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Original
Role of the cerebellum in high stages of motor planning hierarchy / Casartelli, Luca; Federici, Alessandra Enrica Chiara; Cesareo, Ambra; Biffi, Emilia; Valtorta, Giulia; Molteni, Massimo; Ronconi, Luca; Borgatti, Renato. - In: JOURNAL OF NEUROPHYSIOLOGY. - ISSN 0022-3077. - 117:4(2017), pp. 1474-1482. [10.1152/jn.00771.2016]

Published
DOI:10.1152/jn.00771.2016

Articles in PresS. J Neurophysiol (January 11, 2017). doi:10.1152/jn.00771.2016

THE ROLE OF THE CEREBELLUM IN HIGH STAGES OF MOTOR PLANNING HIERARCHY

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Running Title: Preserved motor planning without the cerebellum

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KEYWORDS:

Cerebellar agenesis, kinematics, mirror neurons, cerebellar syndromes, autism

ABSTRACT

Motor planning is not a monolithic process, and distinct stages of motor planning are responsible for encoding different levels of abstractness. However, how these distinct components are mapped into different neural substrates remains an open question. We studied one of these high-level motor planning components, defined as second-order motor planning, in a patient (R.G.) with an extremely rare case of cerebellar agenesis but without any other cortical malformations. Second-order motor planning dictates that when two acts have to be performed sequentially, planning of the second act can influence the execution of the first. We used an optoelectronic system for kinematic analysis to compare R.G.'s performance with age-matched controls in a second-order motor planning task. The first act was to reach for an object and the second was to place it into a small or large container. Our results showed that despite the expected difficulties in fine-motor skills, second-order motor planning (i.e., the ability to modulate the first act as a function of the nature of the second act) was preserved even in the patient with congenital absence of the cerebellum. These results open new intriguing speculations about the role of the cerebellum in motor planning abilities. Although prudence is imperative when suggesting conclusions based on single-case findings, this evidence suggests fascinating hypotheses about the neural circuits that support distinct stages of the motor planning hierarchy, and regarding the functional role of second-order motor planning in motor cognition and its potential dysfunction in autism.

NEW & NOTEWORTHY

Traditionally, the cerebellum was considered essential for motor planning. By studying an extremely rare patient with cerebellar agenesis and a group of neurotypical controls, we found that high stages of the motor planning hierarchy can be preserved even in this patient with congenital absence of the cerebellum. Our results provide interesting insights that shed light on the neural circuits supporting distinct levels of motor planning. Furthermore, the results are intriguing due to their potential clinical implications in autism.

1. INTRODUCTION

For decades the cerebellum was considered primarily or even exclusively a motor structure involved in the monitoring, control, and execution of movements (Babinski, 1902; Leiner, 2010; Manto et al., 2012). Nowadays, a growing body of data supports the critical role of the cerebellum in cognitive, affective, emotional, and sensory/perceptual domains (Levishon et al., 2000; Tavano et al., 2007; Buckner, 2013; Koziol et al., 2014; Baumann et al., 2015). In the last decade, different and non-mutually exclusive hypotheses have been presented to account for the functional role of the cerebellum (Buckner, 2013). A prominent view suggested that the cerebellum provides "internal models" for different motor/non-motor functions (Ito, 2008; Cerminara et al., 2009; Roth et al., 2013), whereas others hypothesized that the cerebellum is a sort of internal timing device (D'Angelo and De Zeeuw, 2009; De Zeeuw, et al. 2011; Knolle et al., 2013). Interestingly, some authors have proposed general models for the cerebellum operating on different domains, as if a similar circuit structure in different cerebellar areas could achieve various operations using a common computational scheme (D'Angelo and Casali, 2012).

According to the classic view that attributed a critical role in motor functions to the cerebellum, a long-standing clinical tradition considered the cerebellum to be essential for motor planning (Liesberger and Thach, 2013). However, in recent years the assumption that motor planning is a sort of monolithic process has been undermined by the description of models that distinguish different hierarchical levels of motor planning (Sober and Sabes, 2003-2005). These models assume that when one plans goal-directed reaches, an estimation of arm position can be computed by integrating visual and proprioceptive signals. More specifically, each sensory modality contributes to two different stages of motor planning: i) the determination of the desired movement vector, and ii) the transformation of the movement vector into a joint-based motor command (Sober and Sabes, 2003). Intriguingly, the same sensory signals are weighted differently at these two stages of reach planning, and this may reflect a strategy that minimizes errors that can arise during such coordinate transformations (Sober and Sabes, 2005). The possibility of dissociating behavioral deficits in planning movement direction from deficits in generating motor commands, and also the relative role played by visual and proprioceptive information, have been investigated in cerebellar degeneration patients (Taig et al., 2012). Thus, the potential contribution of the cerebellum at different hierarchical levels of motor planning has been tested. The authors found that when provided with vision of the joints, cerebellar patients were less able to use visual information about the joints in generating motor commands (Taig et al., 2012). Contrarily, during many other computational operations at different stages of motor planning, cerebellar patients performed similarly to healthy controls. This seems to lead to two important considerations: according to Sober and Sabes' framework (2003-2005), neural substrates of distinct hierarchical stages of motor planning may be at least partially different. Therefore, although specific levels of motor planning can be compromised after cerebellar degeneration (e.g., see Crus I in Taig et al., 2012), others seem to be unperturbed. These considerations are also interesting in light of a previous study by Rabe et al. (2009), in which both perceptive size-weight illusion (i.e., when the smaller of two equally weighted objects is judged to be heavier when lifted) and force adaption based on object size/weight were preserved in patients with cerebellar degeneration. Taken together, these findings strongly urge a deeper investigation of the cerebellar contribution to different components of motor planning and motor adaption. This investigation can help to shed light not only on potential undetected anomalies but also on underestimated preserved abilities in cerebellar patients.

Our study was specifically designed to explore the role of cerebellum at high hierarchical levels of motor planning. The different hierarchical stages reflect increasing degrees of abstraction, and they represent components of motor planning increasingly more distant from actual motor performance. We tested the cerebellar contribution to different stages of motor planning in R.G., a patient with an extremely rare cerebellar agenesis, and we compared his performance to a group of neurotypical controls. R.G.'s congenital condition offered a unique opportunity to directly test the cerebellar contribution to different aspects of motor planning and specifically allowed us to test the high-level components defined as *second-order motor planning* (Fabbri-Destro et al. 2009; Wilmut et al., 2013a; for a review, Rosenbaum et al., 2012). According to recent studies, second-order motor planning takes into account a distal goal (i.e., what one plans to do in the final part of an action) from the initial phases of the same action. Second-order motor planning thus reflects the ability to encode “external” information (e.g., how much the final part of the action demands from a motor point of view) into the motor system and then translates it into spatiotemporal parameters that drive the upcoming motor program accordingly. Second-order motor planning is reported in adults (Johnson et al., 2004; Ansuini et al., 2006), and some degree of modulation of the first act according to the demand of the final task is present even in children (4-11 years old) (Wilmut et al., 2013a), toddlers (Chen et al., 2010) and infants (Claxton et al., 2003).

In agreement with the evidence accumulated so far in the literature (for a review, see Rosenbaum et al. 2012), we predicted that the control group would modulate the initial phases of the action according to the difficulty of the distal goal. If R.G. also showed such modulation, we could conclude that second-order motor planning is also possible in a brain developed without the cerebellum.

