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RESEARCH ARTICLE

Atrophic degeneration of cerebellum impairs both the reactive and the proactive control of movement in the stop signal paradigm

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Abstract The cognitive control of movement suppression, including performance monitoring, is one of the core properties of the executive system. A complex cortical and subcortical network involving cerebral cortex, thalamus, subthalamus, and basal ganglia has been regarded as the neural substrate of inhibition of programmed movements. Using the countermanding task, a suitable tool to explore behavioral components of movement suppression, the contribution of the cerebellum in the proactive control and monitoring of voluntary action has been recently described in patients affected by focal lesions involving in particular the cerebellar dentate nucleus. Here, we evaluated the performance on the countermanding task in a group of patients with cerebellar degeneration, in which the cerebellar cortex was diffusely affected, and showed that they display additionally a longer latency in countermanding engaged movements. Overall, the present data confirm the role of the cerebellum in executive control of action inhibition by extending the contribution to reactive motor suppression.

Keywords Inhibition · Cortical cerebellar degeneration · Stop signal reaction time · Movement generation · Basal ganglia

Introduction

The cerebellum is involved in motor control, since it is included in important functional loops with both the spinal cord and the cerebral cortex (Bostan et al. 2013; Brodal and Brodal 1981; Caligiore et al. 2017; Ishikawa et al. 2016). One of the key functions in motor control is the ability to suppress a movement in response to contextual information changes (Logan et al. 2015; Verbruggen and Logan 2008). Increasing evidence suggests that the cerebellum, beside its contribution to the online control of movement execution (Ishikawa et al. 2016; Ramnani 2006), could play a role in motor cancellation also before action initiation (Brunamonti et al. 2014; Tanaka et al. 2003). Anatomical studies are in line with this hypothesis. In fact, it has been shown that the cerebellum is connected with cortical and subcortical areas (Barbas and García-Cabezas 2016; Middleton and Strick 2001; Ramnani 2006; Strick et al. 2009) known to provide important contributions to the different phases of both movement generation and suppression (Aron and Poldrack 2006; Bostan et al. 2013; Li et al. 2008; Mattia et al. 2013; Mirabella et al. 2011; Pani et al. 2014; Peterburs and Desmond 2016). In particular, the recent observation of

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connections of the cerebellum with basal ganglia (Bostan et al. 2013) seems to support the hypothesis that the cerebellum would exert a higher level of control on movement cancellation, then suggesting that either a delayed execution (longer reaction time after target presentation) or a incomplete action suppression could depend by a modified cerebellar computation of sensorial inputs.

An efficient tool to explore both the reactive and proactive components of movement generation/suppression is the countermanding task (also known as stop signal task; Verbruggen and Logan 2008, 2009). The task requires the participants to promptly respond to a Go signal by making, for example, an arm movement (*go trials*) and to suppress it, if an unpredictable Stop signal countermands the previously presented instruction (*stop trials*). In this task, the inhibitory behavior is evaluated by describing subjects' performance in trials where, after the presentation of a Stop signal, the movement needs to be cancelled during preparation. With a strong theoretical construct, the countermanding task provides good estimates of both the time to respond to the Stop signal presentation (stop signal reaction time, SSRT) referred to as reactive control, and the effect of the *stop trials* on the local and global efficiency of motor generation, an effect known as proactive (strategic) control. The local effect is generally described as a monitoring activity and corresponds to an increased latency in starting a movement after *stop trials* appearance, in particular after errors (Verbruggen and Logan 2009). The global effect refers more to adaptations due to contextual changes.

Recently, it has been shown that patients with cerebellar focal lesions require an increased time to adjust their behavior after the Stop signal but a preserved SSRT, suggesting that the cerebellum could exclusively contribute in the proactive control of movement generation (Brunamonti et al. 2014; Kunimatsu et al. 2016). In the current report, we used the same stop signal task protocol as in Brunamonti et al. (2014) to assess patients affected by cerebellar atrophy and investigate whether a major involvement of the cerebellar cortex could affect all different components of motor inhibition.

Subjects and methods

Participants

Ten patients with cerebellar atrophy (CA) and no clinical or neuroradiological evidence of extracerebellar pathologies were enrolled in the study. The control group comprised 22 healthy subjects (HS) with no history of neurological or psychiatric illness. *T* test for independent samples confirmed that CA patients and controls were well matched for age ($p = 0.4369$) and education ($p = 0.4228$). Demographic, motor, and intellectual level data of each patient and mean values of the control group are reported in Table 1. In the CA group, eight subjects had genetically determined ataxias (2: Friedreich ataxia; 1: spinocerebellar ataxia type 1; 4: spinocerebellar ataxia type 2; 1: ataxia teleangectasia), and 2 presented with an idiopathic form. All patients underwent a neurological examination, and their motor impairments were quantified using a modified version of the cerebellar motor deficit scale per Appollonio et al. (1993), which ranges from 0 (absence of any deficit) to 42 (presence of all deficits to the highest degree) and evaluates eight clinical signs (dysarthria, limb tone, postural tremor, upper and lower limb ataxia, standing balance,

