative Z-scores. These results were confirmed by non-parametric Mann-Whitney U tests that showed significant differences between SCA2 and control subjects in the same sub-components of the attention battery, allowing us to speculate on cerebellar involvement when a high cognitive demand is required (i.e., multisensory integration, sequencing, prediction of events, and inhibition of inappropriate response behaviours).

The voxel-based morphometry analysis showed a pattern of significantly reduced grey matter volume in specific cerebellar lobules. In particular, the SCA2 patients showed significant grey matter loss in bilateral regions of the anterior cerebellar hemisphere (I-V) and in the posterior lobe (VI-IX) and posterior vermis (VI-IX).

Statistical analysis found significant correlations between grey matter reductions in the VIIb/VIIIa cerebellar lobules and impairments in Sustained and Divided Attention tasks and between grey matter reduction in the vermal VI lobule and impairment in the Go/NoGo task.

For the first time, the study demonstrated the involvement of specific cerebellar lobules in different sub-components of the attention domain, giving further support to the inclusion of the cerebellum within the attention network.

Keywords: cerebellum, attention, neurodegenerative disorder, topography, MRI

Highlights

1) SCA2 patients are impaired in specific sub-components of the attention function
2) The cerebellum is involved in attention when a high cognitive demand exists
3) SCA2 shows reductions in grey matter volume in specific cerebellar lobules
4) There is selective topography between cerebellar lobules and specific attentional impairments

Abbreviations: CB = Cerebellar patient; M = Male; F = Female; WAIS-r = Wechsler Adult Intelligent Scale-revised version; IQ = Intelligence quotient; WCST = Wisconsin Card Sorting Test; ToL = Tower of London; SCA 2 = Spinocerebellar ataxia type 2; Ct-Att = Attention control group; v.c. = Verbal condition.

1.1 Introduction

Spinocerebellar ataxia type 2 (SCA2) is a degenerative disorder caused by an expanded CAG trinucleotide repeat in the gene encoding *ataxin-2* (Pulst *et al*., 1996), which causes cerebellar degeneration primarily affecting Purkinje cells, pontine nuclei, and inferior olives (Geschwind *et al*., 1997; Scherzed *et al*., 2012). It is characterized by a progressive cerebellar syndrome and ataxic gait, cerebellar dysarthria, dysmetria, dysdiadochokinesia, and visuospatial impairments, including saccadic and voluntary eye movements (Fernandez-Ruiz *et al*., 2007; Auburger, 2012).

Recent neuropathological studies have revealed an overall reduction in brain size, with significant atrophy of the cerebellum, brainstem, and frontal lobes, along with reductions in cerebral and cerebellar white matter (WM) (Mascalchi *et al*., 2015). Furthermore, a recent study found a disruption in functional connectivity in the fronto-cerebellar network (Hernandez-Castillo *et al*., 2015a) and WM alterations related to the ataxia severity (Hernandez-Castillo *et al*., 2015b).

As reported in the literature, cognitive impairment occurs in 19 to 42% of patients with SCA2 (Dürr *et al*., 1995; Geschwind *et al*., 1997; Bürk et al., 1999), with specific impairments of executive dysfunction, visual memory, and attention (Le Pira *et al*., 2002; Bürk *et al*., 2003; Klinke *et al*., 2010; Fancellu *et al*., 2013; Mercadillo *et al*., 2014; Olivito *et al*., 2017a).

This cognitive profile adheres to the Cerebellar Cognitive-Affective Syndrome (CCAS) described by Schmahmann and Sherman (1998) in patients with cerebellar damage. The cognitive deficits of cerebellar patients with CCAS have been attributed to the disruption of the neural circuits linking prefrontal, temporal, posterior parietal, and limbic cortices with the cerebellum.

A recent study on SCA2 patients found differences in functional connectivity between specific cerebellar and cerebral "nodes" by the network-based statistics (NBS) approach (Olivito *et al.*, 2017b). The authors found altered inter-nodal connectivity between posterior regions in the cerebellum and regions in the cerebral cortex clearly related to cognition and emotion, suggesting that in SCA2, the cerebellar dysfunction affects long-distance cerebral regions and that the clinical symptoms may be specifically related to connectivity changes between motor and non-motor cerebello-cortical nodes.

Although there is clear evidence for the role of the cerebellum in memory, language, emotion, and perceptual functions (Schmahmann & Sherman, 1998; Tedesco *et al.*, 2011; Baumann *et al.*, 2015; Lupo *et al.*, 2015), the cerebellar involvement in attention remains somewhat controversial (Haarmeier & Their, 2007). Specifically, whereas early studies indicated that the cerebellum plays

important roles in both spatial and non-spatial attention (Akshoomoff & Courchesne, 1994; Townsend *et al.*, 1999; Schweizer *et al.*, 2007), subsequent studies failed to replicate many of these findings (Dimitrov *et al.*, 1996; Ravizza and Ivry, 2001; Golla *et al.*, 2005).

It is important to underline that the attention domain *per se* consists of different sub-dimensions (i.e., shifting of attention, sustained attention, and focus of attention), complicating the general study of this function and, even more, the investigation of the underlying networks.

Considering the different theories advanced to distinguish the attentional components, two main models have been taken into account by the scientific literature. The first, proposed by Posner and Petersen (1990), postulates that the brain areas responsible for attention are formed by a specific system of anatomical areas that can be broken down into three networks: the brain stem arousal systems and right hemisphere systems, the frontal and posterior areas, and the midline frontal/anterior cingulate cortex. These systems perform functions related to alerting, orienting, and executive control, respectively (Fan et al., 2002).

Subsequently, in 1994, van Zomeren and Brouwer arranged the different attentional functions along two dimensions: "intensity" and "selectively". The component intensity is subdivided into "alertness" and "sustained attention", while the component selectively is divided into "focused attention" and "divided attention". Such cognitive abilities are strictly linked to the frontal activity; thus, it is difficult to separate them from other executive functions, such as working memory. According to this consideration, the authors postulate that a top-down process, named the "supervisory attentional system" (SAS), consciously co-ordinates and reorganizes new information within the attentional domain.

Thus, considering the difficulties in disengaging the attentional components and the heterogeneity of the cerebellar sample populations enrolled in the different studies (i.e., patients affected by different cerebellar pathologies), until now, it has not been possible to obtain a unique view regarding the roles of cerebellar regions within the attention domain.

For these reasons, studies on the attentional problems of SCA2 patients have also suffered several criticisms (Klinke *et al.*, 2010; Sokolovsky *et al.*, 2010; Almeida-Silva *et al.*, 2013; Moriarty *et al.*, 2016), with consequent controversial results and limited correlational studies between SCA2 patients' attention impairments and anatomical alterations (Mercadillo *et al.*, 2014; Hernandez-Castillo *et al.*, 2016; Moore *et al.*, 2017).

Despite these limitations, there is currently widespread agreement that a specific cortical network is involved in attention and that cerebellar regions might be part of this network (Brissenden *et a*l., 2016). According to this assumption, fMRI studies show activation of the left superior posterior

cerebellum during “focused-attention” tasks (Allen *et al*., 1997) and activation of the right anterior cerebellum during “shifting-attention” tasks (Le *et al*., 1998).
Moreover, the cerebellar involvement in attention is also supported by studies reporting smaller posterior inferior vermis lobules VIII–X in children with attention deficit hyperactivity disorder (ADHD) than in healthy controls (Berquin *et al*., 1998; Castellanos *et al*., 2001).

Taking into account these considerations, the aims of the present study were as follows: within the general cognitive profile of SCA2 patients, investigate the different sub-components of attention and analyse possible correlations between attention deficits and specific cerebellar regions.

2.1 Materials and Methods

2.1.1 *Participants*

We enrolled 11 patients with a genetically confirmed diagnosis of SCA2 recruited from the Ataxia Lab of the Santa Lucia Foundation. Some of these patients had participated in a previous study (Olivito et al., 2017b). Patients’ information are detailed in section 2.1.2.
All control subjects were recruited from the Santa Lucia Foundation and from the Department of Psychology at the Sapienza University of Rome.
In each study section - neuropsychological profile, attentional assessments, and magnetic resonance imaging study - a specific control group has been considered. The detailed inclusion criteria for the enrolment of control subjects have been indicated in each dedicated section.

None of control subjects had a history of neurological or mental illness. In both behavioural conditions (neuropsychological profile and attentional assessments), control subjects were well matched to the SCA2 group regarding age and education.

The experimental procedures were approved by the Ethics Committee of IRCSS Santa Lucia Foundation and by the Institutional Review Board of the Department of Psychology. Written informed consent was obtained from each subject per the Helsinki Declaration.

2.1.2 *Neuropsychological and attention profiles of SCA2 patients*

The demographic characteristics of the patients are reported in Table 1.
At the time of assessment, six months or more had elapsed from the time of diagnosis for all patients. According to the inclusion criteria, patients presented with diffuse cerebellar atrophy and no other brain abnormalities as detected by visual inspection of MRI scans.

Patients' motor impairments were quantified using the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas *et al*., 1997), which ranges from zero (the absence of any deficit) to 100 (the presence of all deficits to the highest degree) (Table 1).

Table 1. Demographic characteristics of SCA2 patients

Group	Age	Education	M/F	Intellectual Level cut off:18,96	ICARS Motor Score
CB1	43	18	F	24.20	26.00
CB2	38	12	F	22.40	33.00
CB3	42	13	F	26.80	47.00
CB4	62	18	M	27.20	27.00
CB5	60	8	F	31.40	31.00
CB6	40	8	M	33.30	18.00
CB7	54	18	F	29.10	27.00
CB8	43	13	F	25.80	28.00
CB9	42	11	M	33.30	24.00
CB10	38	13	F	31.40	39.00
CB11	42	18	M	30.20	17.00
Means (sd)	44.45 (6.82)	12.91 (3.88)	4/7	28.65 (3.65)	28.82 (8.67)

The data are reported as means and standard deviations (sd).