2. METHODS

2.1 Participants

R.G., the patient with cerebellar agenesis, was a 48-year-old right-handed man presenting fair abilities in walking, talking, reading, and writing. For example, he had basic instrumental skills in using a mobile phone, a PC, and the internet. He recently learned how to use a fretsaw to assemble a simple but functional shoe rack (for a detailed clinical description of this case, see Arrigoni et al., 2015). His improvement in motor, cognitive-linguistic, and social skills over the years was difficult to foresee during his childhood, considering that he presented severe delays in the acquisition of neuropsychological and motor developmental milestones (Tavano et al., 2007;

Romaniello and Borgatti, 2013). From a neuroradiological perspective, anatomical sequences confirmed the complete absence of the cerebellum, with a very small component of cerebellar tissue (located posterior to the midbrain, close to the lamina quadrigemina, see Arrigoni et al., 2015). No supratentorial abnormalities were reported, except for a mild enlargement of the lateral ventricles. Also the analysis of structural diffusion tensor imaging (DTI) findings and resting-state functional magnetic resonance imaging (fMRI) data confirmed this neuroradiological picture (Arrigoni et al., 2015) (Fig.1). R.G.'s general cognitive skills were assessed by means of the Wechsler Adult Intelligent Scale-Revised (WAIS-R), and resulted in the following profile: Total-IQ=69, Performance-IQ=82, and Verbal-IQ=65. From a neuropsychological point of view, he showed more difficulties on tasks involving visuomotor integration, motor adaptation and fluency, working memory, and extraction of higher-order semantic inferences. He also had impairment in executive functions, mainly planning and flexibility but also focused attention (Romaniello and Borgatti, 2013). Cerebellar signs, ataxic gait and oculomotor disorders were clearly reported at the neurological examination. The ICARS scale yielded a score of 29/100, which is consistent with a diagnosis of cerebellar ataxia (International Cooperative Ataxia Rating Scale; Trouillas et al. 1997). This clinical picture seems to be compatible with the vascular genesis hypothesis, assuming that the congenital near-total absence of the cerebellum derives from an embryonic cerebellar insult. Accordingly, it would represent a disruption rather than a primary malformation of the cerebellum (Boltshauser, 2004; Yu et al., 2014; Arrigoni et al., 2015).

Ten neurotypical right-handed males comparable to R.G. for age (mean 46.4, range 42-51) were recruited as a control group. These individuals had no history of neurological or psychiatric disorders, and their general cognitive profile was obtained with a shortened version of the WAIS-R employing two verbal (Vocabulary, Similarities) and two performance (Block Design, Picture Completion) subtests (mean 113.6±10.4).

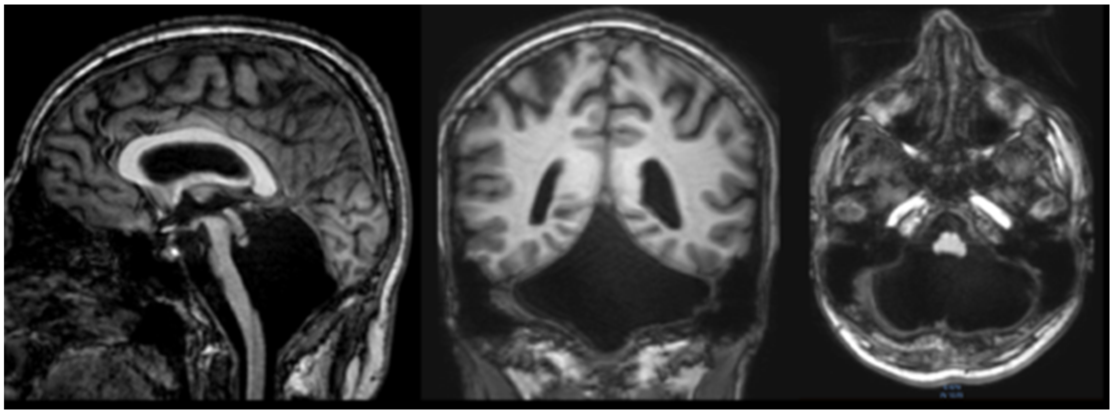


Fig.1 T1-weighted MR sections in the sagittal, coronal and axial planes show the complete agenesis of the cerebellum. The pons is flattened and posterior fossa is filled with cerebrospinal fluid.

The entire research protocol was approved by the local ethic committee and was conducted in accordance to the principles elucidated in the Declaration of Helsinki.

2.2 Task and procedure

Participants sat in front of a table, on which stood a wooden cube and a square cardboard container. In each trial, the subject started with his right hand resting on the starting position (hereafter, start point), with the thumb line close to the edge of the table. The cube (side 3 cm) was placed 12 cm from the hand and the container 20 cm from the cube on the right side. Participants were asked to reach for and grasp the cube and then place it inside the container. Two different-sized containers were alternatively provided (only one container was in front of the participant at any given time): small (4.5 x 4.5 cm) and large (9 x 9 cm). The border of both containers was 0.5 cm tall. The experimental session consisted of 20 trials for each condition (small and large container, 40 trials altogether) executed in random order. Thus, small and large conditions were randomized within 40 trials of each participant (for a similar procedure, see Fabbri-Destro et al., 2009). All participants were unaware of the exact number of trials before the beginning of the experimental task. After each trial, participants returned their right hand to the start point, and the experimenter set up the container (i.e., small or large) for the next trial. Participants were instructed to perform the action accurately but were not given specific instructions regarding velocity (we stated: “as you would in a daily life situation”). Participants were cued to start the trial with a simple “go” signal provided by the experimenter (on average, about 15 seconds elapsed for all participants between one trial and the next). Since we gave no specific instructions regarding speed, participants were free to begin the trial whenever they were ready after the “go” signal. No specific constraints were given to participants while the experimenter placed the container on the table. These instructions, or lack thereof, were intended to avoid excessive stress for our patient, who found the task more difficult than the control group, for obvious reasons in light of his clinical picture and as also demonstrated by our results. This procedure allowed us to obtain excellent compliance and good performance from all participants (only one trial from R.G. was excluded from analysis due to partial dropping of the cube). The experimental session lasted approximately 30 min. In order to verify participants’ compliance, 2D videos were also recorded (see, Fig. 2).

2.3 Equipment and data recording

Following Fabbri-Destro et al. (2009), we considered as an index of preserved second-order motor planning the reduced duration of the first part of the action (i.e., the reaching act) for the easier condition compared to the more difficult one (i.e., placing the cube in the large or small container, respectively). The kinematic of the movements was recorded using an optoelectronic system for motion capture (OEP System, BTS Bioengineering, Milan, Italy), and spatiotemporal parameters were computed. This system (spatial resolution 0.3 mm) was composed of eight charge coupled device (CCD) cameras with axial LEDs that emit infrared light.