Table 1 Demographic and intellectual data of cerebellar CA patients and controls

	Etiology	M/F	Age	Education (years)	Total motor score	PM (cutoff 18.9)
Patients						
CA1	ND	F	57	5	6.75	27.3
CA2	SCA1	M	50	18	28.5	21.2
CA3	SCA2	F	60	5	19.5	14.5
CA4	ND	M	53	15	23.25	33.8
CA5	FRDA	F	41	13	16.5	30.8
CA6	SCA2	F	44	13	23.75	21.6
CA7	FRDA	M	24	8	26	30.3
CA8	AT	M	30	13	18.5	31.8
CA9	SCA2	F	42	18	12	24.2
CA10	SCA2	M	58	5	12	28.6
HS	–	10/12	49.1 (11.4)	12.6 (4.7)	–	31.3 (2.4)

Data of control subjects group are expressed in means and standard deviation

SCA Spinocerebellar ataxia, *FRDA* Friedriech Ataxia, *ND* non-diagnosed, *AT* Ataxia Teleangectasia, *PM* Raven's 47 (progressive matrices), *HS* healthy subjects

gait ataxia, and ocular movements). According to the inclusion criteria, the absence of any extracerebellar abnormalities was investigated by an expert neuroradiologist and performed by visual inspection of brain magnetic resonance imaging scans (MRI—including Spin-Echo, T1- and T2-weighted images) obtained from each patient as part of this research study using a system operated at 1.5 T (Siemens, Magnetom Vision, Erlangen, Germany).

The patients' cognitive profile was evaluated by a battery of tests (Table 2), including WAIS-R total intelligence quotient values (TIQ), immediate (IR) and delayed (DR) recall of Rey's 15 words (Rey 1958), immediate visual memory (IVM; Carlesimo et al. 1996), forward (FDS) and backward digit span (BDS), forward (FC) and backward (BC) Corsi Test (Corsi 1972), Raven's 47 progressive matrices (PM; Raven 1949), freehand copying of drawings (CD; Gainotti et al. 1977), temporal rules induction (Villa et al. 1990), and word fluency (WF; Borkowsky et al. 1967).

Experimental procedures were approved by the ethical committee of the IRCCS Santa Lucia Foundation (CE-PROG.2-AG4-187); written consent for anonymous use of clinical data was obtained from each subject.

Apparatus and task

Visual stimuli were presented to participants, seating in a dimly lit room with their eyes 45 cm from a PC monitor (CRT noninterlaced, refresh rate 85 Hz, 1024 × 768 resolution), using the psychtoolbox software (psychtoolbox.org). A joystick was fixed to the table and aligned to the body midline of participants. Data from the joystick were acquired by a USB port and interpreted by MATLAB-based routines (see also Brunamonti et al. 2011a, b, 2014; Mione et al. 2015 for similar approaches).

Participants performed two types of task (Fig. 1) using the right or left arm in separated blocks. In the Go only task (GOT), participants moved the joystick (leftward or rightward) in response to a directional Go signal (*go trials;* 12 × 12 pixels left/right oriented arrow) appearing after a fixation cue. The joystick movements were transformed in voltage values ranging from −10 mV (leftmost bar position) to +10 mV (rightmost bar position). We defined as central starting position of the joystick, all the voltage values within the interval from −2 mV to +2 mV. Each movement of the joystick providing voltage values lower than −2 mV or higher than +2 mV was taken as leftward or rightward movement onset, respectively. In the countermanding task (CMT), subjects responded to the Go signal (*go trials*), as in the GOT, but withheld the movement when, in 25% of the overall trials (*stop trials*), a Stop signal (200 × 200 pixels red square) was presented after delays of variable duration (stop signal delay; SSD). In the CMT, correctly cancelled ($stop_{correct}$) and not cancelled ($stop_{error}$) *stop trials* were detected. In the *go trials*, if the RT exceeded 1s, the trial was aborted and the subject received an acoustic error feedback. Successfully performed *go trials* were signaled using a different acoustic feedback. An acoustic stimulus also sounded when the RT exceeded 500 ms, as a warning for the participant to respect the primary task's demand of responding as quickly as possible. The initial SSD was always 17 ms (1 unit of refresh rate) on each CMT block (as in Brunamonti et al. 2014). To adapt the SSD duration to subject performance, we used a staircase algorithm (Brunamonti et al. 2012, 2014)

Table 2 Neuropsychological assessment

Patients	TESTs									
	IR	DR	IVM	WF	CD	FDS	BDS	FC	BC	TIQ WAIS-R
CA1	37.8	5.7	14.2	25.8	4.8	4	4	4.8	4.6	79
CA2	29.1	8.1	13	25	**7**	4	4	4	4	95
CA3	31.4	9.2	19.4	29.3	**7**	7	5	6	4.6	77
CA4	38.2	10	21	22.3	11.4	6	5	6	6	104
CA5	53.8	12.1	19.6	24.9	7.2	5.2	4.6	5	6	84
CA6	42.8	10.1	17.6	16.5	8.2	4	6	5	5	87
CA7	33.9	9.2	18.2	36.4	10.6	7	4	5	5	102
CA8	37.2	11.9	20.2	32.5	3.9	5.2	4.6	5	4	83
CA9	38.2	10	18.8	17.3	8.7	5	3	5	4	81
CA10	39.8	14.3	21.2	9.8	7.8	5.2	4.6	4	4	88
Cutoff	28.53	4.69	13.85	17.35	7.18	7 ± 2	5 ± 2	7 ± 2	5 ± 2	70

Mean values (standard deviation)

IR Rey's 15 mots short term (immediate recall), *DR* Rey's 15 mots long term (delayed recall), *IVM* immediate visual memory, *WF* word fluency, *CD* copying drawings, *FDS* forward digit span, *BDS* backward digit span, *FC* forward Corsi, *BC* backward Corsi, *PM* progressive matrices, *TIQ WAIS—R* Wechsler adult intelligence scale revised. Scores below the cutoff are marked in bold

