RESEARCH ARTICLE

Temporal disruption of upper-limb anticipatory postural adjustments in cerebellar ataxic patients

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Abstract Voluntary movements induce postural perturbations, which are counteracted by anticipatory postural adjustments (APAs) that preserve body equilibrium. Little is known about the neural structures generating APAs, but several studies suggested a role of sensory–motor areas, basal ganglia, supplementary motor area and thalamus. However, the role of the cerebellum still remains an open question. The aim of this present paper is to shed further light on the role of cerebellum in APAs organization. Thus, APAs that stabilize the arm when the index finger is briskly flexed were recorded in 13 ataxic subjects (seven sporadic cases, four dominant ataxia type III and two autosomal recessive), presenting a slowly progressive cerebellar syndrome with four-limb dysmetria, and compared with those obtained in 13 healthy subjects. The pattern of postural activity was similar in the two groups [excitation in triceps and inhibition in biceps and anterior deltoid (AD)], but apparent modifications in timing were observed in all ataxic subjects in which, on average, triceps brachii excitation lagged the onset of the prime mover flexor digitorum superficialis by about 27 ms and biceps and AD inhibition were almost synchronous to it. Instead, in normal subjects, triceps onset was synchronous to the prime mover and biceps and AD anticipated it by about 40 ms. The observed disruption of the intra-limb APA organization confirms that the cerebellum is involved in APA control and, considering cerebellar subjects as a model of dysmetria, also supports the view that a proper APA chain may play a crucial role in refining movement metria.

Keywords APA · Ataxia · Cerebellum · Motor control · Human

Introduction

It is well known that a voluntary movement induces reactive forces that are discharged on various body segments. In movements involving large masses, these forces may cause a whole-body equilibrium disturbance (Bouisset and Zattara 1987; Bouisset and Do 2008; see also Hess 1943) which is counteracted by *inter-limb* anticipatory postural adjustments (APAs) (see also Massion 1992). More recently, it has been demonstrated that an accurate stabilization of the segments is performed also in motor tasks which do not involve the whole-body equilibrium. Indeed, Caronni and Cavallari (2009) reported that an *intra-limb* APA chain develops in several upper-limb muscles also when simply flexing the index finger. In this case, the prime mover flexor digitorum superficialis (FDS) is clearly preceded by a major postural inhibitory activity in biceps brachii (BB) and anterior deltoid (AD) and by an excitatory burst in triceps brachii (TB). Such *intra-limb* APAs would not only guarantee the maintenance of the arm posture but are also very important in controlling the trajectory and the final position of the moving segment, i.e., *metria*.

Studies regarding the neural structures generating the APA command are surprisingly rare. Severe APA impairments in patients with Parkinson's disease suggested a role of the basal ganglia in the anticipatory postural control (Viallet et al. 1987). Similar APA impairments were also

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observed in patients with a lesion of the primary motor cortex (M1) or of the supplementary motor area (SMA) (Viallet et al. 1992). With regard to pre-movement brain activity associated with APAs in healthy subjects, a functional MRI study by Schmitz et al. (2005) reported that APAs were associated with activation of sensorimotor areas, SMA and the cerebellum, while a magnetoencephalographic study by Ng et al. (2012) found anticipatory brain activity in basal ganglia, SMA and thalamus. It is apparent that the neural network generating APAs is still debated and, from the scarcely available data, it is particularly challenging to describe the functional role of each structure taking part in the anticipatory postural control.

For this reason, we thought interesting to shed further light on the involvement of the cerebellum in the APAs generation, also because it is known that the cerebellar circuitries play a major role in controlling the movement metria. Indeed, considering that the cerebellum controls rate, smoothness and coordination of the voluntary movement (Manto 2006; Morton and Bastian 2007) and that APAs and voluntary movement are part of a unique motor command (Bolzoni et al. 2012; Bruttini et al. 2014), it should be expected that cerebellum, especially in its role in distributing and temporizing the motor command, contributes in organizing APAs and, accordingly, also in refining movement metria.