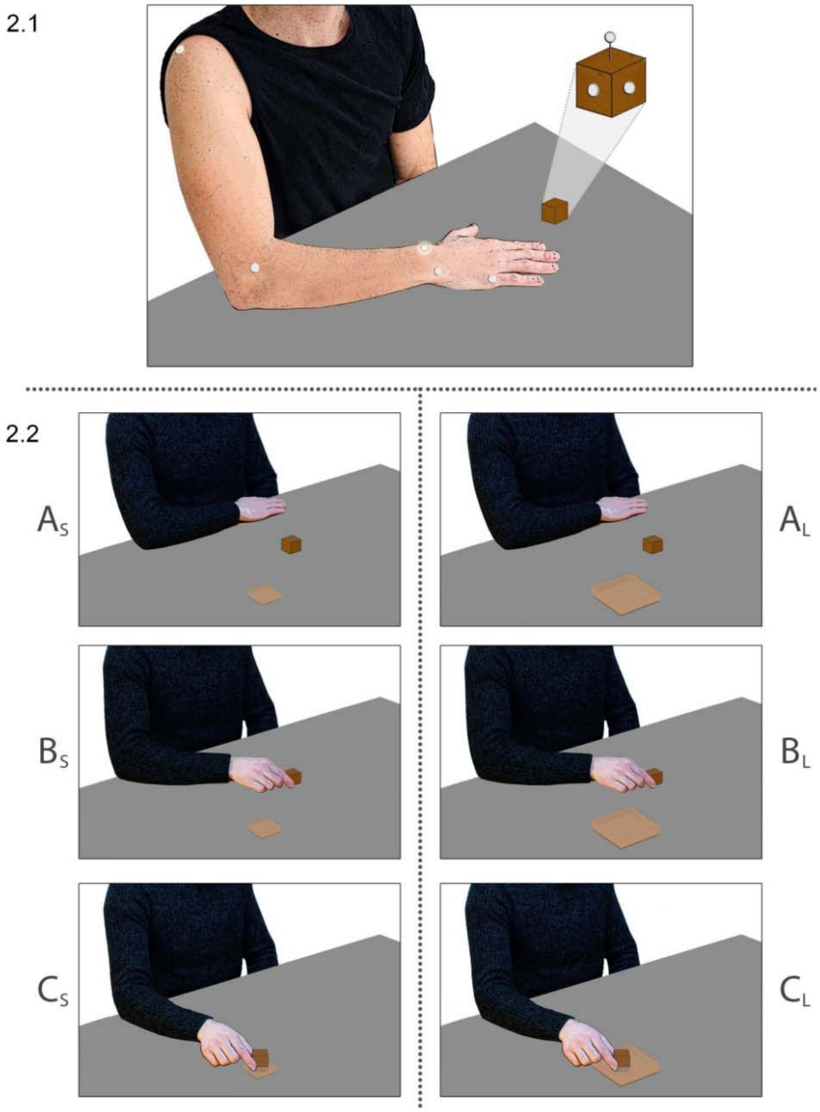


Fig. 2 Marker set and the Experimental Design.

Fig. 2.1 A marker-set of five markers was predisposed: one on the shoulder (ACR), one on the elbow (ELB), two on the wrist ($_U$WRI and $_R$WRI), and one on the hand (HAND). Three markers were placed on the cube: one on two adjacent sides and one on the top. For our aims, the analysis was computed on the $_U$WRI marker (highlighted in the figure). **Fig. 2.2** The figure represents the experimental design for each condition: small (A_S, B_S, C_S) and large (A_L, B_L, C_L). For the small and large condition, respectively: A_S and A_L represent the starting phases in which each participant keeps his hand on the starting point, B_S and B_L indicate the reaching phases, and C_S and C_L are the phases in which participant places the cube in the container. The first act ($Act_{1\text{-}R}$) is defined as the part of action from the starting point to cube grasping (i.e., small: $A_S + B_S$, large: $A_L + B_L$); and the part of the action from the cube grasping to its placement in the container (i.e., small: $B_S + C_S$, large: $B_L + C_L$) is defined as the second act ($Act_{2\text{-}P}$).

The beam of infrared light emitted by the camera flash was reflected by each marker and captured by the cameras working at a sampling rate of 60 Hz. Each marker consisted of adhesive plastic spheres or hemispheres (diameter 10 mm) covered with reflective paper. The 3D coordinates of each marker were determined by stereophotogrammetry using at least two CCD cameras. A set of five markers was placed on specific body landmarks: one on the shoulder (acromion, hereafter ACR), one on the elbow (lateral epicodyle, hereafter ELB), two on the wrist (ulnar and radial styloid processes, hereafter $_{U}$WRI and $_{R}$WRI), and one on the hand (fifth metacarpal head, hereafter HAND). Moreover, there were three markers on the cube: one on two adjacent sides and one on the top (see, Fig. 2.1).

2.4 Data analysis

In this study, we focused on a specific spatiotemporal parameter, which is movement time (MT). MT is a reliable measure of second-order motor planning, as suggested by several findings in the literature (Ansuini et al., 2006; Fabbri-Destro et al., 2009; Wilmut et al., 2013a-b; for a review see Rosenbaum et al., 2012). Noteworthy, MT is a reliable and conservative parameter to study patients with fine motor and motor control difficulties in our (or a comparable) task (for a similar approach, see Fabbri-Destro et al., 2009), given that these difficulties should impact both conditions identically (large and small container). More specific and “subtle” parameters, such as peak of velocity or acceleration, have been sometimes investigated in neurotypical population. However, given that their reliability to assess second-order motor planning is controversial, even in the TD population, we focused our analysis on MT. Each motor action was divided into two motor acts that correspond to the reaching (hereafter, $\text{Act}_{1\text{-R}}$) and placing (hereafter, $\text{Act}_{2\text{-P}}$) phases: the first act duration ($\text{MT-Act}_{1\text{-R}}$) referred to the time between the start position and the point in which the cube was grasped, whereas the second act duration ($\text{MT-Act}_{2\text{-P}}$) referred to the time between the point in which the cube was grasped and the point in which the cube was placed in the (small or large) container (see, Fig. 2).

The marker set of five markers is routinely used for clinical practice in our institute during upper limb kinematic analysis, and then we decided to keep this setting in order to preserve the possibility of qualitative clinical comparisons with other patients. In contrast, for our research project, we were not interested in angular kinematics (i.e., ACR and ELB), and among the remaining markers (i.e., $_U$WRI, $_R$WRI, and HAND) we chose to consider the $_U$WRI one, given that preliminary analysis indicated that it was the most reliable marker (i.e., its tracing was the more solid across all participants).

Particularly, the MT-Act$_{1\text{-R}}$ and the MT-Act$_{2\text{-P}}$ were computed as the difference between the end and the onset of the $_U$WRI marker movement during the Act$_{1\text{-R}}$ and the Act$_{2\text{-P}}$, respectively. As the movement onset, we considered the first frame where the displacement of the marker along any axis (X,Y,Z) exceeded the value of spatial resolution of the system (0.3 mm). As the end of the movement, we considered the first frame – following the onset - where displacements on the three axes were less than 0.3 mm (Barbieri et al., 2007). This procedure was also accurate in establishing potential intermediate intervals between the reaching and the placing phases (i.e., Act$_{1\text{-R}}$ and Act$_{2\text{-P}}$). As Fabbri-Destro et al. (2009), we considered these putative intervals negligible for our specific aim (i.e., to test distal planning ability). Our choice was motivated by the fact that any putative intermediate interval (i.e., the interval – if any - in which the participant has already grasped the cube but he has not yet begun the placing phase) would be very close to zero. Moreover, if any effect existed and could be reliably measured, it would be more parsimonious to hypothesize that such an intermediate interval would be more influenced by the proximal planning stage of the placing act (Act$_{2\text{-P}}$), and thus less relevant for our experimental question.

2.5 Statistical analysis

In the light of the difficulty in predicting R.G.'s boredom, reduced concentration, and potential motor learning in a similar task, we split the 20 trials of each condition into four bins: Bin$_1$ was composed by the first five trials (from 1 to 5), Bin$_2$ by the second five trials (from 6 to 10), and so on until Bin$_4$