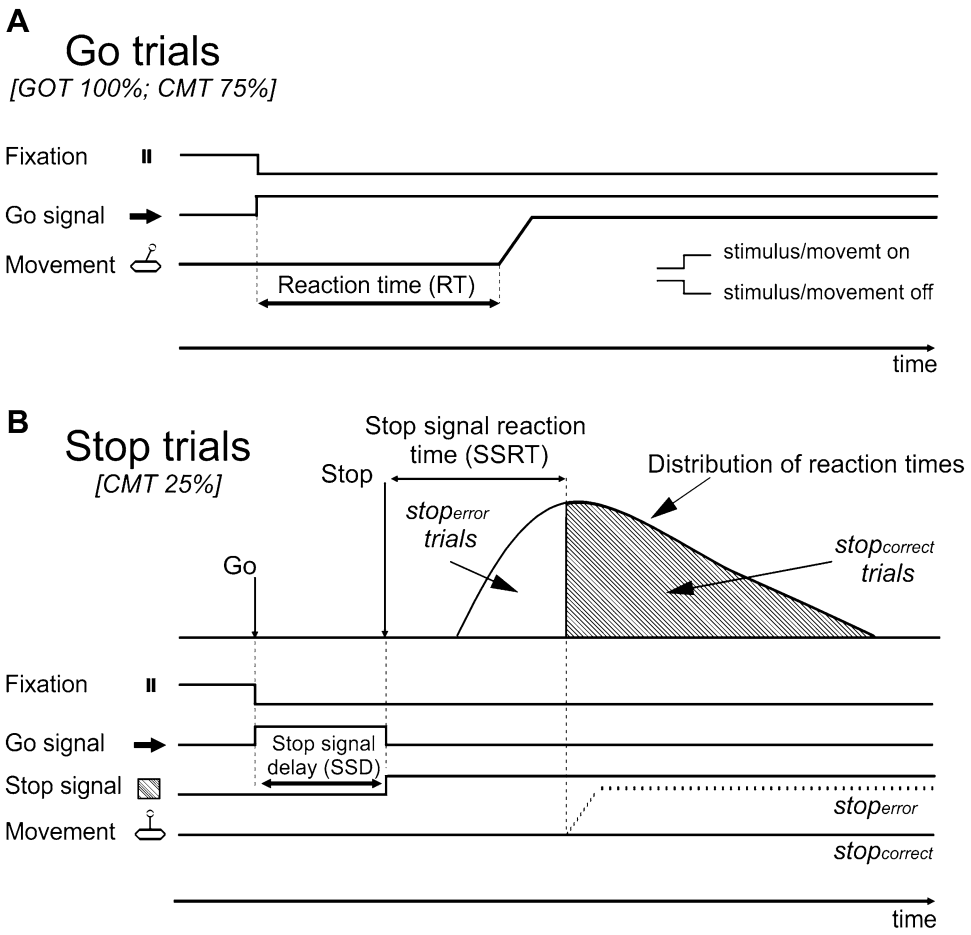

Fig. 1 Experimental tasks and variables. **a** Time evolution of *go trials* events. After a fixation/holding period (800–1200 ms), a directional Go signal (*leftward/rightward oriented arrow*) replaced the fixation stimulus (*double vertical parallel lines*) at the center of the screen, cuing the participants to move the joystick toward the direction indicated. This behavior was required in the totality of trials of the Go only task (GOT) and in 75% of trials of the countermanding task (CMT). **b** Time evolution of *stop trials* events. In 25% of the CMT trials, at variable intervals from the presentation of the Go signal (stop signal delay; SSD), a *red square* (shown as a grey square in the figure) Stop signal replaced the *oriented arrow* instructing the participant to hold joystick in the resting position. Using the integration method, the reaction time to the Stop signal (stop signal reaction time; SSRT) for a given SSD was estimated as the point in time that divided the proportion of the *go trials* reaction times sufficiently fast to avoid the stop process, and corresponding to the proportion of error trials ($stop_{error}$ *trials*; empty portion in the reaction time distribution), from the longer reaction times putatively influenced by the stopping process ($stop_{correct}$ *trials*; striped portion in the reaction time distribution)

increasing by 50 ms the SSD after each $stop_{correct}$ trial and decreasing by 50 ms the SSD after two consecutive $stop_{error}$ trials. We adopted this tracking algorithm to rapidly obtain SSD values with oscillations (Levitt 1970; see below) having decided to start each block from the easy (short) SSD values.

Each participant performed two sessions of six blocks with the right and left arms, respectively. Each session included 5 blocks of CMT (80 trials each) and 1 block of GOT (60 trials each). The order in which the arms were used was counterbalanced across subjects, and the GOT always preceded the CMT for each arm. A resting period (2 min) between blocks was allowed.

Data analysis

We investigated RT differences among *go trials* in the GOT and *go trials* in CMT paradigms. To this aim, we analyzed changes in both the RT average and variability (RT_{var}; estimated as standard deviation) for all subjects.