All patients underwent a neuropsychological evaluation to evaluate their cognitive profile (see 2.2.1 section), while the control subjects underwent Raven's Progressive Matrices '47 (Raven, 1949) to verify a normal intellectual level as an inclusion criterion.

2.1.3 *Magnetic resonance imaging examination of SCA2 patients*

For the study of the voxel-based morphometry (VBM) correlational analysis, nine of the 11 SCA2 patients of the previous study (SCA2-MRI) were enrolled (mean age/SD: 44.44/7.14; M/F:

three/six). Indeed, CB2 and CB11 (Table 1) were excluded because they failed to carry out the MRI examination.

A new group of 33 control subjects (Ct-MRI) with no history of neurological or psychiatric illness was enrolled as the control group for the MRI examination (mean age/sd: 50.55/6.6; M/F: 12/21). A t-test analysis ensured that there was no significant difference in the mean age between the two groups (p= 0.39).

2.2 *Behavioural measures*

2.2.1 *Neuropsychological assessments*

The neuropsychological assessment included the following tests:

Intellectual level: Wechsler Adult Intelligence Scale-Revised Intelligence Quotient (WAIS-r IQ) (Wechsler, 1981; Orsini & Laicardi, 1997, 2003); Raven's Progressive Matrices '47 test (Raven, 1949).

Language: WAIS-r vocabulary subtest (Wechsler, 1981; Orsini & Laicardi, 1997, 2003).

Verbal Memory: Immediate and delayed recall of Rey's 15 words (Rey, 1958); forward and backward digit span (Wechsler, 1945; Orsini *et al*., 1987).

Visuospatial Memory: Rey-Osterrieth Complex Figure Test (recall) (Caffarra *et al.*, 2002); forward and backward Corsi (Corsi, 1972).

Executive Functions: Stroop Test ("time effect" and "error effect") (Caffarra *et al*,. 2002); semantic fluency (Borkowsky *et al*., 1967); phonological fluency (Borkowsky *et al*., 1967); verbal fluency (Woods *et al*., 2005); Wisconsin Card Sorting Test (WCST) (number of perseverations and perseverative errors) (Heaton *et al*., 2000); Tower of London procedure (TOL) (Krikorian *et al*., 1994).

Visuospatial abilities: Rey-Osterrieth Complex Figure Test (copy) (Caffarra *et al.*, 2002); WAIS-r block design subtest (Wechsler, 1981; Orsini & Laicardi, 1997, 2003).

Sequencing Abilities: WAIS-r picture arrangement subtest (Wechsler, 1981; Orsini & Laicardi, 1997, 2003).

2.2.2 *Attention assessments*

To evaluate attention abilities, the patients underwent two phases of testing.

In the first phase, they performed the neuropsychological tests classically used for the screening of attention deficits, i.e., the WAIS-r arithmetic subtest (Wechsler, 1981; Orsini & Laicardi, 1997, 2003), the Multiple Features Target Cancellation task (Gainotti *et al*., 2001), and the Trail Making Test B-A (TMT B-A) (Giovagnoli *et al*., 1996).

In the second phase, both the patients and the matching control subjects performed “Testbatterie zur Aufmerksamkeitsprüfung” (TAP) (Zimmermann & Fimm, 1992).
TAP is a commonly used computerized attention battery that includes 13 subtests, where the subject's responses are given by a simple keypress of one or two buttons placed in front of the subject.
In the present study, five out of the 13 subtests were excluded because they were involved in more specific investigations of the presence of hemispatial deficits; thus, they will not be described in the present section.
Of the remaining eight subtests, Alertness, Covert Shift of Attention, and Eye Movement were used as inclusion criteria to ensure that both patients and control subjects were able to respond quickly and to exclude the possibility that problems in gaze movements interfered with the ability to complete the tasks.

Go/NoGo, Working Memory, Divided Attention, Flexibility (both “verbal” and “non-verbal” conditions), and Sustained Attention were used to analyse specific attention sub-components.

Alertness: Reaction time is examined under two conditions, with and without stimulation warning. The first condition concerns simple reaction time measurements, in which a cross appears on the monitor at randomly varying intervals and to which the subject is required to respond (“intrinsic alertness”). In the second condition, reaction time is measured in response to a critical stimulus preceded by a cue stimulus presented as a warning tone ("phasic arousal").
Covert shift of attention: This task measures the ability to shift focus in response to a critical stimulus with or without a correct predictor for the side of the appearance of the critical stimulus. A central cue (an arrow directed to the left or right) indicates the expected side of the target stimulus.
Eye Movement: This task evaluates the ability to move the eyes to the right, left, and centre of the screen when a critical stimulus is presented alone or together with a distractor. The subject is required to respond as soon as the critical stimulus appears.
Go/NoGo: This is a selective attention task. Five similar patterns are presented in a random order. Two of the five are target stimuli. The three non-target stimuli have to be ignored. The subject is required to respond to the critical stimuli.
Working memory: A list of digits is randomly presented. The subject is instructed to press the response key in those cases where the digit is equal to the penultimate digit shown. This task requires the continuous remembering and comparing of the digits.
Divided attention: Stimuli of two different modalities (visual and acoustic) must be simultaneously

processed to solve the task. In the visual part, the subject must press the key when different “x” symbols in movement form a square. The acoustic part consists of two notes of different pitch (high and low) presented alternately, and the subject is required to press the key after two successive notes of the same pitch.

Flexibility: This is a "set-shifting" task. Either letters and numbers ("verbal" condition) or angular and round figures ("non-verbal" condition) are simultaneously presented to the right and left of the centre of the monitor. For both conditions, the subject responds to alternating types of target stimuli and has the possibility to press a left or a right key according to whether the target stimulus appears to the left or the right of the centre of the monitor following a specific sequence.

Sustained attention: A sequence of stimuli is presented on the monitor. The stimuli vary on a range of features: colour, shape, size, and filling. The subject is required to respond whenever a stimulus occurs with the same shape or colour as the previous one.

In all tasks, the subject was instructed to respond by pressing the button as quickly as possible. When the subject's ability allowed it, all tests were administered in the most difficult version. Accuracy, omissions, and reaction times were recorded. The patients’ performances were compared to those of the matched control group for all parameters (described in the 2.4.2 section).

2.3 *MRI analysis*

2.3.1 *MRI data acquisition protocol*

Both patients and controls underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany) that included the following acquisition parameters: 1) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); 2) fast-FLAIR (TR = 8170 ms, 204TE = 96 ms, TI = 2100 ms); and 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR = 1338 ms, TE = 2.4 ms, matrix = 256 × 224 × 176, in-plane FOV = 250 × 250 mm2, slice thickness = 1 mm). To verify patients’ eligibility, the TSE scans, acquired as part of this research study, were visually inspected and reviewed by an expert neuroradiologist to characterize the brain anatomy and to ensure the absence of any macroscopic extracerebellar abnormalities.

According to the including criteria, conventional MRI images of the Ct-MRI group were also inspected to exclude any pathological conditions.

2.3.2 *Image processing*

The cerebellum was pre-processed individually using the Spatially Unbiased Infratentorial Template (SUIT) toolbox (Driedrichsen *et al*., 2009) implemented in Statistical Parametric

Mapping [Wellcome Department of Imaging Neuroscience; SPM-8 (http://www.fil.ion.ucl.ac.uk/spm/). The procedure involved the following steps: cropping and isolating the cerebellum from the T1 anatomical images, normalizing each cropped image into the SUIT space, and reslicing the probabilistic cerebellar atlas into individual subject space using the deformation parameters from normalization. Finally, the images were smoothed using an 8-mm FWHM Gaussian kernel.

2.4 **Statistical analysis**

2.4.1 *Neuropsychological assessments*

To evaluate the general neuropsychological profiles of SCA2 patients, the raw scores of each test were converted to Z-scores, according into the following formula: (subject raw score – population mean) / population standard deviation (sd).

Published normative data were used for the following tests: immediate and delayed recall of Rey's 15 words, Rey-Osterrieth Complex Figure Test, recall and copy versions, phonological fluency, and the Multiple Features Target Cancellation task. The tests that lacked published normative data are listed in Table 2 with demographic and performance data from specific neuropsychological control groups (Ct-NPS). Since not all of the subjects were available to perform all of the tests, the number of control subjects for each test is also reported. All controls were well matched to the SCA2 group with regard to age and education (independent-sample t-test: p = n.s.).

For each cognitive domain, a single Z-score was obtained by calculating the mean Z-scores of the tests included in each specific domain.