Thus, we analyzed the well-known intra-limb APA chain that stabilizes the arm when the index finger is briskly flexed (Caronni and Cavallari 2009) in a group of ataxic subjects affected by a slowly progressive cerebellar degeneration, as well as in an equal number of healthy subjects. In fact, considering cerebellar subjects as a model of dysmetria, a disruption of the intra-limb APA organization would (1) prove the cerebellum involvement in APA control and (2) support the view that a proper APA chain may play a crucial role in refining movement metria (as proposed by Caronni and Cavallari 2009).

Methods

Thirteen adult subjects with cerebellar ataxia (ATAXIA) were analyzed in this study. All subjects gave written consent to the procedure, after being informed about the nature of the experiments. The local ethical committee approved the procedure in accordance with the 1964 Declaration of Helsinki.

All ATAXIA subjects (age 48.5 years ± 13.0 SD, six females) suffered from a slowly progressive adult-onset cerebellar syndrome, without any other involvement of the sensory and motor systems. Seven cases were sporadic and four had a positive family history for autosomal dominant cerebellar ataxia type III (Fujioka et al. 2013) and two for autosomal recessive ataxia. Mean age at onset

was 23.2 ± 12.4 years. All subjects presented gait ataxia, four-limb dysmetria, mild dysarthria and occasionally mild increase in deep tendon reflexes, without spasticity. Cognition was normal. Neurophysiological evaluations showed normal sensory and motor conduction velocities and no signs of axonal neuropathy. Scale for the Assessment and Rating of Ataxia (SARA; Schmitz-Hübsch et al. 2006) was applied in all subjects. All patients were ambulatory; the mean total SARA score was 8.0 (range 3–20, median 6.0). The SARA scores measuring upper-limb dysmetria ranged from 0.5 to 2 in all cases.

Brain 1.5-T MRIs imaging showed mild-to-severe cerebellar atrophy, mainly affecting the cerebellar vermis, in all subjects. In the majority of the cases, a mild atrophy of the cerebellar hemispheres was also visible. Cerebral cortex, basal ganglia, pons, medulla and cerebral white matter showed no focal lesions or pathological signal intensity changes.

Experimental procedure

The experimental arrangement has been fully described in a previous paper (Caronni and Cavallari 2009). ATAXIA subjects sat on a chair with both arms along the body, elbow flexed at 90°, hand prone in axis with the forearm and the index finger extended. All subjects involved in the experiment were tested on the dominant limb. The index finger was kept in contact with a proximity switch (Pepperl and Fuchs, CJ10-30GK-E2), so that the metacarpophalangeal joint angle was about 180°, all other fingers hanging. Subjects were explicitly asked to keep their back supported, the upper-limb still and both feet on the ground throughout the experiment. The chair was height adjustable and the proximity switch screwed on an articulated arm (Manfrotto 143 MAGIC ARM® + 035 Superclamp Kit®); both were adapted to the different body dimensions of the subjects. The subject position was always visually controlled by the experimenter. Subjects were asked to flex their index finger at the metacarpophalangeal joint so as to gently tap and rest on a flat surface.

Each movement was self-paced and performed after an acoustic signal delivered every 7 s. Subjects were instructed to wait for the acoustic go-signal and then flex the finger at will, within 4 s. This procedure was adopted to exclude any reaction time. In each experiment, index finger flexion was performed 45 times. Subjects never complained about fatigue.

Given the well-known bradykinesia of cerebellar subjects, recordings in ATAXIA subjects were matched to those in an equal number of healthy subjects (CTRL), selected within our database, who performed the brisk finger flexion with a comparable speed. Mean speed (±SE) was 420 ± 34°/s for CTRL and 412 ± 43°/s for ATAXIA; the unpaired t test with common variance estimate led to

$t_{24} = 0.14$, $P = 0.9$. Levene's test showed no difference in the variances of movement speed ($F_{1,24} = 0.53$, $P = 0.47$).