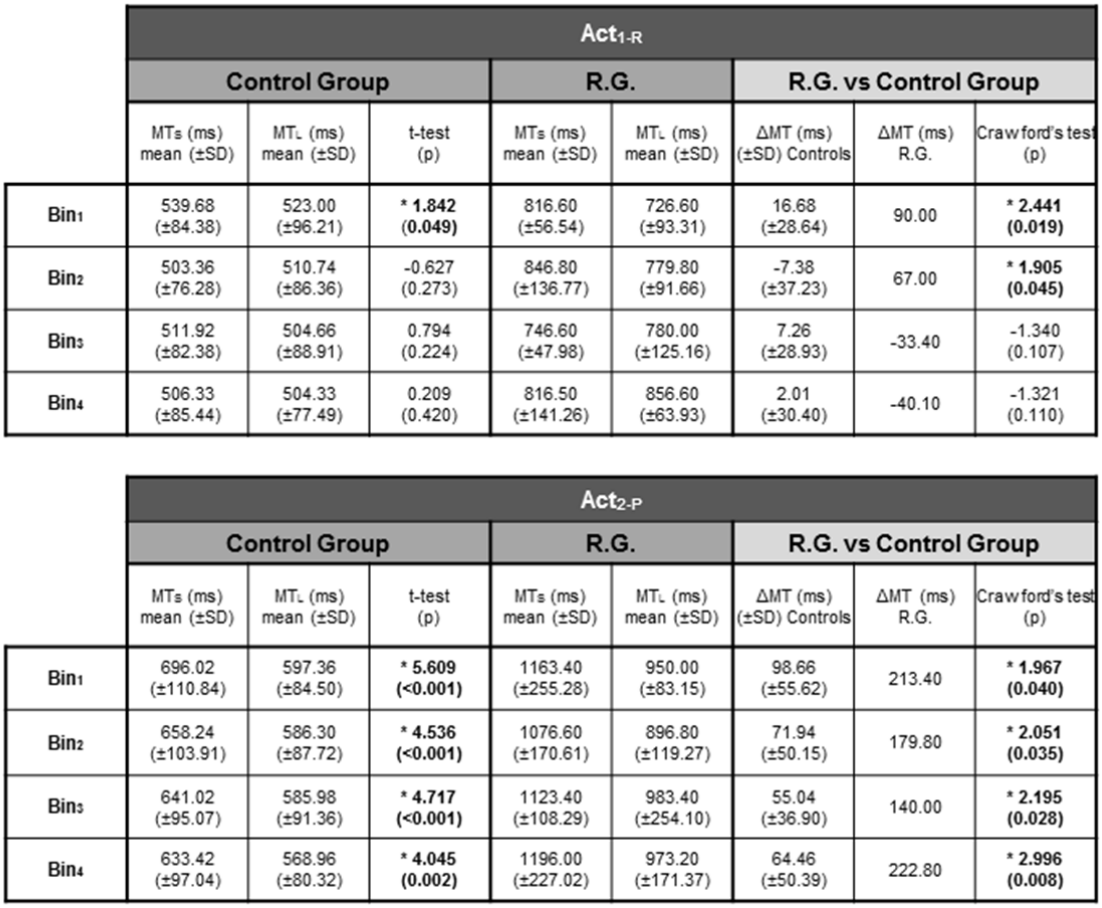
(from trials 16 to 20). For each bin, the mean of the five trials was computed and the data are shown as mean (±standard deviation). A paired t-test was performed within each bin of the control group in order to test the difference in the MT-Act$_{1\text{-}R}$ between the small and the large condition. The same analysis was conducted on the Act$_{2\text{-}P}$.

To compare R.G.'s performance to that of the control group, we used the robust procedure for the single-case vs. control testing described by Crawford et al. (2010), based on a modified t-test procedure outlined by Crawford and Howell (1998). The same statistical method was used in our previous study (Ronconi et al., 2016a). In order to rule out the individual differences in the overall kinematic profile, we computed two differential indexes of the MT as the difference between the MT in the small and in the large condition (hereafter, MT$_s$ and MT$_L$). Specifically, ΔMT-Act$_{1\text{-}R}$ ($MT_S Act_{1\text{-}R} – MT_L Act_{1\text{-}R}$) and ΔMT-Act$_{2\text{-}P}$ ($MT_S Act_{2\text{-}P} – MT_L Act_{2\text{-}P}$) indicate this difference for the first and second act, respectively. We did not directly compare the patient's MT obtained in the small vs. the large condition, since the non-parametric tests, which have been sometimes used for intra-individual analysis (e.g., Wilcoxon signed rank test), require the assumption that each pair of observations is chosen randomly and independently, which is violated in this case (see Laws et al., 2005).

3. Results

3.1 Within control group

The analysis performed on the control group aimed to test the difference between the MT in the small (MT$_S$) and in the large condition (MT$_L$) (see, Table 1), both in the Act$_{1\text{-}R}$ and the Act$_{2\text{-}P}$. In the Act$_{1\text{-}R}$, the analysis pointed out that the MT$_S$ was significantly different from the MT$_L$ in the Bin$_1$ ($t_{(9)}$=1.842, p=0.049), whereas no difference was found in the Bin$_{2.}$, Bin$_3$, and Bin$_4$. For the Act$_{2\text{-}P}$, the paired t-test performed on each bin highlighted the difference between the MT$_S$ and the MT$_L$ in all bins (Bin$_1$: $t_{(9)}$=5.609; Bin$_2$: $t_{(9)}$=4.536; Bin$_3$: $t_{(9)}$=4.717; Bin$_4$: $t_{(9)}$= 4.045; all ps<0.003). These results indicate that, in the first trials (Bin_1), the MT of the control group was modulated by the final goal already in the Act_{1-R}.



	Act1-R							
	Control Group			R.G.		R.G. vs Control Group		
	MTs (ms) mean (±SD)	MTL (ms) mean (±SD)	t-test (p)	MTs (ms) mean (±SD)	MTL (ms) mean (±SD)	ΔMT (ms) (±SD) Controls	ΔMT (ms) R.G.	Crawford's test (p)
Bin1	539.68 (±84.38)	523.00 (±96.21)	*** 1.842 (0.049)**	816.60 (±56.54)	726.60 (±93.31)	16.68 (±28.64)	90.00	*** 2.441 (0.019)**
Bin2	503.36 (±76.28)	510.74 (±86.36)	-0.627 (0.273)	846.80 (±136.77)	779.80 (±91.66)	-7.38 (±37.23)	67.00	*** 1.905 (0.045)**
Bin3	511.92 (±82.38)	504.66 (±88.91)	0.794 (0.224)	746.60 (±47.98)	780.00 (±125.16)	7.26 (±28.93)	-33.40	-1.340 (0.107)
Bin4	506.33 (±85.44)	504.33 (±77.49)	0.209 (0.420)	816.50 (±141.26)	856.60 (±63.93)	2.01 (±30.40)	-40.10	-1.321 (0.110)

	Act2-P							
	Control Group			R.G.		R.G. vs Control Group		
	MTs (ms) mean (±SD)	MTL (ms) mean (±SD)	t-test (p)	MTs (ms) mean (±SD)	MTL (ms) mean (±SD)	ΔMT (ms) (±SD) Controls	ΔMT (ms) R.G.	Crawford's test (p)
Bin1	696.02 (±110.84)	597.36 (±84.50)	*** 5.609 (<0.001)**	1163.40 (±255.28)	950.00 (±83.15)	98.66 (±55.62)	213.40	*** 1.967 (0.040)**
Bin2	658.24 (±103.91)	586.30 (±87.72)	*** 4.536 (<0.001)**	1076.60 (±170.61)	896.80 (±119.27)	71.94 (±50.15)	179.80	*** 2.051 (0.035)**
Bin3	641.02 (±95.07)	585.98 (±91.36)	*** 4.717 (<0.001)**	1123.40 (±108.29)	983.40 (±254.10)	55.04 (±36.90)	140.00	*** 2.195 (0.028)**
Bin4	633.42 (±97.04)	568.96 (±80.32)	*** 4.045 (0.002)**	1196.00 (±227.02)	973.20 (±171.37)	64.46 (±50.39)	222.80	*** 2.996 (0.008)**

Table 1

The table reports the analyses within the control group and the R.G. vs. control group comparison in the first (Act_{1-R}) and in the second (Act_{2-P}) act. The analyses were performed on four different bins of subsequent trials: Bin_1 (trials from 1 to 5), Bin_2 (trials from 6 to 10), Bin_3 (trials from 11 to 15), and Bin_4 (trials from 16 to 20). Mean values of the movement time in the small (MT_S) and in the large (MT_L) condition are reported for the analysis within the control group, whereas the differences between MT_S and MT_L (ΔMT) are reported for the R.G. vs. control group comparison. MT values are reported in milliseconds.

