The Oneness of Posture and Voluntary Movement

are APAs and prime mover recruitment parts of the same motor program?

Carlo Bruttini

UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

DOTTORATO DI RICERCA IN FISIOLOGIA

Dottorando: dott. CARLO BRUTTINI

Matricola: R09680

Tutor: prof. Paolo Cavallari

Coordinatore: prof. Michele Mazzanti

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Summary

Forewords

During my PhD studies, I have dealt with several aspects of the relationship between posture and voluntary movement. In particular, the main subject of my work has been to analyze the functional role of the Anticipatory Postural Adjustments (APAs) within the motor act and how these are programmed by the central nervous system.

In the past literature, it has been described that APAs are unconscious muscular activities aimed to maintain the equilibrium of the whole body (Massion 1992). The role of the APAs has been first disclosed in movements involving relatively large masses, such as an upper-limb flexion (see for a review, Bouisset and Do 2008). In this case, the shoulder flexion may displace the projection of the center of mass to ground, eventually causing an imbalance of the whole body. Therefore, in order to counteract such a perturbation, the recruitment of the prime mover (Anterior Deltoid) is normally preceded by a specific pattern of EMG activities, defined as APAs, developing in the lower limbs, the hips and the trunk. This inter-limb APA chain is thus able to induce a forward displacement which prevents the backward perturbation caused by the focal movement.

More recently, Caronni and Cavallari (2009a) demonstrated that an APA chain also develop for very simple movements such as a finger flexion, in which small masses are involved and in which the whole-body equilibrium is not threatened. Indeed, the index-finger flexion, performed with the hand prone, has been found being preceded by an excitatory burst in Triceps Brachii, while Biceps Brachii and Anterior Deltoid showed a concomitant inhibition. This APA pattern, shaped in the primary motor cortex (Caronni and Cavallari 2009b), contrasts the flexion of elbow and shoulder induced by the upward perturbation that the index-finger flexion causes on the metacarpo-phalangeal joint.

Caronni and Cavallari papers (2009a, b) contributed to arise three questions: i) do inter-limb and intra-limb APAs share similar control mechanisms? If yes, ii) what

is the functional role of intra-limb APAs, since it is hard to keep considering intra-limb APAs simply as a counter-perturbation aiming to maintain the whole-body equilibrium and iii) does the prime mover recruitment and its associated postural adjustments result from two different central commands, as classically proposed (Babinski 1899; Hess 1943; Cordo and Nashner 1982; Brown and Frank 1987) or are they both controlled by a unique motor command, as suggested by more recent evidences (Aruin and Latash 1995; Petersen et al. 2009; Caronni and Cavallari 2009b; Leonard et al. 2011)?

Aim of the present thesis is to shed further light on these questions with the specific target of investigating a possible role of APAs in refining movement accuracy and demonstrating the oneness of the motor command for both anticipatory postural adjustments (APAs) and prime mover recruitment. Thus, I will illustrate: i) the key role of a properly-tailored APA chain on prime mover recruitment in refining movement accuracy, ii) the superposition of the neural network responsible for controlling the voluntary movement and the APAs, focusing on Supplementary Motor Area and Cerebellum, iii) the disruption of both the postural chain and the prime mover recruitment after a period of immobilization and iv) the APAs adaptation to the intended movement, i.e. the expected perturbation. These observations have been already published or are at this moment submitted to publication.

The thesis has been divided in four sections: 1) the Introduction, which includes a review on the existing literature on inter- and intra-limb APAs, and explains my working hypothesis; 2) the Experimental Procedure, which describes how data were collected and analyzed.; 3) the collection of the original papers, and finally 4) the Conclusion, in which I will explain the interpretation of the present results and develop possible conclusions, with special regards on the relationship between postural and prime mover command[1].

[1] The experimental work has been performed at the Human Physiology Section of the DePT

Posture and Voluntary Movement

When we perform a voluntary movement our CNS has to deal with different variables to perform a correct action, for example: 1) what is the goal of our movement, 2) which are the muscles that have to be recruited to achieve the goal, 3) what is the functional state of the body (e.g., in equilibrium or in unstable posture) and 4) which is the environmental context in which we are acting and which are the available fixation points. From the success of this analysis, and the appropriateness of the solutions stems the correct movement outcome.

Since the human body is a multi-link structure of different rigid segments interacting each other in an articulated chain, every mechanical action on any of these body segments is discharged to the adjacent articulated segment. In other words, if a muscular contraction provokes a joint movement, for instance an upper limb flexion, the rest of the body tends to move in the opposite direction. In the period between movement on-set and off-set, this articulated chain is in state of transient disequilibrium.

Therefore, a correct execution of a voluntary movement needs postural adjustments able to counterbalance, at the appropriate time, the perturbation induced by the primary movement on adjacent segments, and then discharged on all segments constituting the postural chain (cfr. Bouisset et Zattara, 1981; Massion 1992).

Historical background of posture and voluntary movement

To the best of my knowledge, the first to describe the rules that governs postural and voluntary movement controls was Leonardo Da Vinci, in his "*Libro A, Trattato della Pittura*", which is now conserved within the *Codex Urbinas Latinus 1270* (1r-329r: Leonardo da Vinci, 1452-1519, lib. I-VIII. sec. XVI, Biblioteca Apostolica Vaticana). Leonardo stated: "*I say that if a motionless figure is poised on his feet, and his arm is extended in front of the chest, he will throw backward as much natural*

weight as the natural and accidental weight which he thrusts forward. And I say the same of each part that projects more than usual beyond the whole". Moreover, Leonardo continued: "*Never will a weight be lifted and carried by a man, without his extending outside himself more than as much weight as that which he wishes to lift, and he thrust it on the side opposite the one where he lifts the weight*". A couple of centuries later, Giovanni Alfonso Borrelli followed the pathway of Leonardo Da Vinci in his *De Motu Animalium,* where he described some principles that govern the voluntary movement. In particular, Borelli considered the skeleton as multi-linked system of levers, which can maintain *per se* the body balance as far as the center of mass falls within the support base.

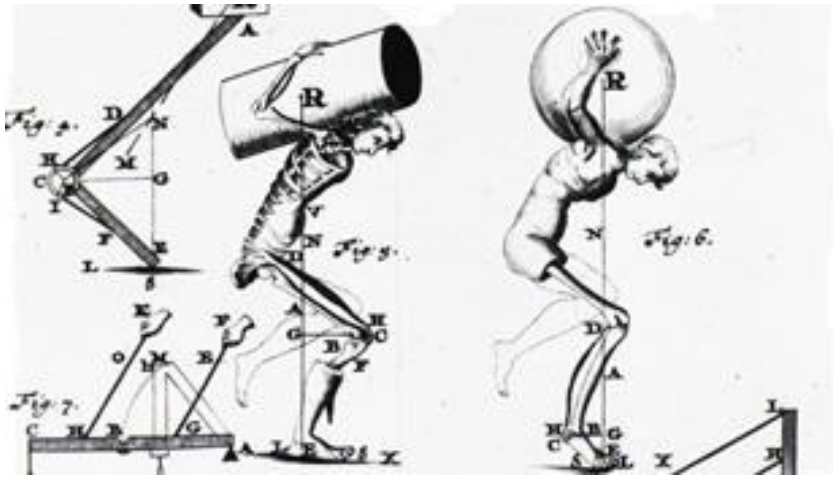

Figure 1. Historical artwork of two humans bearing loads. This illustration is taken from De Motu Animalium (On Animal Motion, 1680) by Alfonso Borelli (1608-1679). The illustration demonstrates how the leg is a twin-lever system controlled by muscles in which the hip (D) and knee (C) are both pivots.

After the observation of Leonardo da Vinci and Borelli, we had to wait until the end of the nineteenth century for having the first clinical observation of the importance of a correct tailoring of posture and voluntary movement in order to correctly execute a successful motor act. Indeed, Joseph Babinski (1857-1932), in his "*De l'asynergie cérebelleuse,* 1899", was the first who described the lack of harmonious synergies in cerebellar patients; in particular he observed the forward

displacement of the knees and hips to compensate for the backward displacement of the trunk, neck and head when asking a subject to look upward. Babinski also observed that cerebellar patients, who were asked to perform the same "*looking upward*" task, were unable to coordinate the upper part of the body to their hip and lower limb, so that they were used to fall. However, Babinski did not analyze the temporal relationship between the postural adjustments and the voluntary movement, and therefore he lacked to observe that also an anticipatory postural control, adjusted in a feed-forward manner, is needed when performing a voluntary movement.

In the twentieth century all studies about the relationship between posture and voluntary movement, as described by Stuart 2005 (*Integration of posture and movement: Contributions of Sherrington, Hess, and Bernstein*), stands on the shoulders of three giants, who were trained in several countries and in different fields. In particular, Charles Sherrington (1857–1952) was more in favor of the idea of a dual coordinated control system: one for movement, and the other for posture. This idea was in agreement with the proposals of Walter Hess (1881–1973), who held the view that without anticipation of postural adaptations (a component of his ereismatic-supporting function system), goal-directed movements were doomed to failure. On the other hand, the Russian scientist Nikolai Bernstein (1896–1966) was the first to propose a unique motor command for both posture and voluntary movement, even if

Nikolai Aleksandrovic Bernstein

his ideas were not know to the western scientist till recently. Indeed, despite Bernstein received a Stalin Prize Award in 1948, his papers and books were translated into English only several years after his death. Bernstein was in favor of the idea of a hierarchical control of both posture and movement stating "*movements are not chains of details but structures which are differentiated into details; they are structurally whole*'' (pg. 69, in Bernstein, 1967).

The organization of posture and movement control

The question of whether the single or the dual command theory should be preferred still remains open. According to the interpretation of Gelfand et al. (1971), motor control would include two different components: a "*primary or focal*" and a "*postural*" one. On these bases, the focal component is relative to the body segment(s) that are mobilized in order to perform a voluntary movement; instead, the postural component interests the rest of the body, which is involved in the reactions of stabilization. Following this idea, the prime mover activity and its associated postural adjustments result from two different central commands, which are independently dispatched to the prime mover and to the muscles generating the postural chain, respectively (Babinski 1899; Cordo and Nasher 1982; Brown and Frank 1987). The division between a postural chain and a focal chain is a direct consequence of this hypothesis.

According to this idea, the scheme illustrated in Figure 3 shows how the motor programs would be transformed into physical parameters for the regulation of the movement from an internal model of body dynamics governed by the central nervous system. The motion parameters include the direction and magnitude of the primary movement (focal sets), the accompanying postural adjustments (postural set) and the temporal relationship between these events. The postural accompaniments may be absent, inappropriate or out of time, as it happens when we apprehend novel motor tasks, or in case of pathologic dysfunction of the CNS, e.g. cerebellar patients. The postural and focal "*sets*" lead to the selection of specific motor patterns that regulate muscle contraction and the following joints displacement, on one hand stabilizing

posture, and on the other to allow a correct execution of the movement. Proprioceptive, vestibular and visual information, are compared with an internal model of sensory dynamics in order to assess the select the pattern of muscular activities which permits a successful execution of the movement (Frank et Earl, 1990).

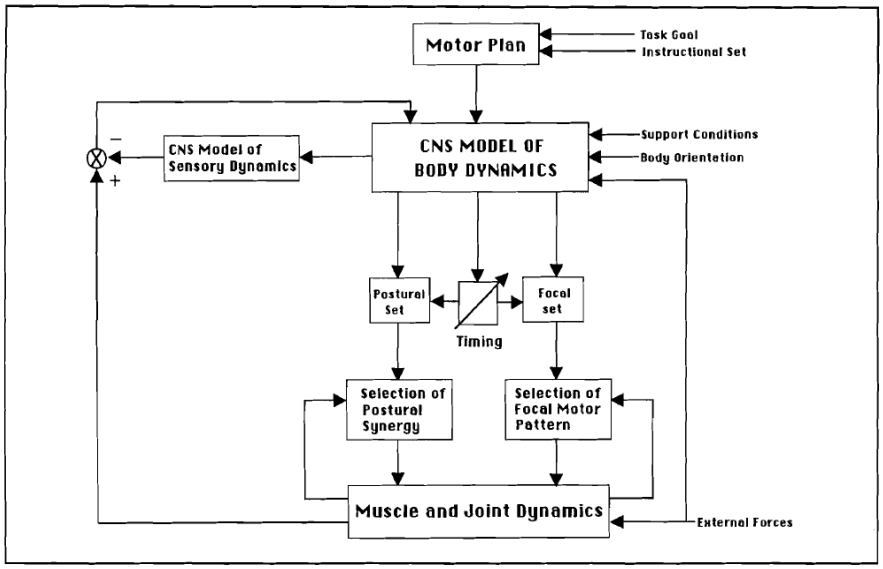

Figure 3. Coordination of the postural and focal sets. The central nervous system (CNS) model of body dynamics translates cognitive motor plans into physical parameters which allow the correct execution of the voluntary movement. Adapted from Brown and Frank, 1990.

Considering the temporal relationship between the development of the *focal* movement and the associated synergies, postural adjustments may be divided in three categories: Anticipatory Postural Adjustments (APAs), which precede the onset of the voluntary movement, Synchronous Postural Adjustments (SPAs) and Consecutive Postural Adjustments (CPAs), which develop after the movement initiation and therefore can be influenced by feed-back proprioceptive loops such as reflexes.

Anticipatory Postural Adjustments

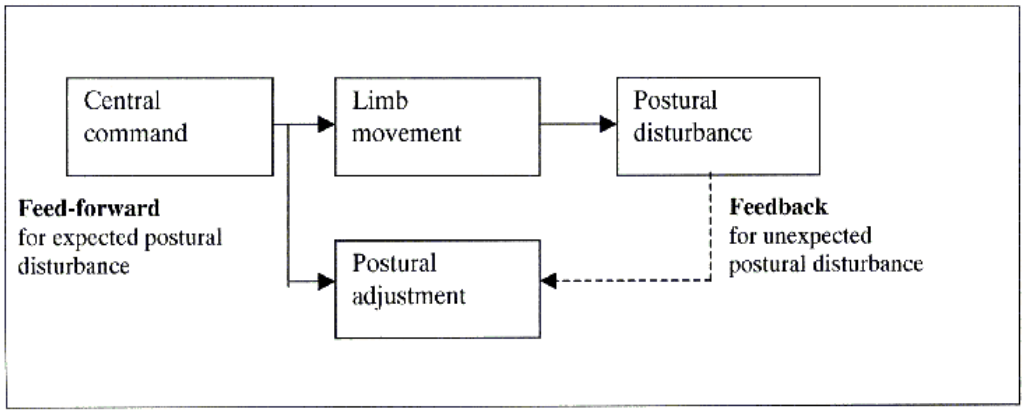

Figure 4. Feed-forward command for APAs and feed-back control of the outcome The Central Nervous System dispatch a fee-forward motor command to the postural muscles, Anticipatory Postural Adjustments, aiming to counteract the perturbation induced by the primary movement (limb movement). The postural disturbance following the movement act as a feed-back signal, which refine the Synergic Postural Adjustments (SPAs) and Consecutive Postural Adjustments (CPAs).

The majority of the literature regarding Anticipatory Postural Adjustments (APAs) analyzes the postural chain developing in the lower limbs, hips and trunk when performing a shoulder flexion. As we mentioned above, since this movement involve a relatively large mass, the perturbation induced by the primary movement may displaces the projection on the ground of the whole-body centre of mass (CoM; e.g. Bouisset and Zattara, 1987) and cause a whole-body equilibrium disturbance (Bouisset and Zattara, 1981; Bouisset and Do, 2008; see also Hess, 1943). Therefore, the prime mover activation is preceded by *inter-limb* anticipatory postural adjustments. When we consider a pointing movement, the recruitment of the prime mover, the Anterior Deltoid, would provoke an upper limb flexion but, contemporarily, a backward displacement of the shoulder, and thus could make the subject to miss the target or even to fall down. Recruitment of Anterior Deltoid is thus preceded by a specific pattern of EMG activities developing in the lower limbs and

trunk, the APA chain, which induce a forward displacement able to counteract the backward perturbation caused by the *primum movens segment.*

The APA chain starts with an inhibition of the tonically active ipsilateral Soleus, between 50 to 100 ms prior the prime mover onset. Then, there is a sequence of excitatory and inhibitory EMG activities, beginning with activation of the contra-lateral *Tensor Fasciae Latae* and *Rectus Femoris*. This APA pattern starts with the contralateral lower limb and hip, the ipsilateral ones, and ending with the ipsilateral shoulder, follows a bottom-up progression, as the postural segment accelerations follows a "*posture-focal gradient*", starting from the support base (ground, seat, etc…), proceeding through the postural chain and then terminating on the prime mover (Figure 5). As expressed by Gray: "*In order to subject the body to a propulsive force, it is necessary to exert an exactly equal but opposite force against his external environment. The reaction is equal to the subject's action (action and reaction principle)*". APAs are efficient in counteracting the perturbation induced by the voluntary movement only if the APA chain encounters resistance originating from the environment, usually a physical support (fixation point/s), which offers the appropriate reaction to the forces generated by APAs. Therefore, APAs could be considered as a fixation chain connecting the moving segment to a firm support (Baldissera et al. 2008), which follows a "*posture-focal gradient*", starting from the available support base (ground, seat, etc…), proceeding through the postural chain and then terminating on the prime mover (see for a Review Bouisset and Do, 2008).

The timing and magnitude of APAs are rapidly tailored according to the characteristics of the prime mover contraction, i.e. the expected intensity of the perturbation induced by the primary movement. Indeed, postural adjustments that develop at an inappropriate time or with incorrect amplitude, may themselves be a source of destabilization and thus be considered as a perturbation. Therefore, to ensure the effectiveness of these postural actions, the central nervous system requires information on the motor task to be performed and the likely interaction of the single body segments (Mille & Mouchnino 1998). The correct analysis of these information within the CNS predispose a correct direction, timing and magnitude of postural

adjustments that precede prime mover activation and therefore permits the correct execution of the voluntary movement (Frank et Earl , 1990; Dietz and Colombo, 1996).

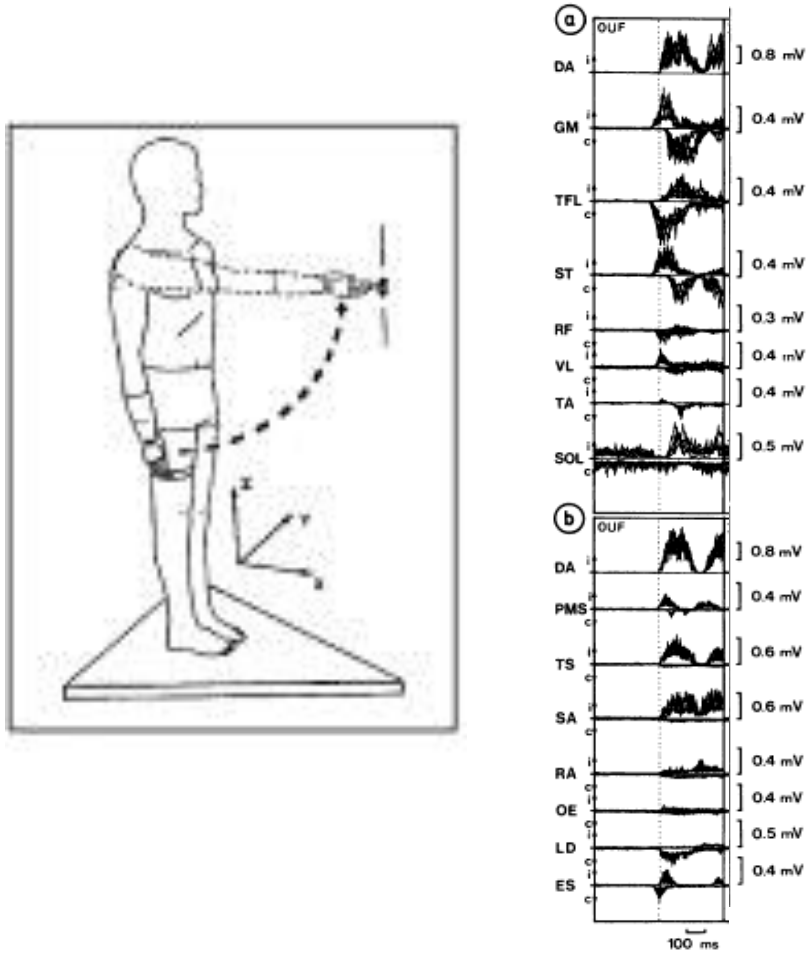

Figure 5. Anticipatory postural adjustments in lower limbs, hips and trunk before the execution of a shoulder flexion The prime mover activation (DA) is preceded by an inhibition in the tonically active Soleus (SOL) and by an increase of the EMG activity of the muscles which cross the hip joint: Tensor Fasciae Latae (TFL); Gluteus Maximus (GM), Semitendinosus (St). Other muscles, such as Vastus Lateralis (VL), Tibialis Anterior (TA) and Rectus Femoris (RF), showed occasionally anticipatory activity. Getting closer to the *primum movens segment* some of the muscles showed en EMG onset: syncronysed Trapezius Superior (TS), Serratus Anterior (SA), and Latissimus Dorsi (LD). Only two muscles showed an anticipatory postural EMG activity: Sternal portion of the pectoralis maior (PMS) and Erectro Spinae (ES) Adapted from Zattara and Bouisset, 1988-

It is worth noting that the temporal coupling between the primary movement and postural responses does not depend only on the physical requirements of the task. Indeed, when the voluntary movement is self-paced, APAs usually precede the EMG onset of prime mover by about 50-90 milliseconds (Horak et al., 1984). Instead, if the subject is instructed to perform the movement as fast as possible in response to an external signal (reaction time movement), the postural response occurs simultaneously with the focal response (Lee et al., 1987). These observations support the hypothesis that posture and movement are controlled by the nervous system independently, as originally proposed Babinski and subsequently endorsed by other researchers such as Brown and Frank (1987).

APAs classification

Considering the fundamental role of the fixation point as the pivot from which the APA chain starts, it is apparent that the distance between the available support base(s) and the *primum movens* segment imply the development of *inter-* or *intra-limb* APAs. As we have mentioned above, a pointing movement performed while standing would be preceded by an APA chain starting from the ground, with the EMG activities developing from the lower limbs according to the *posture-focal gradient*. Therefore, these muscular activities will create an *inter-limb* APA chain. Instead, when we perform a wrist flexion while sitting on a chair with a backrest, the fixation point would be placed at the shoulder level and the Flexor Carpi Radialis activation would be then preceded by an inhibition of the tonic EMG of the Braachioradialis (Br) coupled to the excitation of the Triceps Brachii (TB), i.e. an intra-limb APA chain.

The large majority of the studies regarding APAs were devoted to *inter-limb* APAs, while, at the moment, only a few description of intra-limb APAs have been performed. For this reason, we will first introduce the basic knowledge about the *inter-limb* APAs, then APAs preserving the whole body equilibrium in a bimanual coordination task and we will finally focus on the *intra-limb* APA chain, i.e. APAs developing in the same limb in which the voluntary movement is performed.

Inter-limb APAs – These are the most frequently studied APAs. For example, when we intend to perform a shoulder flexion and extension (Belenkii et al. 1967; Bouisset and Zattara 1981; Lee 1980; Lee et al 1987; Maki 1993), or lateral abduction (Aruin and Latash 1995; Vernazza et al. 1996), the CNS develop an anticipatory postural command for the muscles in the lower limb, hips and trunk. A variety of experimental situations in which the voluntary movement was preceded by an inter-limb APA chain has been also study studied. In some, it was asked to push or pull a handle with the upper limb in normal subjects (Cordo and Nashner 1982; Lee et al 1987), and in patients with Parknison disease (Dick et al 1986). In a paper of Nouillot et al. (1992), it was demonstrated that fast voluntary movements do not require APA when the postural equilibrium is unstable (unipedal stance). According to the interpretation of these results of Nouillot and collaborators, the absence of APAs when flexing the lower limb in unipedal stance, in contrast to the presence of APA in the more stable bipedal stance, suggests that the postural command and the voluntary one are organized in a parallel process. Inter-limb APAs are known to decrease in size as the accuracy demand increases (i.e. when pointing smaller and smaller targets), a feature which has been shown both in the upper-limb (Bonnetblanc et al. 2004) and in the lower-limb (Bertucco & Cesari 2010). Lower limb pointing was also investigated by Duarte and Latash (2007), who have shown that the faster the movement, the larger the APAs variability. It is also well described the relation between movement speed and scattering of the final position around a target (Fernandez & Bootsma 2004, Schmidt et al. 1979). In the other way round, all these observations suggest that small and less variable APAs should accompany slow, but precise movements. Berrigan and colleagues (2006) reported that when pointing is performed towards small targets (i.e. under high accuracy constraints) from an "unstable" position (i.e. standing vs. sitting), slowing movement speed actually represent a strategy to reduce the equilibrium disturbance and, consequently, the associate APAs. Moreover, other studies on inter-limb involved a whole body movement, such as locomotion (Breniere et al. 1987), in which there is a periodic support base transfer that corresponds to a succession of balance losses and recoveries. It should be noted that in both these last experiments the

differentiation between APAs and prime mover's activities is just artificial, since in both case APAs created necessary angular momentum of body segments for the effective task execution.

APAs in a bimanual task: the barman task - It is well known that APAs are associated with movement involving a bimanual load-lifting task, when participants hold an object in one hand and then lift it with the other hand. In such a task, as shown in Figure 6, the subject is asked to maintain a stable posture of the right forearm while a weight is applied to the omo-lateral wrist, a procedure that generates a tonic contraction of the right BB.

The observed motor behavior depend on whether the unloading is carried out actively and voluntarily by the same person (active lifting) or by the experimenter (passive lifting). In the first case, the prime mover activation on one hand is synchronous with an inhibition of BB when the forearm is voluntary unloaded (Hugon et al. 1982). The goal of such an anticipatory adjustment in this task is to minimize the perturbation of forearm posture that occurs during unloading, and thus avoiding an uncontrolled flexion of the elbow. The central organization of such a movement is based on two parallel commands (Massion 1992). Therefore, when self-unloading, a feed forward command is sent in order to preserve the upper limb posture. On the contrary, if the experimenter unexpectedly lifted the object, the inhibition of BB is still present, but starts only about 50 ms after the unloading. If we consider the position of the forearm, as shown in the same figure, the degrees of elbow rotation are lower when the subject unloads the forearm by using its own left hand.