Movement and EMG recordings

The onsets of the fingertips movement were monitored by the proximity switch. Flexion–extension of right metacarpophalangeal joint was recorded by a strain-gauge goniometer (mod. F35, Biometrics Ltd®, Newport, UK), taped to the joint. Angular displacement was DC amplified (P122, Grass Technologies®, West Warwick, RI, USA), and gain was calibrated before each experimental sequence. Pairs of pregelled surface electrodes, 24 mm apart (H124SG, Kendall ARBO, Tyco Healthcare, Neustadt/Donau, Germany), were used to record the EMG signal from the right FDS, the prime mover, and from some of the ipsilateral postural muscles: BB, TB and AD. A good selectivity of the EMG recordings was achieved both by careful positioning of the electrodes and by checking that activity from the recorded muscle, during its phasic contraction, was not contaminated by signals from other sources. The EMG was amplified (IP511, Grass Technologies®, West Warwick, RI, USA; gain 2–10 k) and band-pass filtered (30–1,000 Hz, to minimize both movement artefacts and high-frequency noise). Goniometric and EMG signals were A/D converted at 2 kHz with 12-bit resolution (PCI-6024E, National Instruments®, Austin, TX, USA), visualized online and stored for further analysis.

Data analysis

On each sequence, the 45 EMG traces of the prime mover and those simultaneously recorded from the postural muscles were digitally rectified and integrated (time constant: 25 ms).

The onset of FDS activity was detected by a software threshold set at ± 2 SD of the mean reference signal level, calculated from 1,000 to 500 ms prior to the movement onset. Traces collected from each muscle were then averaged in the temporal window from 1,000 ms before to 300 ms after FDS onset. Latency of the postural activity was measured off-line on the averaged traces by using the same criteria applied to FDS and visually validated.

The latency variances of APAs and movement were compared between ATAXIA and CTRL groups by means of Levene's test. Mean latency values were compared by unpaired t tests with separate variance estimates. Statistical significance was set at $P < 0.05$.

Results

In the representative CTRL subject illustrated in Fig. 1, the FDS muscle activation was (1) preceded by clear inhibitory postural adjustments in BB and AD muscles and (2) almost synchronous to the excitatory postural adjustment in TB; this APA pattern preceded index finger flexion of about 100 ms. Instead, in the ATAXIA subject, APAs maintained their pattern but were clearly delayed: In AD, APA was almost synchronous to the prime mover, while in BB and TB APAs were so delayed that they even lagged the index finger flexion.

The behavior of individual CTRL and ATAXIA subjects is shown in Fig. 2. Despite comparable movement latencies, ATAXIA subjects overall showed a clearly delayed pattern of postural adjustments; indeed, APAs often lagged the FDS and, in some cases, occurred close to the movement onset. Moreover, some ATAXIA subjects lacked inhibitory APAs. In fact two of them did not show APAs in both BB and AD, two lacked APA in BB only and other two lacked it solely in AD. No case of APAs reversal, from inhibitory to excitatory or vice versa, was observed. It is also apparent from the same figure a higher variability in TB and BB APAs latencies in the ATAXIA group. Levene's test found significant ATAXIA versus CTRL differences of latency variability in TB and BB ($F_{1,24} = 4.67$, $P = 0.04$; $F_{1,20} = 8.13$, $P = 0.01$, respectively) but not in AD, nor for movement ($F_{1,20} = 0.04$, $P = 0.84$; $F_{1,24} = 1.39$, $P = 0.25$, respectively).