We used two methods to estimate the time needed to cancel a commanded movement in response to the Stop signal (SSRT). The first method of estimate was the widely used integration method (Logan 1994). Shortly, for all blocks of CMT *go trials* and for the same arm, we first obtained a representative SSD. To compute the representative SSD, we tracked the oscillations of the single

SSDs presented by the staircase procedure to capture the value at which the oscillation of the SSDs inverted its trend (i.e., the upwards and downwards peaks of the SSD fluctuation; Levitt 1970). The average value of the upwards and downwards peaks, calculated on the SSDs occurred at least 10 times across the sessions, has been taken as representative SSD (Brunamonti et al. 2014; Mirabella et al. 2006). This value was used to compute the $SSRT_{integration}$ by integrating CMT *go trials* RT distribution until the integral equals the observed proportion of $stop_{error}$ *trials* for the estimated representative SSD (integration method; Logan 1994; Fig. 1b). As a second method of estimate of the SSRT ($SSRT_{Bayesian}$), we used a Bayesian model approach that accounts for the failing in triggering the stop process (Matzke et al. 2013). Here, we used all SSD values, including early SSDs to maximize the validity of the estimated value (see Matzke et al. 2017).

To evaluate the efficiency of the proactive control, i.e., the effect of the previous trial in the performance, we computed post-$stop_{error}$ slowing (*PostE*) and post-$stop_{correct}$ slowing (*PostC*). The *PostC* and the *PostE* values were calculated first by finding in the data set triplets of *go-stop*$_{correct}$-*go* and *go-stop*$_{error}$-*go trials* and then by subtracting from the RT measured in the *go trials* following the *stop*$_{correct}$ or the *stop*$_{erros}$ *trials*, the RT of the *go trials* preceding them (Dutilh et al. 2012; Mione et al. 2015; Montanari et al. 2017; Nelson et al. 2010). This procedure excluded the contamination of the global fluctuations of the RT over the course of the test on the estimate of the post-*stop trial* RT (Nelson et al. 2010). We also computed the *Post-Go* effect by looking at the RT difference obtained by subtracting the RT in the first and last positions of the triplets *go–go–go*.

Finally, for each participant, the performance in stopping movements at each SSD [*Inhibition function: probability of* $stop_{error}$ − $p(stop_{error})$*—for each SSD*] was normalized by computing the z-score relative finish time (*ZRFT*) by subtracting the SSD and the SSRT from the mean RT in the *go trials* and dividing this difference by the standard deviation of the *go trials* RTs. The slope of the linear portion of the normalized inhibition function (i.e., the part of the inhibition function ranging from 15 to 85% of $stop_{error}$ *trials*) is normally used as a further measure of the inhibitory control. A steeper slope should indicate a better inhibitory control (including less variability in the stop process and stop trigger failure; Band et al. 2003). Multifactorial analysis of variance (ANOVA) was used to test significance in the RT and SSRT comparisons between pathological and control groups (or tasks and arm used). Analysis of covariance (ANCOVA) was used to examine differences in the slope of the linear portion [$0.15 < p(stop_{error}) < 0.85$] of the ZRFT function between groups (Zar 2009).

Estimates of $SSRT_{integration}$ and post-*stop trials* slowing for each participant were obtained by ad-hoc scripts implemented in Matlab (www.mathworks.com). The Bayesian estimate of SSRT was obtained by the BEESTS software (Matzke et al. 2013), available at http://dora.erbe-matzke.com/software.html. Between-groups multifactorial ANOVAs were performed by the statistical package Statistica (www.statsoft.com).

Results

We performed a two-way ANOVA (Arm x Group) statistical test between the stopping accuracy of patients and controls and detected that the average probability of success [$p(stop_{correct})$], as determined by the adaptive SSD algorithm, in patients was significantly higher than in healthy subjects (CA: $p(stop_{correct}) = 0.50$; HS: $p(stop_{correct}) = 0.43$; main effect Group: $F(1,30) = 5.48$; $p = 0.03$). No significant differences for the two arms ($F(1,30) = 0.017$; $p = 0.90$) or significant interactions were detected ($F(1,30) = 0.34$; $p = 0.56$). A very low proportion of omitted *go trials* (number of omitted *go trials*/total number of *go trials*) was detected in both experimental groups [average proportion of omissions of CA: 0.017 (0.032); average omissions rate of HS: 0.0016 (0.003)]. The proportion of omitted *go trials* did not differ between groups (Mann–Whitney U Test: $p = 0.16$), suggesting that on average, the individuals of both groups were approaching the task using comparable strategies.

Neuropsychological assessment

The neuropsychological assessment revealed the presence of selective and very slight impairments in some patients but did not show clear evidence of general cognitive impairment. Indeed, some patients displayed values below the cutoff in copy drawings (CA1, CA2, CA3, and CA8) and in word fluency tests (CA6, CA9, and CA10) (see Table 2). These results are consistent with findings that patients who are affected by cerebellar damage do not present with intellectual deterioration (Tedesco et al. 2011). Indeed, mostly standard norms of testing do not detect cognitive impairments in cerebellar cohorts, because cerebellar patients' symptoms are present in selective domains and, very often, they can be detected only when the patients are compared to matched healthy controls.