Table 2. Demographic characteristics of Ct-NPS subjects for each test

Test	**N°**	**Age**	**Education**	**Raw score**
WAIS-r IQ	96	45.18 (14.70)	11.65 (3.80)	104.45 (11.83)
WAIS-r vocabulary	96	45.18 (14.70)	11.65 (3.80)	52.31 (9.58)
Digit span (forward)	93	45.31 (14.47)	11.49 (3.83)	5.86 (1.23)
Digit span (backward)	93	45.31 (14.47)	11.49 (3.83)	4.45 (1.02)
Corsi Test (forward)	125	45.26 (16.05)	13.32 (4.44)	5.82 (1.19)

Corsi Test (backward)	125	45.26 (16.05)	13.32 (4.44)	5.34 (1.09)
Stroop Test (time effect)	43	47.44 (12.11)	13.91 (3.48)	22.38 (8.45)
Stroop Test (error effect)	43	47.44 (12.11)	13.91 (3.48)	0.89 (1.75)
Semantic fluency	72	48.14 (12.70)	13.42 (3.66)	29.53 (8.50)
Phonological fluency	72	48.14 (12.70)	13.42 (3.66)	40.77 (10.18)
Verbal fluency	43	47.44 (12.11)	13.91 (3.48)	18.09 (5.13)
WCST (perseveration)	43	47.44 (12.11)	13.91 (3.48)	8.50 (8.44)
WCST (perseverative errors)	43	47.44 (12.11)	13.91 (3.48)	7.95 (6.85)
ToL	43	47.44 (12.11)	13.91 (3.48)	31.02 (2.50)
WAIS-r block design	96	45.18 (14.70)	11.65 (3.80)	28.95 (8.30)
WAIS-r picture arrangement	96	45.18 (14.70)	11.65 (3.80)	13.05 (3.91)
WAIS-r arithmetic	96	45.18 (14.70)	11.65 (3.80)	11.10 (3.33)

The data are reported as means and standard deviations (sd).

2.4.2 *Attention assessments*

To obtain the general attention profiles of SCA2 patients, the accuracy score of each attention subtest of the TAP battery was converted into a Z-score according to the formula reported above. Demographic characteristics of the control group tested in the attention battery (Ct-Att) are reported in Table 3.

Ct-Att subjects were well matched to the SCA2 group regarding age and education (independent-sample t-test: p = n.s.).

Table 3. Demographic characteristics of SCA2 patients and Ct-Att subjects in the attention battery

Group	**N°**	**Age**	**Education**	**M/F**	**Intellectual**	**ICARS**

					Level cut off:18.96	Motor Score
SCA2	11	44.45 (6.82)	12.91 (3.88)	4/7	28.65 (3.65)	28.82 (8.67)
Ct-Att	33	46.36 (11.25)	13.55 (3.18)	13/20	32.14 (1.72)	--

The data are reported as means and standard deviations (sd).

The non-parametric Mann-Whitney U test for independent samples was used to detect differences in accuracy rates between SCA2 patients and Ct-Att. For the Sustained Attention task, the statistical analysis was performed only on the number of omissions in three time periods (0-5 minutes, 5-10 minutes, and 10-15 minutes), as required by the TAP battery protocol.

In addition, the same statistical comparison was performed to match the differences in the median reaction time between SCA2 patients and Ct-Att in all tasks of the battery. Furthermore, to exclude the influence of motor impairment on SCA2 patients' attention performance, we calculated the delta reaction time (Δ) according to the following formula: (subject's reaction time in the task – subject's reaction time in the "intrinsic alertness" condition). We considered the reaction time obtained in the "intrinsic alertness" condition to be the pure motor ability of the subject to respond to a target stimulus; thus, by subtracting it from the reaction time obtained in each other attention task, it is possible to detect the reaction time linked to the pure cognitive demand.

The non-parametric Mann-Whitney U test for independent samples was used to detect Δ differences between the SCA2 patients and Ct-Att.

Finally, the correlations between ICARS total and partial scores, Δ, and accuracy were calculated.

2.4.3 *Voxel-based morphometry*

To identify differences between SCA2-MRI patients and the Ct-MRI group in regional cerebellar grey matter (GM) volume, VBM was performed on individual GM maps entered into a voxel-wise two-sample t-test analysis. Age and sex were set as variables of no interest. The results were considered significant at p values < 0.05 after FWE cluster-level correction (clusters formed with $p < 0.005$ at the uncorrected level).

Moreover, to control for the effect of concomitant cortical atrophy in SCA2 patients, a whole brain VBM was also performed.

2.4.4 *Behavioural and motor correlations with regional GM*

Based on VBM results, the lobular volumes of significantly reduced GM areas in patients were extracted using the FSL command line "fslstats" from the FMRIB software library (FSL,

www.fmrib.ox.ac.uk/fsl/), and Spearman's correlations were computed to determine the relationship between such volumes and the mean of accuracy, calculated on the raw scores of the SCA2 performances on each attentional task in which SCA2 performances resulted in significant difference from Ct-Att performances (Go/NoGo and Divided Attention) and the mean number of omissions in three time periods for Sustained Attention.

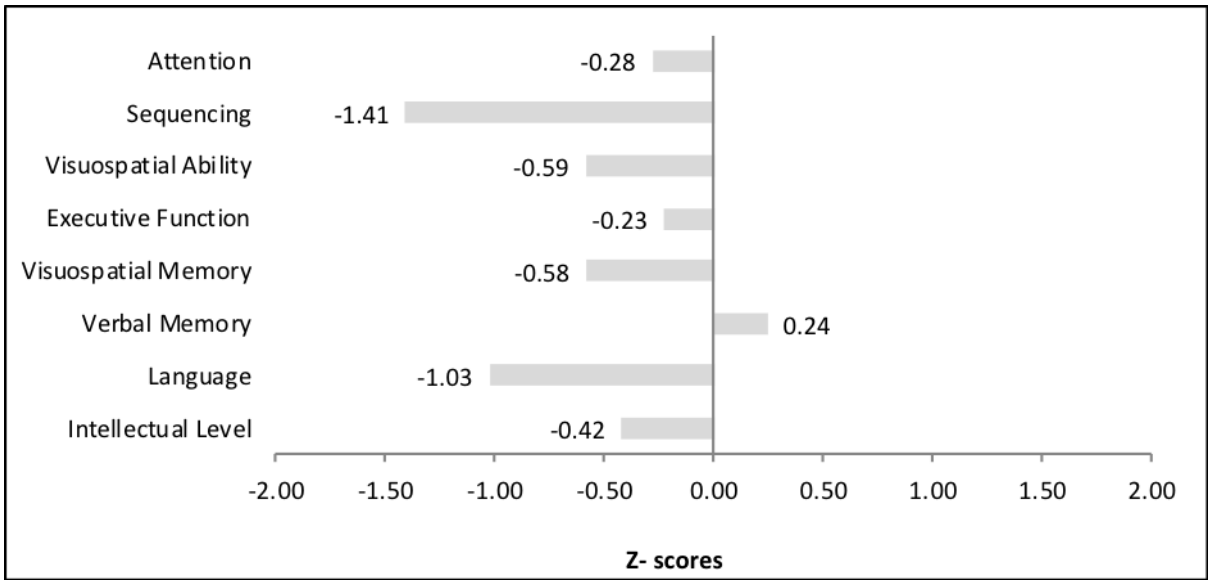
Additionally, the relationship between GM atrophy and ICARS motor scores was also tested. Correlations significant at $p < 0.05$ are reported.

3.1 Results

3.1.1 *Neuropsychological assessments*

SCA2 patients obtained negative Z-scores for all cognitive domains except for Verbal Memory. In particular, simply pathological scores (<-1) were detected for linguistic and sequencing abilities (Fig. 1).

Fig. 1 Neuropsychological profile of SCA2 patients

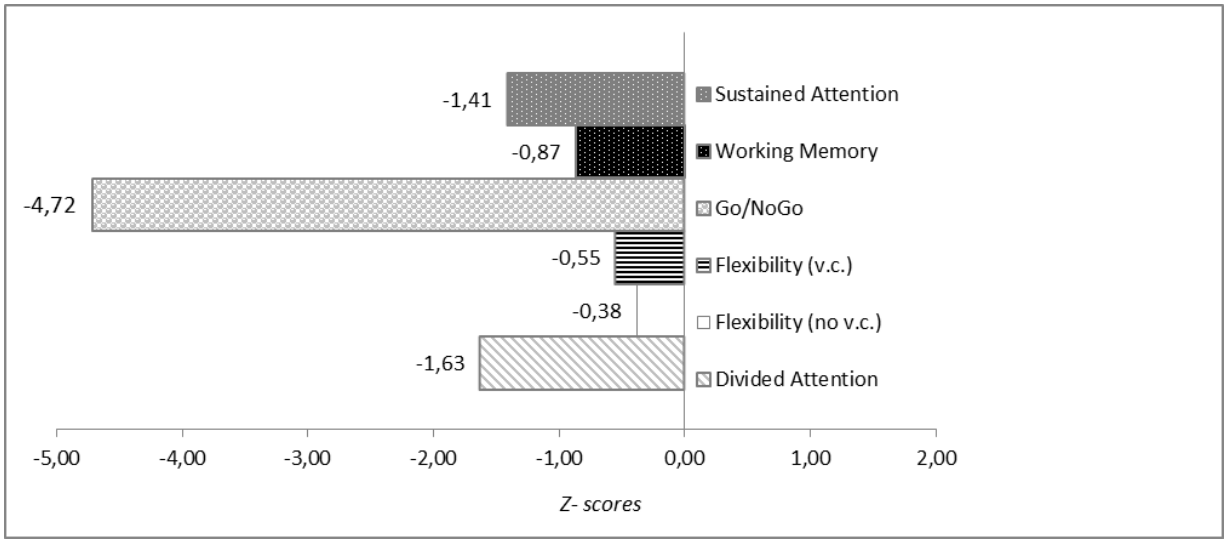


3.1.2 *Attention assessments*

The pattern of attention performances within the SCA2 group showed negative accuracy Z-scores in all TAP tasks (Fig. 2).

In particular, a highly pathological Z-score (-4.72) was found in the Go/NoGo task. Impaired scores (<-1) were also shown in the Sustained Attention and Divided Attention tasks.