Mean latency for APAs and movement in the two groups are plotted in the lowermost panel of Fig. 2. Despite movement latency was at all similar in the two groups ($t_{21.78} = 1.06$, $P = 0.3$), excitatory APA in TB was almost synchronous to FDS in CTRL while it lagged FDS of about 27 ms in ATAXIA subjects. Inhibitory APAs in BB and AD, which led the FDS of about 40 ms in CTRL, were almost synchronous to FDS in ATAXIA subjects. In each muscle, APA latency in ATAXIA was significantly different from that observed in CTRL ($t_{17.07} = 2.26$, $P = 0.037$; $t_{10.81} = 3.53$, $P = 0.005$ and $t_{15.03} = 4.45$, $P < 0.001$, for TB, BB and AD, respectively). No significant correlation between changes in APA timing and SARA score was found.

Discussion

When performing a brisk index finger flexion, ATAXIA subjects showed a timing disruption of *intra-limb* APAs, while their pattern (excitation in TB; inhibition in BB and AD) was unmodified. Since APAs are known to be scaled in amplitude and latency according to the speed of the motor action (Horak et al. 1984; Shiratori and Aruin 2007), the speed effect was excluded by matching ATAXIA to CTRL subjects who displayed comparable speeds. Moreover, the similarity of speed variability grants that the significant difference found in the variability of APA latency stems from the cerebellar dysfunction.
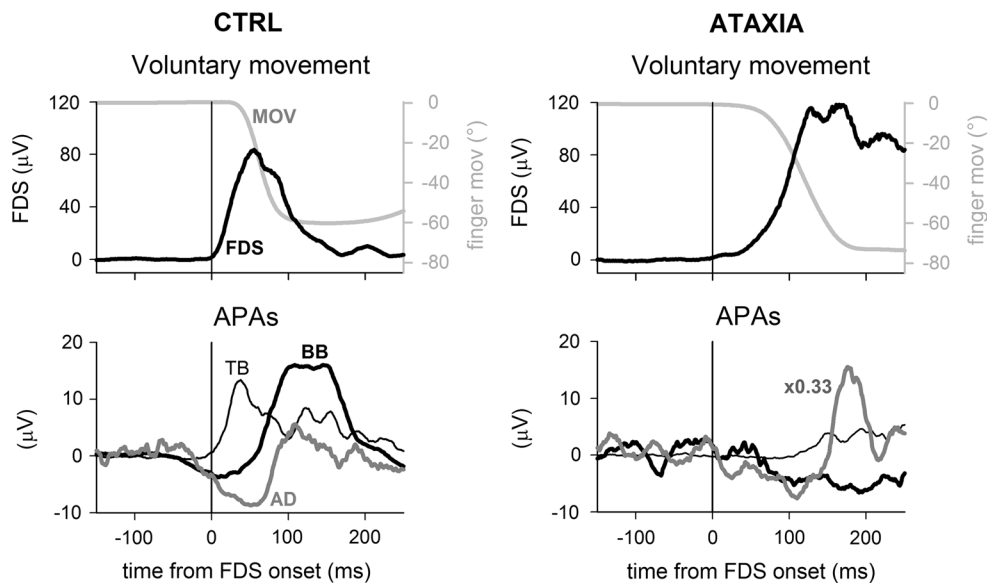
CTRL

Voluntary movement

APAs

ATAXIA

Voluntary movement

APAs

Fig. 1 Changes in intra-limb APAs latencies in cerebellar subjects. Recordings from one representative subject of the healthy group (CTRL) are compared to recordings of a cerebellar subject (ATAXIA). Note that in the healthy subject the prime mover activation is preceded by inhibitory APAs in biceps brachii (BB) and anterior deltoid (AD) and by an excitatory APA in triceps brachii (TB). In the cerebellar patient, a various degree of disruption in APAs timing and a delayed finger flexion are observed. In each subject, *top panel* shows the activation of the prime mover flexor digitorum superficialis (FDS), matched to the ensuing finger flexion (MOV); *bottom panel* illustrates the APAs in elbow and shoulder muscles. Mean reference signal level has been subtracted from each EMG trace. AD amplitude in ATAXIA has been scaled by a factor 3

Altogether, these data sustain the hypothesis that the cerebellum is essential in tailoring the timing of APAs with respect to prime mover activation, and open the question whether the cerebellar dysmetria may stem from an erroneous timing of APAs.