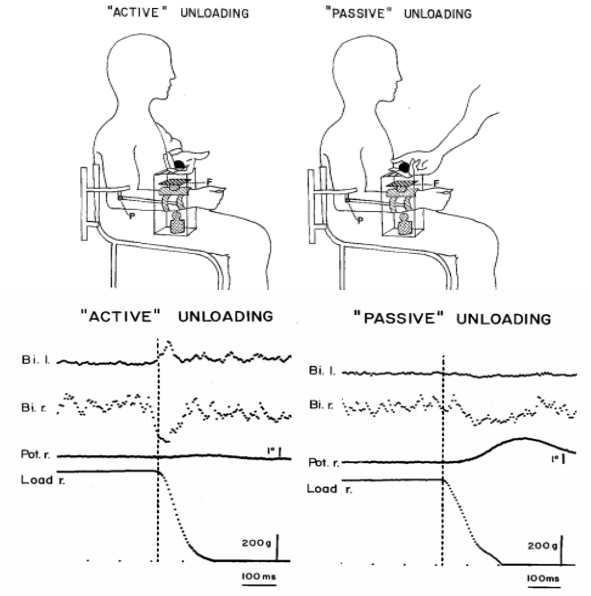

Figure 6. APAs in elbow flexor muscles precede a forearm self-unloading The subject maintains the posture of its right forearm while holding a weight applied at the wrist. When the forearm is self-unloaded (unload "active" on the left), the weight lift (indicated by the dotted line in the graph below) is preceded by an inhibitory APA in the tonically active right biceps brachii (Bi r). Note that the inhibition of the Bi r is synchronous recruitment of the left biceps brachii (Bi l, prime mover). If the weight is instead removed by the experimenter ("passive" unloading, on the right), Bi r inhibition begins approximately 50 ms after the weight removal. Traces related to the elbow angular displacement (Pot.r.) shows that the displacement of the forearm is minor in the self-unloaded (left trace). Adapted from Hugon et al., 1982.

Considering what has just been observed, the passive and unexpected removal of the weight involves an impaired balance for the body segment, and therefore constitutes a disturbance that can only be compensated with mechanism that implies a sensory feed-back of the unexpected perturbation. On the contrary, when the subject was able to actively unload its own forearm, a feed forward command is generated and APAs develop in the right Biceps Brachii. This mechanism of feed-forward has greater efficacy in the stabilization of balance. The described experiment, known as "*the barman task*" allows us to make two conclusions: First, even a movement that does not lead to a whole body imbalance is preceded by APAs, aimed at preserving the single segments balance; second, APAs may develop also in muscles that

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Intra-limb APAs - Aoki (1991) reported that wrist movement was preceded by anticipatory postural adjustments in muscles acting on the elbow. More recently, Caronni and Cavallari (2009a and 2009b) reported that also when the sole index-finger is flexed, an APA chain develops in several upper-limb muscles to stabilize the *segmental* equilibrium of the arm. Indeed, these authors described that a brisk finger flexion was preceded by an excitatory burst in Triceps Brachii (TB), while Biceps Brachii (BB) and Anterior Deltoid (AD) showed a concomitant inhibition.

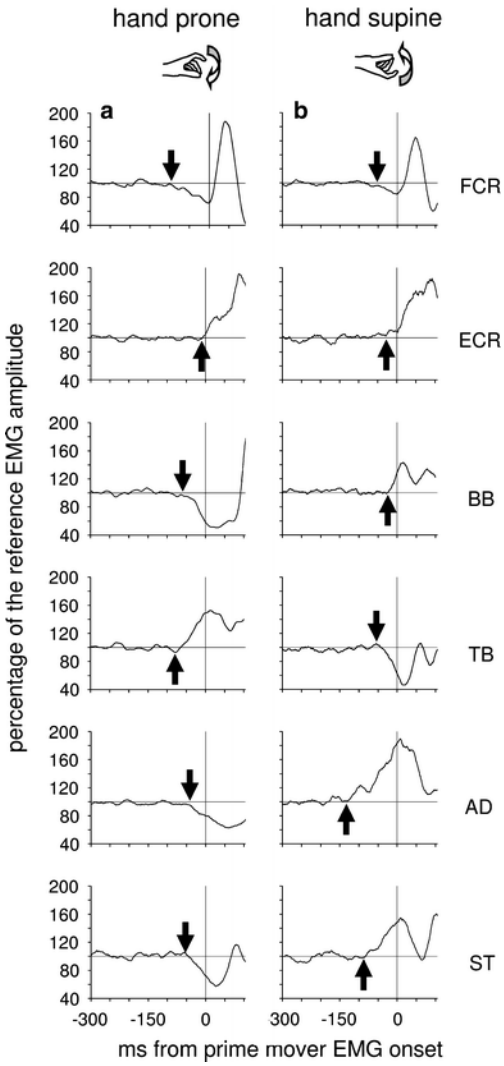

Figure 7. Postural adjustments in upper-limb muscles preceding an index-finger tap with the prone or supine hand. Each graph displays the APA onset (*arrow*) and its development on the tonic EMG from different postural muscles, of a single representative subject, with the hand resting prone (**a**) or supine (**b**). The vertical line at 0°ms marks the onset of the prime mover activity. Note that in the muscles acting at the elbow, the shoulder and the trunk APAs reverts in sign when hand posture changes from prone to supine. EMG is rectified, integrated and averaged (75 trials) and its size expressed in percentage of the mean EMG level recorded 1 s before the go signal. Adapted from Caronnni and Cavallari 2009a

As shown in Figure 7, this APA pattern was shown to revert in sign when hand posture was changed from prone to supine, i.e. when the direction of the focal movement was inverted. In fact, when passing from prone hand to supine hand, BB and AD were regularly excited and TB inhibited.

Such *intra-limb* APAs not only would guarantee the maintenance of the arm posture, but should also be very important in controlling the trajectory and the final position of the moving segment, i.e. metria (Figure 8).

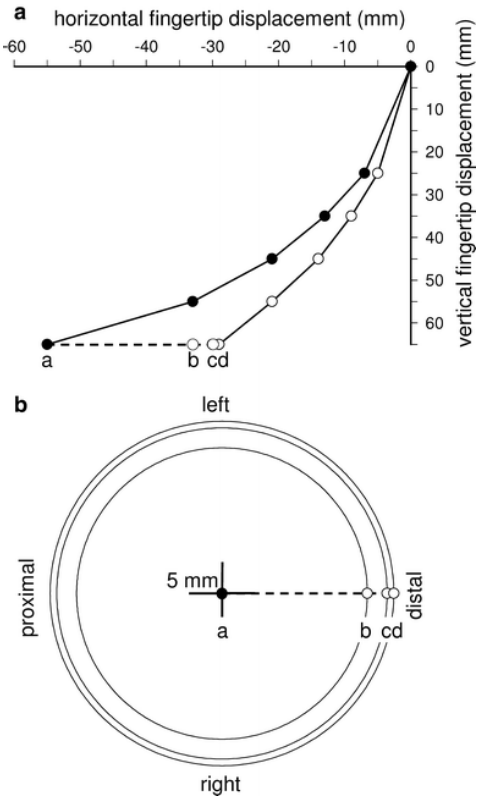

Figure 8. APA and dysmetria. Model simulation of the horizontal fingertip displacement, as function of different strokes, when the proximal segments are immobilized (**a**, fictive APAs, *filled circle*), and when they are free to rotate (**a**, *empty circle*). Note that for a vertical displacement of 65 mm, the fingertip hits the table surface (*dashed line*) more proximally with APAs (*a*) then when no-APAs are involved (*d*). Dots b and c mark the hitting position when the APAs concern the sole shoulder or shoulder plus elbow, respectively. In the planar graph (**b**), in which also lateral segment displacements are considered, the *filled circle* is the univocal target position resulting from a fully correct APA control, a disturbance of the APAs chain would necessarily produce the impact of the fingertip in any other point Adapted from Caronni and Cavallari 2009a.

Indeed, when simulating an index-finger flexion using a four-joint software mechanical model of the arm, in which only the prime mover was recruited, a clear disturbance of both focal movement and upper-limb posture was observed, with

relevant changes at wrist and elbow level. This would affect the final position of the intentional finger movement. In the model, the only way to prevent these "*collateral effects*" was to block all segments but the finger, preventing the proximal joints from rotating (fictive intra-limb APAs). Since this observation derived from a very simplified system, Caronni and Cavallari (2009a) also looked for a more realistic situation: a finger tap was electrically evoked in a real arm by stimulating the median nerve; such an experiment showed recordings comparable in sign and size to those predicted by the software mechanical model, including the dysmetric motor output (Figure 9). However, both the *software simulation* and the *electrically evoked tap* paradigms did not faithfully represent the "natural" dysmetric behavior, since in the two cases no voluntary command is modelled or generated, respectively.

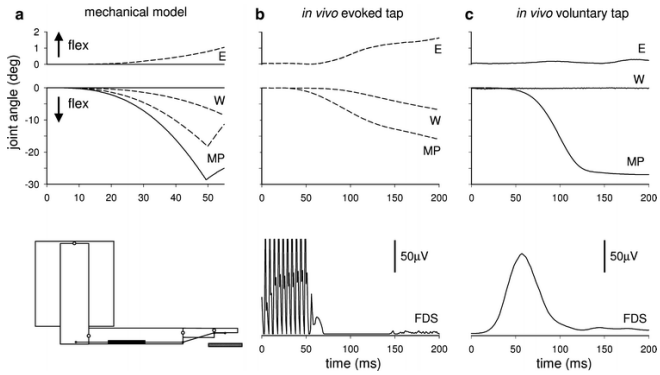

Figure 9. Angular displacements at metacarpo-phalangeal, wrist and elbow joints during simulated, evoked and voluntary index-finger tap. Time course of a simulated finger flexion at the MP joint and the related changes at wrist (W) and elbow (E) level, all in degree of angular rotation, measured when segments were free to rotate (a, dashed lines) or immobilized (a, fictive APA, solid lines). The modeled arm is sketched in the bottom left inset. Angular displacements of the three joints were also recorded when an index-finger tap was passively evoked in vivo by the median nerve electrical stimulation (b) and when it was voluntary performed (c). Rectified FDS activity in the two lower graphs. Note that the mechanical model well predicts the displacements of the proximal joints both during passive (solid lines) and during voluntary (dashed lines) index-finger tap. Adapted from Caronni and Cavallari 2009a.

Finally, *intra-limb* and *inter-limb* APAs seem to share similar control mechanisms and, therefore, their division seems to be inappropriate. Indeed, similarly to inter-limb APAs (Cordo and Nashner 1982; Brown and Frank 1987; see for a review Bouisset and Do, 2008), intra-limb APAs (1) are distributed to several upper-limb muscles creating a postural chain aiming to prevent the effects of the interaction torques generated by the voluntary movement; (2) reverted in sign when movement

direction is reverted and (3) changed in amplitude according to the level of postural stability (Caronni and Cavallari 2009a).

However, other experimental data may help to strengthen the argument that intra and inter limb APAs are controlled in the same manner.

Neural pathways involved in APA programming

Studies regarding the neural structures generating the APAs are surprisingly rare. From the scarce available data, it is possible to hypothesize a superposition of the neural structures for APAs and those for voluntary motor command. This view is supported by evidences suggesting an involvement for APAs generation of both the basal ganglia-thalamo-cortical network and the cerebellum.

Basal Ganglia – Severe APA impairments in patients with Parkinson's disease suggested a role of the basal ganglia also in the anticipatory postural control in movement involving a bimanual coordination task, such as the barman task. (Viallet et al. 1987). More recently, anticipatory brain activity before the execution of a bimanual load-lifting task was recently localized in basal ganglia, SMA, and thalamus in the hemisphere contra lateral to the load-bearing arm (Ng et al. 2012).). It is worth noting that these areas are component nodes of the basal ganglia-thalamo-cortical motor network, which is implicated in well-learned finger movements (Boecker et al. 1998), thus supporting the idea of a superposition of the neural structures for APAs and those for voluntary motor command, and indirectly supporting the view of a oneness of the motor command for both posture and primary movement.

Supplementary Motor Area - Several studies support the idea that Supplementary Motor area (SMA) is involved in the neural circuitry that is involved in the APAs generation. Severe APA impairments in a barman task, i.e. a bimanual unloading task, were observed in patients with a lesion of the SMA (Massion et al, 1989; Viallet et al. 1992). A 1-Hz repetitive stimulation with the TMS, which is able to induce an

inhibitory effect of the SMA, reduces duration of APAs prior to stepping, without affecting their peak amplitude (Jacobs et al. 2009).

Cerebellum - The role of the cerebellum in the genesis or in the transmission of the APAs remains an open question. The debate regarding cerebellum role in the postural control started about one century ago. Babinski (1989) reported that a cerebellum lesion disrupted the coordination between voluntary movement and equilibrium stabilization. Using functional magnetic resonance imaging, Schmitz et al. (2005) reported that APAs were associated with activation of sensorimotor areas, SMA and the cerebellum. On the contrary, Ng et al. (2010) found no evidence of cerebellar involvement during APAs using magnetoencephalography in a bimanual coordination task. However, several studies on patients positively concluded for a cerebellum role

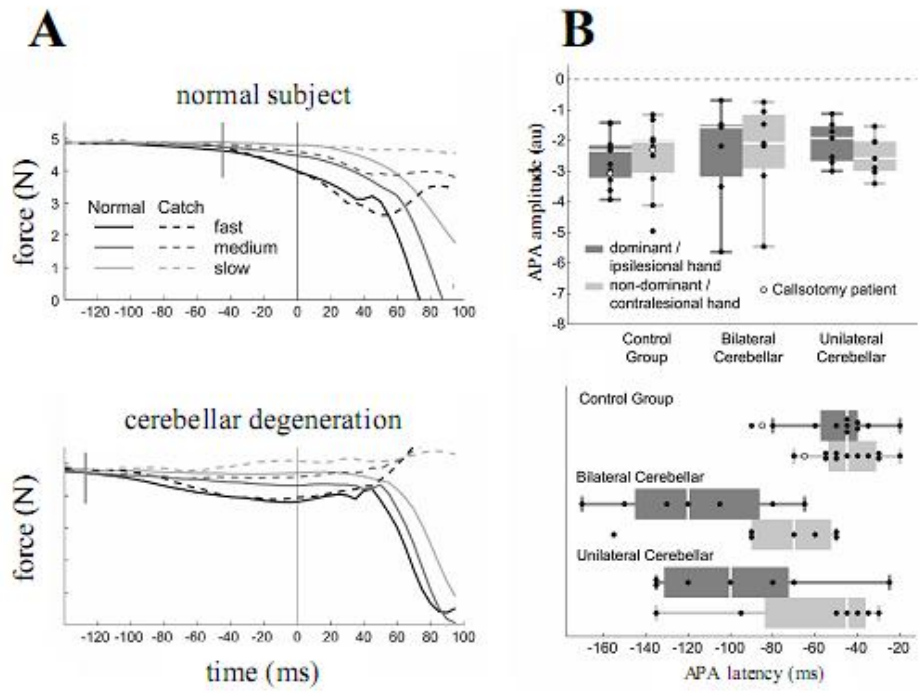

Figure 10. Time course of APAs in healthy and cerebellar subjects. The postural forces in a self unloading task in the health subjects (Top) starts about 40-50 ms before the lift onset. In cerebellar patients (down) the APA effects beginning well in advance, about 100 ms, of the movement onset. Adapted from Diedrichsen et al. 2005.

in APAs control. Indeed, patients with cerebellar lesions fail to show a normal anticipatory adjustment in grip force when lifting or moving an object (Babin-Ratte et al. 1999; Muller and Dichgans 1994). It was also found that cerebellar lesions abolish APAs plasticity in a bimanual unloading task when participants hold an object in one hand and then lift it with the other hand (Figure 10, Diedrichsen J, 2005). Congruently, Diener et al. (1990) also reported that cerebellar patients produce a normal pattern of APAs, but with abnormalities in their timing relationship with the onset of the prime mover. Further support on the role of cerebellum in temporizing APAs come from animal studies; Yamaura et al. (2013) showed that during a reaching task, WT mice show a clear APA in which the EMG activities of the hind limb muscles are synchronized with those of the neck muscles, agonists for the reaching movement, while in conditional transgenic mice of spinocerebellar ataxia type 3, the onset of hind limb EMG activity occur markedly later than that of neck muscle activity, suggesting that mice do not generate the appropriate APA for the reaching task. Indirect support for the cerebellum involvement in APAs comes also from the study of Boendermaker et al. (2014). These authors applied a pressure on three lumbar spinous processes and observed significant activation patterns in the somatosensory cortices (S1 and S2), supplementary motor area and anterior cerebellum. The CNS should reasonably interpret the pressure as a new fixation point on the back and thus trigger a predictive APA adaptation, based on the new postural context. The cerebellum activation suggests its involvement into this process. This view also agrees with the idea that the cerebellum contains forward internal models that could predict the consequences of an action (according to the perceived postural context) and can be used to overcome time delays associated with feedback control (Imamizu et al. 2000; the Wolpert et al. 1998).

Motor cortex - The role of the primary motor cortex in generating APAs has been suggested by both human and animal studies. The stimulation of the primary motor cortex in the intact cats was indeed able to evoke movement in the controlateral side and APAs in the supporting limbs (Gaehry and Nieullon, 1978), suggesting that the primary motor cortex in cats is able to control for both the voluntary prime mover and

the postural control that precede and accompany the primary movement. Moreover, it has been illustrated that cat pyramidal neurons (PT) changes their discharge frequency with a dynamic that is time locked with the time course of the displacement of the centre of vertical pressure (CVP), a parameter that is frequently associated to the mechanical effects of APAs in the whole body equilibrium. Also the discharge frequency was directly dependent on the amplitude of the CVP displacement, a result that strengthens the argument that PT neurons are involved in the APAs production (Yakovenko and Drew, 2009). The role of the primary motor cortex in the anticipatory postural control was observed also in human studies. Indeed, a stimulation with the Transcranic Magnetic Stimulation (TMS) on M1, which is known to induce an initial increase of the cortical excitability followed by a period of inhibition, further support the role of M1 in generating APAs (Palmer et al 1994). These authors asked to seated subjects to abduct their left arm, which is known to be preceded by APAs in the contra lateral right latissimus Dorsi muscle. Then they stimulate with the TMS the left motor cortex, ipsilateral to the prime mover and contra lateral to the postural muscle, recording a delay of the APA onset, while the prime mover was not modified in its timing effects. When instead stimulating the right motor cortex, a delay of the prime mover EMG onset with only minor changes on the time course of APAs were observed.

These results strongly suggest that the primary motor cortex plays a crucial role for both APAs and primary movement production. Other studies also favor the view of the key role of the motor cortex in generating APAs. By testing spinal and corticospinal excitability in humans performing voluntary movement by measuring the change in amplitude of the H-reflex and the amplitude motor evoked potential elicited by the TMS over the primary motor cortex, respectively. For both excitatory (Petersen et al 2009) and inhibitory APAs (Caronni and Cavallari 2009b) it has been illustrated that T-reflexes falling in the APA temporal window were un-modulated, while the MEP significantly increase and was inhibited 50 to 70 ms before the APA onset, respectively for excitatory and inhibitory APAs. Therefore, also these results suggest a

key role of the motor cortex in controlling both primary movement and the associated postural control (see Figure 11).

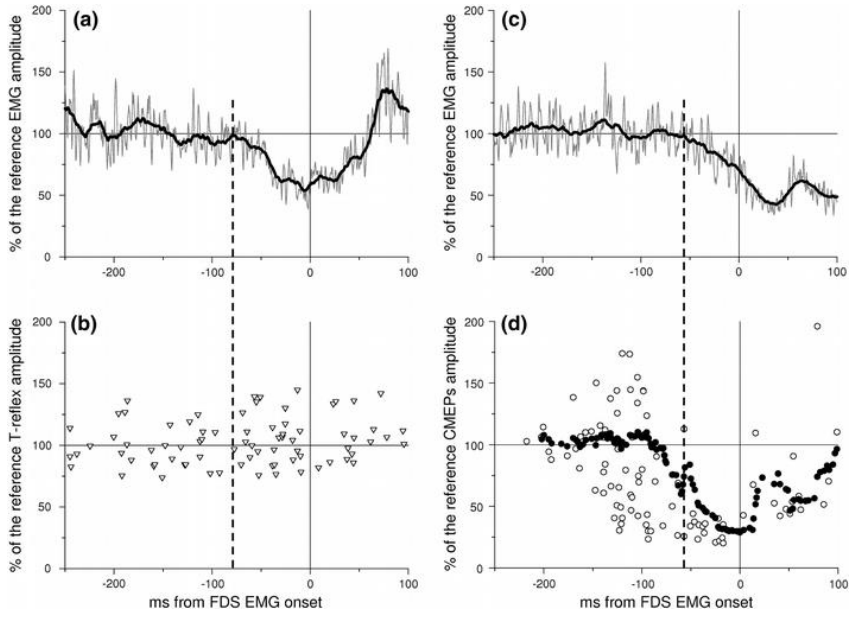

Figure 11. Time course of spinal and cortico-spinal excitability in the resting BB before an index-finger flexion (experiments A and B). An inhibitory APA carves the BB EMG in two representative subjects (**a**, **c**): in both cases rectified (*grey trace*) and integrated (*black trace*) EMG activity (average of 40 trials) is strongly reduced well in advance to FDS onset (0 ms). The time course of the BB spinal excitability has been tested by means of the T-reflex (*triangles*, **b**), while that of the BB cortico-spinal excitability by CMEPs (*open circles*, **d**). Each symbol marks amplitude and latency of one single evoked potential. Note that T-reflexes are un-modulated in size in the iAPA window, edged by the iAPA onset (*vertical dashed line*) and prime mover onset (*vertical continuous line*), whereas CMEPs are strongly inhibited. To better identify the onset of this inhibitory effect, the CMEPs time course has been integrated with the same time constant used for the EMG (*filled circles*). Both EMG and evoked potential amplitude are expressed as a percentage of their mean reference amplitude i.e. that measured before the acoustic signal. Adapted from Caronni and Cavallari 2009b.

Physiological role of APAs

The anticipatory postural adjustments aim generate inertial forces that, when appropriate, will counterbalance the changes in postural balance due to the voluntary movement (Bouisset et Zattara, 1981). According to this hypothesis, the voluntary movement is considered as a perturbation and the anticipatory postural adjustments would have a stabilizing function. Since the anticipatory postural adjustments

originate from a feed forward command and adapt APAs to changes in the postural demand of the motor task, such as speed, amplitude and movement direction (Belen'kii et al. 1967; Cordo and Nashner 1982; Aruin and Shiratori 2004; Shiratori and Aruin 2007), they have to be determined by previous knowledge of its effects of disturbance. Anticipatory postural adjustments seem therefore to be programmed in relation to intended perturbation, rather than the actual one.

During locomotion, transient change in the centre of body mass is needed and in this situation the anticipatory postural adjustments are related not only to the action of contrast of the perturbation linked to the next movement, but also the phenomenon of transferring the body weight to the forthcoming stance foot. When walking it is recognizable a succession of losses and recoveries of equilibrium, which corresponds to the periodic transfer of the support base. Therefore, anticipatory postural adjustments induce a postural destabilization that is necessary to starts the locomotion (Bouisset and Do, 2008).

Taking into consideration the two roles of anticipatory postural adjustments previously mentioned, it seems that APAs may be involved in both functions, i.e. to counteract the primary movement perturbation, e.g. in a shoulder flexion (see Massion 1992), and/or to directly cause a perturbation which initiate the execution of the movement, like in locomotion (Brenière and Dietrich, 1992). The dual role of anticipatory postural adjustments is therefore both to facilitate postural stabilization and to create propulsive forces. Which of the two roles would be played by the APA chain depend on the parameters of the motor task.

Role of Vision

Vennila and Aruin (2011) studied the effect of visual information on the mantainance of the whole-body balance. When exposing subjects to an external perturbation induced by an aluminum pendulum attached to the ceiling with or without holding onto a walker, no significant differences in the APAs activity was found when a full vision was available. These results suggested that vision could overrule the

proprioceptive information and/or an additional support in setting the anticipatory postural control to counteract an incoming postural perturbation. In a similar experimental set-up, APAs were found to be greater when providing dynamic visual cues (high- frequencies strobe light) than with static visual cues (low-frequency strobe light), supporting the importance of vision in the adaptation of APAs (Mophatra and Aruin 2012). Finally, it has been illustrated the importance of visual acuity in a correct tailoring of APAs (Mophatra et al. 2012). Indeed, the anticipatory postural control changes when asking the subject to wear eye-glasses with negative or positive powered lenses. The above described literature suggest that the CNS rely upon vision for tailoring a correct APA pattern when it has to counteract an external perturbation or when it has to deal with a voluntary movement oriented to a target, thus interacting with external objects.

Role of proprioception

According to literature, in a well-lit environment with a firm base of support healthy individuals, which are asked to maintain a bipedal up-right stance, rely on a combination of somatosensory (70%), vestibular (20%) and only 10 % of visual feed-back (Peterka 2002). For what regard APAs, it has been shown that cutaneous inputs provide sufficient information to plan APAs the anticipatory postural adjustments for gait initiation (Mouchnino & Blouin 2013). Similar conclusions were obtained by Lin and Yang (2011), who showed that insufficiency in plantar afferent inputs strongly impair the capability of the CNS in setting a correct APA pattern during the anticipatory phase of gait, which could not be compensated by visual inputs. These observation support the view that proprioceptive inputs are sufficient to modulate the APA pattern that precede gait initiation.

Modulation of APA in timing and amplitude

The CNS is able, within few movement repetitions, to adapt APAs to changes in the postural demand of the motor task, i.e. the ensemble of mechanical actions

required for counteracting the perturbation induced by the primary movement (Belen'kii *et al.* 1967, Cordo & Nashner 1982, Aruin & Shiratori 2004, Shiratori & Aruin 2007). Clear signs of this adaptative process have been observed even after the very first movement trial (Hall *et al.* 2010). In this section it will presented an overview over the mechanical parameters that are able to induce an APA adaptation.