3.2 R.G. vs. control group

Using the Crawford test for the single-case vs. controls, we compared R.G.'s ΔMT with the ΔMT of the control group, both in the $Act_{1\text{-}R}$ and the $Act_{2\text{-}P}$. In the $Act_{1\text{-}R}$, R.G.'s performance differed from the performance of the control group in both Bin_1 (t=2.441, p=0.019) and Bin_2 (t=1.905, p=0.045). Conversely, no significant differences were found in Bin_3 and Bin_4 (see, Fig. 3, left panel). In $Act_{2\text{-}P}$, the difference between R.G. and the control group was significant in all bins (Bin_1: t=1.967; Bin_2: t=2.051; Bin_3: t=2.195; Bin_4: t=2.996; all ps<0.05). These results indicate that, in Bin_1 and Bin_2, R.G. already modulated the final goal in the $Act_{1\text{-}R}$. More specifically, these data indicate that, in R.G., the modulation is in the expected direction (MT_S>MT_L) and is more pronounced relative to the control group (i.e., a larger difference between the small and large condition). Not surprisingly, R.G. was slower than the controls in $Act_{2\text{-}P}$ in all bins (see, Fig. 3, right panel).

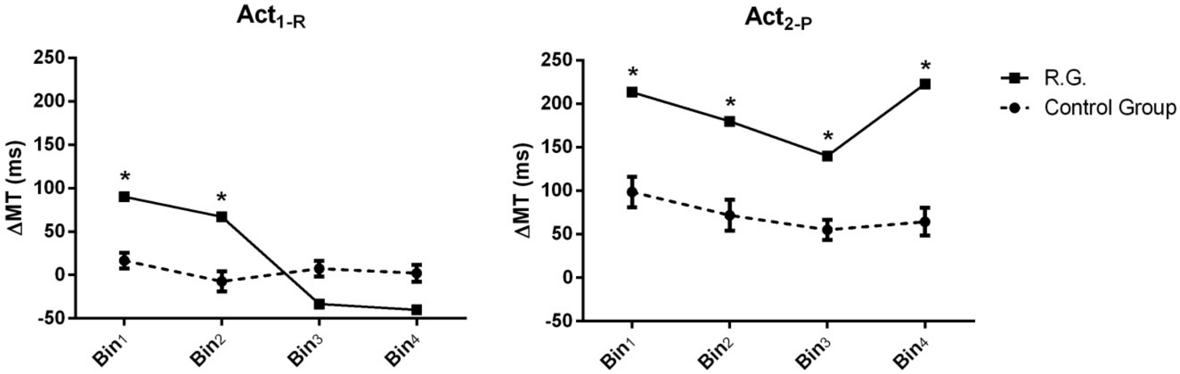


Fig. 3

The graphs show the mean values of the difference between the movement time in the small (MT_S) and in the large (MT_L) condition (ΔMT) of the control group compared to R.G. These analyses were computed in both acts ($Act_{1\text{-}R}$ and $Act_{2\text{-}P}$) for each bin: Bin_1 (trials from 1 to 5), Bin_2 (6 - 10), Bin_3 (11 - 15), and Bin_4 (16 - 20). Error bars represent the mean standard errors of the control group and * indicates a significant difference between R.G. and the controls. **Left Panel**: in the first act ($Act_{1\text{-}R}$), R.G.'s ΔMT value is significantly larger than the ΔMT values of the control group in Bin_1 and Bin_2. **Right Panel**: in the second act ($Act_{2\text{-}P}$), R.G.'s ΔMT value is significantly larger than the ΔMT values of the control group in all bins.

4. DISCUSSION

4.1 High-level motor planning hierarchy in the absence of cerebellum

We went beyond the idea that motor planning is a monolithic process, tackling the hierarchical organization of motor planning at distinct levels of abstraction (Sober and Sabes, 2003-2005). We compared an extremely rare patient with cerebellar agenesis to a group of neurotypical controls in a second-order motor planning task. We found that despite the absence of the cerebellum since birth, R.G. showed preserved second-order motor planning. The results that we observed in the neurotypical control group members showed that they took into account the distal goal of an action (e.g., to place an object in a small or large container) from the very beginning phase of that action (i.e., in $Act_{1\text{-}R}$). However, notwithstanding obvious differences in fine-motor aspects, R.G. took into account the distal goal from the initial phase of the action as well; thus, showing significant second-order motor planning. Specifically, he exhibited a significant modulation of the first act ($Act_{1\text{-}R}$) in relation to the distal goal (to place an object in the small or large container), so that the expected difference in movement time between the small and the large conditions ($MT_S > MT_L$) was evident and even larger than in the control group. The fact that cerebellar patients may have preserved abilities at high levels of motor planning as well as significant difficulties in motor performance is not unexpected, as reported by Taig et al. (2012).

We set the experimental protocol (i.e., distance and difficulty of the task) taking into account R.G.'s clinical picture. As a result, the task was appropriate for R.G., though consequently easier for the neurotypical age-matched control group, which to some extent prematurely stopped planning the distal goal from the beginning phases (see $Act_{1\text{-}R}$), as if the two conditions became equally simple/demanding for them. Our findings support this hypothesis at multiple levels. First, R.G. was significantly slower compared to the control group in both the first and second acts of the two conditions (i.e., $MT_SAct_{1\text{-}R}$, $MT_SAct_{2\text{-}P}$, $MT_LAct_{1\text{-}R}$, $MT_LAct_{2\text{-}P}$). Second, in the final act, which putatively did not take into account the second-order planning but only more basic components of motor control and motor execution, R.G.'s movement time difference between large and small conditions was persistently higher than in the control group (see, Table 1 and Fig.3, right panel). This is clear evidence that the task was more demanding for R.G. In addition, consistently with a number of studies in the literature (Ansuini et al., 2006; Fabbri-Destro et al., 2009; Wilmut et al., 2013a-b; Rosenbaum et al., 2012), the control group tailored the movement time of the first act according to the size of container in Bin_1. Second-order planning was only evident during the initial trials when no further confounding elements (e.g., motor learning, lack of concentration, boredom) were present (Bin_2, Bin_3, and Bin_4 were not statistically different) (Table 1).

Thus, the main result of this study argues for a preserved second-order motor planning ability in R.G. based on the difference, in the expected direction, between R.G. and the controls. Focusing on the $Act_{1\text{-}R}$, in Bin_1 and Bin_2 the difference between the small and large conditions in R.G. is higher than in the control group. This indicates that R.G. tailored the duration of the first act according to the final task demand ($MT_S > MT_L$, see Table 1), and this tailoring is significantly higher than the control group (Fig.3, left panel). These results suggest that, at the beginning, R.G. needed a higher degree of second-order planning than the control group in order to gauge the difficulty of the task (Bin_1 and Bin_2), but this difference gradually collapsed during the course of the experiment (Bin_3 and Bin_4 were not significantly different). This study does not enable testing whether the results showing no statistically significant differences in Bin_3 and Bin_4 between R.G. and the controls (Table 1 and Fig.3, left panel) are due to boredom, reduced concentration, or motor learning (or a combination thereof). While our experiment was not designed to test this question, one could interpret R.G.'s findings in Bin_3 and Bin_4 as the corresponding flattening effect was also already found for the control group in Bin_2. Accordingly, second-order motor planning would only be observable in the initial trials, and the number of trials in which second-order motor planning is noticeable would be directly related to the difficulty of the task perceived by each participant. Past this threshold, participants would simply stop planning the distal goal (i.e., to place the object in the small vs. large container) from the beginning phase of the action (i.e., from the reaching phase), and the kinematics of the reaching act would only be influenced by motor control and proximal planning (i.e., to grasp the cube). Interestingly, this could be considered as further indirect evidence that this task was simpler for the neurotypical control group than for R.G., given that our patient reached this flattening of performance later. Thus, these data could also be considered concordant with previous clinical studies, indicating that the major limitation for R.G. is the longer time he needs to learn and consolidate his skills compared to neurotypical individuals (Tavano et al., 2007; Romaniello and Borgatti, 2013; Arrigoni et al., 2015; Ronconi et al., 2016a).