Fig. 2 Attention profile of SCA2 patients



The statistical analysis on accuracy showed significant differences between SCA2 and Ct-Att groups in specific tasks. Indeed, significant differences were found in the Go/NoGo, Divided Attention, and Sustained Attention tasks ($p = 0.01$, $p = 0.05$ and $p = 0.00$, respectively), with SCA2 patients displaying lower performance.

Furthermore, in the three time periods of the Sustained Attention task, the statistical comparison of the omissions showed that a significantly higher number of stimuli were omitted by SCA2 patients [0-5 minutes ($p = 0.05$), 5-10 minutes ($p = 0.01$), and 10-15 minutes ($p = 0.00$)].

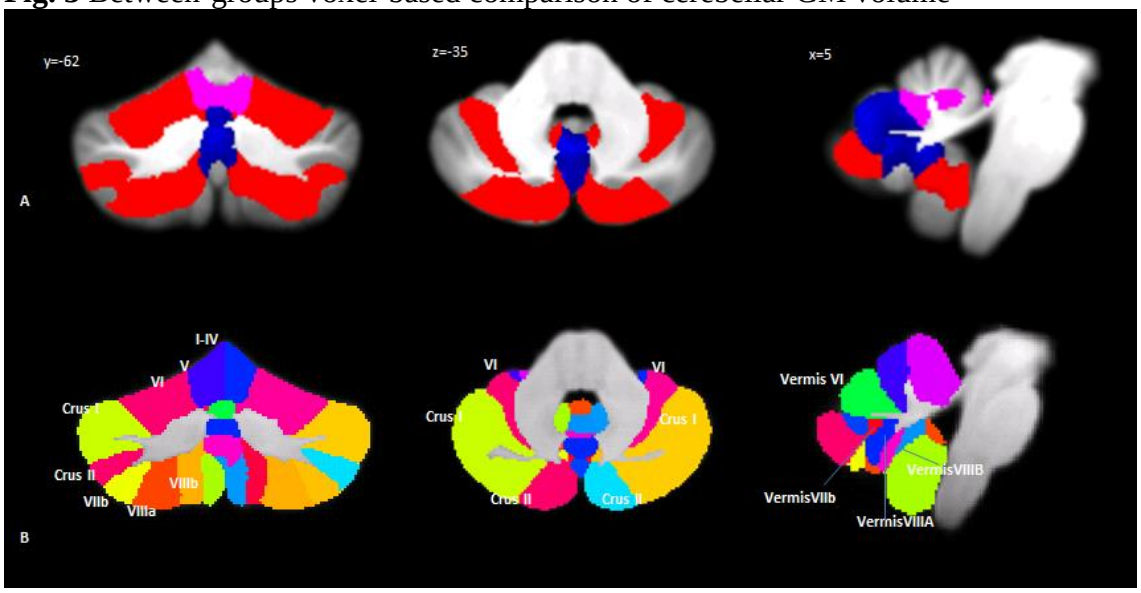
Regarding the analysis on the Δ score, SCA2 patients and Ct-Att significantly differed in Δ of the Flexibility [both verbal ($p = 0.00$) and non-verbal conditions ($p = 0.00$)] and the Divided Attention tasks ($p = 0.00$), with SCA2 patients displaying a higher Δ score.

No relevant correlation was observed between ICARS motor scores and attention assessments.

3.1.3 *Voxel-based morphometry*

As assessed by voxel-wise analysis of GM maps, SCA2-MRI patients showed a significant GM loss in the cerebellar cortex in comparison to the Ct-MRI group. More specifically, a large cluster of significantly decreased GM volume (FWE $p = 0.05$) included bilateral regions in the anterior cerebellar hemisphere (I-V) and in the posterior lobe (VI-IX) and posterior vermis (VI-IX). The results of VBM are shown in Fig. 3. All cerebellar regions with GM reductions are listed in Table 4. Moreover, when looking for voxel-based patterns of GM reductions in the whole brain of SCA2, only one cluster of reduced GM volume was found in SCA2 patients compared with controls, centered at -15 -100 22 (left occipital pole). No other pattern of GM loss was detected throughout the cerebral cortex of SCA2 patients.

Fig. 3 Between-groups voxel-based comparison of cerebellar GM volume



A) Cerebellar regions showing patterns of significantly reduced GM in SCA2-MRI compared with Ct-MRI are reported and superimposed on the Spatially Unbiased Infratentorial Template (SUIT) (Diedrichsen *et al.*, 2009). Regions of reduced GM volume involved both anterior (violet) and posterior (red) lobules of the cerebellar hemispheres and posterior regions of the vermis (blue). Statistical significance was found at cluster level (FWE= 0.05; cluster size: 68396), with peak voxels centred in the right lobules V-VI (x = 24 y = -47 z = 25), left I-IV (x = -9 y = -35 z = -19), and left crus II (x = -14 y = -89 z = -29). B) Cerebellar lobular subdivision shown in coronal (y), axial (z), and sagittal (x) slices from the SUIT cerebellar atlas.

Table 4. Cerebellar regions of reduced GM.

	CLUSTER LEVEL					
FWE-corr	**Size (NoV)**	**Peak Z-score**	**Coordinates (mm)**			**Regions**
			x	**y**	**z**	
0.000	**68396**	**7.30**	**24**	**-47**	**-25**	**Right VI**
		7.24	-9	-35	-19	Left I-VI
		6.93	-14	-89	-29	Left Crus II

Results significant at cluster level 0.05 FWE corrected. Regions with a peak Z-score in the cluster (size: 68396) were centered in the Right VI, Left I-VI, and Left Crus II.

3.1.4 *Behavioural and motor correlations with regional GM*

The significant correlations between left and right cerebellar regions with preserved GM volumes and SCA2-MRI patients' performances on each subtest are shown in Table 5 and Fig. 4. Notably, the correlations between cerebellar lobules and SCA2-MRI patients' scores were performed by

restricting the analysis only to the subregions that in showed significant GM reductions within each lobule compared with the controls.

Regarding the cerebellar motor impairment, significant correlations between ICARS scores are reported in Table 6.

Table 5. Correlational analysis between cerebellar GM volumes and accuracy of attention evaluations in SCA2 patients

TAP subtest	Lobules	Spearman	*p*-value
Divided Attention	Right_VIIB	0.678	0.045
Go/NoGo	Vermis_VI	0.690	0.040
Sustained Attention Omissions 5-10 minutes	Left_VIIIB	-0.834	0.005
	Right_V	-0.690	0.040
Sustained Attention Omissions 10-15 minutes	Left_VIIB	-0.700	0.036
	Left_VIIIA	-0.692	0.039
	Right_VIIB	-0.895	0.001
	Right_VIIIA	-0.802	0.009

Fig. 4 Correlational analysis between cerebellar GM volumes and Attentional sub-components in SCA2 patients

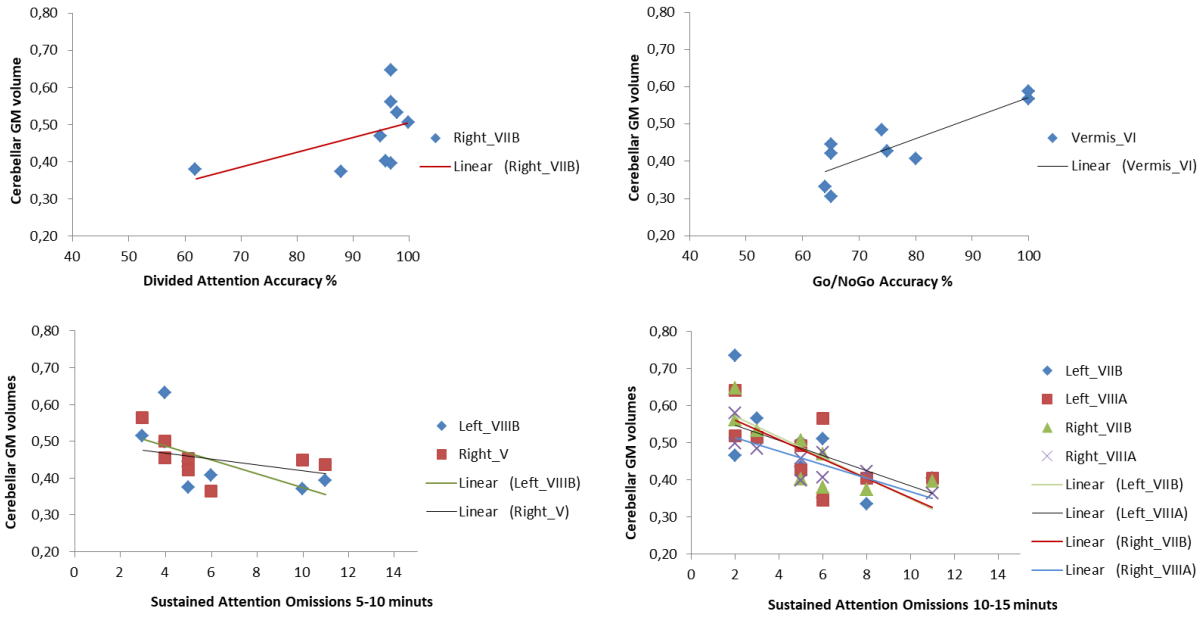


Table 6. Correlational analysis between cerebellar GM volumes and ICARS motor scores in SCA2 patients

ICARS scores	Lobules	Spearman	*p*-value
Posture & Gait	Left_I_IV	-0.698	0.037
Speech	Left_I_IV	-0.671	0.048
Oculomotor	Left_I_IV	-0.791	0.011
Total score	Left_I_IV	-0.695	0.038
	Right_VIIB	-0.770	0.015

4.1 Discussion

The main aim of the study was to define the attention profiles of SCA2 patients, which first made it necessary to depict their general cognitive abilities.