Role of cerebellum in APA control

The cerebellum is fundamental for controlling rate, smoothness and coordination of voluntary movement (Manto 2006; Ramnani 2006; Morton and Bastian 2007) as well as in preparation, initiation and timing of motor acts (Ivry and Keele 1989; Ivry 1997; Timmann et al. 1999; Cerri et al. 2005; D'Angelo 2010). Cerebellar damage appears to disrupt different movement features, generally ascribed to an altered timing–scaling and amplitude–scaling of agonist and antagonist activity (e.g., Brown et al. 1990; Manto et al. 1994; Flament and Hore 1986). Cerebellum may predictively scale recruitment of different muscles in relation to the mechanical demands (Bastian et al. 1996; Massaquoi and Hallett 1996; Topka et al. 1998), and thus, ataxia should be more pronounced in those movements requiring coordination of many muscles (Thach et al. 1992). One of the typical signs observed in cerebellar patients is dysmetria, i.e., the inability to properly reach a given target. Cerebellar dysmetria occurs both proximally and distally in upper and lower limbs and affects single-joint as well as multi-joint movements (Blouin et al. 2004; Ullén et al. 2003).

As stated in the introduction, the role of cerebellum in APA control is instead an open question. Indeed, Mummel et al. (1998) reported normal APAs in patients with cerebellar pathology, and also Timmann and Horak (2001) found that the temporal parameters of APSs were preserved in cerebellar subjects performing unperturbed steps. However, several other studies positively concluded for a cerebellum role in APAs control. Indeed, patients with cerebellar lesions fail to show a normal anticipatory adjustment in grip force when lifting or moving an object (Müller and Dichgans 1994; Babin-Ratté et al. 1999). Moreover, Davidson and Wolpert (2005) suggested a stronger role of feedforward internal models versus sensory feedback in several aspects of human motor control. The cerebellum is one of the most likely site for storing forward models (Kawato et al. 2003, see also Bastian 2006). Finally, Asaka and Wang (2011) found that cerebellar ataxic patients showed altered feed-forward muscle synergies and multi-mode coordination when compared to healthy subjects, witnessing a disorganization of feed-forward muscular control.

Our data agree with the above conclusions, in particular supporting that the cerebellum plays a crucial role in setting the temporal distribution of APAs while not affecting the APA pattern. On the other hand, delayed APAs during finger flexion seem to contrast with the anticipation of APAs

Fig. 2 Comparison of the APA chain in healthy and in cerebellar ▶ subjects. Latencies of finger flexion (MOV) and APA onsets in TB, BB and AD are plotted with respect to onset of FDS. Each single subject is represented. *Dashed line marks* the average movement latency for either group of subjects. Note that in ATAXIA APAs are delayed and absent in four cases (marked with an X). The lowermost panel shows mean latency (±SE) of the onset of finger flexion and APAs. *Asterisks* mark significant differences found by unpaired *t* test

found by Diedrichsen et al. (2005) in the bimanual barman task. However, Diedrichsen interpreted the premature APAs in cerebellar subjects as a safety strategy to avoid a violent elbow flexion when unloading the hand; such strategy is clearly useless in our finger flexion task; hence, there is no need to anticipate APAs.

Instead, the delayed APAs described in the present study conform to those described by Yamaura et al. (2013), in transgenic spinocerebellar ataxic mice which had to reach and drink from a flask while standing. Different from the wild type, ataxic mices activated hindlimb postural muscles markedly later than neck prime movers, i.e., they showed delayed APAs.

A last remark regards the significantly larger inter-subject variability in APAs timing observed in ATAXIA versus CTRL subjects. This finding agrees with previous literature (Diener et al. 1992; Diedrichsen et al. 2005; Asaka and Wang 2011) and may be due to a different clinical expression of the cerebellar degeneration.