Go process duration was impaired in patients affected by cerebellar atrophy

Preliminarily, to obtain a reliable estimate of the variables playing a role in the race, we assessed that the participants

complied the prediction of the race model (Logan 1994). To this end, we controlled across participants of each group that the mean $stop_{error}$ RT was significantly lower than the mean *go trials* RT (CA: mean $stop_{error}$ RT = 579 ± 114); mean *go trials* RT = 621 ± 98); paired *t* test: t (1,9) = 2.26; p = 0.018); HS: mean $stop_{error}$ *RT* = 422 ± 38; mean *go trials RT* = 456 ± 40; paired *t* test: t (1, 21) = 2.08; $p < 0.001$). We also controlled for an increase of the $stop_{error}$ RT with SSD duration. Across participants of each group, a regression analysis detected a significant linear increase of the $stop_{error}$ RT with the SSD (CA: $stop_{error}$ *RT* = 0.79 * *SSD* + 367; $F(1,71) = 42.15$; $p < 0.001$; $R^2 = 0.4$; HS: $stop_{error}$ *RT* = 0.74 * *SSD* + 267; $R^2 = 0.6$; $F(1,151) = 226.48$; $p < 0.001$).

A three-way ANOVA (factors: Task, Group, Arm) showed that the RT of patients was significantly longer compared to HS (Group: F (1, 30) = 51.47, $p < 0.001$), and that the RT in the CMT (RT_{CMT}) was longer than RT in the GOT (RT_{GOT}) in both groups (Task: F (1, 30) = 20.93, $p < 0.001$). However, no difference between arms emerged (Arm: $F(1,30) = 1.55$, $p = 0.22$). No significant effect between variables interactions [Task and Group: $F(1,30) = 2.60$, $p = 0.12$; Task and Arm: $F(1,30) = 1.88$, $p = 0.18$; Group and Arm: $F(1,30) = 0.04$, $p = 0.85$; Task and Group and Arm: $F(1,30) = 0.82$; $p = 0.37$] was detected.

Similarly, a three-way ANOVA (factors: Task, Group, Arm) showed that the RT variability (RT_{var}) was higher both in the CMT than in the GOT (Task: $F(1,30) = 6.68$, $p = 0.015$) and in the group of patients than in the group of controls (Group: $F(1,30) = 11.9$, $p = 0.002$). No difference between arms emerged (Arm: $F(1,30) = 1.27$, $p = 0.27$) in this measure. No significant interactions between Task and Group: $F(1,30) = 1.47$, $p = 0.23$; Task and Arm: $F(1,30) = 1.66$, $p = 0.29$; Group and Arm: $F(1,30) = 0.18$, $p = 0.68$; Task and Group and Arm: $F(1,30) = 0.01$; $p = 0.91$, were detected. Figure 2 shows relevant values for RT and RT_{var} after pulling together data from the two arms. Further details are reported in Table 3.

In the analysis of trial sequences (Fig. 3), a three-way ANOVA (factors: Trial type, Group, Arm) revealed that the post-$stop_{error}$ trials slowing (*PostE*) was significantly longer than the post-$stop_{correct}$ trials slowing (*PostC*) and that both these indexes were significantly higher than the RT of a *go trial* following another *go trial* (*PostGo*) (main effect Trial type: $F(2,58) = 32.70$; $p < 0.001$). *PostGo*, *PostE,* and *PostC* RT changes did not significantly differ between arms (main effect Arm: $F(1,29) = 0.30$; $p = 0.59$). Furthermore, a significant main effect between groups (main effect Group: ($F(1,29) = 7.12$; $p = 0.012$) and interaction between groups and Trial type ($F(2,58) = 3.39$; $p = 0.040$) were detected. Tukey HSD post hoc comparisons revealed that *PostE* RT slowing was longer in CA than HS ($p = 0.04$). *PostGo* and *PostC* did not significantly differ between groups ($ps > 0.05$). Significant interactions between Group and Arm ($F(1,29) = 0.60$; $p = 0.44$), Group and Arm ($F(1,29) = 0.60$; $p = 0.44$) or Group, Trial type, and Arm ($F(2,58) = 2.34$; $p = 0.10$) were not detected. One patient (CA 2; Table 1) was excluded from this analysis due to the outlier values of *PostC* and *PostE* that fell below the first quartile of the distribution.

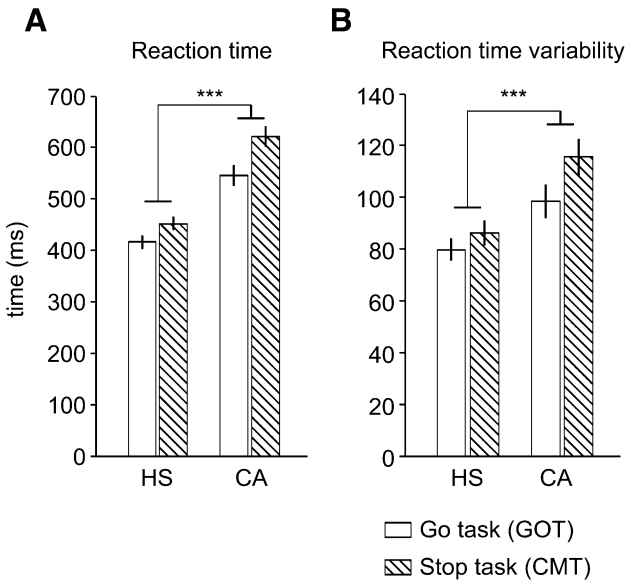

Fig. 2 Reaction time duration and variability in *go trials*. **a** RT of *go trials* in GOT (Go only task; empty) and CMT (countermanding/stop task; striped). **b** RT variability; convention and symbols as in **a**. Data for left and right arms are pooled together. *Vertical bars* indicate SEM. Significance between main groups is indicated (***$p < 0.0001$). The significance between tasks' main effects is not shown

We explored the relationship between RT_{var} in the CMT block and all effects analyzed for the trial sequence. Interestingly, the only factor that significantly correlated (Spearman's correlation) with the RT_{var} was the *PostE* slowing [RT_{var}—*PostGo*: $R = -0.3$ ($p = 0.1$); RT_{var}—*PostC*: $R = 0.34$ ($p = 0.18$); RT_{var}—*PostE*: $R = 0.54$ ($p = 0.002$)], suggesting that RT variability is mainly determined by the changes in RT duration after errors.