General postural context - The characteristics of the general postural context depend on both the physical properties of the support base and the interface between the body and the support. The first depends on the characteristics of the environment in which we are moving: properties and geometrical parameters of the available fixation points, such as flatness or curvature, inclination and stability of the support bases. The second depends on our own body posture, i.e. depend on whether we are firmly standing on two feet or in an unstable posture on only one; if we are seated, with or without a backrest, or if there are any other reliable fixation points on which we could rely on. Indeed, the amplitude of the anticipatory postural adjustments is affected by the whole body stability at the time of the movement execution. APAs are reduced in size when performing a movement in a stable postural context. A view that agrees with the arm-pull experiment in standing subjects by Cordo and Nashner (1982) in which the Soleus APAs were strongly reduced when adding a fixation point to the trunk. In this situation, the oscillation caused by pulling the handle is prevented thanks to the presence of the additional support and, therefore, reduces the importance of the intervention of the posterior muscles of the lower limb (Figure 12). Furthermore, the length of the APA chain depends on the position of the fixing point to which it is anchored. In this experiment the fixation point is located in proximity of the moving segment, thus shortening the fixation chain length .If the condition in which the subject is unstable, i.e. when reducing the support base area, APAs are usually reduced in amplitude. Indeed, since the APA themselves determine movement (Bouisset and Do, 2008), when the support base is small the APA themselves could cause a CoM displacement, potentially threatening the whole body balance. The importance of an adequate support base to ensure a reliable fixation point for the APA

chain is suggested by Dietz & Colombo (1996), who showed that no APAs in lower limbs could be observed when performing push/pull movements when the body fully immersed in water. It is thus apparent that moving without any fixation point is not an adequate condition for the APA chain to develop.

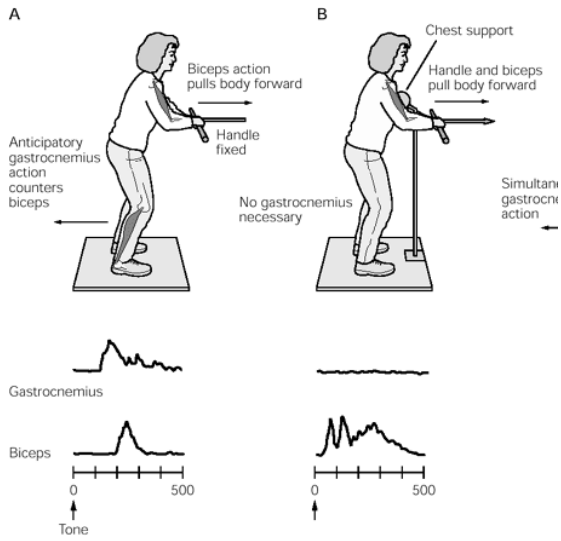

Figure 12. Anticipatory motor action in response to postural disturbance adapts to the behavioral context. The illustrations show the postural activity of the gastrocnemius muscle in four behavioral contexts:A. The subject stands on a firm platform and pulls on a fixed handle as soon as possible after an auditory cue. To maintain posture, backward-acting contraction of the leg muscle (gastrocnemius) starts before the biceps begin pulling the handle. B. When the chest is supported and the handle is suddenly pulled forward, there is a very early reflex response in the biceps and the gastrocnemius remains silent. Adapted from Cordo and Nashner 1982.

Kinematic properties of voluntary movement - APAs are known to be tuned depending on several kinematic aspects of the primary movement. Specifically, they augment their amplitude when increasing the amplitude of motor action (Aruin and Shiratori 2004), the movement speed (Shiratori and Aruin 2007) and the mass of the segmented moved (Friedli et al, 1984). Moreover, an increase of APAs was shown when the voluntary movement was performed against resistance (Baldissera et al. 2008). Instead, when the movement velocity is voluntary lowered, APAs decrease their anticipation and some muscles with early activity prior the movement show no activity at all (Horak et al 1984). The relationship between latency and amplitude of

APAs from one hand and from the other the strength of the prime mover contraction is clearly understandable when considering that APAs are tailored to the expected perturbation. Since the strength of prime mover activation influence the magnitude of the perturbation on the other body segments, and would potentially cause a displacement of the CoM, a greater and more anticipation generates by the APA chain, which compensates for the disturbing forces and presumably provides stability for the ensuing movement

Movement direction - A modification of APAs could be also observed when considering movement with different direction (Aruin et Latash, 1995; Pozzo et al. 2002). In the experiment of Aruin and Latash, illustrated in Figure 13, the subject was asked to perform a bilateral movement of the shoulders in three different directions. In Figure 13 the EMG traces of erector spinae muscles (ES) and rectus abdominis (RA) were illustrated in relation to different movements directions. When flexing the upper limb an excitatory APA in the ES muscle, without any activation in the RA muscle. Instead, when extending the shoulder, the APA pattern is inverted with respect to the upper limb flexion, with an excitatory APA in the rectus abdominis and no activation for the erector spinae muscle. The reversal of the APA sign is the result of the inversion of the movement direction, which reflects the different perturbation induced by the moving segment. Finally, when synchronously abducting both the arm, the whole body perturbation is not threatened since the CoM should not virtually change. For this reason, no APAs were needed and indeed no EMG activities in any of the two muscles considered were recorded. The APAs adaptation to movement direction is also visible in *intra-limb* APAs. As illustrated by Caronni and Cavallari (2009a, see Figure 7), indeed, when changing the hand position from prone to supine the APA pattern changes accordingly, with inhibitory APAs in TB and excitatory APAs in BB and AD.

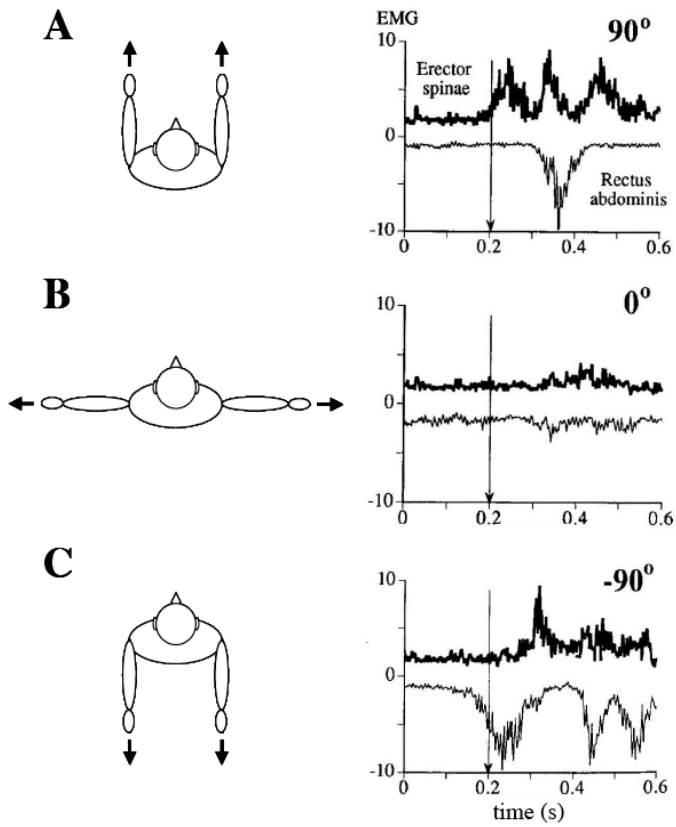

Figure 13. The reversal of the direction of movement leads to the reversal of the APA sign. Subjects performed bilateral shoulder movements in three different directions (flexion, in the upper picture; abduction, in the intermediate image and extension, in the image below). Graphs on the right show APA recorded in the erector spinae muscles (Erectors Spinae, ER) and rectus abdominis (Rectus Abdominis, RA), two antagonist trunk muscles. The flexion of the shoulder (A) was accompanied by an excitatory APA in ES, while no APA was recorded in the rectus abdominis. The shoulder extension (C) was preceded by anticipatory activity of the RA, without any APA in ER. It may be noted that in the case of bilateral shoulder abduction (B) no APAs were not recorded neither the APA sacrospinalis nor in the rectus abdominis. Adapted from Aruin et Latash, 1995.

APAs role in movement accuracy

According to Soechting and Flanders (1989a, b; see also Massion 1992 for a review), when a healthy subject points to a target cross, an eventual error in missing the target derive from an incorrect sensorimotor transformation from the visual representation of the target to the kinematics representation of the planned trajectory. Indeed, these authors showed that when subjects have to reach a position which has been previously appreciated kinesthetically (thus after having empirically built up the

exact transformation), pointing errors dramatically reduce. In particular, several evidences showed that the parietal cortex play a critical role in integrating visual and somatic inputs for building up this sensorimotor transformation (see Kalaska et al. 1997 for a review).In this context, the sensorimotor transformation is co-adiuvated by the skin receptors which detect the torsion forces that act on the skin of the feet in contact with the soil.

Era and co-workers (1996) have reported that top-level rifle shooters stabilize their whole body balance better than naive shooters, particularly in the last seconds before the shot. This and other studies investigating the same topic (e.g. Aalto et al., 1990; Mononen et al., 2007) give evidence that shooting accuracy relies on the accurate trunk and lower-limb posture control, allowing coordination of these body segments with the focal trigger pull.

On these premises, APAs may represent the earliest part of the motor command necessary for proximal and distal body segments coordination. Only in recent years, some Authors suggested that APAs function is not limited to ensure the whole-body balance, but may as well encompass the ability to provide the most appropriate conditions to guarantee an accurate movement execution. APAs decrease in size as the accuracy demand increases (i.e. when pointing smaller and smaller targets), a feature that has been shown both in the upper-limb (Bonnetblanc et al., 2004) and in the lower-limb (Bertucco and Cesari, 2010). Lower limb pointing was also investigated by Duarte and Latash (2007), which have shown that the faster the movement, the larger is the APAs variability. It is also well described the relation between movement speed and scattering of the final position around a target (Fernandez and Bootsma, 2004; Schmidt et al., 1979). All these observations suggest that small and less variable APAs should accompany slow, but precise movements. Finally, Berrigan and colleagues (2006) reported that when pointing is performed towards small targets (i.e. under high accuracy constraints) from an “unstable” position (i.e. standing vs. sitting), slowing movement speed actually represent a strategy to reduce the equilibrium disturbance i.e. the associate APAs. Thus, when the accuracy demand increases, peak movement velocity decreases, as already described

by the Fitts' law (1954). However, since APAs amplitude is known to be proportional to focal movement velocity (Shiratori and Aruin, 2007; Lee et al., 1987), its reduction might be not directly related to the increased accuracy demand, but to the associated reduction in movement speed.

Caronni and Cavallari (2009a) proposed that during a brisk index-finger flexion, *intra-limb* APAs play a crucial role in controlling the finger trajectory and final position. Indeed, when simulating an index-finger flexion using a four-joint software mechanical model of the arm, in which only the prime mover was recruited, a clear disturbance of both focal movement and upper-limb posture was observed, with relevant changes at wrist and elbow level. This would affect the final position of the intentional finger movement. In the model, the only way to prevent these "collateral effects" was to block all segments but the finger, preventing the proximal joints from rotating (fictive *intra-limb* APAs). Since this observation derived from a very simplified system, Caronni and Cavallari (2009a) also looked for a more realistic situation: a finger tap was electrically evoked in a real arm by stimulating the median nerve; such an experiment showed recordings comparable in sign and size to those predicted by the software mechanical model, including the dysmetric motor output. However, both the *software simulation* and the *electrically evoked tap* paradigms did not faithfully represent the "natural" dysmetric behavior, since in the two cases no voluntary command is modelled or generated, respectively.

Working Hypothesis

Data illustrated in the present thesis aim to shed further light on the neural mechanisms that control APA and the relationship of the APA command with the voluntary movement.

As it has been pointed out above, studies regarding the neural structures generating the APA command are surprisingly rare. From the available data, it was supposed a key role of supplementary motor area (SMA) and cerebellum in the APA control. In the present thesis, it is shown from one hand that a tDCS stimulation over the SMA modulates the APAs associated to a finger flexion and, from the other, that the cerebellum plays a role in controlling APAs, specifically in temporizing their activities with respect to the prime mover activation. Therefore, the superposition of the neural structures controlling APAs and the voluntary motor command indirectly supports the above described hypothesis of the oneness of the command for both posture and primary movement. To prove the SMA involvement in the APA control a tDCs was applied over the SMA in order to investigate if this stimulation would induce a modification of the well-known intra-limb APA chain that stabilize the arm when briskly flexing the index-finger (Caronni and Cavallari 2009a). A change in the APA pattern when stimulating with the tDCS would be a further evidence that this area is involved in the APAs network.

Also the involvement of the cerebellum in the APAs generation was still an open question. Considering that the cerebellum controls rate, smoothness, and coordination of the voluntary movement (Manto MU, Bastian AJ, 2007) and the APAs and voluntary movement are part of a unique motor command (Aruin and Latash 1995; Petersen et al. 2009; Caronni and Cavallari 2009b), it should be expected that the cerebellum, especially in its role in distributing and temporizing the motor command, plays a role in the organization of APAs and, specifically, in refining movement metria. To shed further light on this working hypothesis, we analyzed the upper-limb APA chain that stabilize the arm when briskly flexing the index-finger

(Caronni and Cavallari 2009a) in a group of dysmetric patients (detected clinically using the SARA score) with slowly progressive cerebellar degeneration and on an equal number of healthy subjects. A disruption of the organization of the intra-limb APA chain in cerebellar dysmetric subjects would support the idea that i) cerebellum is involved in the anticipatory postural command and ii) a properly tailored intra-limb APA chain plays a key role in refining movement metria, as originally suggested by Caronni and Cavallari (2009a). If the above described hypothesis are confirmed, the idea of a superposition of the neural networks controlling both APAs and prime mover recruitment would be strengthened.

Consequently, it was also hypothesized that APAs would not only aim to counteract the perturbation induced by the primary movement, as often proposed in previous literature, but would be the first part of the motor program which start from a fixation point, develop through the APA chain and include also the command for the focal movement. Indeed, according to the classical view, the prime mover activity and its associated postural adjustments result from two different central commands, which are independently dispatched to the prime mover and to the muscles generating the postural chain, respectively (Babinski 1899; Hess 1943; Cordo and Nasher 1982; Brown and Frank 1987). On the other hand, a growing body of recent evidences favours the view that APAs and prime mover recruitment are both controlled by a unique motor command (Aruin and Latash 1995; Petersen et al. 2009; Caronni and Cavallari 2009b). This latter view is also supported by Yakovenko and Drew (2009), who studied the discharge properties of cat pyramidal tract neurons (PTN) and their temporal linkage with APAs associated with reaching movements. These authors found a strong linear relationship between the onset of PTN discharge and the APA onset, strengthening the idea that the motor cortex contributes to generate the APAs. Moreover, Schepens and colleagues (Schepens and Drew 2004; Schepens et al. 2008) emphasized the role of pontomedullary reticular formation (PMRF) in the coordination of posture and movement. In particular, they suggested that PMRF is a site of integration of signals from both cortical and subcortical structures and that

these signals ensure that APAs are appropriately scaled in time and magnitude to the intended movement, contributing to integrate the control of posture and movement. However, whether the single or the dual command theory should be preferred, it remains an open question.

To verify the working hypothesis of the oneness of postural and movement command, we analysed the well-known intra-limb APA chain that stabilise the arm during an index-finger flexion (Caronni and Cavallari 2009a) in an experimental condition in which the voluntary command was normally dispatched but the prime mover was unable to contract. In this aim, subjects were asked to repeatedly flex their index-finger under two different conditions: i) before an ischemic block of the forearm, ii) when ischemia had suppressed the finger movement and the ensuing postural perturbation.

On this basis, the experimental paradigm may have lead to two alternative scenarios. Following the dual command view, one should expect that under ischemia APAs are suppressed after few repetitions, since the postural activity on the upper limb is useless (no real perturbation on the more proximal segments) and also uneconomical. Indeed the CNS is able, within few movement repetitions, to adapt APAs to changes in the postural demand of the motor task, i.e. the ensemble of mechanical actions required for counteracting the perturbation induced by the primary movement (Belen'kii et al. 1967; Cordo and Nashner 1982; Aruin and Shiratori 2004; Shiratori and Aruin 2007). Moreover, clear signs of this adaptive process were observed even after the very first movement trial (Hall et al. 2010). On the other hand, following the idea of the oneness of voluntary and postural commands, APAs would have be expected to remain manifest in the proximal arm muscles, and tailored to the intended movement (i.e. to the expected perturbation stemming from the voluntary command), despite the absence of the real perturbation. The persistence of APAs even after several attempts to flex the index finger under forearm ischemia would provide a novel indication that, during the execution of a voluntary movement, the recruitment of postural and prime mover muscles is driven by a functionally unique motor

command. Thus, APAs and prime mover activation could be seen as parts of the same muscular chain.

In this regard, it is a common opinion that APAs are programmed according to the velocity of the voluntary movement (Horak et al. 1984, Lee et al. 1987, and also appreciable in figure 2a of Shiratori and Aruin 2007). However, in the above cited papers, information about the linkage between APAs and speed of voluntary movements was obtained by instructing subjects to voluntarily change the movement speed; therefore, it is impossible to discern whether the key factor determining the modification in APA latency is the change in the movement instruction or the change of the actual movement speed. Therefore, the present thesis also aims to distinguish between these two factors. To address this issue, it was analysed the well known intra-limb APA chain that stabilise the arm during a brisk index-finger flexion in two groups of subjects: 1) the 29 composing database of previous experiments published by my group, who received the same "go-fast" instruction but actually performed the movement with different velocities (238 to 1371°/s) and 2) 10 new subjects who performed the "go-fast" flexion at more than 500°/s and were then asked to "go-slow" at about 50% of their initial speed. Data from the first group allowed testing the correlation between APA latency and movement speed, while those from the second group the effect of movement instruction on APA latency. Moreover, since the velocity range was similar in the two groups, a last comparison was drawn between subjects moving at the same speed but obeying to different instructions: go fast or go slow. Results from these experiments would thus allow to properly distinguishing if APA latency depends on movement velocity, movement instruction or both.

Therefore, the observed oneness of the motor command for both APAs and prime mover recruitment, let my group to hypothesize that a correct tailoring of the APA chain on the ensuing voluntary movement might have a role in the enhancement of the accuracy of the voluntary movement. Indeed, one of the aims of the present thesis is to search for a direct proof of the relationship between the APAs amplitude and the endpoint of a target reaching movement. Consequently, it is shown that a small pointing error specifically underlies changes in APAs amplitude with no

changes in the prime mover activation, thus sustaining the hypothesis that a successful and accurate pointing movement relies upon a specific tuning between APAs and prime mover activation (see Caronni & Cavallari 2009a).

Finally, it is illustrated that 12-hours of wrist and fingers immobilization is able to provoke changes in the cortical organization of anticipatory postural adjustments, developing in the elbow and the shoulder, accompanying a brisk flexion of the index finger. Since Moisello et al. (2008) reported that 12h of immobilization are sufficient to modify the kinematic variables of a voluntary movement, the results illustrated in the present thesis would provide new evidences that the voluntary movement and the associated anticipatory postural adjustments are strongly correlated, although scaled in different manners.

In the following section, data and methods of the experiments performed, and the results will be compared with the working hypothesis and the available literature in the Conclusions section.

Experimental Procedure

The experiments of the present thesis share some methodological features, which will briefly reviewed here and will be detailed in the article section.

In all works the electromiographical activity of prime mover and postural muscles were recorded with couples of pre-gelled surface electrodes (H124SG, Kendall ARBO, Tyco Healthcare, Neustadt/Donau, Germany) carefully positioned on each muscle belly. EMG was AC amplified (IP511, Grass Technologies®, West Warwick, Rhode Island, USA; gain 2–10 k) and band-pass filtered (30–1000 Hz, to minimize both movement artefacts and high frequency noise). In five of these studies, subjects was sitting on a chair with the elbow flexed at 90° and the prone hand in axis with the forearm. Subjects were asked to flex their index-finger at the metacarpophalangeal joint after an acoustic signal. Flexion-extension of metacarpophalangeal and elbow joints was recorded by strain-gauge goniometers (mod. F35 and SG110, respectively, Biometrics Ltd®, Newport, UK) fixed to the respective joint. Goniometric and EMG signals were A/D converted at 2 kHz with 12 bit resolution (PCI-6024E, National Instruments®, Austin, Texas, USA), visualized online and stored for further analysis.

In three works, a control condition in which healthy subjects performed a sequence of self paced index-finger flexions was compared to recordings obtained during and/or after an experimental condition. Among these: i) a tDCS stimulation, with the active electrode placed on the supplementary motor area (SMA), ii) a cast immobilization of the metacarpo-phalangeal and radio-carpal joints for 12 hours, and iii) ischemic block of the forearm, which abolish the voluntary EMG activity in the prime mover Flexor Digitorum Superficialis. In one experiment, recordings from healthy subjects were compared with an equal number of ataxic patients with a cerebellar syndrome. In Esposti et al. (2014), the effect of movement velocity vs. movement instruction was analysed in two groups of subjects: one composed by our database of subjects, who all were asked to briskly flex the index-finger (“go-fast” instruction), and the other who

were asked to perform the “go-fast” finger flexion and then asked to “go-slow” at about 50% of their initial speed.

Finally, in Caronni et al. (2013) subjects were asked to perform a pointing movement with their right arm. The task was performed while wearing and after doffing prismatic goggles (Fresnel 3M® Press-On, 20 dioptres) which produced a rightward shift of the binocular eye-field of about 11°. This corresponds to a 12cm linear shift of the target, placed at 60cm (about one arm length) in front of the subject. While wearing prisms, subjects realized the shifting in the binocular eye-field only when they performed the first pointing movement. Indeed, only when the finger reached the Plexiglas screen they became aware they had missed the target, also because the fingertip underwent the same visual position bias as the target itself. Electromyographic (EMG) activity, right upper-limb movement, target position and the forces exerted onto the ground were synchronously recorded. A 3D motion analysis system (SMART-D, BTS®; 6 infrared cameras) was used to record both the right upper-limb movement and the target position. A dynamometric platform (AMTI® OR6-7) was used to record forces (F) and moments (M) discharged to the ground with reference to the above axes. Data acquisition was accomplished by the SMART-D workstation.

Results

The current thesis aim to shed further light on the neural control of the anticipatory postural command and provide experimental evidences that APAs and prime mover activation are seemingly part of a unique motor command, which drives the muscular chain starting from the fixation point(s) and including the moving segment and permits an accurate execution of a voluntary movement. A detailed description of the results obtained in each work could be found in the article section.

In Bolzoni et al. (2012), it has been shown that this procedure interferes in parallel with the postural muscles which are recruited to stabilize the limb. Since Moisello et al. (2008) showed that 12h of immobilization are able to interfere with the kinematic variables of a voluntary movement, this result strengthens the idea of a shared command for both the control of APAs and voluntary movement.

In Caronni et al. (2013), it has been shown that out-of-target movements were associated to changes in the APAs size, not in prime mover recruitment, as it might be expected. This observation reinforces the hypothesis that a successful on-target pointing movement relies upon a specific tuning between APAs and prime mover activation.

In Bruttini et al. (2014a) it has been illustrated that the intra-limb APAs stabilising the arm when producing a brisk index-finger flexion were still present under an ischemic block of the forearm that suppressed the prime mover EMG, the finger movement and the related mechanical perturbation. Given the well-known ability of the CNS to adapt APAs to changes in the postural demand of the motor task within few movement repetitions (Cordo and Nashner 1982; Hall et al. 2010), one could have expected that in these conditions APAs were suppressed, since unnecessary and uneconomical. Intriguingly, even after 60 movement trials, accomplished in more than 10 minutes, the CNS did not adapt APAs to the new postural demand, failing to properly suppress the postural chain. Instead, in the same

work, it was illustrated that that APAs were deeply reduced when adding a new fixation point at the wrist, i.e. closer to the *voluntary moving* segment, witnessing the well-known ability of the CNS to adapt APAs to the environment, and in particular according to the available fixation points.

In Bruttini et al. (2014b), it has been demonstrated that when performing a brisk index-finger flexion, cerebellar subjects showed a timing-disruption of intra-limb APAs, while their pattern (excitation in TB; inhibition in BB and AD) was unmodified. These data sustain the hypothesis that the cerebellum is essential in tailoring the timing of APAs with respect to the prime mover activation, and open the question whether the cerebellar dysmetria may stem from an erroneous timing of APAs.

Finally, in Esposti et al. (2014) it has shown that the key factor which determines the modification in APA latency when performing a voluntary movement is the change in the movement *instruction (“go-fast” vs. “go slow”)*, not its *actual* velocity. This conclusion stems from three observations: i) there is no correlation between APA latency and movement speed when subjects obeyed the same instruction, ii) APAs were delayed when subjects reduced their movement velocity because they obeyed to a go slow instruction, iii) given a certain speed APA latency depend on the instruction since go fast subjects showed earlier APA than go slow. In other words, APAs seem to be tailored to the expected perturbation, much more than on the real one, strengthening the idea that the postural and prime mover muscles are driven by a functionally unique command.

Article section

The studies presented in this thesis have been also exposed in several congress, both as short talk posters and as oral presentations. Specifically:

Short talk posters

"Changes in "intra-limb" anticipatory postural adjustments after a short-term immobilization of both wrist and fingers", 8 th International Brain Research Organization (IBRO) World Congress of Neuroscience, Firenze, 14-18 July, 2011.

"Immobilization of the hand affects arm and shoulder postural control", 8 th Fens Forum of Neuroscience, Barcelona, Spain, 14 – 18 July, 2012.

"Disrupt of anticipatory postural adjustments in cerebellar ataxia", ESF-FENS Forum: The Neurobiology of Action, Stresa (VB), 20-24 October 2013.

"The ischemic block of the forearm abolishes index-finger's movement but not its associated APAs", 9th FENS Forum of Neuroscience, Milan, 5-9 July, 2014.