The neuropsychological assessment confirmed the slight cognitive alterations of language, executive functions, visuospatial memory, and intellectual level that were already reported in SCA2 patients (Gambardella *et al*., 1998; Le Pira *et al.*, 2002; Kawai *et al.*, 2009; Sokolovsky *et al.*, 2010; Mercadillo *et al.*, 2014). These results are in line with the view that cerebellar damage does not dramatically impair a cognitive function but does increase the suboptimal variability when mental tasks are performed (Courchesne & Allen, 1997; Tedesco *et al*., 2011). Interestingly, sequencing abilities, investigated for the first time in SCA2 patients, resulted in clear impairments, accordingly with the cerebellar sequence theory (Leggio *et al.*, 2008; Tedesco *et al.*, 2011).

The attention domain has been analysed by means of a broad and detailed assessment that, for the first time, allowed us to define the sub-components of attention that are affected in SCA2 patients. In particular, our results showed alterations in only three attention tasks, i.e., Go/NoGo and Divided and Sustained Attention. It is worth noting that these tasks evaluate attention sub-components characterized by a cognitive processing modality known to be affected by cerebellar damage. According to the van Zomeren and Brouwer model (1994), we can assume that the Go/NoGo and Divided and Sustained Attention tasks fall inside the two dimensions of this theoretical model. Specifically, according to the description of the attentional tasks of the TAP battery, while the Go/NoGo and Divided Attention tasks have features that are part of the selectivity component of

attentional function, the Sustained Attention task mainly requires the intensity component of attentional function.

As previously described, each of these components is strictly linked to specific anatomical areas, which include thalamic, frontal, and parietal regions (Posner & Petersen, 1990; Fan et al., 2002). Although most of the neuroanatomical and neurophysiological data suggest that the prefrontal and parietal cortices are the main cognitive nodes interacting with the cerebellum (O' Reilly *et al.*, 2010; Ramnani *et al.*, 2006), several studies also underline the presence of direct reciprocal connections between the cerebellum and temporal cortex that are specific to some aspects of the attentional function (Kellermann *et al.*, 2012; Sokolov *et al.*, 2012*;* Sokolov *et al.*, 2014). According to these anatomical connections, Kellermann and colleagues (2012), upon analysing the connectivity of the cerebellum with the temporal and frontal areas, concluded that crus I supplies a temporal signal to the cortical network engaged in spatial orienting and concluded that the intrinsic processing in the cerebellum would show attention-related effects and that the output of this processing to motion-sensitive areas in the visual system would be enabled selectively during attention.

Despite the accumulating evidence of cerebellar contributions to attention processes (Schweizer *et al.*, 2007; Kellermann *et al.*, 2012; Striemer *et al.*, 2015a), only a few studies have used neuroimaging techniques to investigate the involvement of specific cerebellar lobules in the attention domain (Kellermann *et al.*, 2012; Brissenden *et al.*, 2016; Hernandez-Castillo *et al.*, 2016; Kansal *et al.*, 2017). In particular, Brissenden, Levin, Osher, Halko, and Somers (2016) demonstrated a clear involvement of specific cerebellar regions in the widely known attentional network, namely, the "dorsal attention network" (DAN) or the frontoparietal network, a cortical network that supports sustained attention and working memory functions (Courtney *et al.*, 1998; Sprague & Serences, 2013). According to task-based and resting-state fMRI studies, in humans, the DAN includes four regions: the intraparietal sulcus and superior parietal lobule, the superior pre-central sulcus, the inferior pre-central sulcus, and the motion-sensitive area middle temporal (MT) complex. The authors note that whereas subcortical structures, such as the superior colliculus and pulvinar, are often implicated in attention, cerebellar structures are not typically discussed among the attention neural substrates. Furthermore, although previous studies have implicated cerebellar regions, i.e., lobule VI/crus I, in working memory and attention (Allen *et al.*, 1997; Townsend *et al.*, 1999; Chen & Desmond, 2005a,b; Kirschen *et al.*, 2005; Striemer *et al.*, 2015a,b; Kansal *et al.*, 2017), there is no consensus about the specific cerebellar contribution to attention abilities. Considering that the cerebellum is not a unitary structure, multiple association networks, including the DAN, share intrinsic functional connectivity with distinct cerebellar regions, namely, lobules

VIIb and VIIIa (Habas *et al.*, 2009; Buckner *et al.*, 2011; Olivito *et al.*, 2017b). Based on these results, Brissenden et al. (2016), using an fMRI protocol, demonstrated that lobules VIIb/VIIIa not only showed a strong intrinsic functional connectivity with the cortical DAN but also displayed task-driven responses that mirrored those of the cortical DAN, extending the DAN to the cerebellum (Brissenden et al., 2016).

In line with this suggestion, the present results show that specific attention tasks (i.e., Divided Attention and Sustained Attention tasks) correlate with specific cerebellar regions, mainly VIIb/VIIIa. Upon analysing the characteristics of these tasks in detail, it is understandable that the attentional problems of SCA2 patients are linked to specific underlying processes.
Specifically, the Go/NoGo task requires participants to memorize and recognize two targets among distractors by the inhibition of inappropriate responses. The role of the cerebellar-cortical connections in inhibition is widely known (Tanaka *et al*., 2003; Rubia *et al*., 2007; Hirose *et al*., 2014). Very recently, Olivito and colleagues (2017) provided further evidence of the cerebellar role in motor execution and inhibition in a sample of patients affected by degenerative cerebellar atrophy, demonstrating specific impairments in action inhibition. The authors proposed that the defective inhibitory control is likely due to an alteration of the cortico-subcortical network that involves the cerebellum, which intervenes in the executive control of movement generation (Olivito *et al*., 2017c).
In the present work, we found a direct correlation between the performance in the Go/NoGo task and vermal lobule VI, indicating that good accuracy in this task correlates with preserved volume in vermal lobule VI. It is important to emphasize that in healthy subjects, Habas and colleagues (2009) indicated that the vermis and paravermal lobules (i.e., lobule VI) act within a network involved in the regulation of executive decisions, such as working memory, attention, emotion evaluation, and response selection (van Harskamp *et al.*, 2005; Habas *et al.*, 2009; Hernáez-Goñi et al., 2010). These processes are needed to correctly solve the Go/NoGo task that requires response selection and executive decisions by inhibiting an inappropriate behaviour against irrelevant stimuli. Moreover, Brissenden and colleagues (2016) also indicated the involvement of a specific portion of lobule VI and crus I in attention domains, showing a functional connectivity of these portions with the cortical DAN (Brissenden *et al.*, 2016).

Furthermore, in SCA2 patients, we found clearly impaired accuracy when performing the Divided Attention task. In this task, participants must simultaneously keep in mind two different types of information (visual and auditory targets). Considering the characteristics of the task and the

underlying mechanisms required to solve it, we note some similarities with the results of Ronconi and colleagues (2017), who found an impairment in multisensory integration in a case of cerebellar agenesis, highlighting the essential contribution of the cerebellum to this process. Moreover, Akshoomoff and Courchesne (1992) already demonstrated how an intact neocerebellum was fundamental for cognitive operations that require a quick shift in the focus of attention between different sensory channels. According to this view, the impairments in integrating basic information from different sensory modalities may affect—with cascading effects—higher-order abilities (Wang *et al.,* 2014; Ronconi *et al*., 2017). These considerations can also explain the higher Δ score of SCA2 patients in comparison with that obtained by Ct-Att. Indeed, it is probable that this task requires such cognitive effort that it cannot be executed in a short time by SCA2 patients, making it impossible to respond both accurately and quickly.

Anatomically, we found a correlation between this task and the right cerebellar lobule VIIb. Specifically, we found a direct correlation between the GM in the lobule VIIb and accuracy in the Divided Attention task, indicating that a good percentage of accuracy in this task correlates with the presence of a preserved volume in this lobule.

Additionally, we found impaired performances in the Sustained Attention task; a deepening of the processes required to solve the task can explain the result. Indeed, cerebellar patients' performances were impaired when they had to process different information that needed to be integrated and compared with stored templates, as shown in mismatch negativity tasks (Restuccia *et al.*, 2007; Molinari *et al.*, 2009). Specifically, these studies have shown that cerebellar patients fail in the matching process, namely, in the ability to predict the changes between stored information and those derived from the environment. In line with this idea, if the predicted and actual signal match, the afferent signals can be cancelled (Brooks, *et al.,* 2013; Sokolov *et al.,* 2017). When they mismatch, the difference constitutes a sensory prediction error. These error signals are essential for sensorimotor control, allowing rapid adjustment in the motor output. Very recently, Wagner and colleagues (2017) provided neurophysiological evidence in mice that the cerebellar granule cells encode non-motor expectations and predictions.

Although this condition has been mainly described in motor and sensory processing, there are also similar hypotheses in cognitive tasks (Molinari *et al.,* 2009). It is important to note that the Sustained Attention task requires a subject to keep in mind more information at the same time (i.e., shape and colour) while omitting irrelevant information (i.e., size) and to compare the present stimulus with the previous one to respond correctly. Thus, to solve the task, the subject needs to mentally compare the figure that he/she is watching with the previous one, which may differ in all

or some features, matching only the relevant characteristics and omitting the others in a short amount of time. The presence of cerebellar damage could produce a delay in detecting this matching, especially when the subject has a very short time to respond, such as in the Sustained Attention task. This hypothesis can explain the higher number of omissions made in all three time periods of the task by SCA2 patients.

Also in this case, we found specific correlations between the performance obtained in the Sustained Attention task and lobules VIIb/VIIIa. Specifically, we found an inverse correlation between the amount of residual GM in these lobules and the number of omissions made in the task; indeed, a low number of omissions is an index of good performance.