4.2 Functional, neurophysiological, and clinical considerations.

The results of our study can be interesting from different perspectives. First, in light of the functional value of second-order motor planning in motor cognition (i.e., the ways in which the motor system contributes to understanding and shaping social actions, see Casartelli and Chiamulera, 2016). Second-order motor planning facilitates proficient anticipation of the final phase of the action in order to accomplish it more efficiently (Wilmut and Barnett, 2014). In other words, when two acts must be performed sequentially, planning the final act can influence the execution of the first one[1]. The consistent body of experimental studies supports the presence of second-order motor planning ability in typically developing (TD) individuals (Claxton et al. 2003; Johnson et al., 2004; Ansuini et al., 2006; Fabbri-Destro et al., 2009; Chen et al., 2010; Wilmut et al., 2013a; for a

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[1] Let’s take our experimental setting as a reference point. In the final act (i.e., $Act_{2\text{-}P}$), movement time is influenced by the “execution phase” (i.e. motor control) and by the “proximal planning phase” (i.e., to place the cube in the small or large container, which can be defined as “first-order motor planning”). As in $Act_{2\text{-}P}$, the movement time of the first act (i.e., MT-$Act_{1\text{-}R}$) is influenced by the “execution phase” (i.e., motor control) and by the “proximal planning phase” (i.e., grasping the cube). For these phases (i.e., motor control + proximal planning), the two conditions (i.e., $Act_{1\text{-}R}$ large condition, and $Act_{1\text{-}R}$ small condition) can be assumed to be identical, given that participants have to grasp the same cube. However, $Act_{1\text{-}R}$ is also influenced by the “distal planning phase” (i.e., the “future” need to place the cube in the small/large container in the subsequent phase of action). We used the notion of “second-order motor planning” ability to refer to this “distal planning phase” of the $Act_{1\text{-}R,}$ representing a more abstract and subtle motor planning ability that reflects a function situated at a high level of the motor planning hierarchy.

In sum, we can assume that the influence of first-order planning (also defined as “proximal planning phase”) and motor control in $Act_{1\text{-}R}$ is identical for both conditions (large and small container), and we can reasonably claim that differences in movement time in $Act_{1\text{-}R}$ ($MT_S > MT_L$) must be attributed exclusively to second-order planning (i.e. to the “distal planning phase”).

review, Rosenbaum et al., 2012). Further support of this view is provided by a study by Cohen et al. (2004) in which TD adults were invited to grasp a cylinder with the goal of placing it in a new position which differed in height. The authors found that the grasp height on the cylinder was inversely related to the height of the target position. This finding demonstrates that participants grasp the cylinder in a specific position based on their ability to gauge the final destination of the act. Taken together, these studies support the existence of a series of subtle motor mechanisms (at different levels of abstraction) that contribute to shaping the way in which we interact with the world.

Second, our data on R.G.'s preserved second-order motor planning are intriguing in view of the potential neural circuits supporting this ability. As second-order motor planning is a component of the high stages of motor planning (Sober and Sabes, 2003-2005), and considering the results of degenerative cerebellar studies (Taig et al., 2012), we may expect that the congenital absence of the cerebellum could impede the preservation of such an ability (Wilmut et al., 2013a). However, our data do not support the hypothesis that the cerebellum is essential for second-order motor planning, although no definitive conclusions about the role of cerebellum can be inferred from our results. Rather, our data suggest that distinct stages of motor planning can be supported to varying degrees by different neural substrates. This may also induce speculation about alternative hypotheses on the brain circuits supporting second-order motor planning. It has been hypothesized that the parieto-frontal mirror circuit, which includes the inferior parietal lobule, the ventral premotor cortex, and the caudal part of the inferior frontal gyrus (Rizzolatti et al., 2014), is not only able to encode the goal of a single motor act (e.g., reaching, grasping, throwing, etc.), but also the final goal of a sequence of motor acts (e.g., grasp-to-eat vs. grasp-to-place) (Rizzolatti and Sinigaglia, 2010; Sinigaglia, 2013). This view is supported by single-neuron-recording studies in macaques that showed how a subset of neurons in the inferior parietal cortex (area PFG) and the F5 spiked in a markedly different way (i.e., stronger or lower activation) when the same act (e.g., to grasp) was part of an action with different goals (e.g., grasp-to-eat vs. grasp-to-place) (Fogassi et al., 2005;

Bonini et al., 2010). Compelling evidence supporting the presence of a similar mechanism in humans was obtained by electromyography (EMG) studies in human children (Cattaneo et al., 2007), and even in infants (Turati et al., 2013; Natale et al., 2014). In R.G.'s case, his preserved second-order motor planning ability may be considered direct evidence that this ability can be preserved even in the absence of the cerebellum, which thereby supports the hypothesis that the parieto-frontal mirror circuit – apparently not compromised in R.G. – plays a critical role in second-order motor planning. A recent study by Bruni et al. (2015) seems to suggest that the ventrolateral prefrontal cortex (VLPFC), a region anatomically connected with the parietal and premotor areas (Petrides and Pandya, 1984; Borra et al., 2011), may also play a role in second-order motor planning. The study tested an elegantly modified version of the grasp-to-eat/grasp-to-place paradigm (Fogassi et al., 2005; Bonini et al., 2010) also involving a go/no-go condition (see also Bonini et al., 2014). The authors concluded by proposing that the VLPFC may also host a kind of abstract "vocabulary" of the intended goals (Bruni et al., 2015; see also Rizzolatti and Sinigaglia, 2016).

Finally, our study is also interesting from a clinical point of view in regards to the role of second-order motor planning in autism spectrum disorder (ASD). Children with ASD show anomalies in second-order motor planning ability at both the behavioral (Fabbri-Destro et al., 2009) and electrophysiological (Cattaneo et al., 2007) level. R.G.'s performance may be considered similar to the performance of TD children in Fabbri-Destro et al. (2009), and it clearly differs from the ASD children group (Casartelli et al., 2016). In early childhood, ASD-like behaviors were reported in R.G. (Tavano et al., 2007, Arrigoni et al., 2015), even if the clinical picture radically evolved over the years. At the time of his last clinical visit (Ronconi et al., 2016a), the patient did not present any significant ASD signs, as confirmed by his Autism Quotient score (Baron-Cohen et al., 2001). Anomalies in second-order motor planning in children with ASD (Cattaneo et al., 2007; Fabbri-Destro et al., 2009), combined with our results demonstrating R.G.'s preserved second-order motor planning, could be of great interest for disentangling subtler impairments that characterize ASD and cerebellar-induced autistic-like symptomatology (Riva and Giorgi, 2000; Tavano et al., 2007; Limperpoulos et al., 2014; Bolduc et al., 2011-2012; Chlebowski et al., 2013; Casartelli and Molteni, 2014; Wang et al., 2014; Ronconi et al., 2016b).

5. Conclusion and limitations

In this study, we explored the contribution of the cerebellum to high stages of the motor planning hierarchy, and we found that second-order motor planning is preserved in a patient with congenital near-total absence of the cerebellum. Exploring motor planning as a process constituted by different but interdependent components was useful for disentangling neural substrates of distinct levels of motor planning. In light of the functional role of second-order motor planning in motor cognition and its potential clinical implications in ASD, this result may represent an important contribution to future research.

Our results support the idea that the cerebellum is not essential for this specific high-level stage of motor planning. Nonetheless, we cannot infer definitive conclusions on the role of the cerebellum in high levels of the motor planning hierarchy. An important limitation in approaching congenital agenesis is that we cannot definitively exclude that some long-term reorganization of R.G.'s brain may have resulted in phenomena of functional compensation. R.G. clearly benefited from impressive cortical compensatory plasticity, as demonstrated by his abilities in daily life activities. Thus, we cannot exclude the fact that R.G.'s cortical circuits have fully taken charge of operations normally supported – at least in part - by the cerebellum. This alternative explanation of our results must be attentively considered, and we need further evidence to definitely disentangle this point and confirm what this preliminary evidence suggests. On the other hand, the fact that R.G.'s condition is congenital (Arrigoni et al., 2015) allows us to exclude the hypothesis that his preserved second-order motor planning was the result of an ability learned before acquired lesion, a problem which is common to many studies involving patients with cerebellar degenerative or acquired lesion (for a critical comparison of strengths and limitations of studies with different cerebellar populations, see Timmann et al., 2009). A further point for future research may concern the comparison between healthy participants and cerebellar patients in encoding subtler kinematic parameters (e.g., peak velocity). To study kinematics in cerebellar patients is always difficult in light of ataxic signs that usually are relevant in these patients. However, one might also hypothesize that typical kinematic laws (e.g., increased decelerating time indicates a more difficult act) are not respected in these patients, or at least seriously perturbed.