Oral presentations

"Hand immobilization affects arm and shoulder postural control", Annual Meeting of Young Researchers in Physiology (YRP 2012), Sestri Levante (GE), 1 June, 2012.

"Ischemic block of the forearm abolishes finger movements but not their associated anticipatory postural adjustments", Young Researchers Meeting, Anacapri (NA), 21-24 May, 2013.

"Ischemic block of the forearm abolishes finger movements but not their associated anticipatory postural adjustments", 64° Congresso nazionale SIF, Portonovo (AN), 18-20 September, 2013.

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RESEARCH ARTICLE

Hand immobilization affects arm and shoulder postural control

Francesco Bolzoni · Carlo Bruttini · Roberto Esposti · Paolo Cavallari

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Abstract It is a common experience, immediately after the removal of a cast or a splint, to feel motor awkwardness, which is usually attributed to muscular and joint immobilization. However, the same feeling may also be perceived after a brief period of immobilization. We provide evidence that this last effect stems from changes in the cortical organization of the focal movement as well as in the associated anticipatory postural adjustments. Indeed, these two aspects of the motor act are strongly correlated, although scaled in different manners. In fact, they are both shaped in the primary motor cortex, they both undergo similar amplitude and latency modulation and, as we will show, they are both impaired by the immobilization of the lone prime mover. Neuromuscular effects of limb immobilization are well known; however, most papers focus on changes occurring in the pathways projecting to the prime mover, which acts on the immobilized joint. Conversely, this study investigates the effect of immobilization on anticipatory postural adjustments. Indeed, we show that 12 h of wrist and fingers immobilization effectively modify anticipatory postural adjustments of the elbow and the shoulder, that is, those joints not immobilized within the fixation chain. Accordingly, the motor impairment observed after short-term immobilization most likely stems from the unbalance between anticipatory postural adjustments and the focal movement.

Keywords Motor control · Posture · APAs · Immobilization · Human

F. Bolzoni · C. Bruttini · R. Esposti · P. Cavallari (✉)
Dipartimento di Fisiologia Umana, Università degli Studi di Milano, Via Mangiagalli 32, 20133 Milan, Italy
e-mail: paolo.cavallari@unimi.it

Introduction

It is well known that joint immobilization leads to significant modification to the muscular and nervous system. Over the past few decades, several authors have documented modifications in skeletal muscle properties such as atrophy (White et al. 1994; Hather et al. 1992), increasing in the intramuscular connective tissue (Józsa et al. 1990) and reduction in the maximal voluntary contraction strength (Veldhuizen et al. 1993; Hortobàgyi et al. 2000) after cast immobilization.

In contrast, only a few papers have examined the neural adaptations to immobilization. Liepert et al. (1995) showed that immobilization leads to a reduction of the cortical area of the inactivated muscle, while Facchini et al. (2002) demonstrated a decrease in the cortical excitability, without affecting nerve or muscle excitability, after only 4 days of motor restriction. Huber et al. (2006) found that these changes may even occur after 12 h of immobilization. Moisello et al. (2008) demonstrated that short-term immobilization affects inter-joint coordination by acting on feed-forward mechanisms, while Avanzino et al. (2011) showed that a brief period (10 h) of right-hand immobilization decreased the excitability of left primary motor cortex and reduced interhemispheric inhibition from left-to-right hemisphere. Finally, Langer et al. (2012) illustrated that the left cortical thickness of the sensorimotor cortex changed during right arm immobilization.

We hypothesize that postural control, and especially anticipatory postural adjustments (APAs), may play a key role in the process leading to the motor impairment induced by immobilization. In fact, APAs are considered intimately coupled to several kinematics aspects of the primary movement, such as speed and trajectory (Kaminski et al. 1995; Pozzo et al. 2002; Bortolami et al. 2008; Kim et al.

2009). Recently, it has also been described that APAs may either be openly manifest or subliminal for motor effects in resting muscles (Caronni and Cavallari 2009b). Although in the latter case generation of the APAs command seems to be uneconomical, it highly simplifies and speeds up the postural control, which only requires a gain adjustment at each potential fixation chain (Esposti and Baldissera 2011). This result also confirms two previous observations in which cortical excitability of resting hand movers has been shown to fluctuate under threshold for the motoneuronal firing when the ipsilateral foot is voluntarily oscillated (Baldissera et al. 2002) and in which the "hidden effect" develops in an overt APA once the hand is recruited in a postural act (Baldissera and Esposti 2005).

In the present paper, a simple paradigm of index finger flexion and the related APAs chain was studied before and after applying a splint to the metacarpophalangeal and radiocarpal joints for 12 h. Indeed, we have recently shown (Caronni and Cavallari 2009a) that even a gentle index finger flexion is preceded by a complex fixation chain, which distributes to several upper limb muscles. In that paper, we predicted that the central activity supporting APAs might be intimately coupled to voluntary movement, also when its effect on motoneurons is subliminal. That expectation has been confirmed by showing that when a postural muscle is not explicitly recruited, an excitatory or an inhibitory APAs activity develops along with the primary motor command (Caronni and Cavallari 2009b).

The aim of this work is to investigate whether a brief immobilization affects the postural control performance as well as the primary movement. If so, the hypothesis of the strict parallelism between APA control and the focal movement would be confirmed.

Materials and methods

Experiments, carried out in 5 male and 5 female adult volunteers, were approved by the Ethical Committee of the University of Milano, School of Medicine, in accordance with the standards laid down in the 1964 Declaration of Helsinki. All subjects gave a written consent to the procedure, after being informed about the nature of the experiments; none of them had any history of neurological disease. Their mean (±SD) anthropometric characteristics were age, 29.4 ± 9.4 years; weight, 64.8 ± 14.2 kg; height, 169 ± 10 cm; index finger length, 9.2 ± 0.7 cm; and arm length, 76.9 ± 7.1 cm.

Experimental procedure

The subject was sitting in a chair with his dominant arm lying along the body, the elbow flexed at 90°, and the prone hand in axis with the forearm. The index finger was kept extended and in contact with a proximity switch (CJ10-30GK-E2, Pepperl and Fuchs®, Mannheim, Germany), so that the metacarpophalangeal joint angle was about 180°, all other fingers hanging. Subjects had their eyes open throughout the whole experiment and 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 (143 MAGIC ARM + 035 Superclamp Kit, Manfrotto®, Cassola, Italy); both were adapted to the different body dimensions of the subjects. A wrist weight of 0.5 kg (Domyos Gym Weight, Decathlon®, Villeneuve d'Ascq, France) was then wrapped around the distal end of the forearm. 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. The time between the beep and the movement onset varied according to the subject will. This procedure was adopted to exclude any reaction time.

In each experiment, index finger flexion was performed 120 times, divided into 4 sequences of 30 movement trials. The 30 trials were accomplished in a temporal window of about 2 min, and then the subject had time to rest (about 3 min) before undergo a new sequence. Subjects never complained about fatigue.

Movement and EMG recordings

The onset of the fingertip movement was monitored by the proximity switch. Flexion–extension of metacarpophalangeal and elbow joints was recorded by strain-gauge goniometers (mod. F35 and SG110, respectively, Biometrics Ltd®, Newport, UK) fixed to the respective joint. Angular displacements were DC-amplified (P122, Grass Technologies®, West Warwick, Rhode Island, USA), A/D converted at 2 kHz with 12-bit resolution (PCI-6024E, National Instruments®, Austin, Texas, USA), and stored. Goniometer calibration was undertaken before each experimental session.

Couples of pre-gelled surface electrodes, 24 mm apart (H124SG, Kendall ARBO, Tyco Healthcare, Neustadt/Donau, Germany), were used to record the EMG signal from the prime mover Flexor Digitorum Superficialis (FDS) and from the following muscles that had an anticipatory postural activity: Biceps Brachii (BB), Triceps Brachii (TB), and Anterior Deltoid (AD). A good selectivity of the EMG recordings was achieved both by a careful positioning of the electrodes and by checking that activity from the recorded muscle, during its phasic contraction, was not contaminated by signal from other

sources. FDS activity was selectively recorded by positioning the electrodes on its course in the distal third of the forearm. To probe both excitatory and inhibitory APAs, the subject was requested to maintain a constant level of EMG activation in the BB muscle against the 0.5 kg weight suspended to the distal end of the forearm. The EMG was AC-amplified (IP511, Grass Technologies®, West Warwick, Rhode Island, USA; gain 2–10 k) and band-pass filtered (30–1000 Hz, to minimize both movement artifacts and high-frequency noise), A/D converted at 2 kHz, 12-bit (PCI-6024E), visualized, and stored for further analysis.

M_{max}-wave recording

The amplitude of the surface EMG reflects the impedance of the structures interposed between the electrodes and the muscle (skin and fat). To exclude impedance variability from subject to subject, EMG amplitude was normalized to the maximal motor response (M_{max}) evoked by orthodromic nerve stimulation (S8800 stimulator + SIU5 isolation unit, Grass Technologies®, West Warwick, Rhode Island, USA). M_{max} was recorded at the beginning of each experiment. The subject was seated with both arms at sides and muscles relaxed; the experimenter positioned the stimulating anode dorsal to the clavicle and the cathode in the underarm. The M-wave was recorded through the same pre-gelled electrodes used during the experiment. The intensity of stimulation (duration 0.8 ms) was gradually increased, by controlling the resulting M-wave on an oscilloscope. Once exceeded the intensity necessary to elicit M_{max}, the track was acquired at 10 kHz, 12 bits (PCI-6024E), and stored. M-waves were measured peak-to-peak in mV.

Immobilization

At the end of the first part of the experiment (session PRE), performed during the morning hours, the subject was disconnected from the instruments, but the pre-gelled electrodes and the electrogoniometers were left on the skin.

In the late afternoon, the metacarpophalangeal and radio-carpal joints were then immobilized by a splint made of synthetic plaster (Dynacast, BSN medical®, Hamburg, Germany), closed by an elastic bandage, whose length was equal to the distance between the distal ends of the fingers and the proximal third of the forearm. The splint kept wrist and fingers in mid-range (neutral) position. Anyway, this apparatus allowed flexion–extension and pronation–supination at the elbow level.

The subject was then free to return to his/her normal daily activities. After 12–14 h, that is, during the successive morning, the splint was removed and the subject again performed 4 sequences of 30 finger flexions (session POST), followed by the evaluation of the M_{max}.

Data analysis

In each session, the 120 EMG traces of the prime mover and those simultaneously recorded from the postural muscles were digitally rectified and integrated (time constant: 25 ms). Traces collected from each recorded muscle were then averaged in a fixed temporal window (−2000 to +300 ms from the onset of index finger flexion, detected by the proximity switch). The period from −1500 to −1000 ms, free from APAs, was utilized to calculate a mean reference level that was subtracted from for each EMG trace.

In each experiment, latency and amplitude of the postural activity were measured off-line on the averaged EMG trace. The onset of an effect in the postural muscle was identified by a software threshold set at ±2 SD of the reference signal level and visually validated. Latency of the APA was referred to the movement onset, thus assuming negative values. APA amplitude was measured as mean level of the trace in the temporal window from APA to movement onset and normalized to M_{max}. In the same temporal window, for each subject, the SD resulting from averaging the EMG traces was used to estimate their within-session variability. Pooled within-session variability for each muscle was then computed as the RMS of the individual values.

To assess whether APAs well balanced the reaction forces of the primary movement, the peak-to-peak angular excursion of the elbow joint was measured from the onset of finger flexion to the moment when flexion started to be braked, that is, when its acceleration zeroed.

All comparisons between the two experimental sessions were performed either by paired *t* tests (session PRE vs. session POST) or by a repeated measures ANOVA with factors *muscle* (BB vs. TB vs. AD) × *session* (PRE vs. POST).

Results

The aim of this paper is to assess whether a 12-h immobilization of a segment changes in parallel the circuits controlling the activation of both the prime mover muscle (responsible for a given movement) and the postural muscles, which are recruited to stabilize the limb.

APAs prior to index finger flexion with the hand prone

Figure 1 shows the pattern of APAs, observed in a representative subject, when an index finger tap is performed. The activation of the prime mover FDS was constantly preceded by APAs at the elbow level: a clear inhibition of BB EMG was mirrored by a facilitation of TB. These two

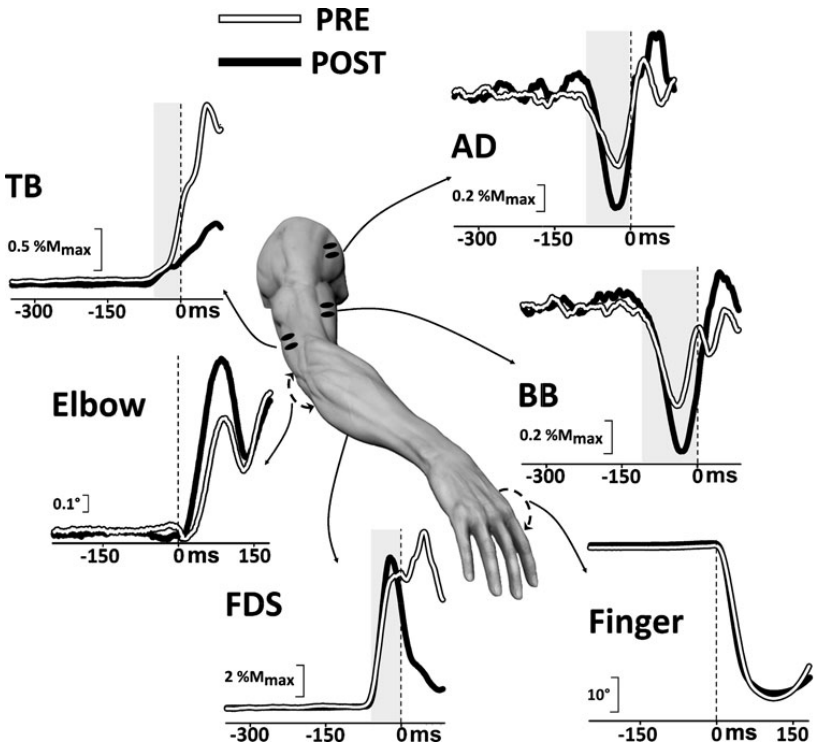

Fig. 1 Intralimb APAs change after short-term immobilization. Average recordings in a representative subject before (PRE, *white*) and after (POST, *black*) immobilization. When rapidly flexing the index finger (Flexor Digitorum Superficialis, FDS, prime mover), the arm equilibrium is preserved thanks to APAs (shaded area), which are excitatory in Triceps Brachii (TB) and inhibitory in Biceps Brachii (BB) and Anterior Deltoid (AD). After 12-h immobilization, FDS activation preceding the movement onset and index finger movement was unchanged. Instead, inhibitory APAs in BB and AD apparently increased, while excitatory APA in TB was marginally decreased. The changes in the postural chain lead to a less effective fixation of the elbow joint, which showed a larger displacement during index finger acceleration

effects were similar for both timing and (normalized) amplitude. An important anticipatory reduction in the EMG activity could also be observed in the more proximal AD muscle. Thus, the reciprocal modulation at the elbow and the inhibitory effect at the shoulder would in fact counteract both the arm flexion and the scapular elevation, which is developed when the index finger is flexed, so that the full APA chain stabilizes the more distal joints (Caronni and Cavallari 2009a).

APAs after 12-h immobilization: EMG recordings

Figure 1 reports also the comparison of the rectified and integrated EMG traces recorded before (PRE) and after (POST) immobilization. It is apparent that in both conditions, activation of the FDS muscle, which starts about 14 ms before the index finger flexion, is clearly preceded (by about 30 ms) by a major postural inhibitory activity in BB and AD muscles, which is almost synchronous to an excitatory postural adjustment in TB muscle. Note, however, that in the time window between APAs and movement onsets, the inhibition of BB and AD is increased after immobilization, while the activity remains unchanged in FDS; on the other hand, TB excitation is reduced. These data testimony that a short-term immobilization of the distal joints interferes with the motor program that generates the proximal components of the postural control.

The effect of immobilization has been regularly observed, although to varying degree, in all ten subjects. Figure 2b shows the mean amplitude of the APAs, expressed as a percentage of the average value of the maximum motor-evoked potential (M_{max}) recorded in the two sessions. Figure 2a shows that the average level of FDS muscle activation does not reveal significant changes ($t_9 = 1.46$, $P = 0.18$), before and after immobilization. The average inhibitory effects on BB and AD and excitation on TB are instead compared on the right. A two way, *muscle* x *session* ANOVA with repeated measures showed a significant main effect for both factors (*muscle*: $F_{2,18} = 18.65$, $P < 0.0001$; *session*: $F_{1,9} = 14.73$, $P = 0.004$) and the absence of any *interaction* ($F_{2,18} = 0.23$, $P = 0.79$). Thus, after immobilization of the wrist, inhibition of BB and AD significantly increased (+19.4% and +30.3%, respectively) and excitation of TB significantly decreased (-36.0%). The only significant Tukey's post hoc tests are those comparing excitation in TB versus inhibition in BB and AD. Pooled within-PRE and within-POST session variability (in $\%M_{max}$) was 1.64 and 1.40 in FDS, 0.23 and

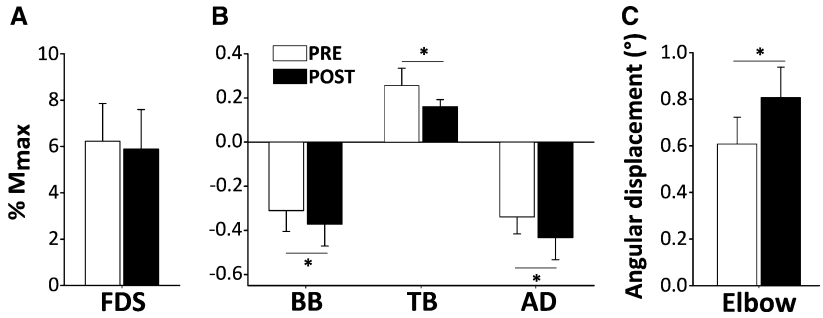

Fig. 2 Amplitude of voluntary activation in FDS, of APAs in BB, TB and AD, and of elbow displacement, before (PRE, *white*) and after (POST, *black*) immobilization. Mean values ± SEM. Paired *t* tests found no PRE versus POST difference in FDS activation, but a significant increase of APAs in BB and AD. The change in TB did not reach significance. APAs changes lead to a significant increase of elbow displacement

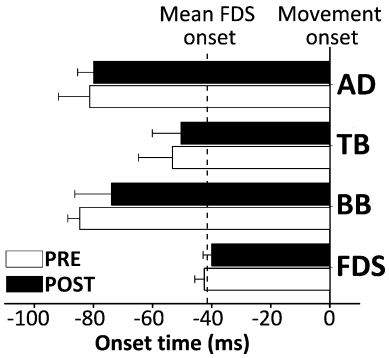

Fig. 3 Timing of FDS voluntary activation and of APAs in BB, TB, and AD before (PRE, *white*) and after (POST, *black*) immobilization Mean values ± SEM. Paired *t* tests showed no PRE versus POST differences. Time 0 marks the onset of finger flexion

0.25 in BB, 0.26 and 0.16 in TB, and 0.26 and 0.29 in AD, respectively.

The time course of the effects was similar in the two experimental sessions. Figure 3 shows the average latency of the APA onset in the individual muscles: note that EMG activation in the prime mover is constantly preceded by the APA in BB, TB, and AD muscles.

APAs after 12-h immobilization: goniometric recordings

The clear changes observed in the APAs in response to immobilization are evidently expected to cause an altered fixation of the proximal joints, leading to a less accurate execution of the finger flexion. The kinematics consequences induced by immobilization were easily highlighted by comparing the angular excursion of the elbow recorded in two experimental sessions. Figure 2c shows that, after removing the plaster, the amplitude of elbow excursion was significantly higher (0.798° ± 0.12° vs. 0.628° ± 0.11°; $t_9 = 2.55$, $P = 0.031$).

Control measurements

Table 1 reports the control measurements concerning the substantial stability of the amplitude and duration of the index finger flexion; the amplitude of the M_{max} waves and the level of EMG activity in the muscle that receive inhibition. For all parameters, statistics showed no difference between the PRE- and the POST-immobilization values. This will exclude changes in the kinematics parameters of the movement, in the interface between electrodes, skin,

Table 1 Control measurements

	PRE	POST	t_9	*P*
Finger movement amplitude (°)	46.6 ± 3.4	45.6 ± 3.2	0.92	0.38
Finger movement duration (ms)	129.4 ± 15.0	124.4 ± 15.0	1.32	0.22
M_{max} in FDS (mV)	1.8 ± 0.3	1.7 ± 0.3	0.51	0.62
M_{max} in BB (mV)	3.8 ± 0.9	3.2 ± 0.6	0.72	0.49
M_{max} in TB (mV)	2.5 ± 0.4	2.6 ± 0.4	0.57	0.58
M_{max} in AD (mV)	2.3 ± 0.3	2.1 ± 0.3	1.12	0.29
Background EMG level in BB (%M_{max})	0.9 ± 0.2	1.0 ± 0.3	0.88	0.40
Background EMG level in AD (%M_{max})	1.0 ± 0.3	1.1 ± 0.3	1.03	0.33

Amplitudes and durations of index finger movement, amplitude of M_{max} waves, and reference EMG level in BB and AD (which receive inhibition). Mean values ± SEM. Paired *t* tests found no differences in PRE versus POST values, excluding that the changes in APAs size could be ascribed to a difference in movement kinematics, a change in skin impedance or a difference in the number of recruited motoneurons

and muscles and in the level of background motoneurons activity recruited in the two situations.

Discussion

The aim of this study was to determine whether a short-term immobilization (12 h) interferes in parallel with both the activation of the prime mover muscle, responsible for a given movement, and with the postural muscles that are recruited to stabilize the limb. For this purpose, a known experimental paradigm was used (Caronni and Cavallari 2009a), in which index finger flexion promoted by the FDS muscle evokes APAs in BB, TB, and AD. To the best of our knowledge, this is the first paper that shows that a short-term immobilization interferes with the control of the postural muscles. In the past, Moisello et al. (2008) have demonstrated that short-term immobilization effectively modifies the focal movement concerning the sole kinematic variables. Our results, instead, do not show a modification to the focal movement kinematics (controlled with a goniometer), simply because subjects were explicitly asked to perform finger flexion in a way that the movement was mechanically comparable before and after immobilization.

After wrist immobilization, inhibitory APAs in BB and AD muscles were increased, while facilitation of the TB muscle was decreased; this was also paralleled by an increase of the elbow excursion. The data presented here are in agreement with those reported by Moisello et al. (2008) in which immobilization was shown to produce changes in the coordination of adjacent joints leading to a decline in the accuracy of the trajectory, and ultimately to a scarce precision of the voluntary movement, similar to that already described in patients with proprioceptive deafferentation (Ghez et al. 1995; Gordon et al. 1995; Sainburg et al. 1995). However, our results disclosed that the trajectory impairment has to be attributed to focal as well as postural components of the movement. Few days of immobilization seem to decrease the somatosensory cortex excitability (Facchini et al. 2002), but according to Huber et al. (2006) even 12 h of immobilization were already effective in decreasing the amplitude of both the somatosensory and motor evoked potentials, suggesting that a synaptic depression has developed in the cortex. According to Huber, the short-term immobilization lessens the amplitude of the P45-wave in median somatosensory evoked potentials, which represents the processing of the proprioceptive information in the sensory-motor areas (Allison et al. 1992). Moreover, the P45 reduction was closely related with the inaccuracy of voluntary movement. As a whole, these authors suggested that short periods of immobilization trigger a synaptic depression upon the primary sensory-motor cortical representations of the immobilized segment. We propose that in a situation of synaptic depression of the above sited areas, to obtain a quantitatively similar voluntary movement before and after immobilization (as we got in the present study) an increase in the central voluntary command is needed.

Since APAs are scaled to prime mover activation (Aruin and Shiratori 2004), a parallel change should then occur in APAs too, but this would lead to a significant increase of both excitatory APAs in TB and inhibitory APAs in BB. The unbalanced effect showed in the antagonistic muscles BB and TB suggests, in agreement with the results of Facchini et al. (2002), that immobilization triggers a tonic enhancement of inhibitory drive involving not only the cortical representation of the immobilized joint but also the adjacent areas. In BB, in which a tonic voluntary drive maintains the elbow at the requested 90°, the tonic enhancement of inhibition that might decrease the EMG background level and affect the elbow angle is instead compensated by a comparable increase of the tonic voluntary drive. In this condition, the increase in central commands for the focal movement and for the associated APAs (required for overcoming the depression of the FDS representation) would simply lead to an increased inhibitory APA in BB. On the other side in TB, which is at rest before the movement, the enhancement of inhibition would not affect the background EMG level but would offset the increase in the central commands, thus affecting the excitatory APA. This tonic enhancement of inhibition may stem from an increased intracortical inhibition, as observed after immobilization by Clark et al. (2010), but may as well come from an increased cerebellar activity.

Our results deserve some further brief comments. First, the reciprocal effect on biceps (more inhibition) and triceps (less excitation) may be due to the general increase of descending inhibition distributing upon the two motoneuronal pools, but may as well as be the expression of a change in spinal reciprocal inhibitory circuits (Katz et al. 1991), which are known to be fed by cortico-spinal projections (Cavallari et al. 1984; Kudina et al. 1993). However, the first hypothesis seems to be preferred, taking into account that AD activity is also more inhibited and spinal reflexes seems unmodulated during the whole period of motor preparation (Caronni and Cavallari 2009b). Second, a series of control measurements allows us to exclude that other factors may have influenced our results. In particular, the constancy of M_{max} in the PRE and POST sessions revealed a substantial stability of the recording apparatus all along the 12-h period, as observed also by Facchini et al. (2002) after 3 days of immobilization. Moreover, since movement amplitude and duration may affect the precision of the movement itself as well as the characteristics of APAs (Lee et al. 1987; Aruin and Shiratori 2004), it has also been verified that the kinematics of index finger

flexion did not change in the two experimental conditions. Last, the level of the background EMG activity in BB and AD was found to be analogous in the two sessions, the sensitivity of the pool to facilitation or to inhibition being thus comparable in the two situations (Crone et al. 1990).