As previously discussed, Divided and Sustained Attention tasks are more difficult for SCA2 patients, likely due to the high cognitive load required to link the specific internal features of these tasks, i.e., the capacity to integrate the processing of multisensory information and to match and predict changes in the environment compared with the information stored in one's own template. Thus, the prediction error signals improve future predictions and produce on-line changes in processing of behaviour in response to the error predictions generated in the cerebellum. In the presence of a cerebellar lesion, this prediction is altered, and the subjects will likely need more time for changes to their responses.

Anatomically, our finding is in line with the Brissenden group's argument that the activation in cerebellar lobules VIIb/VIIIa is significantly higher during high-load tasks, exhibiting a high degree of specificity (Brissenden *et al.*, 2016).

Regarding the Flexibility task, peculiar patterns have been seen in both verbal and non-verbal conditions. Indeed, SCA2 patients obtained normal accuracy, but their Δ scores were significantly longer than those of the Ct-Att group. According to the Posner and Petersen model (1990) and to the van Zomeren and Brouwer (1994) model, this tasks requires a top-down process of executive control, the "supervisory attentional system", to co-ordinate and reorganize new information, thus requiring sequential processing (Leggio *et al.*, 2008; Molinari *et al.*, 2008; Leggio *et al.*, 2011; Tedesco *et al.*, 2011) and prediction ability to coordinate motor responses and cognitive stimuli (Restuccia *et al.*, 2007; Molinari *et al.*, 2009; Sokolov *et al.*, 2017). Taking into account these considerations, it is possible to hypothesize that the cerebellum supports cortical activity, ensuring smooth, coordinated processing within the fronto-parietal networks. However, different from the other TAP tasks, the Flexibility task does not require an answer within a defined time limit. Thus, even if the task implies a high cognitive demand for cerebellar patients since it involves abilities such as sequencing and coordination, it is the only TAP task that allows the subjects to determine

their own response time. In this condition, the reaction time delay, shown by the Δ score analysis, could facilitate the maintenance of a normal accuracy.

Regarding the SCA2 patients' motor impairment, specific anatomical correlations between anterior lobules (i.e., left I-IV) and ICARS motor scores were detected. These data confirm the topographical and functional distinctions inside the cerebellum between the anterior and posterior lobules, with the former involved in motor information processing and the latter in cognition (Stoodley *et al.*, 2012; Olivito *et al.*, 2017b).
Finally, the results of the VBM analysis of GM reductions in the whole brain of SCA2 patients did not show a significant pattern of cortical atrophy. Indeed, only one cluster in the left occipital pole and no other pattern was detected throughout the cerebral cortex, and considering the attentional function, in the frontal lobes. Thus, it could be reasonable to think that this finding is not specific to SCA2 and may also be due to the close anatomical proximity between the cerebellum and the occipital pole. Furthermore, considering the absence of cortical structural changes at our patients' stage of disease, it is reasonable to hypothesize that the cerebellar damage impacts the cerebellar modulation of the cerebral cortex, thus resulting in functional impairment of cerebello-cerebral networks relevant to different cognitive functions (Olivito *et al.*, 2017a,b; Olivito *et al.*, 2018).

5.1 Conclusions

The present study investigated the cognitive patterns of the neuropsychological and, more specifically, attentional abilities in SCA2 patients. The profiles shown demonstrated that these abilities are impaired only in tasks with higher cognitive demands and those requiring skills and cognitive processes linked to the basic mode by which the cerebellum operates in motor and cognitive functions (Restuccia *et al.*, 2007; Leggio *et al.*, 2008; Molinari *et al.*, 2009; Tedesco *et al.*, 2011; Kellermann *et al.*, 2012; Wang *et al.*, 2014; Olivito *et al.*, 2017c; Ronconi *et al.*, 2017; Sokolov *et al.*, 2017). According to the existent attentional models, we found selective alterations in some components of these models, but not in all.

Indeed, our results showed that SCA2 patients have defective performances when they have to process information in sequential ways, inhibit an inappropriate response behaviour, operate a multisensory integration, and predict and compare different information with a stored template. These abilities are typically demanding of attention resources, as demonstrated by the impairments of the related attention subtests of the TAP battery, and are strictly linked to the frontal activity, making it difficult to separate the study of attentional function from other frontal abilities. (i.e., executive functions).

Furthermore, the relevance of this study is the novel result of a strong correlation between Divided and Sustained attention and the VIIb/VIIIa lobules, which have been proposed to be part of the DAN (Brissenden *et al*., 2016), and between selective attention and vermis VI.
Thus, the MRI findings allow the involvement of specific cerebellar regions in the attention impairments of SCA2 patients to be demonstrated and give further support to the inclusion of the cerebellum within the DAN network.

It is important to emphasize that although supratentorial atrophy has been described in many subtypes of cerebellar ataxias (Dayan *et al.*, 2016), including SCA2 patients (Brenneis *et al.*, 2003), none of our SCA2 patients presented with atrophy at the level of the cerebral cortex at either visual MRI inspection or voxel-based grey matter quantifications, thus allowing us to address the relationship between cerebellar damage and attentional impairment in SCA2. However, future research will be needed to investigate the mechanism through which the cerebello-cerebral interactions account for specific cognitive impairments in greater detail.

A limitation of the present study is the small sample of patients. Nevertheless, the highly significant differences between the performances of SCA2 patients and controls together with the selective alterations in SCA2 patient attentional profiles and the topographical concordance with previous fMRI studies converge to give support to the present data.

Overall, the present results confirmed the relationship between the cerebellar structural alterations associated with SCA2 neurodegeneration and the functional outcomes of the patients (Olivito *et al.*, 2017a). Specifically, it is proposed that the attention deficits found in SCA2 patients are subsequent to the disruption of cerebro-cerebellar circuitry and are influenced by the specific site of cerebellar degeneration (Kawai *et al*., 2009; Olivito *et al.*, 2017a).

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Declaration of interest

The authors have no conflicts of interest to declare.

Reference list

Akshoomoff, N.A., & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. Behav Neurosci, 106(5), 731-738. doi: http://dx.doi.org/10.1037/0735-7044.106.5.731

Akshoomoff, N.A., & Courchesne, E. (1994). ERP Evidence for a Shifting Attention Deficit in Patients with Damage to the Cerebellum. J Cogn Neurosci, 6(4), 388-399. doi:10.1162/jocn.1994.6.4.388

Allen, G., Buxton, R.B., Wong, E.C., & Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. Science, 275,1940-1943. doi:10.1126/science.275.5308.1940

Almeida-Silva, U.C., Hallak, J.E., Júnior, W.M., & Osório, Fde L. (2013). Association between spinocerebellar ataxias caused by glutamine expansion and psychiatric and neuropsychological signals - a literature review. Am J Neurodegener, 2(2), 57-69. www.AJND.us

Auburger, G.W. Spinocerebellar ataxia type 2. (2012). Handb Clin Neurol, 103,423-436. doi:10.1016/B978-0-444-51892-7.00026-7.

Baumann, O., Borra, R.J., Bower, J.M., Cullen, K.E., Habas, C., Ivry, R.B., *et al*. (2015). Consensus paper: the role of the cerebellum in perceptual processes. Cerebellum, 14(2),197-220. doi:10.1007/s12311-014-0627-7

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., *et al*. (1998). The cerebellum in attention-deficit/hyperactivity disorder: a morphometric study. Neurology, 50,1087-1093.

Borkowsky, J.G., Benton, A.L., & Spreen, O.(1967).Word fluency and brain-damage. Neuropsychologia, 5,135-140.

Brenneis, C., Bösch, S.M., Schocke, M., Wenning, G.K., & Poewe, W. (2003). multisensory integration pattern in SCA2 determined by voxel-based morphometry. Neuroreport, 14(14), 1799-1802. doi:10.1097/01.wnr.0000094105.16607.18

Brissenden, J.A., Levin, E.J., Osher, D.E., Halko, M.A., & Somers, D.C. (2016). Functional Evidence for a Cerebellar Node of the Dorsal Attention Network. J Neurosci, 36(22), 6083-6096. doi:10.1523/JNEUROSCI.0344-16.2016

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., & Yeo, B.T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol, 106,2322-2345. doi:10.1152/jn.00339.2011

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

Bürk, K., Globas, C., Bösch, S., Klockgether, T., Zuhlke, C., Daum, I., *et al*. (2003). Cognitive deficits in spinocerebellar ataxia type 1,2, and 3. J Neurol, 250,207-211. doi:10.1007/s00415-003-0976-5

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci, 22,443-447. doi:10.1007/s100720200003

Castellanos, F.X., Giedd, J.N., Berquin, P.C., Walter, J.M., Sharp, W., Tran, T., *et al.* (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry, 58(3),289-295. doi:10.1001/archpsyc.58.3.289

Chen, S.H., & Desmond, J.E. (2005a). Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. Neuroimage, 24(2),332-338. doi:10.1016/j.neuroimage.2004.08.032

Chen, S.H., & Desmond, J.E. (2005b). Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. Neuropsychologia, 43(9),1227-1237. doi:10.1016/j.neuropsychologia.2004.12.015

Corsi, P.M. (1972). Human memory and the medial temporal regions of the brain. Dissertation Abstract International, 34,891B.

Courchesne, E., & Allen, G. (1997). Prediction and preparation, fundamental functions of the cerebellum. Learning and Memory, 4,1-35.