Stop process duration was impaired in patients affected by cerebellar atrophy

When looking at the duration of the stop process (Fig. 4), a two-way ANOVA (factors: Group and Arm) revealed that the SSRT of CA patients was significantly longer than the SSRT of HS (Group: $F(1,30) = 26.5$, $p < 0.001$). No significant difference between arms was observed (Arm: $F(1,30) = 1.95$, $p = 0.17$) (Table 3). The interaction between Group and Arm variables was not significant

Table 3 Across groups mean values (standard deviation)

Estimate	Non-dominant hand mean (SD)	Dominant hand mean (SD)
HS		
RT-GOT	418 (44)	412 (54)
RT-CMT	457 (49)	446 (37)
RT_{var}-GOT	85 (25)	75 (31)
RT_{var}-CMT	88 (25)	84 (24)
Representative SSD	421 (95)	209 (87)
$SSRT_{integration}$	311 (14)	299 (12)
$SSRT_{Bayesian}$	299 (14)	287 (12)
PostGo slowing	−7 (12)	−5 (6)
PostC slowing	13 (31)	22 (21)
PostE slowing	42 (41)	42 (52)
CA		
RT-GOT	546 (104)	546 (104)
RT-CMT	632 (109)	610 (88)
RT_{var}-GOT	102 (24)	94 (34)
RT_{var}-CMT	115 (25)	116 (22)
Representative SSD	311 (48)	156 (47)
$SSRT_{integration}$	421 (21)	408 (17)
$SSRT_{Bayesian}$	429 (15)	419 (17)
PostGo slowing	−10 (12)	−10 (9)
PostC slowing	43 (47)	32 (48)
PostE slowing	69 (53)	99 (49)

RT-GOT and RT_{var}-GOT: mean reaction time and standard deviation at *go trials* in the Go only paradigm; RT-CMT and RT_{var}-CMT mean reaction time and standard deviation at *go trials* in the countermanding task; Representative SSD: estimated SSD by tracking the single SSD fluctuations; $SSRT_{integration}$ and $SSRT_{Bayesian}$ estimates of the stop signal reaction time using the integration and the Bayesian method, respectively; *PostGo* slowing, *PostC* slowing, and *PostE* slowing: average reaction times in the *go trials* following *go trials*, $stop_{correct}$ *trials*, and $stop_{error}$ *trials*, respectively (for further details, see "Methods")

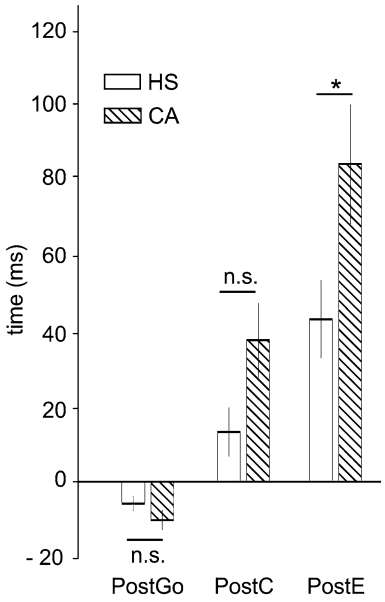

Fig. 3 Analysis of trial sequences. RT changes after *go trials* (*PostGo*), $stop_{correct}$ trials (*PostC*) and $stop_{error}$ trials (*PostE*) in patients with atrophic cerebellum (CA) and controls (HS). Data for left and right arms are pooled together. *Vertical bars* indicate SEM. Significance between trial type main effects is indicated (***$p < 0.05$)

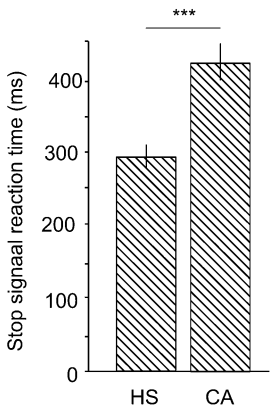

Fig. 4 SSRT in patients with CA and controls. Data for left and right arms are pooled together. Significance between groups' main effects is indicated (***$p < 0.0001$). *Vertical bars* indicate SEM

($F(1,30) = 0.005$, $p = 0.94$). The finding that the SSRT of CA was longer than HS was confirmed by the statistical analysis on the $SSRT_{Bayesian}$. $SSRT_{Bayesian}$ of AC was higher than HS [main effect of Group: $F(1,30) = 21.4$, $p < 0.001$]. Similar to $SSRT_{integration}$, neither a significant main effect of the Arm factor [$F(1,30) = 2.03$, $p = 0.16$] nor that of the interaction between Group and Arm [$F(1,30) = 0.023$, $p = 0.88$] was detected on the duration of $SSRT_{Bayesian}$.