Seki et al. (2001a, b) reported that, after immobilization, the properties of the muscle underwent changes in the ratio between fast and slow muscle fibers, but these changes took place only after 3–4 weeks. In animal studies, researchers have also shown that 12 h of decreased muscle activity produced some disturbances in intracellular levels of messenger RNAs for members of the aspects of metabolism and muscle structure, but these changes needed several weeks to produce changes at the level of the muscle fiber (Bey et al. 2003). The changes in motor performance found in our study occur, instead, too early to be related to changes in muscle structure.

In conclusion, differently from other papers (Brown and Frank 1987), our work strengthens the argument that APAs may be organized similar to voluntary movement: in fact, although they may be scaled in a different manner, both are shaped in the motor cortex (Caronni and Cavallari 2009b; Petersen et al. 2009), undergo similar amplitude and time modulations (Caronni and Cavallari 2009a), and, as shown here, are affected in parallel by immobilization.

It is worth noting that, although the prime mover activation remains unchanged after the immobilization, the trajectory described by the index finger is most likely changed between the two sessions due to the modification in the postural control that led to a less effective stabilization of the proximal joint, as was suggested by the mechanical model designed by Caronni and Cavallari (2009a).

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Accuracy of pointing movements relies upon a specific tuning between anticipatory postural adjustments and prime mover activation

A. Caronni, F. Bolzoni, R. Esposti, C. Bruttini and P. Cavallari
Human Physiology Section of the DePT, Università degli Studi di Milano, Milan, Italy

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Correspondence: P. Cavallari, Human Physiology Section of the DePT, Università degli Studi di Milano, 32, Via Mangiagalli, 20133 Milano, Italy.
E-mail: paolo.cavallari@unimi.it

Abstract

Aim: Equilibrium-perturbing forces associated with a voluntary upper-limb movement can be strong enough to displace the whole-body centre of mass. In this condition, anticipatory postural adjustments (APAs), developing in muscles other than the prime mover, are essential in maintaining the whole-body balance. Here, we test the hypothesis that APAs preceding an upper-limb target-reaching movement could play a role also in controlling the movement accuracy.

Methods: Standing subjects (10) were asked to flex the right shoulder and touch with the index fingertip the centre of a target positioned in front of them. The reaching task was also performed while wearing and after doffing prismatic lenses (shifting the eye field rightward). EMGs from different upper- and lower-limb muscles and the mechanical actions to the ground were recorded.

Results: (i) Before wearing prisms, subjects were very accurate in hitting the target, and the pointing movements were accompanied by APAs in quadriceps (Q) and tibialis anterior (TA) of both sides, and in right hamstrings (H) and soleus (SOL). (ii) After donning prisms, rightward pointing errors occurred, associated with a significant APA increase in right Q and TA, but without changes in the recruitment of right anterior deltoid (prime mover) and biceps brachii. (iii) These pointing errors were progressively compensated in about 10 trials, indicating a sensorimotor adaptation, and APAs returned to values recorded before wearing prisms. (iv) After doffing prisms, pointing errors occurred in the opposite direction but changes in APAs did not reach significance.

Conclusion: We propose that, besides preserving the whole-body balance, APAs are also tailored to obtain an accurate voluntary movement.

Keywords anticipatory postural adjustment, human, pointing, prismatic lenses, sensorimotor adaptation, voluntary movement.

Anticipatory postural adjustments (APAs) are known to be unconscious muscular activities, preceding any voluntary movement, aiming to prevent the *segmental* and *whole-body* equilibrium disturbances caused by the movement itself (see Massion 1992).

In a multilink structure as the human body, movement may perturb the equilibrium because (i) the contraction of the prime mover exerts forces on both the distal and the proximal tendon (typically, the former transmits the intended movement, while the latter acts on the posture of more proximal segments; Zatsiorsky 2002), (ii) the forces acting on one segment not only arise from the pertinent muscles but also include the 'interaction forces' deriving from movement of other distal segments (Hollerbach & Flash 1982) and (iii) by changing the body geometry, movement

displaces the projection of the whole-body centre of mass on the ground (CoM; e.g. Bouisset & Zattara 1987; see also the next paragraph).

The importance of proper *whole-body stabilization* is immediately apparent when considering standing subjects performing voluntary movements that involve large masses. In such motor acts, the equilibrium-perturbing forces would cause a whole-body imbalance, by displacing the trunk and the whole-body CoM (Bouisset & Zattara 1987, Bouisset & Do 2008, see also Hess 1943). On the other hand, in those motor tasks in which the whole-body balance is not threatened, the importance of an accurate *segmental stabilization* might look less obvious. In our previous papers (Caronni & Cavallari 2009a,b), it has been reported that when the index finger is flexed, an APA chain develops in several upper-limb muscles to stabilize the *segmental* equilibrium of the arm. According to a mechanical simulation showing the consequences of a poor APA control on the movement trajectory (Caronni & Cavallari 2009a), we proposed that APAs could be crucial to guarantee movement accuracy by an appropriate stabilization of the proximal segments. Further studies showed that a short-term immobilization of the wrist and fingers leads to a APAs impairment in proximal arm muscles, resulting into an impaired fixation of the elbow joint (Bolzoni *et al.* 2012). Moreover, a growing body of evidence clarifies the contribution of the proximal segments on both movement trajectory and speed of distal segments (e.g. Kaminski *et al.* 1995, Archambault *et al.* 1999, Pigeon *et al.* 2000, Pozzo *et al.* 2002, Bortolami *et al.* 2008, Kim *et al.* 2009).

At our knowledge, information about the linkage between APAs and accuracy of voluntary movements may only be figured out from studies analysing the pointing to targets of different size (e.g. Bonnetblanc *et al.* 2004, Nana-Ibrahim *et al.* 2008, Bertucco & Cesari 2010). Indeed, these studies show that Fitts' law[1] (1954) governs both the prime movement speed and the associated APAs. This observation actually provides an indirect suggestion that APAs are involved in attaining the movement precision necessary to accomplish the imposed accuracy constraint. However, APAs are known to be scaled according to movement speed (Lee *et al.* 1987, Shiratori & Aruin 2007); thus, the linkage between target and APAs size could then be just an epiphenomenon of the former relationship.

Aim of the present study is to seek a direct proof of the relationship between the APAs amplitude and the endpoint of a target-reaching movement. A reaching task was thus performed with the upper limb, before and after donning prismatic lenses, which are known to shift the binocular eye field and cause the subject to miss the target (Redding *et al.* 2005). After some movement repetitions, subjects adapted to the new condition, compensating for the prisms effect and hitting the target again. As a novelty, we will show that the prism-induced pointing error specifically underlies changes in APAs amplitude with no changes in the prime mover activation, thus sustaining the hypothesis that a successful and accurate pointing movement relies upon a specific tuning between APAs and prime mover activation (see Caronni & Cavallari 2009a). Moreover, we also ruled out any bias caused by changes in movement velocity because prismatic lenses do not affect the target size, thus leaving the movement speed unchanged.

Materials and methods

Ten right-handed subjects (four women) were engaged (mean age ± SD: 26.9 ± 3.28 years). They reported no history of orthopaedic or neurological disorder; none of them reported a reduction in the visual acuity. Each volunteer gave his/her informed consent to the experiment. This study is conform with Good Publishing Practice in Physiology (Persson & Henriksson 2011).

Motor task

Subjects stood barefoot on a force platform, with the feet normally apart in a natural upright position, and both upper limbs lying along the body. After an acoustic *go signal*, delivered every 5 s so as to mark the overall temporal cadence, subjects had to perform a self-paced index-finger pointing movement, using right shoulder flexion, which was as fast and accurate as possible. Subjects never anticipated the go signal. A variation of the 'Belen'kii *et al.* (1967) has been adopted: subjects were asked to point-and-touch a target placed in front of them, watch the final position they attained for no more than 1 s, return to the initial position at their preferred speed and finally relax before starting a new movement. The task was also performed while wearing and after doffing prismatic goggles.

By monitoring the EMG traces during the experiment, it was apparent that they returned to their baseline within 3 s from the movement onset. The target consisted in two lines drawn on a Plexiglas screen, 1 mm thick × 2 cm long, one vertical and one horizontal, so that its centre was clearly visible. The anterior–posterior, vertical and lateral position of the target was regulated for each subject: the target was

[1]Movement duration increases with movement amplitude and decrease when the target size increases, i.e. when the accuracy constraint loosens.

positioned at the shoulder height on the subject's midline, one upper-limb length from the subject's shoulder. Care was taken to align the subject's sagittal plane to the platform midline; feet position was then marked on the platform and checked throughout the experiment. Before starting each exercise, care was taken that the CoP position (calculated online by the SMART system) fell on the platform midline.

Experimental design

A couple of prismatic lenses (Fresnel 3M® Press-On, St. Paul, MN, USA, 20 dioptres) were mounted on conventional safety goggles to produce a rightward shift of the binocular eye field of about 11°. This corresponds to a 12-cm linear shift of the target, placed at 60 cm (about one arm length) in front of the subject. While wearing prisms, subjects realized the shifting in the binocular eye field only when they performed the first pointing movement. Indeed, only when the finger reached the Plexiglas screen, they became aware they had missed the target, also because the fingertip underwent the same visual position bias as the target itself. Subjects were asked to close their eyes when donning and doffing goggles and not to move their arms before the new recording session started.

Each experiment was arranged into three sessions of repeated target reaching: before donning (BEFORE), while wearing (DURING) and after doffing (AFTER) goggles with prismatic lenses. In each session, 25 trials of the target-reaching task were performed. Between two subsequent sessions, subjects did rest for 5–10 min. Subjects donned the goggles just before starting the DURING session and kept them on throughout the following rest period. Goggles were removed only right before starting the AFTER session. No subject reported fatigue. They were allowed to familiarize with the motor task by practicing, without goggles, at least 15 target-reaching movements before the first experimental session.

Recordings

In each experiment, electromyographic (EMG) activity, right upper-limb movement, target position and the forces exerted onto the ground were synchronously recorded.

Electromyographics were recorded from two muscles of the right upper limb (anterior deltoid, AD; biceps brachii, BB) and four muscles of both the right and left lower limbs (quadriceps, Q; hamstring, H; tibialis anterior, TA; soleus, SOL). For each muscle, conventional disposable bipolar electrodes (1 cm diameter) were glued 25 mm apart on the skin covering the muscle belly. Skin was cleaned with abrasive cotton discs and alcohol. The EMG system was a set of customized BTS pre-amplified electrodes (gain ×10, pass band 30–500 Hz), followed by GRASS IP511 amplifiers (total gain 1-10k).

A 3D motion analysis system (SMART-D, BTS®, Garbagnate Milanese, Italy; six infrared cameras) was used to record both the right upper-limb movement and the target position. Reflecting spherical markers (1.5 cm ∅) were taped to the dorsal aspect of the metacarpophalangeal joint of the second finger, radius distal end, olecranon and acromion. Reflective tape was applied directly to the distal phalanx of the index finger so as to resemble a hemispherical marker. This avoided placing a marker directly on the fingertip, which could interfere with the pointing movement. This method allowed the kinematics acquisition device to track the centre of the fingertip as all the other markers, with the same accuracy (±0.5 mm). A positive deflection on the marker trace indicates a leftward (x, right–left axis), forward (y, posterior–anterior axis) or downward (z, up–down axis) displacement. To identify target position, two hemispherical markers were glued on the Plexiglas screen, equidistantly above and below the target cross. Thus, target position was recognized as the xyz coordinates of the 'virtual' marker placed midway on the line connecting the two.

A dynamometric platform (AMTI® OR6-7, Watertown, MA, USA) was used to record forces (F) and moments (M) discharged to the ground with reference to the above axes.

Data acquisition was accomplished by the SMART-D workstation. EMG and platform signals were A/D converted at a sampling frequency of 1120 Hz, while cameras sampling rate was 70 Hz. EMG, kinematics and force signals were digitalized with 16-bit resolution and stored on a PC for offline measurements.

Data analysis

As stated above, subjects were asked to start the target-reaching movement with a right shoulder flexion. Thus, AD muscle will be referred to as the pointing *prime mover*.

Movement onset (0 ms) was identified as the time when the y position trace of the elbow marker crossed a threshold (set at the mean elbow position in the 500 ms preceding the go signal +2 SDs) for at least 100 consecutive ms. *Movement end* was instead identified, by the same threshold method, from the y coordinate of the target 'virtual' marker, signalling the impact of the index finger on the Plexiglas screen. Systematically, timing measurements were visually checked and independently confirmed by two of the authors (AC and FB). The pointing movement was assumed to terminate when the finger touched the Plexiglas screen.

We define *pointing error* the distance between the index-fingertip position on the screen and the target (see, for example, Luauté *et al.* 2009, Chapman *et al.* 2010, Ronchi *et al.* 2011). For each trial, the horizontal (x) and vertical (z) components of the pointing error were measured. Movement onset was chosen as reference point to leave enough time for APAs to fully develop. Moreover, this reference allowed us to quantify the amplitude and latency of the premovement activation of AD and BB. In addition, this analysis allowed quantifying APAs amplitude in their mechanical actions on the ground, which develop together with or even after the prime mover activation.

Platform recording analysis was conducted on the three components of the forces exerted to the ground (*Fx, Fy and Fz*), on the displacement of the centre of pressure (*CoPx, CoPy*) and on the torque exerted about the z axis passing through the CoP (*Tz*). The position of the CoP and the value of Tz were derived from the recorded platform signals; Tz was calculated according to the following formula:

$$\mathrm{Tz} = \mathrm{Mz} + \mathrm{CoPy} * \mathrm{Fx} - \mathrm{CoPx} * \mathrm{Fy} \quad (1)$$

with Mz: moment about the vertical axis passing through the platform centre; CoPx and CoPy: right–left and posterior–anterior CoP coordinates in the platform plane respectively.

CoP coordinates were calculated as CoPx = –My/FzandCoPy = Mx/Fz; being Mx and My the moments about the x and y axes passing through the centre of the platform surface. For each trial, both EMGs and platform recordings were re-aligned on movement onset (0 ms). EMGs were rectified and then smoothed by a running average (time window 35 ms).

In each session, analysis of EMG and platform recordings was performed on trials 1–5 (1st BLOCK), in which pointing error resulted to be significantly different among sessions, and trials 11–15 (2nd BLOCK), in which the pointing error was similar in the three sessions.

The EMG and the platform traces within each block were then averaged to obtain a *block mean trace (BMT)*. For each muscle, BMTs were normalized on the mean amplitude of the BMT recorded in the 1st BLOCK of the BEFORE session, thus allowing comparison between EMGs recorded from different subjects. Background activity (i.e. the mean amplitude of the BMT from −1000 to −500 ms) was finally subtracted from the EMG and platform BMTs. Voluntary *EMG onset* in arm muscles and *APA onset* in postural muscles, as well as in force platform traces, were identified as the time when the BMT crossed ±2 SDs of the mean background activity level and remained above that threshold for at least 50 ms. All *onset timings* were visually checked and independently confirmed by two of the authors (AC and FB). *APAs amplitude*, or amplitude of premovement activation in AD and BB, was quantified as the mean amplitude of the BMT in a time window arbitrarily set from −25 to 0 ms (see also Caronni & Cavallari 2009a). It is also worth to note that in the great majority of recordings (except for left Q in BEFORE), APAs and prime mover activation level at the 0 ms corresponded to the highest premovement amplitude, and that APAs onset in EMG and platform recordings were, on average, much earlier than −25 ms. Data were analysed by a custom-made software.

Statistical analysis

A two-way repeated-measures ANOVA, with prisms (BEFORE, DURING and AFTER) and trials (1–25) as factors, was applied to horizontal and vertical pointing errors. A similar test *prisms* (BEFORE, DURING and AFTER) × *blocks* (1st and 2nd BLOCK) was also applied to (i) the *amplitude* and *timing* of APAs, or of premovement activation in AD and BB and (ii) the mean movement duration of trials 1–5 and 11–15. When ANOVA resulted in a significant main effect and/or interaction, Tukey's HSD test was used for post hoc comparisons. Significance level was set at 0.05.

Results

Prismatic lenses induce pointing errors in a target-reaching movement

Before wearing prismatic lenses, subjects were very accurate in reaching the target: in each of them, the index finger final position scattered within a circle of 15 mm radius from the target centre (white dots in Fig. 1a,b). When the same movement was performed while wearing goggles (Fig. 1b, black dots), the index fingertip hit the Plexiglas screen to the right of the target. However, within ten trials (*prisms adaptation*, see Fig. 1c,d), pointing fell again within the 15-mm circle. Pointing after goggles removal (Fig. 1b, grey dots) caused the subject to hit to the left of the target and, also in this case, the error faded away (*recovery from prisms after-effect*) after a few movement repetitions.

The mean time course of the horizontal and vertical components of the pointing error (H and V respectively) for each of the three experimental conditions (BEFORE, DURING and AFTER wearing prisms) is detailed in Figure 1c,d. When subjects performed the motor task before wearing prismatic lenses, neither the mean H-error (2.0 ± 1.6 mm, mean ± SEM) nor the mean V-error (0.9 ± 1.0 mm) was different from 0 (one-sample t-test, $P > 0.25$ for both variables).

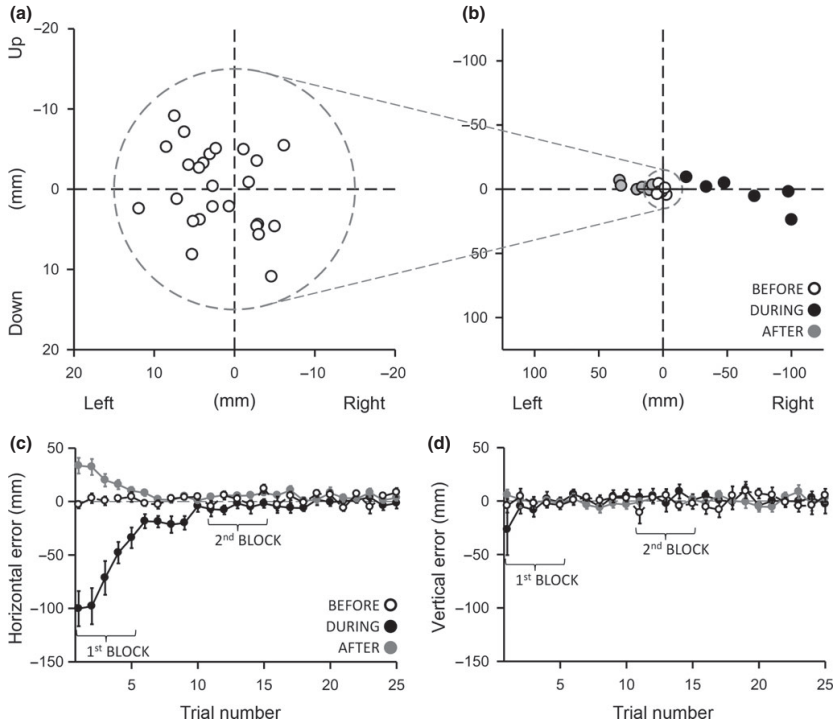


Figure 1 (a) Final position of the index finger (average of all subjects) in each of the 25 pointing movement trials performed BEFORE wearing goggles with prismatic lenses (white dots). All points fell within a circle of 15 mm radius from the target centre (grey dashed circle). (b) Final position of the index finger (average of all subjects) in the first six pointing trials, performed in the three successive experimental sessions (BEFORE, DURING and AFTER wearing prismatic goggles). While wearing prisms (DURING, black dots), the index fingertip missed the target and pointing terminated on its right. After doffing prisms (AFTER, grey dots), the error reversed and pointing terminated on the target left, signalling an after-effect. (c, d) Average horizontal and vertical pointing errors (±intersubject SEM) in each movement trial for the three experimental sessions (same labels and symbols as in b). The rightward horizontal pointing error observed in the DURING session recovered, in about 10 trials, to values comparable to those of the BEFORE session. The leftward error in the AFTER session had a lower amplitude than that in the DURING one and recovered more quickly. A *prisms* × *trial* ANOVA found that the horizontal pointing error was significantly different among sessions only in trials 1–5. The same ANOVA design, instead, did not found any significant change in vertical pointing error. Thus, electromyographic (EMG) and platform data from trials 1–5 (1st BLOCK) were matched to those of other five trials (11-15, 2nd BLOCK), in which pointing error was comparable among sessions, that is, both adaptation to prisms and recovery from after-effect were completed.

When subjects performed the first target-reaching trial while wearing the prismatic lenses, a large rightward H-error occurred (-100.3 ± 16.4 mm; $P < 0.001$), while V-error was not different from 0 (-26.7 ± 23.9 mm; $P > 0.25$). Also after doffing goggles, a considerable H-error occurred (33.5 ± 7.3 mm; $P < 0.001$), but now all subjects ended the pointing to the left of the target. Conversely, V-error (5.7 ± 5.1 mm; $P > 0.25$) was again not different from 0.

Two-way ANOVA on H-error showed a significant effect of both *prisms* ($F_{2,18} = 26.19$, $P < 0.001$) and *trials* ($F_{24,216} = 8.18$; $P < 0.001$), as well as a significant interaction ($F_{48,432} = 14.92$, $P < 0.001$). Post hoc comparisons revealed that *trials* (i.e. time) had no effect in the BEFORE session, while there was a significant difference between BEFORE and DURING sessions for trials 1–5 (P always < 0.001) and, only for trial 1, between BEFORE and AFTER ($P < 0.002$). Note also that the adaptation process (trial 1–5 with prisms) is considerably longer as compared to the after-effect recovery (trial 1, after prisms). As a two-way ANOVA showed no significant modification on the V-error, the following analysis will focus on the H-error only.

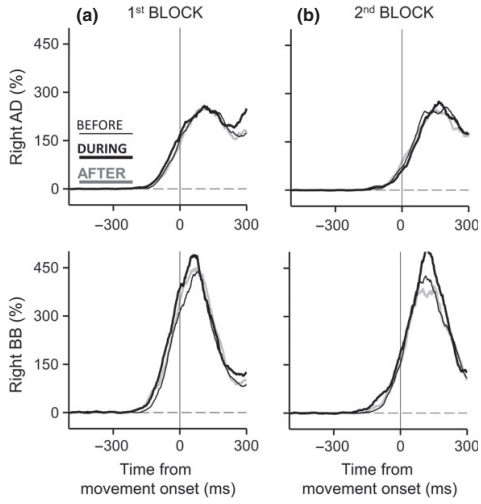


Figure 2 Rectified and smoothed (see Methods) electromyographic (EMG) recordings from the prime mover anterior deltoid (AD) and from the biceps brachii (BB) muscles. Averaged traces of one representative subjects, obtained in trials 1–5 (a – 1st BLOCK) and in trials 11–15 (b – 2nd BLOCK) of the three experimental sessions: BEFORE (thin black line), DURING (thick black line) and AFTER (thick grey line) wearing prismatic goggles. Note that in each BLOCK, the premovement (before 0 ms) EMG activity was nearly indistinguishable in all sessions.

Prismatic lenses modify APAs of a target-reaching movement

As shown above, pointing errors of trials 1–5 were significantly different among sessions, thus a comparison of EMG and platform data from these trials (1st BLOCK – BEFORE, DURING and AFTER sessions) was carried out. Similar *between-sessions* comparisons were also drawn in a second BLOCK of five trials (11–15, 2nd BLOCK), in which adaptation to prisms and after-effect recovery were apparently completed, and pointing errors were comparable among sessions.

EMG recordings. The EMG activity recorded in the prime mover AD and in BB muscle when the right shoulder is flexed and the index finger points to the target is shown in Figure 2 for a representative subject. Note that in both muscles, premovement activity in the 1st BLOCK (before 0 ms) was nearly indistinguishable in all sessions, thus pointing errors were not due to changes in the prime mover activation.

For what concerns lower-limb muscles (Fig. 3), when the reaching movement was performed without prisms, so that pointing was accurate, excitatory or inhibitory APAs developed in all muscles, except left H and left SOL (1st BLOCK, BEFORE). The latter two will be then ruled out from analysis, because EMG amplitude at movement onset was not significantly different from the background activity (paired *t*-test, $P > 0.5$ for both muscles). When reaching was performed immediately after donning prisms and the subject's index fingertip hits the Plexiglas screen to the right of the target (1st BLOCK, DURING), APAs in Q and TA of both sides increased in amplitude (compare thick to thin black lines). When prisms were removed and subjects missed the target to the left (1st BLOCK, AFTER), APAs in Q and TA of both sides decreased to values similar to those observed in the BEFORE session. It is worth noting that the leftward deviation induced by the after-effect recovered much more quickly than the rightward deviation. To group together the same number of trials in each BLOCK, the 1st BLOCKs of the AFTER session had to include four trials in which the leftward deviation was not significant. The absence of significant APAs' changes in the AFTER vs. BEFORE session may be seemingly ascribed to this. In contrast, both when adaptation to prisms completed and when after-effect recovered (2nd BLOCK; Figs 2b and 3b,d), premovement EMG activities in AD and BB, as well as APAs in lower-limb muscles, were similar in all experimental sessions.

In summary, when prisms induce a pointing error, the movement seems to be associated with stronger lower-limb APAs, not paralleled by changes in the activation of the prime mover.

Quantitative analysis of the EMG recordings. Figure 4a, c shows the mean amplitudes of the premovement activation in AD and BB and of the APAs in lower-limb muscles. Two-way ANOVAs (*prisms* × *blocks*), computed on premovement EMG amplitude of the two upper-limb muscles, showed no *prisms* nor *interaction* effect, while a significant *blocks* factor resulted for both AD ($F_{1,9} = 117.13$, $P < 0.001$) and BB muscles ($F_{1,9} = 52.74$, $P < 0.001$). Two-way ANOVAs (*prisms* × *blocks*) on the right Q and the right TA resulted in a non-significant *prisms* main effect, a significant *blocks* main effect ($F_{1,9} = 5.67$, $P < 0.05$ and $F_{1,9} = 11.72$, $P < 0.01$ respectively) and a significant *interaction* ($F_{2,18} = 3.57$, $P < 0.05$ and $F_{2,18} = 4.81$, $P < 0.05$ respectively). According to the post hoc comparisons, *prisms* affected only the 1st BLOCKS, in which right Q EMG was larger in the DURING than in both BEFORE and AFTER sessions, while right TA was larger in DURING than in BEFORE session only. ANOVAs on right H, right SOL and left Q showed neither main effects nor interactions, while a significant *blocks* main effect was found in left TA ($F_{1,9} = 7.6$, $P < 0.05$).