Courtney, S.M., Petit, L., Maisog, J.M., Ungerleider, L.G., & Haxby, J.V. (1998). An area specialized for spatial working memory in human frontal cortex. Science, 279(5355), 1347-1351. doi:10.1126/science.279.5355.1347

Dayan, M., Olivito, G., Molinari, M., Cercignani, M., Bozzali, M., & Leggio, M. (2016). Impact of cerebellar atrophy on cortical gray matter and cerebellar peduncles as assessed by voxel-based morphometry and high angular resolution diffusion imaging. Funct Neurol, 31(4), 239-248. doi:10.11138/FNeur/2016.31.4.239

Diedrichsen, J., Balsters, J.H., Flavell, J., Cussans, E., & Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. Neuroimage 2009; 46, 39-46. doi:10.1016/j.neuroimage.2009.01.045

Dimitrov, M., Grafman, J., Kosseff, P., Wachs, J., Alway, D., Higgins, J., *et al*. (1996). Preserved cognitive processes in cerebellar degeneration. Behav Brain Res, 79(1-2), 131-135.

Dürr, A., Smadja, D., Cancel, G., Lezin, A., Stevanin, G., Mikol, J., *et al*. (1995). Autosomal dominant cerebellar ataxia type I in Martinique (French West Indies). Clinical and neuropathological analysis of 53 patients from three unrelated SCA2 families. Brain, 118 (Pt 6),1573-1581.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., & Posner, M.I. (2002). Testing the efficiency and independence of attentional networks. Journal of Cognitive Neuroscience, 14, 340-347. doi: 10.1162/089892902317361886

Fancellu, R., Paridi, D., Tomasello, C., Panzeri, M., Castaldo, A., Genitrini, S., *et al*. (2013). Longitudinal study of cognitive and psychiatric functions in spinocerebellar ataxia types 1 and 2. J Neurol, 260(12), 3134-3143. doi:10.1007/s00415-013-7138-1

Fernandez-Ruiz, J., Velásquez-Perez, L., Díaz, R., Drucker-Colín, R., Pérez-González, R., Canales, N., *et al*. (2007). Prism adaptation in spinocerebellar ataxia type 2. Neuropsychologia, 45(12), 2692-2698. doi:10.1016/j.neuropsychologia.2007.04.006

Gainotti, G., Marra, C., & Villa, G. (2001). A double dissociation between accuracy and time of execution on attentional tasks in Alzheimer's disease and multi-infarct Dementia. Brain, 124, 731-738.

Gambardella, A., Annesi, G., Bono, F., Spadafora, P., Valentino, P., Pasqua, A.A., *et al*. (1998). CAG repeat lenght and clinical features in three Italian families with spinocerebellar ataxia type 2 (SCA2): early impairment of Wisconsin Card Sorting Test and saccade velocity. J Neurol, 245,647-652.

Geschwind, D.H., Perlman, S., Figueroa, C.P., Treiman, L.J., & Pulst, S.M. (1997).The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. Am J Hum Genet, 60(4), 842-850. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1712476/

Giovagnoli, A.R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. Ital J Neurol Sci, 17(4),305-309.

Golla, H., Their, P., & Haarmeier, T. (2005). Disturbed overt but normal covert shifts of attention in adult cerebellar patients. Brain, 128(Pt 7),1525-1535. doi:10.1093/brain/awh523

Haarmeier, T., & Their, P. (2007). The attentive cerebellum - myth or reality? Cerebellum, 6(3),177-183. doi:10.1080/14734220701286187

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., *et al*. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. The Journal of Neuroscience, 29,8586-8594. doi:10.1523/JNEUROSCI.1868-09.2009

Heaton, R.K., Chelune, G., Talley, J.L., Kay, G.G., Curtiss, G. (2000). In: M.C. Hardoy, M.G. Carta, M.J. Hardoy, & P.L. Cabras, editors. WCST: Wisconsin Card Sorting Test. Forma completa revisionata. It. O.S. Organizzazioni Speciali.

Hernandez-Castillo, C.R., Galvez, V., Mercadillo, R.E., Díaz, R., Yescas, P., Martinez, L., *et al*. (2015a). Functional connectivity changes related to cognitive and motor performance in spinocerebellar ataxia type 2. Mov Disord, 30,1391-1399. doi:10.1002/mds.26320

Hernandez-Castillo, C.R., Galvez, V., Mercadillo, R.E., Díaz, R., Campos-Romo, A., & Fernandez-Ruiz, J. (2015b). Extensive White Matter Alterations and Its Correlations with Ataxia Severity in SCA 2 Patients. PLoS One, 10(8), e0135449. doi:10.1371/journal.pone.0135449

Hernandez-Castillo, C.R., Vaca-Palomares, I., Galvez, V., Campos-Romo, A., Díaz, R., & Fernandez-Ruiz, J. (2016). Cognitive Deficits Correlate with White Matter Deterioration in Spinocerebellar Ataxia Type 2. J Int Neuropsychol Soc, 22(4),486-491. doi:10.1017/S1355617716000084

Hernáez-Goñi, P., Tirapu-Ustárroz, J., Iglesias-Fernández, L., & Luna-Lario, P. (2010). The role of the cerebellum in the regulation of affection, emotion and behaviour. Rev Neurol, 51(10),597-609.

Hirose, S., Jimura, K., Kunimatsu, A., Abe, O., Ohtomo, K., Miyashita, Y., *et al*. (2014). Changes in cerebro-cerebellar interaction during response inhibition after performance improvement. NeuroImage, 99,142-148. doi:10.1016/j.neuroimage.2014.05.007

Kansal, K., Yang, Z., Fishman, A., Sair, H.I., Ying, S.H., Jedynak, B.M., *et al.* (2017). Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration. Brain, 140,707-720. doi:10.1093/brain/aww327

Kawai, Y., Suenaga, M., Watanabe, H., & Sobue, G. (2009). Cognitive impairment in spinocerebellar degeneration. Eur Neurol, 61(5),257-268. doi:10.1159/000206850

Kellermann, T., Regenbogen, C., De Vos, M., Mößnang, C., Finkelmeyer, A., & Habel, U. (2012). Effective Connectivity of the Human Cerebellum during Visual Attention. J Neurosci, 32(33):11453-60. doi: 10.1523/JNEUROSCI.0678-12.2012

Kirschen, M.P., Chen, S.H., Schraedley-Desmond, P., & Desmond. J.E. (2005). Load- and practice-dependent increases in cerebro-cerebellar activation in verbal working memory: an fMRI study. Neuroimage, 24(2), 462-472. doi:10.1016/j.neuroimage.2004.08.036

Klinke, I., Minnerop, M., Schmitz-Hübsch, T., Hendriks, M., Klockgether, T., Wüllner, U., *et al*. (2010). Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. Cerebellum, 9,433-442. doi:10.1007/s12311-010-0183-8

Krikorian, R., Bartok, J., & Gay, N. (1994). Tower of London procedure: a standard method and developmental data. J Clin Exp Neuropsychol, 16(6), 840-850. doi:10.1080/01688639408402697

Le, T.H., Pardo, J.V., & Hu, X. (1998). 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. J Neurophysiol, 79(3),1535-1548.

Leggio, M.G., Tedesco, A.M., Chiricozzi, F.R., Clausi, S., Orsini, A., & Molinari, M. (2008). Cognitive sequencing impairment in patients with focal or atrophic cerebellar damage. Brain, 131,1332-1343. doi:10.1093/brain/awn040

Leggio, M.G., Chiricozzi, F.R., Clausi, S., Tedesco, A.M., & Molinari, M. (2011). The neuropsychological profile of cerebellar damage: The sequencing hypothesis. Cortex, 47(1),137-144. doi:10.1016/j.cortex.2009.08.011

Le Pira, F., Zappalà, G., Saponara, R., Domina, E., Restivo, D., Reggio, E., *et al*. (2002). Cognitive findings in spinocerebellar ataxia type 2: relationship to genetic and clinical variables. J Neurol Sci, 201(1-2),53-57. https://doi.org/10.1016/S0022-510X(02)00194-6

Lupo, M., Troisi, E., Chiricozzi, F.R., Clausi, S., Molinari, M., & Leggio, M. (2015). Inability to Process Negative Emotions in Cerebellar Damage: a Functional Transcranial Doppler Sonographic Study. Cerebellum, 14(6),663-669. doi:10.1007/s12311-015-0662-z

Mascalchi, M., Toschi, N., Giannelli, M., Ginestroni, A., Della Nave, R., Nicolai, E., *et al*. (2015). Progression of microstructural damage in spinocerebellar ataxia type 2: a longitudinal DTI study. AJNR Am J Neuroradiol, 36(6),1096-1101. doi:10.3174/ajnr.A4343

Mercadillo, R.E., Galvez, V., Dıaz, R., Hernàndez-Castillo, C.R., Campos-Romo, A., Boll, M.C., *et al*. (2014). Parahippocampal gray matter alterations in spinocerebellar ataxia type 2 identified by voxel based morphometry. J Neurol Sci, 347,50-58. doi:10.1016/j.jns.2014.09.018

Molinari, M., Chiricozzi, F.R., Clausi, S., Tedesco, A.M., De Lisa, M., & Leggio, M.G. (2008). Cerebellum and detection of sequences, from perception to cognition. Cerebellum, 7(4),611-615. doi:10.1007/s12311-008-0060-x

Molinari, M., Restuccia, D., & Leggio, M.G. (2009). State estimation, response prediction, and cerebellar sensory processing for behavioral control. Cerebellum, 8(3),399-402. doi:10.1007/s12311-009-0112-x

Moore, D.M., D'Mello, A.M., McGrath, L.M., & Stoodley, C.J. (2017). The developmental relationship between specific cognitive domains and grey matter in the cerebellum. Dev Cogn Neurosci, 24,1-11. doi:10.1016/j.dcn.2016.12.001