Conversely, the ANCOVA analysis (factors: Slope of inhibition function, Group) revealed that the normalized inhibition function (ZRFT) was comparable between groups. In fact, while both groups displayed a significant linear trend (i.e., a slope significantly different than zero) of their performance in function of the duration of the SSD (factor slope: $F(1,259) = 354.2$, $p < 0.001$), neither the slope of the two groups differed (factor Group: $F(1,259) = 0.28$, $p = 0.28$), nor the average slope of the patients (slope = 0.20) differed significantly from HS (slope = 0.16; interaction between slope of inhibition function and Group: $F(1,259) = 2.68$; $p = 0.10$).

Finally, we explored the relationship between motor scores (MS) and the duration of go (RT) and stop processes (SSRT). Interestingly, no significant correlation emerged between motor scale and behavioral measures, indicating that motor impairment of patients, as measured by the modified version of the cerebellar motor deficit scale, did not influence the performance of patients neither in the RT duration, nor in the inhibition function as measured by Spearman's correlation coefficient [MS-RT_{GOT}: $R = -0.10$ ($p = 0.76$); MS-RT_{CMT}: $R = 0.14$ ($p = 0.68$); MS-SSRT: $R = 0.41$ ($p = 0.23$); MS-*PostGo*: $R = 0.27$ ($p = 0.48$);

MS-*PostC*: $R = -0.35$ ($p = 0.36$); MS-*PostE*: $R = -0.3$ ($p = 0.44$)].

Overall, CA patients showed a slower Go process than HS in the GOT and CMT, accompanied by a significant increase of RT variability to the *go trials*. The analysis of trial history showed that CA patients had a significant increased RT slowing after errors in canceling Stop signals when compared to HS. Finally, our analysis revealed that patients experienced slowing in the SSRT, although the other available measure of inhibitory control, as estimated by ZRFT regression line slope, did not differ from controls.

Discussion

We observed that an extended damage of the cerebellar network, as in cerebellar atrophy, severely impaired the readiness to react to the Stop signal (significantly longer SSRT). However, the length of SSRT was not accompanied by the impairment of the other commonly used measure of inhibition ability, since the slope of ZRFT was comparable between CA and HS. Neither, CA patients showed higher percent of errors than HS participants overall *stop trials*. On the contrary, here, we observed a significantly better performance ($stop_{\text{correct}}$) of CA in *stop trials*, likely due to the tracking algorithm adopted to select the SSD duration (see "Methods") and to the way we organized *stop trials* in each block. In fact, on every experimental CMT block, the SSD was reseted at the minimum value of 17 ms. If, from one side, this approach allowed us to present more frequently to participants *stop trials* with short SSD to try to capture possible failures in triggering the stop process (Matzke et al. 2013, 2017), from the other side, it favored the performance of the CA individuals with longer RTs than HS subjects.

Even though we designed the blocks procedure to obtain growing inhibition functions from each participant, it is worth noticing that the reliability of the slope of ZRFT as a measure of efficiency of movement inhibition could be polluted by the between-group and within-group variability in RT. Therefore, evaluation of inhibitory performance by ZRFT slope should be considered less informative than SSRT (Band et al. 2003). Similarly, the ZRFT slope is unable to discriminate between SSRT variability and trigger failures (Band et al. 2003).

Cerebellar role in motor decision

Our previous results in a group of patients with focal lesions of the cerebellum (Brunamonti et al. 2014) suggested that the cerebellum could play a role in motor inhibition within the framework of the countermanding task thanks either to the connections with prefrontal cortex, via the thalamic relay, or to the connection with the basal ganglia, including both direct and indirect pathways (Bostan et al. 2013; Middleton and Strick 2001). Among the subcortical regions in the basal ganglia, the subthalamic nucleus (STN) is able to act as a gate for the inhibitory control of the internal segment of the globus pallidus (GPi) over the thalamic drive (Aron and Poldrack 2006; Aron et al. 2009). The STN is also directly connected to pontine nuclei influencing both the cerebellar cortex and deep cerebellar nuclei (DCN). The output of the cerebellum, in turn, could influence the 'indirect' pathway by specifically targeting striatal neurons that connect to the external portion of the globus pallidus (GPe) (Alexander and Crutcher 1990; Mink 1996; Nambu et al. 2002). As a consequence, in our previous report, we proposed that cerebellum receives a copy of the cortically originated signal to suppress the movement via the STN (Aron and Poldrack 2006; Bostan et al. 2010, 2013; Brunamonti et al. 2014) and contributes to executive control by modulating the tonic inhibition that is exerted by the cerebellar cortex on the DCN. The results of this process are relayed back to the basal ganglia through the indirect pathway, influencing the basal ganglia inhibitory action. However, in patients with focal cerebellar lesions, we observed a change in the ability to monitor and adjust their current motor behavior as the consequence of the Stop signal appearance and/or error in the previous trial. Instead, a clear effect in the velocity to respond to the Stop signal presentation (SSRT) was not detected. We reported that patients with focal lesions displayed a shallower slope of ZRFT (Brunamonti et al. 2014) suggesting a higher variability in triggering the stop process. However, see comments above about the validity of the ZRFT (see also Band et al. 2003) on the evaluation of the inhibitory performance.