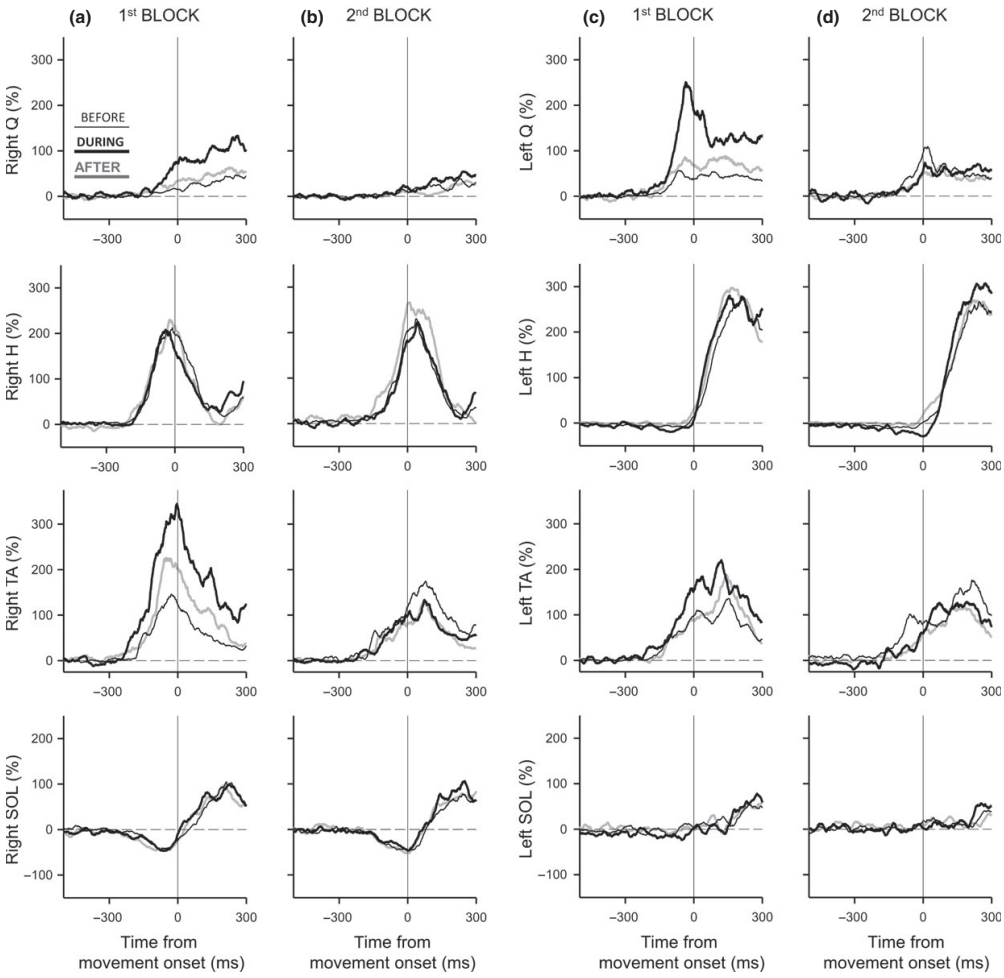


Figure 3 Rectified and smoothed electromyographic (EMG) recordings from the lower-limb muscles quadriceps (Q), hamstring (H), tibialis anterior (TA) and soleus (SOL) of the right (a, b) and left (c, d) sides. Averages of the traces of one representative subjects, obtained in trials 1–5 (a, c – 1st BLOCK) and in trials 11–15 (b, d – 2nd BLOCK) of the three experimental sessions: BEFORE (thin black line), DURING (thick black line) and AFTER (thick grey line) wearing prismatic goggles. BEFORE wearing prisms, excitatory or inhibitory anticipatory postural adjustments (APAs) developed, prior to the movement onset, in all muscles except left H and SOL. In the 1st BLOCK of the DURING session, APAs in Q and TA of both sides increased, while when prisms were doffed (1st BLOCK of AFTER session), APAs decreased to values similar to those of the BEFORE session. In contrast, in the 2nd BLOCK, when adaptation to prisms and after-effect recovery were completed, APAs in lower-limb muscles were similar in all experimental sessions.

Despite the strong increase in APAs strength in left Q and left TA, prisms did not produce significant changes.

Figure 4 summarizes also the latencies of the pre-movement activation and of the APAs. Two-way ANOVAs (*prisms* × *blocks*) resulted in non-significant *prisms* main effect nor interaction, while *blocks* factor was significant in AD, BB, right Q, right TA and left TA (in all cases, $F_{1,9} > 7$, $P < 0.05$), that is, those muscles that showed *blocks* main effect on the EMG amplitude.

Platform recordings. Before wearing prisms, platform recordings changed prior to the movement onset, when all of them significantly differed from the corresponding background level (paired *t*-test, *P* always < 0.05). As shown in Figure 5a – 1st BLOCK, the force vector pointed backward, rightward and downward; the CoP moved backward and rightward, and the vertical torque turned clockwise. The largest prisms effect occurred in the APA revealed by the

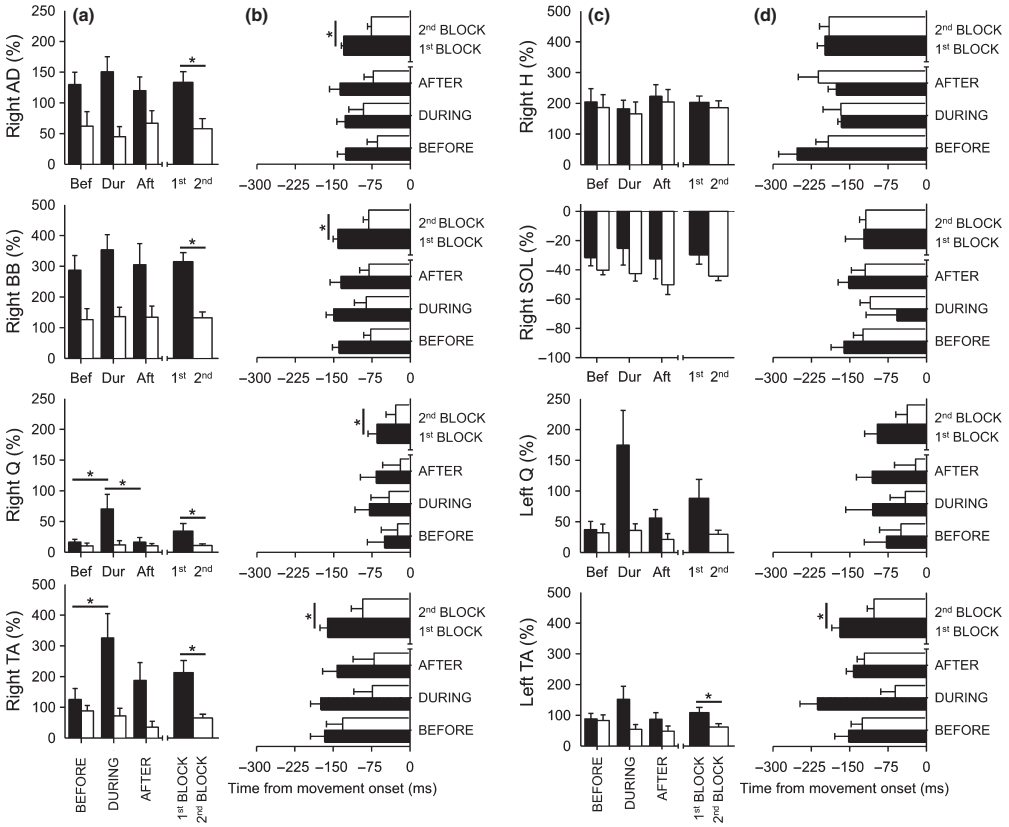


Figure 4 Mean normalized amplitude (a, c) and mean latency with respect to movement onset (b, d) of premovement activation in right arm muscles and of anticipatory postural adjustments (APAs) in lower-limb muscles (raw traces in Figs 2 and 3). Plotted values refer to the 1st and 2nd BLOCK (black and white bars respectively) of each experimental session (BEFORE, DURING and AFTER wearing prismatic goggles). Error bars mark the intersubject SEM. Significant differences (*prisms* × *block* ANOVA on each muscle) are marked by asterisks. For each BLOCK, the average of the values recorded among the three sessions is also reported, after the axis break, so as to illustrate the main effect of the ANOVA *block* factor. The APAs increase in Q and TA muscles of both legs observed in the 1st BLOCK of the DURING session (Fig. 3) reached significance only in the right limb. Moreover, a significant *block* factor was observed in the size and latency of premovement activations in AD and BB as well as in the size and latency of APAs in right Q and in right and left TA. Finally, in the 2nd BLOCK, non-significant effect of prisms was found on size or latency of premovement activations or of APAs, again in agreement with Figures 2 and 3.

CoPy (antero-posterior) displacement. When prisms were just donned (Fig. 5a – 1st BLOCK), the anticipatory displacement increased, while after doffing them, it reduced in size. When adaptation to prisms and after-effect recovery were completed (Fig. 5b – 2nd BLOCK), the APA size in CoPy was again comparable among the three sessions.

Quantitative analysis of platform recordings. Figure 6a shows the mean amplitudes of the APAs in platform recordings. Two-way ANOVA (*prisms* x *blocks*) on APA amplitude in CoPy resulted in a non-significant *prisms* main effect, a significant *block* main effect ($F_{1,9} = 4.93$, $P < 0.05$) and a significant *interaction* ($F_{2,18} = 13.19$, $P < 0.001$). According to the post hoc comparisons, *prisms* affected only the 1st BLOCK, in which the anticipatory displacement was larger in the DURING than in both BEFORE and AFTER sessions. Two-way ANOVAs on the remaining recordings highlighted only a significant *block* main effect in all traces (Fx: $F_{1,9} = 21.33$, $P = 0.0012$; Fy: $F_{1,9} = 12.71$, $P = 0.0060$; Fz: $F_{1,9} = 19.75$, $P = 0.0016$; CoPx: $F_{1,9} = 20.18$, $P = 0.0015$; Tz: $F_{1,9} = 26.80$, $P = 0.0005$). The same ANOVA design on APAs latencies (Fig. 6b) showed no *prisms* main effect nor *interaction*, but a significant *block* main effect in

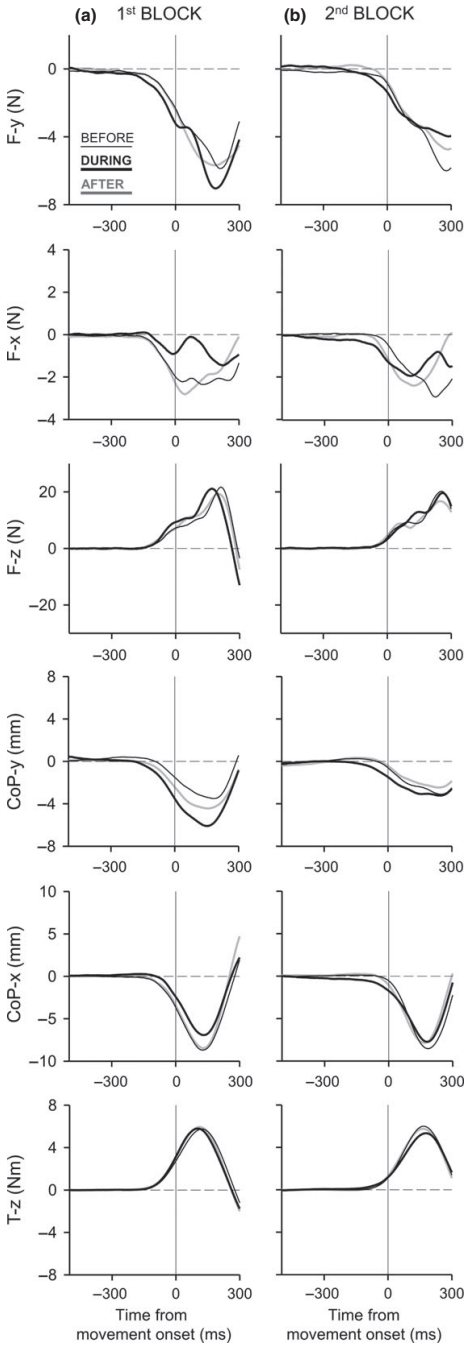


Figure 5 Force platform recordings: components of the force exerted on the ground along the three Cartesian axes (Fy, positive when directed forward; Fx, positive leftward; Fz, positive downward), displacement of the centre of pressure (CoPy, positive forward; CoPx, positive leftward) and torque about the body vertical axis passing through the CoP (Tz, positive clockwise). Averaged traces of one representative subjects, obtained in trials 1–5 (a – 1st BLOCK) and in trials 11–15 (b – 2nd BLOCK) of the three experimental sessions: BEFORE (thin black line), DURING (thick black line) and AFTER (thick grey line) wearing prismatic goggles. BEFORE wearing prisms, all platform recordings changed prior to the movement onset, thus showing APAs. Prismatic goggles induced the largest change in the APA of CoPy, which increased when prisms were just donned (1st BLOCK, DURING) and reduced in size after doffing them (1st BLOCK, AFTER). When adaptation to prisms and after-effect recovery were completed (2nd BLOCK), the size of APA in CoPy was again comparable among the three sessions.

Fy, Fz and CoPy (Fy: $F_{1,9} = 5.90$, $P = 0.038$; Fz: $F_{1,9} = 62.38$, $P < 0.0001$; CoPy: $F_{1,9} = 11.89$, $P = 0.0072$).

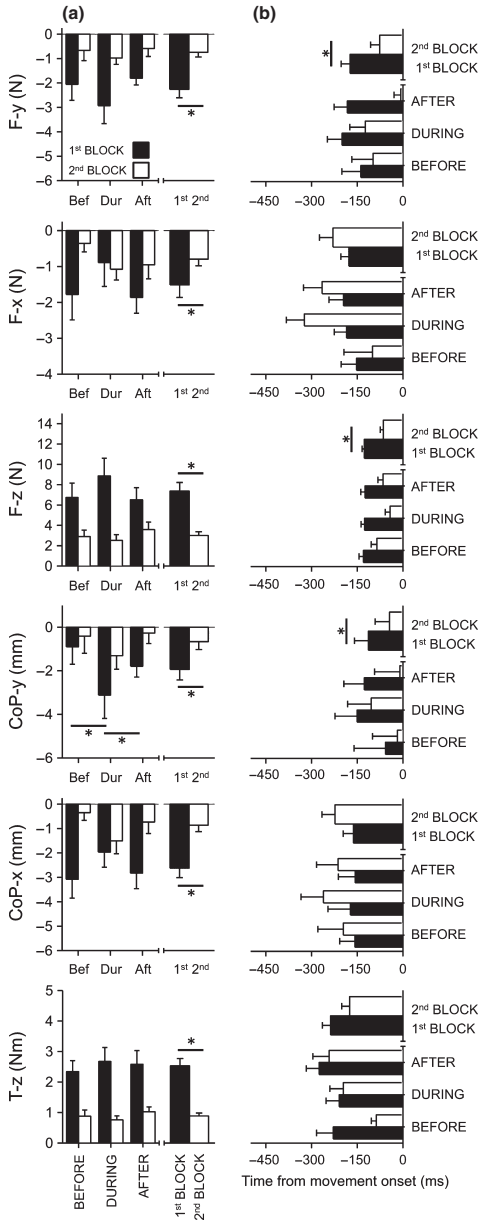
Control analysis – duration of the target-reaching movements

As it is widely reported that APAs are scaled in amplitude to movement duration (faster movements are associated with larger APAs, Lee *et al.* 1987; Shiratori & Aruin 2007), we carefully verified whether this parameter changed during the experiment. Figure 7 shows the mean duration of the target-reaching movement in the two blocks of trials, collected in the three experimental sessions. Two-way repeated-measures ANOVA (*prisms* × *blocks*) highlighted only a significant *blocks* main effect ($F_{1,9} = 63.45$, $P < 0.001$). Thus, within each block, movement duration was similar in the three sessions, indicating that the APAs' changes observed in the EMG and platform recording, within the 1st BLOCK, should not be ascribed to changes in movement velocity. On the other hand, all the APAs' changes between the two blocks (1st BLOCK vs. 2nd BLOCK comparisons) may be affected as well by the increase in movement duration observed in the second BLOCK.

Discussion

The novelty of our study is that by using prisms, we induced out-of-target movements that were found not to be associated with changes in the prime mover activation, as it might be expected, but only to changes in the APAs size. This observation reinforces the hypothesis that a successful on-target pointing movement relies upon a specific tuning between APAs and prime mover activation, as that obtained at the end of the adaptation phase.

In the following, we will first deal with the origin of the pointing error, then we will recall that accurate



motion of a segment (e.g. the hand) requires a proper coordination between distal (e.g. the upper limb) and proximal (e.g. the trunk) body parts. Thereafter, we will examine evidences suggesting a relationship between APAs and movement accuracy, and finally, we will discuss specific aspects of our results and their possible interpretation.

Figure 6 Mean amplitude (a) and mean latency with respect to movement onset (b) of anticipatory postural adjustments (APAs) in the force platform recordings (raw traces in Fig. 5). Plotted values refer to the 1st and 2nd BLOCK (black and white bars respectively) of each experimental session (BEFORE, DURING and AFTER wearing prismatic goggles). Error bars mark the intersubject SEM. Significant differences (*prisms* × *block* ANOVA on each force platform recording) are marked by asterisks. For each BLOCK, the average of the values recorded among the three sessions is also reported, after the axis break, so as to illustrate the main effect of the ANOVA *block* factor. The CoPy APA increase observed in the 1st BLOCK of the DURING session (Fig. 5) reached significance. Moreover, a significant *block* effect was observed in the size of APAs in all platform variables and also in the latency of APAs in Fy, Fz and CoPy. Finally, in the 2nd BLOCK, non-significant effect of prismatic goggles was found on size or latency of APAs, in agreement with Figure 5.

Origin of pointing error

Pointing to a visually displayed target requires a neural transformation from a visual representation of target location to an appropriate pattern of arm muscles activity. According to Soechting & Flanders (1989a,b); see also Soechting & Flanders 1992 for a

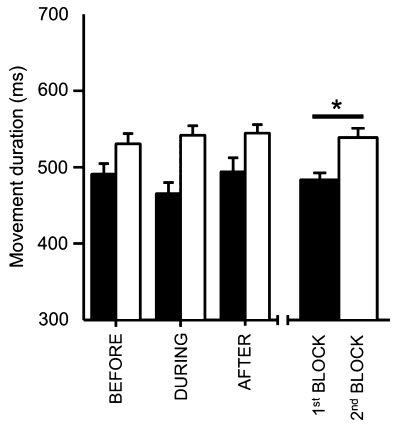


Figure 7 Mean duration of the target-reaching movement. Plotted values refer to the 1st and 2nd BLOCK (black and white bars respectively) of each experimental session (BEFORE, DURING and AFTER wearing prismatic goggles). Error bars mark the intersubject SEM. Significant differences (*prisms* x *block* ANOVA) are marked by asterisks. For each BLOCK, the average of the values recorded among the three sessions is reported, after the axis break, so as to illustrate the main effect of the ANOVA *block* factor. Note that the only significant difference was an increase in movement duration in the 2nd vs. 1st BLOCK, while prisms had no effect in either BLOCK.

review), errors in such a movement derive from errors in the sensorimotor transformation from the visual representation of the target to the kinematics representation of the planned trajectory. Indeed, such transformation is intrinsically nonlinear, but subjects usually employ a linear approximation when they have to remember the target location and point to it. These authors also showed that when subjects have to reach a position, which has been previously appreciated kinaesthetically (thus after having empirically built up the exact transformation), pointing errors dramatically reduce. Several evidences were collected that the parietal cortex plays a critical role in integrating visual and somatic inputs for building up this sensorimotor transformation (see Kalaska *et al.* 1997 for a review).

In our study, pointing errors were apparently due to the changes in the sensorimotor transformation induced by prisms. In a few trials, thanks to the visual feedback, our subjects empirically solved the new sensorimotor transformation and succeeded in reaching the target. The same occurred (in the opposite direction) after doffing goggles. An increase in pointing error when requiring to change the sensorimotor transformation, for instance by asking to reach a target in an horizontal workspace while looking at the initial position of the hand and target on a vertical screen, was also observed by Messier & Kalaska (1997).

Coordination between proximal and distal body segments

There is growing evidence from the literature showing that the performance of dexterous motor tasks, such as pointing and reaching, relies on the exact coordination between proximal (e.g. trunk) and distal body segments (e.g. hand).

Several motor control studies (Ma & Feldman 1995, Archambault *et al.* 1999, Pigeon *et al.* 2000, Robertson & Roby-Brami 2011) provide evidence that motion of the trunk and the upper limb is appropriately scaled each other to ensure the maximal accuracy when moving the hand towards a target. In their seminal paper, Hollerbach & Flash (1982) offer a model, which describes shoulder–elbow coordination in hand-reaching movements. The same model also predicts the modifications of the distal segments trajectory and its final position when the force exerted at proximal joints is inadequate, a condition in which an out-of-target movement would result. Similarly, out-of-target movements are also expected when the Coriolis force acting on the arm during the simultaneous displacement of the upper limb and torso is not compensated in a feed-forward manner (Bortolami *et al.* 2008).

Interestingly, Era *et al.* (1996) have reported that top-level rifle shooters stabilize their whole-body balance better than naive shooters, particularly in the last seconds before the shot. This and other studies investigating the same topic (e.g. Aalto *et al.* 1990, Mononen *et al.* 2007) give evidence that shooting accuracy relies on the accurate trunk and lower-limb posture control, allowing coordination of these body segments with the focal trigger pull. In close relation with the idea that postural stabilization influences movement performance, other authors showed that changes in the size of the base of support (Yiou *et al.* 2007), or the addition of a secondary motor task, which specific APAs may interfere with those of the primary motor task (Yiou 2005) might influence the velocity of the focal arm movement.

On these premises, APAs may represent the earliest part of the motor command necessary for proximal and distal body segments coordination, as also supported by our results.

APAs contribution to movement accuracy

Only in recent years, some authors suggested that APAs function is not limited to ensure the whole-body balance, but might also encompass the ability to provide the most appropriate conditions to guarantee an accurate movement execution.

Anticipatory postural adjustments decrease in size as the accuracy demand increases (i.e. when pointing smaller and smaller targets), a feature that has been shown both in the upper limb (Bonnetblanc *et al.* 2004) and in the lower limb (Bertucco & Cesari 2010). Lower-limb pointing was also investigated by Duarte & Latash (2007), who have shown that the faster the movement is, the larger the APAs variability is. It also well described the relationship between movement speed and scattering of the final position around a target (Schmidt *et al.* 1979, Fernandez & Bootsma 2004). In the other way round, all these observations suggest that small and less variable APAs should accompany slow but precise movements. Berrigan *et al.* (2006) reported that when pointing is performed towards small targets (i.e. under high accuracy constraints) from an 'unstable' position (i.e. standing vs. sitting), slowing movement speed actually represents a strategy to reduce the equilibrium disturbance and, consequently, the associate APAs.

Conversely, other authors showed that decreasing the stability of the initial posture (passing from seating with 100% ischio-femoral contact to 30% contact) might increase both the amplitude of the APAs and the overall performance of an arm movement like, for example, the maximal velocity of a pointing task (Teyssèdre *et al.* 2000) or the isometric maximal force

developed during a pushing task (Le Bozec & Bouisset 2004). Both these effects were ascribed to a greater postural mobility in the unstable (30% contact) condition. However, it should be noted that, in both these studies, subjects were asked to perform as fast as possible movements/pushes, not to exactly reach a particular point or a given force level. Thus, the motor task was quite different from that of Berrigan *et al.* (2006).

Thus, when the accuracy demand increases, movement velocity decreases, that is, movement time increases, as already described by the Fitts (1954). However, as APAs amplitude is known to be proportional to focal movement velocity (Lee *et al.* 1987, Shiratori & Aruin 2007), its reduction might be not directly related to the increased accuracy demand, but to the associated reduction in movement speed. With respect to the above studies, our work is novel because it proves the relationship between APAs and movement accuracy (i.e. the pointing error), rather than the accuracy constraint (i.e. the target size), by ruling out the effect of movement velocity. The latter was indeed constant among sessions thanks to the fact that prismatic lenses influenced just movement direction, as revealed with aiming errors, but did not affect the target.

Further considerations on present results

As pointed out above, a crucial aspect in APAs modulation is movement velocity. However, our experiments show that when movement velocity remains constant among sessions (i.e. within each BLOCK), prism-induced pointing errors are still associated with changes in APA amplitude, thus supporting a linkage between APAs and movement accuracy. When moving fast, stronger prime mover activation is associated with stronger (Lee *et al.* 1987, Shiratori & Aruin 2007) and more anticipated APAs (Horak *et al.* 1984, Zattara & Bouisset 1988). This is in agreement with our results, which show that APAs and prime mover activation in the 1st BLOCK were larger and started earlier than those recorded in the 2nd BLOCK, when movements were slower.

Intriguingly, the relationship between movement speed/prime mover contraction and APAs' changes was limited to Q and TA of both sides (although not significant in left Q), with no modifications in H and SOL, a pattern which suggests that different muscles of the APAs chain could have different roles in equilibrium stabilization. APAs are known to secure the equilibrium in a twofold way (Massion 1992) (i) by counterbalancing the segmental equilibrium disturbance due to the reaction forces developing with the ongoing movement (which grow when movement speed increases) and (ii) by preventing the whole-body CoM displacement produced by the new configuration of the body (regardless the speed with which that configuration has been reached). Considering that 1st and 2nd BLOCK trials have different movement speed, but similar movement amplitude on the sagittal plane, it can be proposed that anterior lower-limb muscles (Q and TA) may neutralize the time-changing perturbation due to prime mover contraction, while posterior muscles (H and SOL) may neutralize the CoM changes as the movement develops.