To summarize, although obvious prudence is generally needed to infer definitive conclusions from single-case vs. control experimental design, our study may represent an important contribution to future research on the role of the cerebellum at different stages of the motor planning hierarchy. Intriguingly, approaching motor planning as a process constituted by different but interdependent components may be useful for disentangling neural substrates of distinct specific levels. Thus, our findings may be a strong catalyst for researches on ASD, on the parieto-frontal mirror circuit, and on their mutual relationship with the cerebellum.

Acknowledgments:

LC was supported by a grant from the Italian Ministry of Health (Ricerca Corrente 2016 to LC). This study was partially supported by the Italian Ministry of Health (Ricerca Corrente grant 01/03/2011 to RB). We also acknowledge the PADAPORT project (to RB) funded by the Pierfranco and Luisa Mariani Foundation.

We would like to thank Filippo Arrigoni, Serena Carna, Courtney Keeling Greenlaw, and Corrado Sinigaglia for their helpful comments. The authors are also grateful to the patient and his family for their kind cooperation.

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Fig.1 T1-weighted MR sections in the sagittal, coronal and axial planes show the complete agenesis of the cerebellum. The pons is flattened and posterior fossa is filled with cerebrospinal fluid.

Fig. 2 Marker set and the Experimental Design.

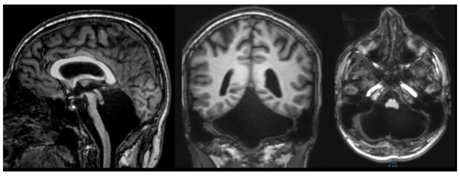
Fig. 2.1 A marker-set of five markers was predisposed: one on the shoulder (ACR), one on the elbow (ELB), two on the wrist ($_U$WRI and $_R$WRI), and one on the hand (HAND). Three markers were placed on the cube: one on two adjacent sides and one on the top. For our aims, the analysis was computed on the $_U$WRI marker (highlighted in the figure). **Fig. 2.2** The figure represents the experimental design for each condition: small (A_S, B_S, C_S) and large (A_L, B_L, C_L). For the small and large condition, respectively: A_S and A_L represent the starting phases in which each participant keeps his hand on the starting point, B_S and B_L indicate the reaching phases, and C_S and C_L are the phases in which participant places the cube in the container. The first act (Act_{1-R}) is defined as the part of action from the starting point to cube grasping (i.e., small: $A_S + B_S$, large: $A_L + B_L$); and the part of the action from the cube grasping to its placement in the container (i.e., small: $B_S + C_S$, large: $B_L + C_L$) is defined as the second act (Act_{2-P}).

Fig. 3

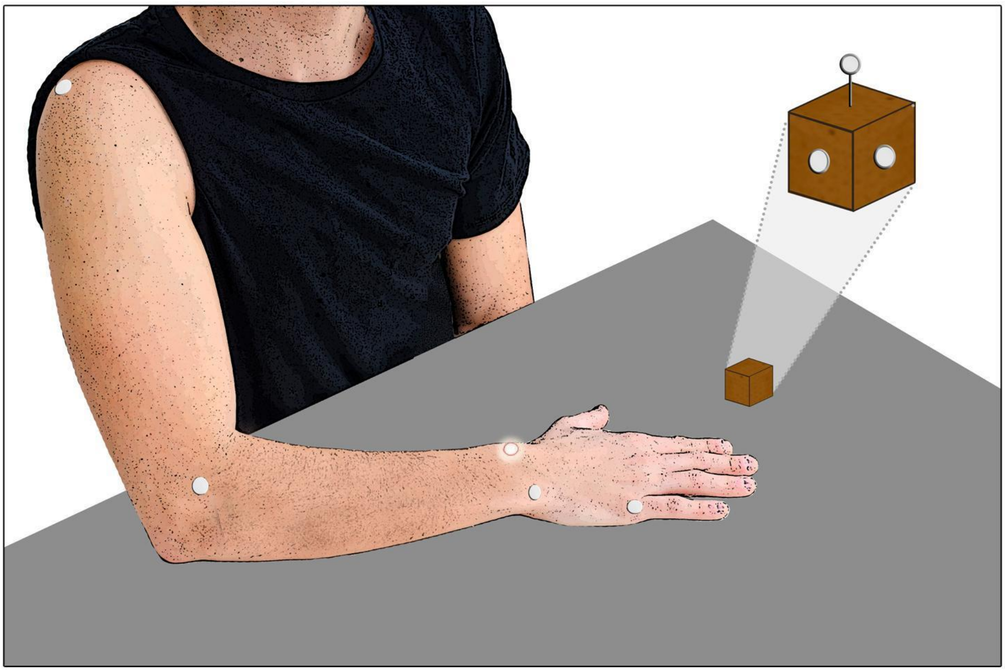
The graphs show the mean values of the difference between the movement time in the small (MT_S) and in the large (MT_L) condition (ΔMT) of the control group compared to R.G. These analyses were computed in both acts (Act_{1-R} and Act_{2-P}) for each bin: Bin_1 (trials from 1 to 5), Bin_2 (6 - 10), Bin_3 (11 - 15), and Bin_4 (16 - 20). Error bars represent the mean standard errors of the control group and * indicates a significant difference between R.G. and the controls. **Left Panel**: in the first act (Act_{1-R}), R.G.'s ΔMT value is significantly larger than the ΔMT values of the control group in Bin_1 and Bin_2. **Right Panel**: in the second act (Act_{2-P}), R.G.'s ΔMT value is significantly larger than the ΔMT values of the control group in all bins.