Here, in AC patients, we observed a clear effect on the duration of the SSRT. Considering that the performances of patients affected by degenerative pathology are different from those of patients affected by focal cerebellar lesion, it has to be taken into account the diffuse involvement of the cerebellar cortex in cerebellar degenerative diseases. Indeed, within the cerebellar cortex, information ultimately converges on Purkinje neurons that are the central computational integrators of the cerebellar system (Chopra and Shakkottai 2014). Projections from Purkinje neurons are channeled through the neurons of the DCN and represent the sole output of the cerebellar cortex. It is through the DCN that the cerebellum communicates with the rest of nervous system with extensive excitatory connections. Purkinje neurons exhibit autonomous high-frequency repetitive spiking (Raman and Bean 1999), a property often referred to as pacemaking. It has been evidenced that abnormal pacemaking is linked to Purkinje neuron atrophy and cell death. As a consequence, normal pacemaking in Purkinje neurons plays a critical trophic function

that is disrupted in cerebellar atrophies, and particularly some types of spinocerebellar ataxias, including SCA1 and SCA2 (Chopra and Shakkottai 2014). When Purkinje cells are underfunctioning, their defective inhibitory control on DCN leads to an increase of excitatory output to all target regions, including cortical areas and striatal neurons. Thus, powerful activation of Purkinje cells is necessary to terminate the unwanted component of the action (Swenson 2006) by suppressing the DCN neurons. In light of these observations, we speculate that the major involvement of cerebellar cortex in the presence of cerebellar degeneration, as opposed to focal lesions, fully alters the control on inhibition exerted by the interplay among cerebellar cortex, DCN, and basal ganglia.

In analyzing the present results, it has to be considered that the different etiology of cerebellar atrophy makes our cohort of patients quite heterogeneous. In spite of this heterogeneity, a prevalent involvement of Purkinje cells has been demonstrated in some cerebellar spinocerebellar atrophies, such as type 1 and 2 (Chopra and Shakkottai 2014) that are prevalent in our sample. However, our findings should be complemented by future studied with a more selected population of cerebellar atrophies.

Cerebellar role in the proactive control of behavior

Post-error slowing, as well as post-*stop trial* slowing in general, could be taken as behavioral adjustments occurring after a deviation from expectancy and, thus, to be related to unexpected novel events (Notebaert et al. 2009). In the behavioral context of the countermanding task, designed to study the efficiency of self-control, post-error slowing occurs, because each error is signalling that the go process is deviating from the average speed value of the subject.

One influential hypothesis concerning cerebellar processing in non-motor domains centers on the idea that the cerebellum enables online prediction of immediately upcoming events and generates estimates of future states, by implementing *internal models* that allow to anticipate predictable events and consequently modify behavior when these predictions are violated (Ghajar and Ivry 2009; Ivry and Spencer 2004; Leggio and Molinari 2015; Moberget et al. 2016; Molinari et al. 2009; Sokolov et al. 2017). For example, several studies revealed that the cerebellum contributes to the decoding of errors and to the consequent behavioral adaptation in both cognitive and motor domains (Blakemore et al. 2001; Doya 2000; Molinari et al. 2008, 2009). In the results of Ide and Li (2011), the cerebellum emerges as an important structure strongly modulated after error experience in the countermanding task, in cooperation with the ventrolateral PFC, and the thalamus (Li et al. 2008). Thus, together with PFC, anterior cingulate cortices, basal ganglia, and supplementary motor areas, the cerebellum is part of a distributed network contributing to the elaboration of errors as '*deviations from what expected*' and, in general, performance monitoring (Aron et al. 2004; Chevrier and Schachar 2010; Marcos et al. 2013; Peterburs et al. 2015).

In a previous work, it has been observed that cerebellar patients with focal damage involving the DCN display an excessive compensation to errors, corresponding to an increased post-error slowing (Brunamonti et al. 2014). This provides evidence that cerebellar patients may experience difficulties in predicting the occurrence, and calibrating the consequence, of future events and, therefore, not be able to properly prepare their behavior. The observation supports the hypothesis that the cerebellum collaborates to the evaluation and internalization of the statistics of recent events for decision making (Ma and Yu 2015).

Here, we aimed at evaluating whether the same ability was impaired even in patients affected by a diffuse cerebellar degeneration. We observed that the ability of evaluate the local and global effects of the Stop signal appearance in the sequence was spared in AC, as indicated by a normal lengthening of the RT in the CMT when compared to the RT in the GOT and by the lack of effect on the *go trials* after $stop_{\text{correct}}$ trials. This last result suggests that AC patients have a preserved function on monitoring novelty in the countermanding task (Notebaert et al. 2009). Conversely, the detection of longer post-$stop_{\text{error}}$ slowing of AC patient is in line with the hypothesis that patients suffering of cerebellar diseases lack of an adequate proactive inhibitory control. We, therefore, conclude that, when DCN are lesioned (Brunamonti et al. 2014) or are under reduced control by the cerebellar cortex, as a consequence of the degenerative process, the internal models used to control, adapt, estimate, and monitor the consequences of rapidly executed movements (Wolpert et al. 1998) are not functionally integrated anymore in the control network formed by the basal ganglia–thalamus–cortical loops (Prevosto and Sommer 2013).

In conclusion, the present study provides further evidence of the cerebellum role in motor execution and inhibition in a sample of patients affected by degenerative cerebellar atrophy, in which the Purkinje cells are more selectively affected. Specifically, our results have shown impaired actions inhibition. We propose that the defective inhibitory control on DCN, due to Purkinje cells degeneration, deteriorates the appropriate output, necessary to inhibit unwanted activity in the deep nuclei. All in all, we advance the hypothesis that the behavioral deficits observed are the consequence of a distributed alteration of the network formed by cortico-subcortical areas interacting for the executive control of movement generation.

Additional investigations including different clinical group with extracerebellar lesion could provide further support to our conclusions.

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