Prisms selectively modulate those APAs sensitive to modification in movement speed. When wearing prisms, APAs amplitude was significantly increased in right Q and TA muscles (1st BLOCK – DURING vs. 1st BLOCK – BEFORE); no changes were instead found in APA latency. Thus, APAs timing and amplitude seem to be independently controllable, as also suggested by Nana-Ibrahim *et al.* (2008). Note also that the TA APA contributes to the backward CoP change, which in turn counteracts the perturbation applied by the arm movement on the shoulder. Indeed, the backward CoP change is responsible for the generation of forward-oriented inertial forces, which act to counteract the perturbing force induced by the arm movement (Bouisset & Zattara 1987).

The backward CoP change is apparently larger when wearing prisms. To explain this behaviour, one should consider that (i) to hit the target on the sagittal plane, the subject has to flex and slightly adduct the arm, so that the resulting perturbation is directed backward and slightly rightward; (ii) when committing rightward pointing errors, the shoulder angle in the horizontal plane seems to be unchanged, so that the fingertip endpoint deviation stems from a rightward rotation of the shoulder girdle (produced by a change in the many degrees of freedom along the body, see next paragraphs). As a consequence, the vector of the perturbation should undergo the same rightward rotation. Its projection along the *y*-axis should then increase, in agreement with the significant increase in TA APAs and CoPy change (Figs 4 and 6). Note also that, in parallel, the projection of the perturbation along the *x*-axis should instead reduce, in agreement with the slight decrease (although not significant) found in CoPx.

A final comment is worthwhile about the invariance of the upper-limb kinematics during the different sessions. In the absence of whole-body kinematic data, allowing to trace the relative position of the upper limb with respect to the trunk, the invariance of the shoulder angle in the horizontal plane (i.e. adduction/abduction of the arm) may be inferred by the observed invariance in the AD and BB activity (see Fig. 2). Indeed, AD and BB are both involved in shoulder flexion and adduction (see Kapandji 1982). Thus, any rightward deviation of

the upper limb in the horizontal plane should have been either negligible or signalled by a de-recruitment in both AD and BB activity. For the same reason, a different recruitment of other muscles acting on the shoulder, or even of other deltoid portions, should have been accompanied by appreciable changes in AD and BB. On this basis, we are rather confident that the pointing movement, with and without prisms, was performed without major changes in the shoulder angle in the horizontal plane.

Therefore, the pointing error should stem from other muscles acting along the body vertical axis, that is, from changes in the APAs chain, as those witnessed by our results. Data provided in this paper are certainly insufficient to fully appreciate the complex biomechanics of the postural chain. In this regard, the invariance of Tz coupled to the asymmetric changes in left and right Q and TA suggests a mechanical action from the legs to the pelvis that should have been accompanied by a counter rotation in one or more of the many degrees of freedom within the chain. Present data do not allow any speculation about this aspect, but in any case, this does not affect the main result of this paper: the accuracy of pointing movements relies upon a specific tuning between APAs and prime mover activation.

Conclusions

Data reported here suggest that by securing the position of the proximal joints, properly tailored APAs contribute to make the focal movement accurate. Indeed, we showed that prisms induce pointing errors in the upper limb by modifying the balance between APAs in lower limb and prime mover contraction. In other words, 'A movement never responds to detailed changes by a change in its detail; it responds as a whole to changes in each small part, such changes being particularly prominent in phases and details sometimes considerably distant both spatially and temporally from those initially encountered' (Bernstein 1967).

Conflict of interest

Research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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RESEARCH ARTICLE

Ischemic block of the forearm abolishes finger movements but not their associated anticipatory postural adjustments

Carlo Bruttini · Roberto Esposti · Francesco Bolzoni · Paolo Cavallari

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Abstract Voluntary movement is known to induce postural perturbations that are counteracted by unconscious anticipatory postural adjustments (APAs). Thus, for every movement, two motor commands are dispatched: a voluntary command recruiting the prime mover and a postural command driving the APAs. These commands are classically thought to be separated; this study investigates whether they could be instead considered as two elements within the same motor program. We analyzed the APAs in biceps brachii, triceps brachii and anterior deltoid that stabilize the arm when briskly flexing the index finger (prime mover flexor digitorum superficialis). APAs and prime mover activation were recorded before, under and after ischemic block of the forearm. Ischemia paralyzed the prime mover, thus suppressing the finger movement and the ensuing postural perturbation. If the two commands had been separated, it would have been expected that after a few failed attempts to flex the index finger, the APAs were suppressed too, being purposeless without postural perturbation. APAs were still present under ischemia even after 60 movement trials. No significant changes were found in APA amplitude in biceps and triceps among different conditions, or in the average APA latency. Inhibitory APA in anterior deltoid was reduced but still present under ischemia. In addition, the pharmacologic block of the sole median nerve produced similar effects. APAs were instead almost abolished when applying a fixation point to the wrist. The observation that APAs remained tailored to the expected perturbation even when that perturbation did not occur supports the idea of a functionally unique motor command driving both the prime mover and the muscles of the APA chain.

Keywords APA · Ischemia · Motor control · Posture · Voluntary movement · Human

C. Bruttini · R. Esposti · F. Bolzoni · P. Cavallari (✉)
Sezione di Fisiologia Umana-DePT, Università degli Studi di Milano, Via Mangiagalli 32, 20133 Milan, Italy
e-mail: paolo.cavallari@unimi.it

Introduction

Any voluntary motor act exerts forces not only upon the external environment but also upon our own body. To compensate for the latter forces, the prime mover activation is preceded by anticipatory postural adjustments (APAs): Unconscious muscular activities aimed at counterbalancing the perturbation induced by the primary movement (Massion 1992). The importance of a proper *whole-body* stabilization is immediately apparent when considering standing subjects performing voluntary movements that involve large masses (e.g., Belen'kii et al. 1967; Cordo and Gurfinkel 2004; see Bouisset and Do 2008 for a review). On the other hand, APAs were shown to develop also in the same limb where movement occurred (intra-limb APAs), in motor tasks in which the whole-body equilibrium was not threatened (Zattara and Bouisset 1988; Chabran et al. 2001).

Moreover, Caronni and Cavallari (2009a, b) reported that intra-limb APAs developed even when moving a very small mass like the index finger. Indeed, a brisk finger flexion was preceded by an excitatory burst in triceps brachii (TB), while biceps brachii (BB) and anterior deltoid (AD) showed a concomitant inhibition. This pattern contrasted the elbow and shoulder flexion induced by the upward perturbation that the index finger flexion caused on the metacarpophalangeal joint. According to Caronni and Cavallari (2009a, b), such APAs 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. Indeed, when simulating an index finger flexion using a four-joint software mechanical model of the arm, in which only the prime mover was recruited, a clear disturbance of both focal movement and upper limb posture was observed, with relevant changes at wrist and elbow level. This would affect the final position, i.e., the precision, of the intentional finger movement. In the model, the only way to prevent these "collateral effects" was to block all segments but the finger, preventing the proximal joints from rotating (fictive APAs). Since this observation derived from a very simplified system, Caronni and Cavallari (2009a) also looked for a more realistic model: A finger tap was evoked in a real arm by electrical stimulation of the median nerve; such an experiment showed recordings comparable in sign and size to those predicted by the software mechanical model.

According to the classical view, the prime mover activity and its associated postural adjustments result from two different central commands, which are independently dispatched to the prime mover and to the muscles generating the postural chain, respectively (Babinski 1899; Hess 1943; Cordo and Nashner 1982; Brown and Frank 1987). On the other hand, a growing body of recent evidences favors the view that APAs and prime mover recruitment are both controlled by a unique motor command (Aruin and Latash 1995; Petersen et al. 2009; Bolzoni et al. 2012; Caronni et al. 2013). This latter view is also supported by Yakovenko and Drew (2009), who studied the discharge properties of cat pyramidal tract neurons (PTN) and their temporal linkage with APAs associated with reaching movements. These authors found a strong linear relationship between the onset of PTN discharge and the APA onset, strengthening the idea that the motor cortex contributes to generate the APAs. Moreover, Schepens and colleagues (Schepens and Drew 2004; Schepens et al. 2008) emphasized the role of pontomedullary reticular formation (PMRF) in the coordination of posture and movement. In particular, they suggested that PMRF is a site of integration of signals from both cortical and subcortical structures and that these signals ensure that APAs are appropriately scaled in time and magnitude to the intended movement, contributing to integrate the control of posture and movement.

Whether the *single* or the *dual* command theory should be preferred, it remains an open question. To verify the working hypothesis of the oneness of postural and movement command, we analyzed the well-known intra-limb APA chain that stabilizes the arm during an index finger flexion (Caronni and Cavallari 2009a) in an experimental condition in which the voluntary command was normally dispatched, but the prime mover was unable to contract. In this aim, subjects were asked to repeatedly flex their index finger under two different conditions: (1) before an ischemic block of the forearm and (2) when ischemia had suppressed the finger movement and the ensuing postural perturbation.

On this basis, our experimental paradigm may lead to two alternative scenarios. Following the *dual command* view, one should expect that under ischemia, APAs are suppressed after few repetitions, since the postural activity on the upper limb is useless (no *real* perturbation on the more proximal segments) and uneconomical. Indeed, the CNS is able, within few movement repetitions, to adapt APAs to changes in the postural demand of the motor task, i.e., the ensemble of mechanical actions required for counteracting the perturbation induced by the primary movement (Belen'kii et al. 1967; Cordo and Nashner 1982; Aruin and Shiratori 2004; Shiratori and Aruin 2007). Moreover, clear signs of this adaptive process were observed even after the very first movement trial (Hall et al. 2010). On the other hand, following the idea of the oneness of voluntary and postural commands, APAs would be expected to remain manifest in the proximal arm muscles and tailored to the intended movement (i.e., to the *expected* perturbation stemming from the voluntary command), despite the absence of the *real* perturbation. The persistence of APAs even after several attempts to flex the index finger under forearm ischemia would provide a novel indication that during the execution of a voluntary movement, the recruitment of postural and prime mover muscles is driven by a functionally unique motor command. Thus, APAs and prime mover activation could be seen as parts of the same muscular chain.

Methods

Experiments were carried out on seven adult volunteers (five males and two females). Their mean (±SD) anthropometric characteristics were age 29.4 ± 7.2 years, weight 72.4 ± 9.3 kg, height 176 ± 11 cm, index finger length 8.4 ± 0.6 cm and arm length 79.5 ± 4.1 cm. All subjects gave written consent to the procedure, after being informed about the nature of the experiments. The local ethics committee approved the procedure in accordance with the 1964 Declaration of Helsinki; none of the subjects had any history of orthopedic or neurological disease.

Experimental procedure

Since in one of our experimental conditions (ischemia/anesthesia of right forearm, see below) no primary voluntary movement was produced, in order to have a reliable time reference for APA identification, a "*work-around*" was needed. Thus, the experimental paradigm described by Caronni and Cavallari (2009a) was modified by asking

subjects to perform a simultaneous flexion of both index fingers. In this way, the onset of the left index finger flexion was used as a time reference for APAs developing in the right side.

Subjects were sitting on a chair with both upper arms lying along the body and hanging down by their sides, elbows flexed at 90° and prone hands aligned with the forearm. The left arm was always supported by an armrest (see below). Subjects could see both their arms during the whole experiment, to be fully aware of their general postural context and of movement performance.

Index fingers were kept aligned with the hand and in contact with two proximity switches (CJ10-30GK-E2, Pepperl and Fuchs®, Mannheim, Germany), all other fingers hanging. Under forearm ischemia (see below), wrist and fingers of the right hand were in mid-range (neutral) position and subjects were instructed not to attempt any effort to keep the hand and fingers aligned with the forearm. Subjects were explicitly asked to keep their back supported and both feet on the ground throughout the experiment. The chair was height adjustable and the proximity switches screwed on articulated arms (143 MAGIC ARM + 035 Super clamp Kit, Manfrotto®, Cassola, Italy); both were adapted to the different body dimension of the subjects.

Subjects were asked to produce a simultaneous brisk flexion with both index fingers at the metacarpophalangeal joint. Each movement was self-paced after an acoustic signal delivered by the software every 6 s. The time between the beep and the movement varied at subject's will, to exclude any reaction time. Amplitude and duration of finger movements were visually controlled throughout the experiment by looking at the index finger movement trace on a computer screen.

Each experiment was arranged in three conditions: before an ischemic block of the forearm (PRE); when ischemia had completely suppressed the prime mover activation (ISC); and after complete recovery from ischemia (REC). On a different day, two of the subjects agreed to undergo the same protocol but with a pharmacologic block of the median nerve at the elbow (anesthesia), instead of ischemia. Subjects always had full view of their performance.

In each condition, a sequence of 30 index finger flexions was performed. Under ischemia/anesthesia, two sequences of 30 movement trials were recorded. The 30 trials were accomplished in a temporal window of about 3 min, and then, the subject had about 5 min of rest before the next sequence.

Ischemia

The ischemic procedure, and its duration, followed the approach of McNulty et al. (2002), Ziemann et al. (2001) and Vallence et al. (2012). After the PRE recordings, the right forearm rested on a support with the hand and fingers aligned with it; a blood pressure cuff, previously placed just below the elbow, was inflated at 250 mmHg. The ischemic block affected first the larger sensory fibers, inducing a clear numbness and anesthesia of the forearm and hand, and then abolished the voluntary EMG activity in the prime mover after an average time of 51 min (±8 min). After suppression of prime mover EMG, the forearm support was removed and the subject performed two ISC sequences (ISC1 and ISC2), separated each other by a temporal window of about 5 min. Throughout both sequences, the subject kept the upper arm along the body and the elbow at 90°, so as to exclude any change in posture that could have affected the APAs in AD, BB and TB.

Pharmacologic block of the median nerve

Lidocaine 2 % was injected in proximity of the median nerve just below the right elbow joint, under guidance of the needle's electrostimulating tip (Echoplex®, REF 6194.35, 23G-L.35 mm, Vygon; stimulator Plexygon®, 7501.31, Vygon). Complete neromuscular block was obtained in about 10 min. Activation of flexor digitorum superficialis (FDS, prime mover) and voluntary finger movements were abolished, as well as the afferences from the median nerve. Complete paralysis lasted for about 25 min. It is worth noting that this procedure did not suppress afferences from the distal part of the upper limb, thanks to the unaffected functionality of radial and ulnar nerves.

Movement and EMG recordings

The proximity switches monitored the onsets of the fingertips movement. Flexion–extension of the right metacarpophalangeal joint was recorded by a strain gauge goniometry (mod. F35, Biometrics Ltd®, Newport, UK) taped to the joint. Angular displacement was DC-amplified (P122, Grass Technologies®, West Warwick, Rhode Island, USA), and gain was calibrated before each experimental sequence. Pairs of pre-gelled surface electrodes, 24 mm apart (H124SG, Kendall ARBO, Tyco Healthcare, Neustadt/Donau, Germany) were used to record the EMG signal from the right flexor digitorum superficialis (FDS) and from some of the ipsilateral postural muscles: biceps brachii (BB), triceps brachii (TB) and anterior deltoid (AD). A good selectivity of the EMG recordings was achieved both by a 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. EMG was AC-amplified (IP511, Grass Technologies®, West Warwick, Rhode Island, 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, Texas, USA), visualized online and stored for further analysis.

Median nerve electroneurogram

A stimulating ring electrode was positioned at the right index fingertip and two pre-gelled recording electrodes (see above) on the surface of the distal third of the forearm, along the course of the median nerve. Simulation was applied by a Grass S8800 device + SIU5 isolation unit, pulse duration 0.8 ms, pulse frequency 4 Hz. Stimulation intensity was set at three times the perception threshold (PT). Electroneurogram (ENG) was amplified by a Grass IP511 device (gain 50 k; filters 1–3,000 Hz). Recorded signal was A/D-converted at 10 kHz, 12 bit, on a PCI-6024E. Median nerve activity was recorded before ischemia, every 10 min during it and at different times during the postischemic recovery. When the afferent volley had disappeared, the stimulation intensity was temporarily raised to 4xPT to check for the complete suppression of the neural transmission.

Control experiments

As stated above, the left arm was always supported by an armrest. Such a setup was conceived (second part of the "*work-around*") to provide a distal fixation point for the postural chain accompanying the left finger flexion and abolish (or deeply suppress) the APAs in the upper arm and trunk muscles. Thus, the APAs in *right* arm muscles preceding the *right* finger flexion should be unaffected by the simultaneous *left* finger flexion. To assess this invariance, all subjects performed a sequence of unilateral right index finger movements (CTRL), keeping both arms in the same position as in PRE, and the outcome was compared (see below) to that of the bilateral PRE condition. This procedure was specifically chosen to assess whether left finger tapping *significantly* affected those APAs in right arm that normally accompanies right finger tapping. Comparison between bilateral and unilateral right finger flexions is reported in the "Control measurements" section of the "Results."

All subjects also performed a sequence of unilateral right index finger movements with the right forearm fixated at the wrist (FIXED). Subjects familiarized with the new condition for several trials, and then, a sequence of 30 trials was recorded.

Data analysis

On each sequence, the 30 EMG traces of the prime mover and those simultaneously recorded from the postural muscles were digitally rectified and integrated (time constant 25 ms). Traces collected from each muscle were then averaged in a fixed temporal window: from −1,000 to +300 ms with respect to the onset of the left index finger flexion. The mean EMG activity in a time window clearly free from APAs (from −1,000 to −500 ms) was utilized to calculate the baseline reference level, which was subtracted from each EMG trace. On each experiment, latency and amplitude of the postural activity were measured offline on the averaged traces. A software threshold set at ±2 SD of the reference signal level, and visually validated identified the onset of an effect in each postural muscle. Latency of the APA was referred to the movement onset, thus assuming negative values. APA amplitude was measured as mean level of the trace in the temporal window from the APA onset to the movement onset and expressed as a percentage of the corresponding amplitude measured in the CTRL sequence. This window was chosen to exclude any reflex component. The same criteria for onset detection and amplitude measurement were applied to voluntary activity in FDS. All comparisons between PRE, ISC1, ISC2 and REC experimental sequences were performed by one-way repeated-measures ANOVA. Whenever significance ($p < 0.05$) was reached, Tukey's HSD test was used for post hoc comparisons. The comparisons CTRL versus PRE and CTRL versus FIXED were performed using a paired *t* test.

Results

Anticipatory postural adjustments before and under ischemic block of the forearm

Figure 1 shows the comparison between the right arm EMG activity recorded in a representative subject before ischemia (PRE) and under ischemic block (ISC2). It is apparent that in PRE, the FDS activation was preceded by a clear postural inhibitory adjustment in BB and AD, paralleled by an excitatory postural activity in TB muscle. Note that in ISC2, the postural activities were qualitatively and quantitatively similar to those recorded in PRE, although the suppression of both the FDS activation and the ensuing finger movement.

Results from all subjects are given in Fig. 2, which also report values obtained in the first sequence under ischemia (ISC1), as well as after complete recovery (REC). Failure of ischemia in suppressing the proximal APA chain, despite the abolishment of FDS activity and finger movement, was systematically observed, although to a various degree in different subjects. On average, amplitude of BB inhibition decreased by ~1 % under ischemia (average PRE and REC: 110 % of CTRL *vs.* average ISC1 and ISC2: 109 %), while TB excitation was reduced by ~33 % (average PRE

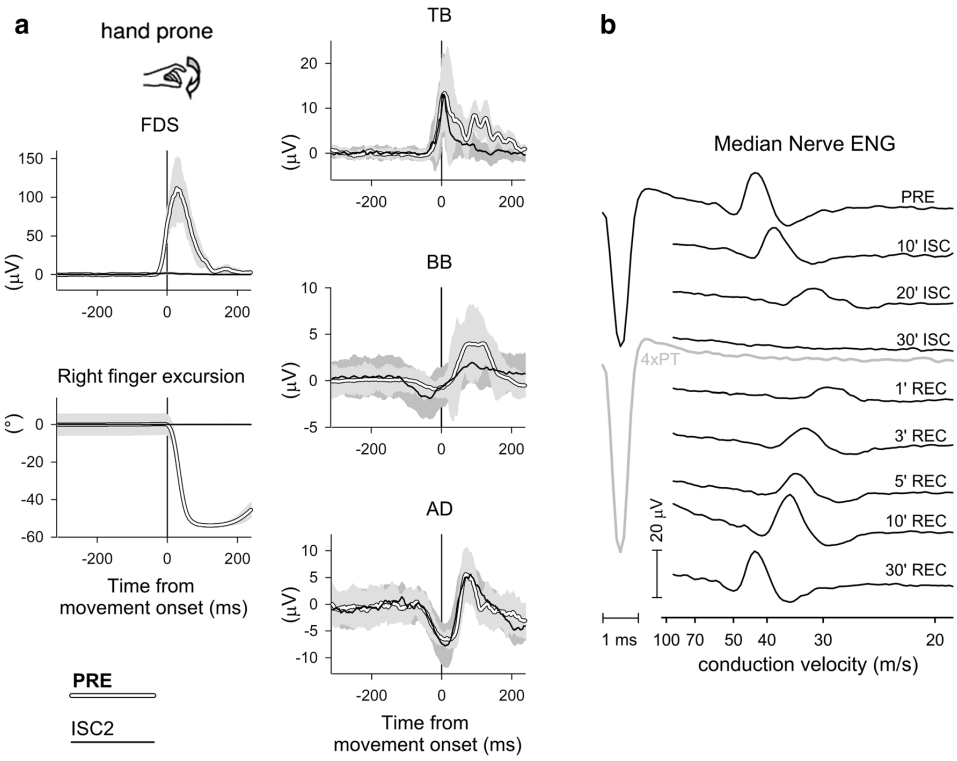

Fig. 1 **a** Rectified and integrated average recordings of EMG in prime mover flexor digitorum superficialis (FDS) and intra-limb APAs in a representative subject. Time 0 = movement onset of the left index finger. When rapidly flexing both index fingers before ischemia (PRE, *white traces*, SD in *light gray*), right FDS muscle was activated and the right arm equilibrium was preserved, thanks to an excitatory APA in triceps brachii (TB) and inhibitory APAs in biceps brachii (BB) and anterior deltoid (AD). Under ischemia of the right forearm (ISC2, *black traces*, SD in *dark gray*), FDS activation and index finger movement were both suppressed, while excitatory APAs in TB and inhibitory APAs in BB and AD were still evident and qualitatively similar to those recorded in PRE. **b** Electroneurogram (ENG) of the right median nerve of one representative subject, showing the effect of ischemia, induced by a pressure cuff, on the afferent volley elicited by electrical stimulation of the index finger skin (3 × perception threshold). Ischemia progressively reduced the volley amplitude until reaching complete suppression after 30 min (even increasing stimulation to 4xPT, gray trace, does not elicit a response). After removing the pressure cuff, the effect of ischemia completely recovered in 30 min

and REC: 106 % *vs.* average ISC1 and ISC2: 67 %). One-way ANOVA found no differences in BB inhibition and TB excitation among PRE, ISC1, ISC2 and REC sequences ($F_{3,18} = 0.055$, $p = 0.98$ for BB; $F_{3,18} = 1.922$, $p = 0.16$ for TB). On average, AD inhibition decreased by ~48 % under ischemia (average PRE and REC: 87 % *vs.* average ISC1 and ISC2: 39 %). One-way ANOVA among sequences found significant differences ($F_{3,18} = 9.033$, $p = 0.0007$) that clearly indicated the ischemic versus non-ischemic conditions; indeed, post hoc tests found no differences PRE versus REC ($p = 0.38$) nor ISC1 versus ISC2 ($p = 0.99$). Nevertheless, AD inhibition remained significantly larger than zero under ischemia ($CI_{95\ \%}$ 14–63 %), attesting the persistence of the APA in this muscle too.

Note also that ischemia was very efficient in suppressing both FDS activity and the subsequent index finger flexion. On average, FDS activation decreased by ~86 % under ischemia (average PRE and REC: 94 % *vs.* average ISC1 and ISC2: 8 %) and mean finger excursion, which was about 56° (average PRE and REC), was annihilated under ischemia. One-way ANOVA found significant differences between the four sequences for FDS EMG amplitude ($F_{3,18} = 43.121$, $p < 0.0001$) and for finger excursion ($F_{3,18} = 258.4$, $p < 0.0001$). The differences indicated the ischemic versus non-ischemic conditions: Post hoc tests found no differences PRE versus REC ($p = 0.81$ and $p = 0.87$, for FDS EMG amplitude and finger excursion, respectively) nor ISC1 versus ISC2 ($p = 0.98$ and $p = 0.99$, respectively).