Table 1

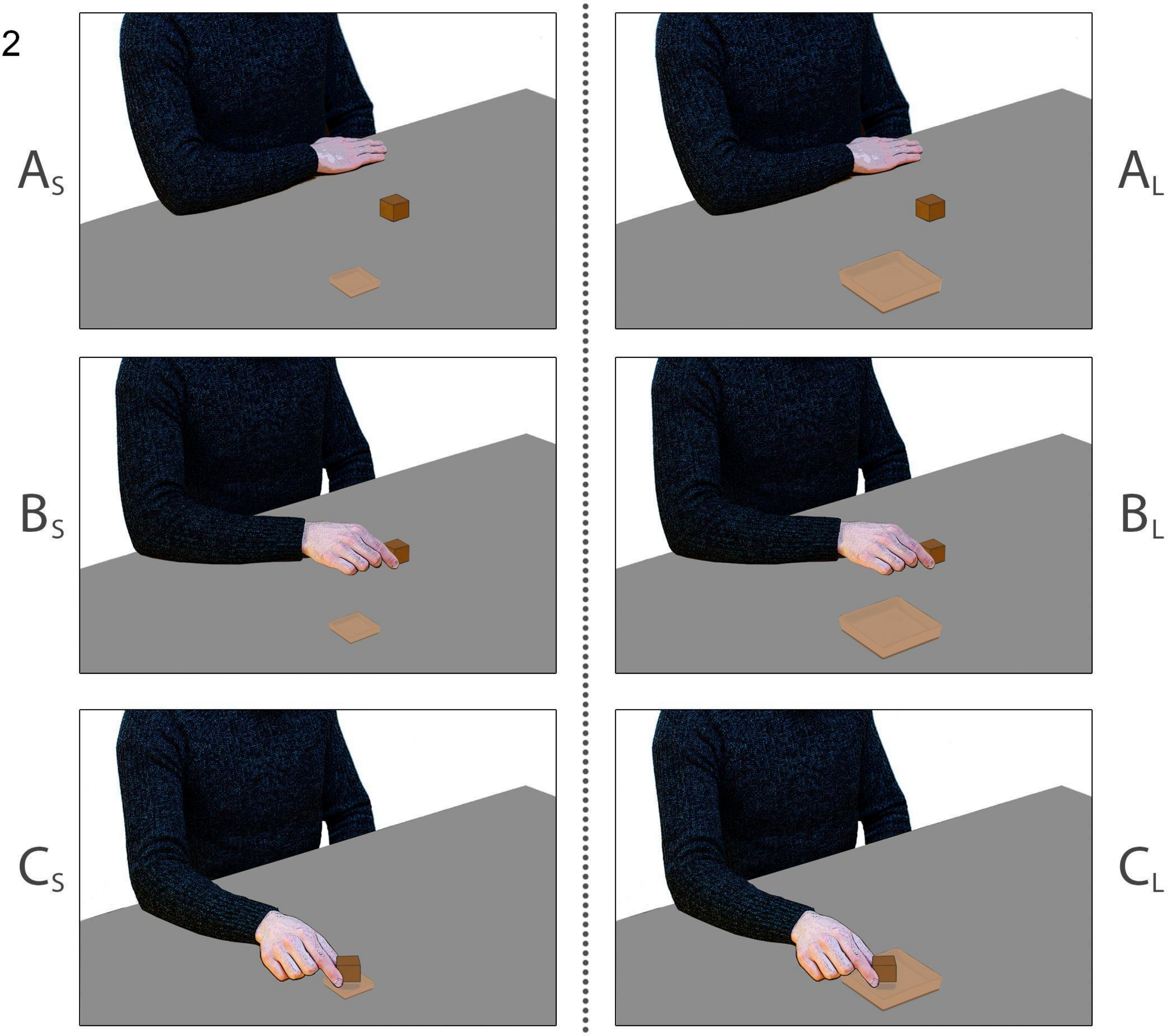
The table reports the analyses within the control group and the R.G. vs. control group comparison in the first (Act_{1-R}) and in the second (Act_{2-P}) act. The analyses were performed on four different bins of subsequent trials: Bin_1 (trials from 1 to 5), Bin_2 (trials from 6 to 10), Bin_3 (trials from 11 to 15), and Bin_4 (trials from 16 to 20). Mean values of the movement time in the small (MT_S) and in the large (MT_L) condition are reported for the analysis within the control group, whereas the differences between MT_S and MT_L (ΔMT) are reported for the R.G. vs. control group comparison. MT values are reported in milliseconds.

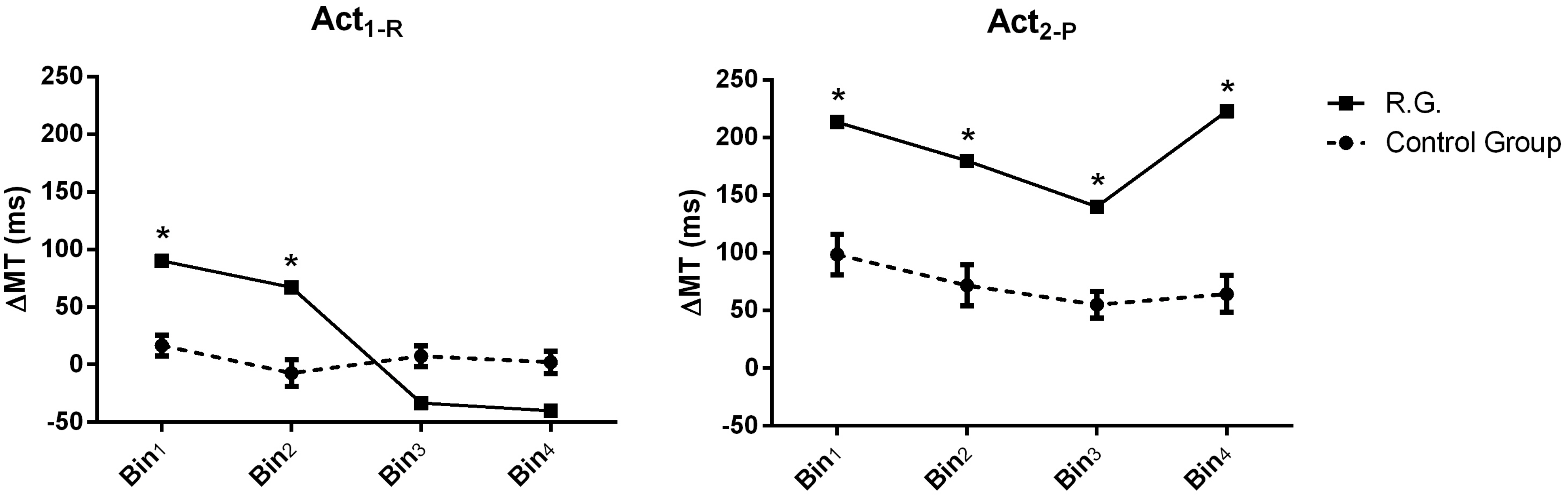


2.1



2.2




Act_{1-R}
Act_{2-P}
ΔMT (ms)
250
200
150
100
50
0
-50
*
Bin_1
Bin_2
Bin_3
Bin_4
R.G.
Control Group

	Act$_{1\text{-}R}$							
	Control Group			**R.G.**		**R.G. vs Control Group**		
	MT$_S$ (ms) mean (±SD)	MT$_L$ (ms) mean (±SD)	t-test (p)	MT$_S$ (ms) mean (±SD)	MT$_L$ (ms) mean (±SD)	ΔMT (ms) (±SD) Controls	ΔMT (ms) R.G.	Crawford's test (p)
Bin$_1$	539.68 (±84.38)	523.00 (±96.21)	* **1.842** **(0.049)**	816.60 (±56.54)	726.60 (±93.31)	16.68 (±28.64)	90.00	* **2.441** **(0.019)**
Bin$_2$	503.36 (±76.28)	510.74 (±86.36)	-0.627 (0.273)	846.80 (±136.77)	779.80 (±91.66)	-7.38 (±37.23)	67.00	* **1.905** **(0.045)**
Bin$_3$	511.92 (±82.38)	504.66 (±88.91)	0.794 (0.224)	746.60 (±47.98)	780.00 (±125.16)	7.26 (±28.93)	-33.40	-1.340 (0.107)
Bin$_4$	506.33 (±85.44)	504.33 (±77.49)	0.209 (0.420)	816.50 (±141.26)	856.60 (±63.93)	2.01 (±30.40)	-40.10	-1.321 (0.110)

	Act$_{2\text{-}P}$							
	Control Group			**R.G.**		**R.G. vs Control Group**		
	MT$_S$ (ms) mean (±SD)	MT$_L$ (ms) mean (±SD)	t-test (p)	MT$_S$ (ms) mean (±SD)	MT$_L$ (ms) mean (±SD)	ΔMT (ms) (±SD) Controls	ΔMT (ms) R.G.	Crawford's test (p)
Bin$_1$	696.02 (±110.84)	597.36 (±84.50)	* **5.609** **(<0.001)**	1163.40 (±255.28)	950.00 (±83.15)	98.66 (±55.62)	213.40	* **1.967** **(0.040)**
Bin$_2$	658.24 (±103.91)	586.30 (±87.72)	* **4.536** **(<0.001)**	1076.60 (±170.61)	896.80 (±119.27)	71.94 (±50.15)	179.80	* **2.051** **(0.035)**
Bin$_3$	641.02 (±95.07)	585.98 (±91.36)	* **4.717** **(<0.001)**	1123.40 (±108.29)	983.40 (±254.10)	55.04 (±36.90)	140.00	* **2.195** **(0.028)**
Bin$_4$	633.42 (±97.04)	568.96 (±80.32)	* **4.045** **(0.002)**	1196.00 (±227.02)	973.20 (±171.37)	64.46 (±50.39)	222.80	* **2.996** **(0.008)**