APAs and metria

It has been suggested that APAs may play a crucial role in controlling the finger final position during a brisk flexion. Indeed, indirect evidences showed that the absence of APAs may induce a dysmetria movement (Caronni and Cavallari 2009). Symmetrically, when inducing dysmetria in healthy subjects by means of prismatic lenses, the APA pattern was altered, without changes in prime mover recruitment (Caronni et al. 2013).

Considering our recent suggestion that APAs and prime mover activation are part of a unique motor command (Bruttini et al. 2014), one should expect that APAs are present also in dysmetria movements, most probably altered in timing and/or pattern. Actually, ATAXIA subjects, clinically classified as dysmetria, showed a temporal disruption in the intra-limb APAs without involvement of the prime mover recruitment. This also agrees with the finding of Bastian et al. (2000), who studied cerebellar subjects performing elbow flexion, with or without shoulder fixation. They showed that cerebellar subjects were dysmetria without shoulder fixation and became 'metric' with it. The
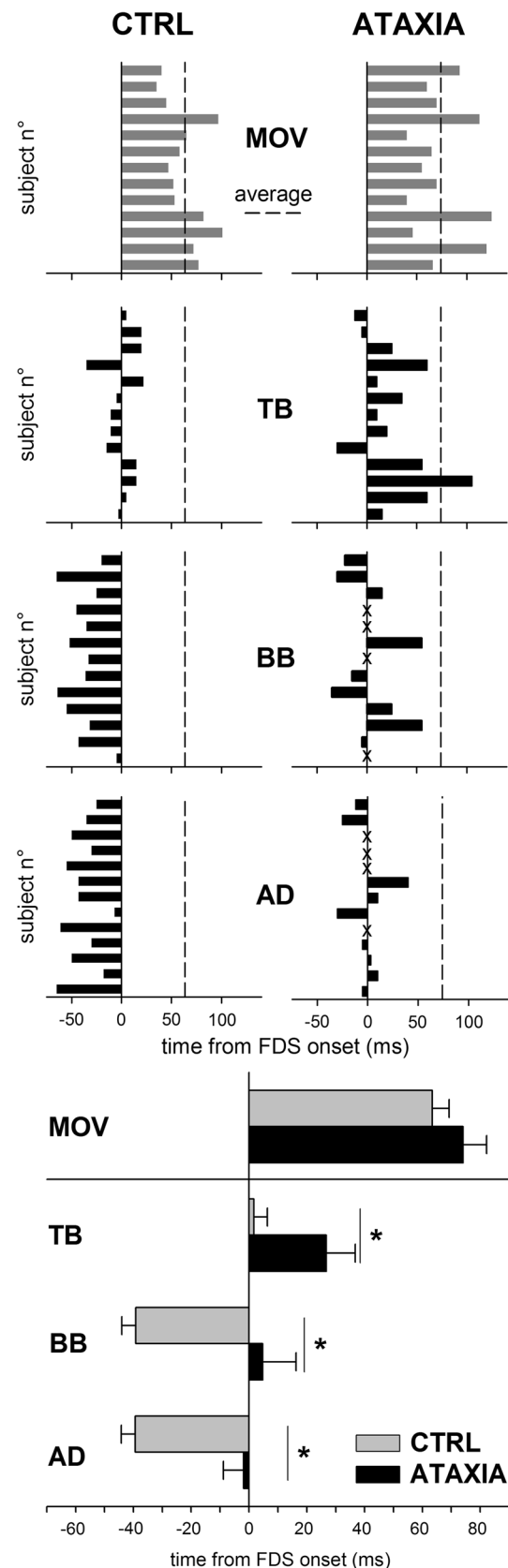
impairment in active shoulder stabilization by interaction torques, shown by the authors, may be seen as an impairment of APAs in proximal muscles.

Conclusion

The present data confirm the hypothesis that the cerebellum is involved in controlling APAs timing with respect to the prime mover activation and also support the view that a proper APA chain may play a crucial role in refining movement metria.

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