Moriarty, A., Cook, A., Hunt, H., Adams, M.E., Cipolotti, L., & Giunti, P. (2016). A longitudinal investigation into cognition and disease progression in spinocerebellar ataxia types 1, 2, 3, 6, and 7. Orphanet J Rare Dis, 11(1),82. doi:10.1186/s13023-016-0447-6

Olivito, G., Lupo, M., Iacobacci, C., Clausi, S., Romano, S., Masciullo, M., *et al*. (2017a). Microstructural MRI basis of the cognitive functions in patients with Spinocerebellar ataxia type 2. Neuroscience, 366,44-53. [Epub ahead of print]. doi:10.1016/j.neuroscience.2017.10.007

Olivito, G., Cercignani, M., Lupo, M., Iacobacci, C., Clausi, S., Romano, S., *et al*. (2017b). Neural substrates of motor and cognitive dysfunctions in SCA2 patients: A network based statistics analysis. Neuroimage Clin, 14,719-725. doi:10.1016/j.nicl.2017.03.009

Olivito, G., Brunamonti, E., Clausi, S., Pani, P., Chiricozzi, F.R., Giamundo, M., *et al*. (2017c). Atrophic degeneration of cerebellum impairs both the reactive and the proactive control of movement in the stop signal paradigm. Exp Brain Res, 235(10), 2971-2981.[Epub ahead of print]. doi:10.1007/s00221-017-5027-z

Olivito, G., Lupo, M., Iacobacci, C., Clausi, S., Romano, S., Masciullo, M., *et al*. (2018). Structural cerebellar correlates of cognitive functions in spinocerebellar ataxia type 2. J Neurol, 265(3):597-606. doi: 10.1007/s00415-018-8738-6

O'Reilly, J.X., Beckmann, C.F., Tomassini, V., Ramnani, N., & Johansen-Berg, H. (2010). Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex 20(4), 953-965. doi: 10.1093/cercor/bhp157

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., & Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. Italian journal of neurological sciences, 8, 539-548.

Orsini, A., & Laicardi, C. Wais-r. (1997). Contributo alla taratura italiana. Firenze: Organizzazioni Speciali.

Orsini, A., & Laicardi, C. (2003). Wais-r e terza età. Firenze: Organizzazioni Speciali.

Posner, M.I.,& Petersen, S.E. (1990). The attention system of the human brain. Annual Review of Neuroscience, 13, 25-42. doi: 10.1146/annurev.ne.13.030190.000325

Pulst, S.M., Nechiporuk, A., Nechiporuk, T., Gispert, S., Chen, X.N., Lopes-Cendes, I., *et al*. (1996). Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet, 14(3),269-276. doi:10.1038/ng1196-269

Ramnani, N., Behrens, T.E., Johansen-Berg, H., Richter, M.C., Pinsk, M.A., Andersson, J.L., *et al.* The evolution of prefrontal inputs to the cortico-pontine system : diffusion imaging evidence from macaque monkeys and humans. (2006). Cereb Cortex 16(6), 811-818. doi:10.1093/cercor/bhj024

Raven, J.C. (1949). Progressive Matrices. Sets A, Ab, B: Board and Book forms. Lewis: London.

Ravizza, S.M., & Ivry, R.B. (2001). Comparison of the basal ganglia and cerebellum in shifting attention. J Cogn Neurosci, 13(3), 285-297.

Restuccia, D., Della Marca, G., Valeriani, M., Leggio, M.G., & Molinari, M. (2007). Cerebellar damage impairs detection of somatosensory input changes. A somatosensory mismatch-negativity study. Brain, 130(Pt 1),276-287. doi:10.1093/brain/awl236

Rey, A. (1958). Memorisation d'une sèrie de 15 mots en 5 rèpètions. In: A. Rey, editor. L'examen clinique en psychologie. Paris: Presses Universiteries de France.

Ronconi, L., Casartelli, L., Carna, S., Molteni, M., Arrigoni, F., & Borgatti, R. (2017). When one is Enough: Impaired Multisensory Integration in Cerebellar Agenesis. Cereb Cortex, 27(3),2041-2051. doi:10.1093/cercor/bhw049

Rubia, K., Smith, A.B., Taylor, E., & Brammer, M. (2007). Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. Hum Brain Mapp, 28(11),1163-1177. doi:10.1002/hbm.20347

Scherzed, W., Brunt, E.R., Heinsen, H., de Vos, R.A., Seidel, K., Bürk, K., *et al*. (2012). Pathoanatomy of cerebellar degeneration in spinocerebellar ataxia type 2 (SCA2) and type 3 (SCA3). Cerebellum, 11(3),749-760. doi:10.1007/s12311-011-0340-8

Schmahmann, J.D., & Sherman, J.C. (1998). The cerebellar cognitive affective syndrome. Brain, 121,561-579.

Schweizer, T.A., Alexander, M.P., Cusimano, M., & Stuss, D.T. (2007). Fast and efficient visuotemporal attention requires the cerebellum. Neuropsychologia, 45(13),3068-3074. doi:10.1016/j.neuropsychologia.2007.05.018

Sokolov, A.A., Erb, M., Gharabaghi, A., Grodd, W., Tatagiba, M.S., & Pavlova, M.A. (2012). Biological motion processing: the left cerebellum communicates with the right superior temporal sulcus. Neuroimage 59(3), 2824-2830. doi: 10.1016/j.neuroimage.2011.08.039

Sokolov, A.A., Erb, M., Grodd, W., & Pavlova, M.A. (2014). Structural loop between the cerebellum and the superior temporal sulcus : evidence from diffusion tensor imaging. Cereb Cortex 24(3), 626-632. doi: 10.1093/cercor/bhs346

Sokolov, A.A., Miall, R.C., & Ivry, R.B. (2017). The Cerebellum : Adaptive Prediction for Movement and Cognition. Trends in Cogn Sci, 21(5), 313-332. doi:10.1016/j.tics.2017.02.005

Sokolovsky, N., Cook, A., Hunt, H., Giunti, P., & Cipolotti, L. (2010). A preliminary characterisation of cognition and social cognition in spinocerebellar ataxia types 2, 1, and 7. Behav Neurol 2010; 23(1-2):17-29. Erratum in: Behav Neurol, 23(3),159. doi:10.3233/BEN-2010-0270

Sprague, T.C., & Serences, J.T. (2013). Attention modulates spatial priority maps in the human occipital, parietal and frontal cortices. Nat Neurosci, 16(12),1879-1887. doi:10.1038/nn.3574

Stoodley, C.J., Valera, & E.M., Schmahmann, J.D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. NeuroImage, 59:1560–1570. doi: 10.1016/j.neuroimage.2011.08.065

Striemer, C.L., Chouinard, P.A., Goodale, M.A., & de Ribaupierre, S. (2015a). Overlapping neural circuits for visual attention and eye movements in the human cerebellum. Neuropsychologia, 69,9-21. doi:10.1016/j.neuropsychologia.2015.01.024

Striemer, C.L., Cantelmi, D., Cusimano, M.D., Danckert, J.A., & Schweizer, T.A. (2015b). Deficits in reflexive covert attention following cerebellar injury. Front Hum Neurosci, 9,428. doi:10.3389/fnhum.2015.00428

Tanaka, H., Harada, M., Arai, M., & Hirata, K. (2003). Cognitive dysfunction in cortical cerebellar atrophy correlates with impairment of the inhibitory system. Neuropsychobiology, 47(4),206-211. doi:10.1159/000071216

Tedesco, A.M., Chiricozzi, F.R., Clausi, S., Lupo, M., Molinari, M., & Leggio, M.G. (2011). The cerebellar cognitive profile. Brain, 134(Pt 12),3672-3686. doi:10.1093/brain/awr266

Townsend, J., Courchesne, E., Covington, J., Westerfield, M., Harris, N.S., Lyden, P., *et al*. (1999). Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci, 19,5632-5643.

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R.D., Subramony, S.H., Wessel, K., *et al*. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci, 145,205-211. doi:http://dx.doi.org/10.1016/S0022-510X(96)00231-6

van Harskamp, N.J., Rudge, P., & Cipolotti, L. (2005). Cognitive and social impairments in patients with superficial siderosis. Brain, 128(Pt 5),1082-1092. doi:10.1093/brain/awh487

Van Zomeren, A.H., & Brouwer, W.H. (1994). Clinical neuropsychology of attention. New York: Oxford University Press.

Wagner, M.J., Kim, T.H., Savall, J., Schnitzer, M.J., & Luo, L. (2017). Cerebellar granule cells encode the expectation of reward. Nature, 544(7648), 96-100. doi: 10.1038/nature21726

Wang, S.S., Kloth, A.D., & Badura, A. (2014). The cerebellum, sensitive periods, and autism. Neuron, 83,518-532. doi:10.1016/j.neuron.2014.07.016

Wechsler, D. (1945). A standardized memory scale for clinical use. Journal of Psychology, 87-95.

Wechsler, D. (1981). Scala di intelligenza Wechsler per adulti rivisitata (WAIS-R). Manuale. Ed. Organizzazioni Speciali.

Woods, S.P., Scott, J.C., Sires, D.A., Grant, I., Heaton, R.K., & Tröster, A.I. (2005). HIV Neurobehavioral Research Center Group. Action (verb) fluency: test-retest reliability, normative standards, and construct validity. J Int Neuropsychol Soc, 11(4),408-415.

Zimmermann, P., & Fimm, B. (1992). Testbatterie zur Aufmerksamkeitsprufung (TAP). Wurselen: Psytest.