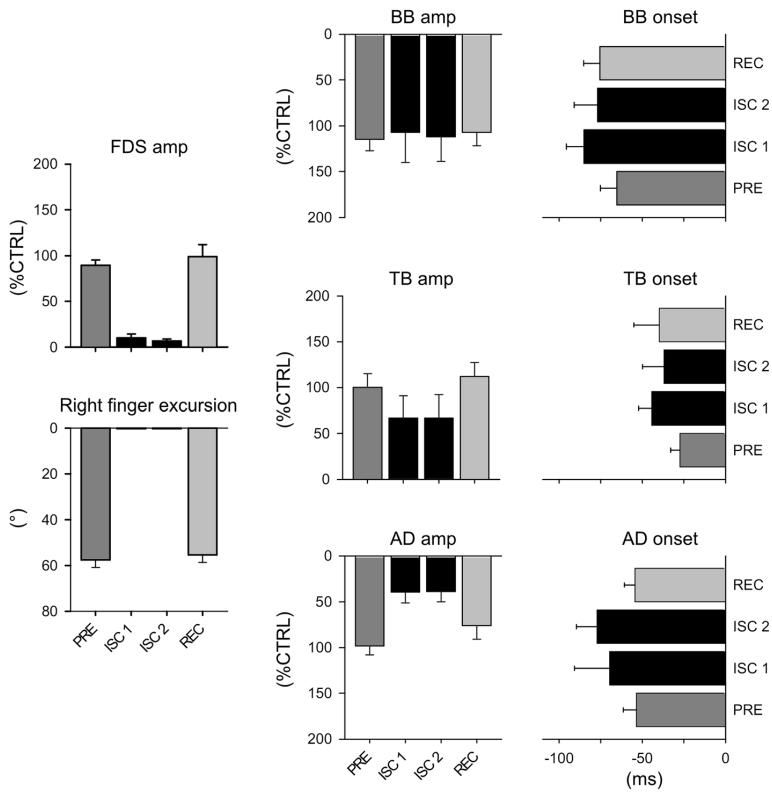

Fig. 2 Mean amplitude of pre-movement EMG activity in prime mover FDS (flexor digitorum superficialis) and of APAs in BB (biceps brachii), TB (triceps brachii) and AD (anterior deltoid). Values in % of the control sequence (CTRL), see "Methods". Mean amplitude of right index finger excursion and mean latency of APAs are also reported. Data were recorded in three conditions: before an ischemic block of the forearm (PRE sequence, *dark gray*), when ischemia completely suppressed both the sensory feedback and prime mover activation (two sequences: ISC1 and ISC2, *black*) and after complete recovery from ischemia (REC, *light gray*). Mean values ± SEM. Under ischemia, FDS activation and right index finger movement were almost suppressed, but APAs in TB, BB and AD were still evident. One-way repeated-measures ANOVA found no differences in APA amplitude and latency among sequences, except for AD that showed smaller APAs during ISC1 and ISC2 than during PRE and REC. However, AD APAs were significantly different from 0 also during ischemia ($CI_{95\ \%}$ on pooled ISC1 and ISC2: 14–63 % CTRL). The same analysis showed no significant differences in APA latencies among sequences

With regard to the timing of anticipatory effects, they were comparable among all sequences (Fig. 2, panels on the right), with no effect of forearm ischemia on the average APA latency in BB, TB and AD muscles ($F_{3,18} = 0.503$, $p = 0.68$; $F_{3,18} = 0.645$, $p = 0.60$; and $F_{3,18} = 0.800$, $p = 0.51$, respectively).

Control measurements

Bilateral versus unilateral right finger flexion

To support the choice of using the left finger flexion as a time reference, further control measurements concerned the synchronism between the right and the left index finger flexions. The mean delay between the signals from right and left proximity switches was not significantly different from 0 in both PRE and REC conditions (paired *t* test: $t_6 = 0.17$, $p = 0.87$; $t_6 = 1.21$, $p = 0.27$, respectively). Moreover, to exclude any effect of the contralateral movement on the right APA chain, we compared right upper limb APAs during PRE and CTRL sequences (bilateral movement *vs.* right finger only, respectively), finding no differences in amplitude ($t_6 = -1.39$, $p = 0.21$; $t_6 = 1.33$, $p = 0.23$; $t_6 = 0.15$, $p = 0.88$ for BB, TB and AD, respectively), nor in latency ($t_6 = -0.05$, $p = 0.96$; $t_6 = -1.15$, $p = 0.29$; $t_6 = -1.33$, $p = 0.23$, respectively). Finally, note that the APAs in arm muscles during PRE were statistically significant. Indeed, when expressed in percentage of

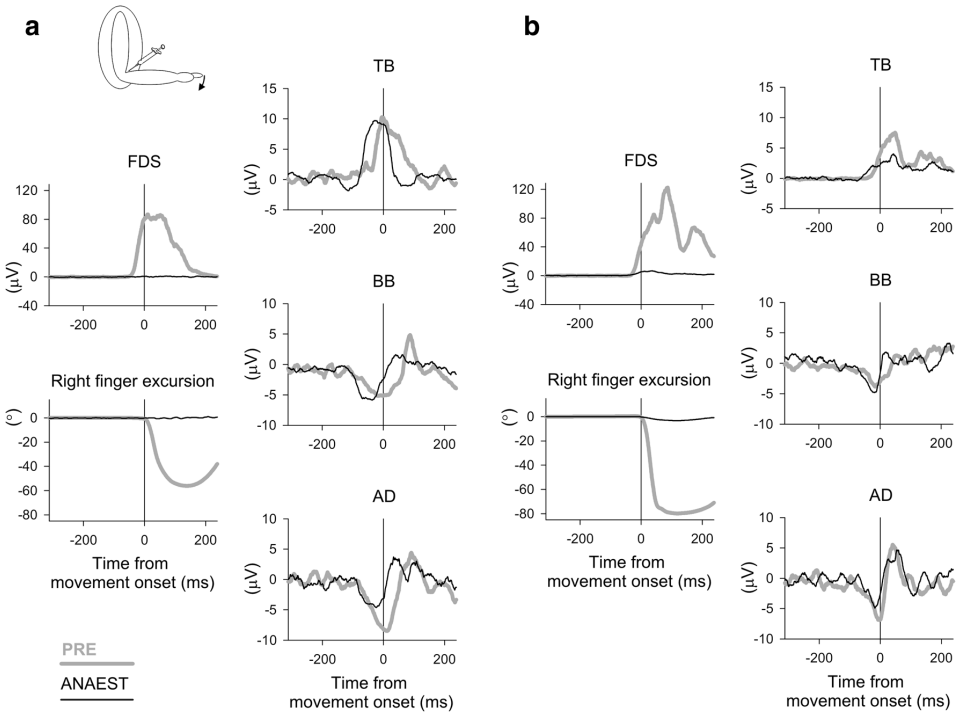

Fig. 3 Recordings of prime mover EMG (FDS) and intra-limb APAs in two subjects (**a**, **b**) when trying to move the right index finger before (PRE, *gray traces*) and under anesthesia (ANAEST, *black traces*). During PRE, activation of the FDS drove a rapid flexion of the index finger. As in Fig. 1, excitatory APAs developed in TB and inhibitory APAs in BB and AD. In ANAEST, FDS activation and index finger movement were both suppressed, but APAs were still evident and qualitatively similar to data recorded in PRE

the baseline reference level, the average size of anticipatory BB inhibition was 41 % with a $CI_{95\ \%}$ of 30–52 %, the size of AD inhibition was 43 % with a $CI_{95\ \%}$ 36–51 %, and the size of TB excitation was 83 % with a $CI_{95\ \%}$ of 42–124 %.

Neurographic control of ischemia

Figure 1b shows an example of the median nerve ENG recorded during the whole duration of one experiment (arm ischemia) when stimulating the index finger skin at 3xPT. A progressive decrease in the evoked potential was evident during the ischemic period. The ENG-wave increased its latency and was completely suppressed after 30 min of ischemia, after which even increasing the stimulation to 4xPT did not elicit a response. Having blocked the tactile Aβ fibers, proprioceptive and motor Aα fibers should have been blocked too. After the removal of the pressure cuff, the ENG-wave recovered and reached the PRE values in <30 min. The same control measurements were taken from all subjects.

APAs under pharmacologic block of the median nerve

The selective block of the median nerve, induced by lidocaine, abolished the prime mover EMG and the ensuing movement, without affecting the functionality of the radial and ulnar nerves. After this procedure, the APA chain was still evident in both subjects (see Fig. 3).

APAs in the presence of a distal fixation point

Figure 4 shows that when keeping the dorsal aspect of the wrist in contact with a rigid frame, the novel fixation point strongly modified the amplitude of APAs: In the illustrated subject (Fig. 4a), APAs were deeply reduced in BB and TB and completely abolished in AD. Mean APA amplitude in the whole population is illustrated in Fig. 4b. Note the APA depression in the three postural muscles with respect to its CTRL condition (arm unsupported), despite the constancy of the FDS recruitment (for statistics, see Fig. 4). It should be also underlined that in the FIXED arm condition, APAs

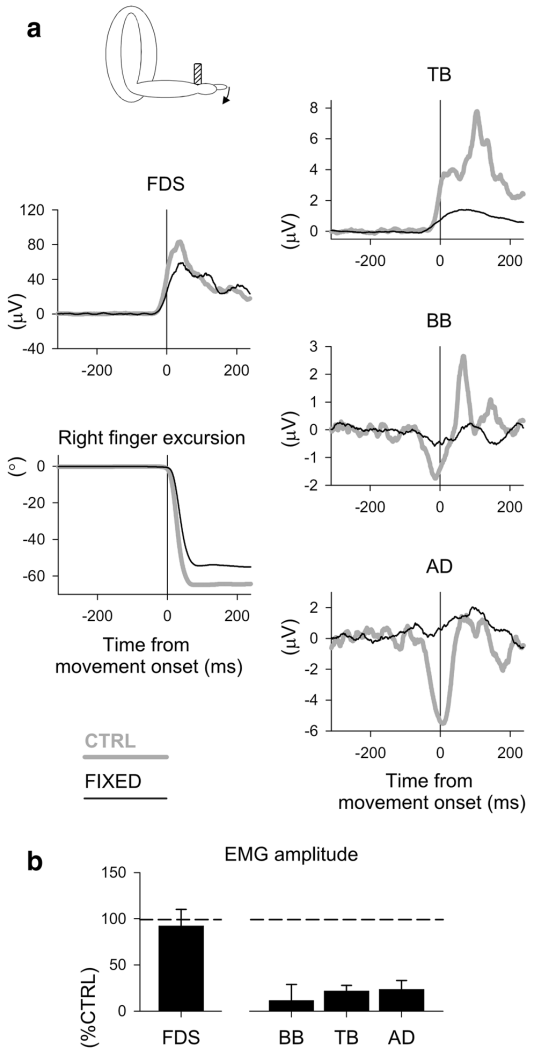

Fig. 4 **a** Recordings of EMG activity in prime mover FDS (flexor digitorum superficialis) and intra-limb APAs in a representative subject with (FIXED, *black*) or without (CTRL, *gray*) a wrist fixation point. It is evident that both the EMG activity in the prime mover and finger movement were comparable in the two conditions, while in the FIXED condition, APAs were deeply reduced in BB (biceps brachii) and TB (triceps brachii) and completely abolished in AD (anterior deltoid). **b** Mean amplitude of pre-movement FDS EMG and of APAs in BB, TB and AD. Values in % of the control sequence (CTRL), see "Methods". A *t* test showed no CTRL *versus* FIXED difference in FDS activation ($t_6 = 0.44$, $p = 0.67$). The average inhibitory effects on BB and AD and excitation in TB revealed significant reduction in the FIXED condition ($t_6 = 5.01$, $p = 0.002$; $t_6 = 12.41$, $p < 0.0001$; $t_6 = 7.80$, $p = 0.0002$, respectively)

changed not only quantitatively but also qualitatively: in three subjects, a small excitatory APA replaced the inhibitory one in BB; the same sign reversal occurred in another subject in AD muscle.

Discussion

This paper illustrated that the intra-limb APAs stabilizing the arm when producing a brisk index finger flexion (cfr. Caronni and Cavallari 2009a) were still present under an ischemic block of the forearm that suppressed the prime mover EMG, the finger movement and the related mechanical perturbation. In this condition, even after 60 movement trials, accomplished in more than 10 min, the CNS did not adapt APAs to the new postural demand, failing to properly suppress the postural chain; instead, the upper arm and shoulder muscles showed EMG activities comparable, in amplitude and latency, to those reported by Caronni and Cavallari (2009a).

Given the well-known ability of the CNS to adapt APAs to changes in the postural demand of the motor task within few movement repetitions (Belen'kii et al. 1967; Cordo and Nashner 1982; Aruin and Shiratori 2004; Shiratori and Aruin 2007; see also Hall et al. 2010), one could have expected that in these conditions, APAs were suppressed, since unnecessary and uneconomical. Intriguingly, when repeatedly trying to flex the index finger under ischemia, significant anticipatory adjustments were still clearly visible in BB, TB and AD. Note that the subjects were asked to generate the same voluntary command in both conditions and any attempt to recruit FDS still resulted in an APA chain, without adaptation to the suppression of finger movement. The similarity of the motor command in the two conditions could not be directly assessed, but it may be inferred from the invariance of APA amplitudes and latencies and the simultaneity and constancy of the contralateral index finger flexion, visually controlled by the subject during the experiment. In this regard, the absence of any significant APA difference between REC and PRE sessions also witnesses that these intra-limb APAs are very stable, i.e., they remain manifest even after repeated "exposure" to index finger flexion.

In this framework, as also suggested by Leonard et al. (2011), it would be difficult to keep strictly divided the control of posture from the control of the primary movement, as instead it was often proposed in previous literature (Hess 1943; Cordo and Nashner 1982; Brown and Frank 1987). Our results seem more in agreement with the proposal by Bouisset and Do (2008) that APA's progression follows a

"posture–focal gradient," starting from the support base (ground, seat, etc), proceeding through the postural chain and then terminating on the prime mover. Indeed, our finding that APAs in the same limb where the voluntary movement occurs (intra-limb APAs) were deeply reduced in the FIXED condition favors the above "posture–focal gradient" view: The new fixation point at the wrist, i.e., closer to the *voluntary moving* segment (index finger), strongly attenuated APAs in the more proximal muscles. A result that agrees with the arm-pull experiment in standing subjects by Cordo and Nashner (1982) in which the soleus APAs were strongly reduced when adding a fixation point to the trunk. The APA adaptation to changes in postural context is usually observed since the first trials, as also shown by Hall et al. (2010). Further support to the "posture–focal gradient" comes from the results by Dietz and Colombo (1996), who showed that no APAs in lower limbs could be observed when performing push/pull movements with the body fully immersed in water. Presumably, moving without any fixation point was not an adequate condition for the APA chain to develop. Sensory information regarding the whole-body postural context is indeed known to play a role in setting and online modifying the feed-forward APA command (Mille and Mouchnino 1998).

Our proposal that the APA–prime mover chain is programmed as a whole fully agrees with the above-described "posture–focal gradient" view. In this regard, it is interesting to mention the studies of Gritsenko et al. (2009) and Leonard et al. (2011) that showed that when it is required to correct an ongoing arm pointing movement, the CNS employs a predictive mode of postural control and consistently adapts the postural muscle activities before correcting the prime mover recruitment. These authors concluded that the postural corrections could be described as being a component of the voluntary movement, rather than ensuring the maintenance of equilibrium. Similar conclusions were reached by Caronni et al. (2013), who showed that small errors in arm pointing movements could be described to changes in the APA pattern, not paralleled by changes in the prime mover recruitment.

Little is known about the neural subsystems governing APAs, but several studies suggested a superposition of the neural structures for APAs and those for voluntary motor command, thus indirectly supporting the above hypothesis of a "global command." 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 observed in patients with a lesion of the motor cortex or of the supplementary motor area, (SMA) (Viallet et al. 1992). The possible involvement of the SMA in the APA network was indicated also by other experiments (Brinkman 1984; Yoshida et al. 2008; Jacobs et al. 2009). Anticipatory brain activity before the execution of a bimanual load-lifting task was recently localized in basal ganglia, SMA and thalamus in the hemisphere contralateral to the load-bearing arm (Ng et al. 2012). It is worth noting that these areas are component nodes of the basal ganglia-thalamo-cortical motor network, which is implicated in well-learned finger movements (Boecker et al. 1998).

Possible criticisms

One possible objection to our interpretation may be that the consistent APA presence under ischemia could be a consequence of a lack of time for adapting to the new postural demand. According to literature (Cordo and Nashner 1982; Hall et al. 2010), adaptation to changes in the postural context occurs within few trials. This was not the case since in our data no adaptation occurred both inter- and intra-sequences (30 trials each, see ISC 1 and ISC 2 in Fig. 1 and 2). It is, however, possible that the CNS might adapt to the new postural demand over longer periods (more than 60 movement trials). Ahmed and Wolpert (2009) asked sitting and standing subjects to perform a reaching task while a force-generating robot was changing the dynamics of their arm, and analyzed how subjects adapted their motor and postural commands to accomplish the task. Results on standing subjects showed that when keeping the same postural context and required movement trajectory but changing the arm dynamics, APAs adapted to the resulting changes in the movement-induced perturbation by following an exponential course with a time constant of about 80 trials. If this had been true also in our experimental condition, clear APA changes would have been observed when comparing ISC1 and ISC2. The absence of such changes may be attributed to the fact that in our study, subjects had to produce the same motor command both before and under ischemia, while in the study by Ahmed and Wolpert, subjects had to change their voluntary motor command to compensate for the altered arm dynamics. In support of this, literature reports that when amputees were asked to voluntarily move their phantom hand, activity in severed motor nerve fibers was recorded (Dhillon et al. 2004). This suggests that when amputees voluntarily move their phantom, they generate activity in the nerves that previously supplied the missing limb. Moreover, it has been shown that the EMG activity in stump muscles followed a pattern correlated with the intended phantom movement (Reilly et al. 2006). From Reilly's data, we observed that this activity was accompanied by a specific activation of the proximal muscles. Such activity could not be precisely timed with respect to the lacking prime mover activity, but from our point of view, it might be in fact the expression of an APA chain. If this is true, Reilly's data will prove that the CNS chronically produces an APA chain every time it dispatches a voluntary command.

Another consideration is worth regarding the perceived hand posture. Throughout the development of the ischemic block, the forearm was supported with the hand and fingers aligned with it. When subjects readopted the position for recording the ISC1 and ISC2 sequences, the hand was in a neutral position and subjects were instructed not to attempt any effort on the ischemic segments before trying to flex the index finger. The hand and fingers were thus perceived as slightly flexed (cfr. Gandevia et al. 2006), and this perception was confirmed by the visual feedback. It should be noted that such neutral position did not interfere with a normal finger flexion.

Finally, based on our results on intra-limb APAs, the conclusion of a unified command driving the APAs and prime mover activity cannot be directly generalized to include APAs developing outside the limb involved in the voluntary movement (inter-limb APAs). Nevertheless, it should be recalled that *intra-limb* APAs (see Caronni and Cavallari 2009a, b) share several properties with inter-limb APAs. Indeed, the brisk finger flexion produced well-defined anticipatory natural synergies that (1) were distributed to several upper limb muscles creating a postural chain aiming to prevent the effects of the interaction torques generated by the voluntary movement; (2) changed in amplitude according to the level of postural stability; (3) reverted in sign when movement direction is reverted and, as shown in this paper, (4) adapted to changes in the postural context within few trials of movement repetition. This actually supports the view that both intra- and inter-limb APAs share similar control mechanisms.

Implications for a predictive model of movement planning and APA updating

Davidson and Wolpert (2005) suggested a stronger role of feed-forward internal models versus sensory feedback in several aspects of human motor control, such as oculomotor and skeletomotor control, perceptual processing, mental imagery and also postural control (see also Wolpert et al. 1995, 2011). In this framework, the persistence of APAs in the absence of a real movement, i.e., without perturbation, sheds further light on the importance of internal models in APAs, actually limiting the role that the sensory feedback from real movement plays in fast APA adaptation. Indeed, we observed that APAs rapidly adapted only when sensory afferences signaled a change in the postural context (FIXED vs. CTRL results, see next paragraph for further considerations on this topic).

More recently, Ahmed and Wolpert (2009) asked subjects to learn to perform a reaching task, while arm dynamics were modified by a force-generating robot and in a sitting position (in which there is no need to produce any APA on the ground); thereafter, the authors asked to repeat the task while standing and subjects produced the correct APAs on the ground since the very first trials. These authors interpreted the transfer of information about movement-induced perturbation from the control of voluntary movement to that of postural actions as a sign that a common dynamic encoding underlies both posture and movement control. From our perspective, on the one hand Ahmed and Wolpert (2009) showed that when the voluntary command has to be changed in order to reach the task goal (because of the modified arm dynamics), the change in voluntary command drives a change in APAs; on the other hand, we showed that when continuing to produce the same voluntary motor command, even when the task goal cannot be reached, the APAs remain unchanged. These seem to us two faces of the same coin: the close linkage between voluntary command and APAs.

It might be wondered whether the APA "survival" under ischemia might result from the impossibility to update the motor program because of the lack of sensory feedback. In this regard, we should distinguish between the sensory afferences regarding the general postural context and those indicating the actual movement outcome.

It should be considered that in this experiment, the general postural context did not change and subjects were fully aware of it: Proprioception from the proximal segments and vision were indeed unaffected. Therefore, those neural mechanisms (see next paragraph) responsible for APA adaptation to the postural context should not be affected by ischemia or anesthesia.

For what concerns the absence of proprioception from distal segments under ischemia, which signaled the loss of actual movement, it can be argued that either the CNS may have been engaged in interpreting a fuzzy afferent signal generated by the ischemic procedure or it may have been completely unaware about the loss of perturbation. However, also in this case, the vision should have been more than enough to inform the CNS that no movement occurred.[1] One should also take into account that the afferents starting more proximally than the pressure cuff might have indirectly signaled the loss of perturbation on the more proximal joints. Therefore, subjects were fully aware also of the loss of movement. Therefore, the persistence of APAs tailored to the expected perturbation suggests that the weight of feedback signals due to the real perturbation plays a minor role in APA adaptation. This view was also

[1] We chose not to restrain the visual feedback so that subjects were always aware about index finger motion; therefore, the persistence of APAs under ischemia should have been attributed only to the persistence of postural context and voluntary command, not to the lack of information about movement suppression. If APAs had disappeared, it would have indicated that they were tailored on the real perturbation, thus being not strictly linked to the voluntary command.

supported by the observation that in the two subjects who underwent median nerve anesthesia, the normal afferent traffic in the radial and ulnar nerves (a further signal of the movement loss) was still not sufficient to update the motor program and suppress APAs. Moreover, in this condition, no fuzzy signal was generated, thus excluding its role in our results. A similar conclusion may be drawn from the work on perceived posture by Gandevia et al. (2006), who observed that subject at rest perceived their ischemic hand in a neutral position between flexion and extension, showing that even under ischemia, a perception of body position persists, even if biased.

Further considerations on APA adaptation

In our experiments, we modified the *postural demand* in two different ways: 1) with the procedure of the nerve block and 2) by adding a fixation point to the wrist; in the former case, there was a change in the *real perturbation,* while in the latter case, there was a change in *postural context*. Instead, in both cases, the voluntary command and, consequently, the *expected perturbation* did not change.

If the recruitment of the postural muscles had involved a separate neural mechanism with respect to that governing the prime mover(s), APAs would have been expected to be suppressed both when no primary movement perturbation occurred (like under ischemia/anesthesia) and when the postural context changed (FIXED condition). Instead, our results showed that in contrast to the rapid adaptation to changes in the postural context, no adaptation occurred to the loss of primary movement perturbation, even after 60 movement trials; thus, if any adaptation should have had occurred, it would have required much longer time than the adaptation to changes in postural context. Therefore, the two adaptation processes should entail different mechanisms.

With regard to the adaptation to postural context, several studies suggested that each voluntary movement is accompanied by widespread descending APA commands, which are then restricted to the appropriate muscles by actively gating at the spinal level the transmission of APAs to the other motoneurone (Schepens and Drew 2006). The single branches of such an "arborized" APA pattern selectively potentiated/suppressed according to the usefulness and reliability of the respective support point (Baldissera et al. 2002; Baldissera and Esposti 2005; Esposti and Baldissera 2011).

Instead, the much slower adaptation (if any) to changes in the *real* perturbation indicates that its relative weight in scaling the APA pattern is much lower than that of the *expected* perturbation. In other words, APAs are tailored to the expected perturbation, much more than on the real one, strengthening the idea that the postural and prime mover muscles are driven by a functionally unique command, where "functional" does not imply a unique neuronal circuit in charge of both voluntary and postural commands (actually we did not identify any anatomical substrate). In fact, even if more than one control center may be involved, the exchange of information between the controllers should be so close and strong that they would behave as a functional unit.

Conclusion

The suppression of the prime mover EMG activity, the finger movement and the related mechanical perturbation, due to ischemia or anesthesia of the forearm, provided a novel opportunity to isolate the role of the APAs within a voluntary motor act. The observation that APAs remained tailored to the intended movement, i.e., to the expected perturbation, even after 60 movement trials in which that perturbation did not occur, supports the idea that the recruitment of postural and prime mover muscles is driven by a functionally unique motor command, according to a well-acquired pattern. Thus, APAs and prime mover activation are seemingly part of a unique motor command, which drives the muscular chain starting from the fixation point(s) and including the moving segment.

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Conflict of interest The authors declare that they have no conflict of interest.

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RESEARCH ARTICLE

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

Carlo Bruttini · Roberto Esposti · Francesco Bolzoni · Alessandra Vanotti · Caterina Mariotti · Paolo Cavallari

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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

C. Bruttini · R. Esposti · F. Bolzoni · P. Cavallari (✉)
Sezione di Fisiologia Umana - DePT, Università degli Studi di Milano, Via Mangiagalli 32, 20133 Milan, Italy
e-mail: paolo.cavallari@unimi.it

A. Vanotti · C. Mariotti
Unità di genetica delle malattie neurodegenerative e metaboliche, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy

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.

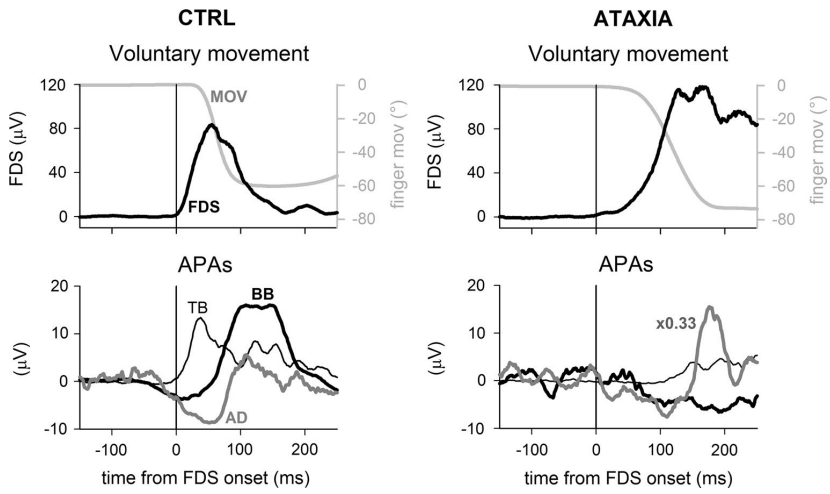

Fig. 1 Changes in intra-limb APAs latencies in cerebellar subjects. Recordings from one representative subject of the healthy group (CTRL) are compared to recordings of a cerebellar subject (ATAXIA). Note that in the healthy subject the prime mover activation is preceded by inhibitory APAs in biceps 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

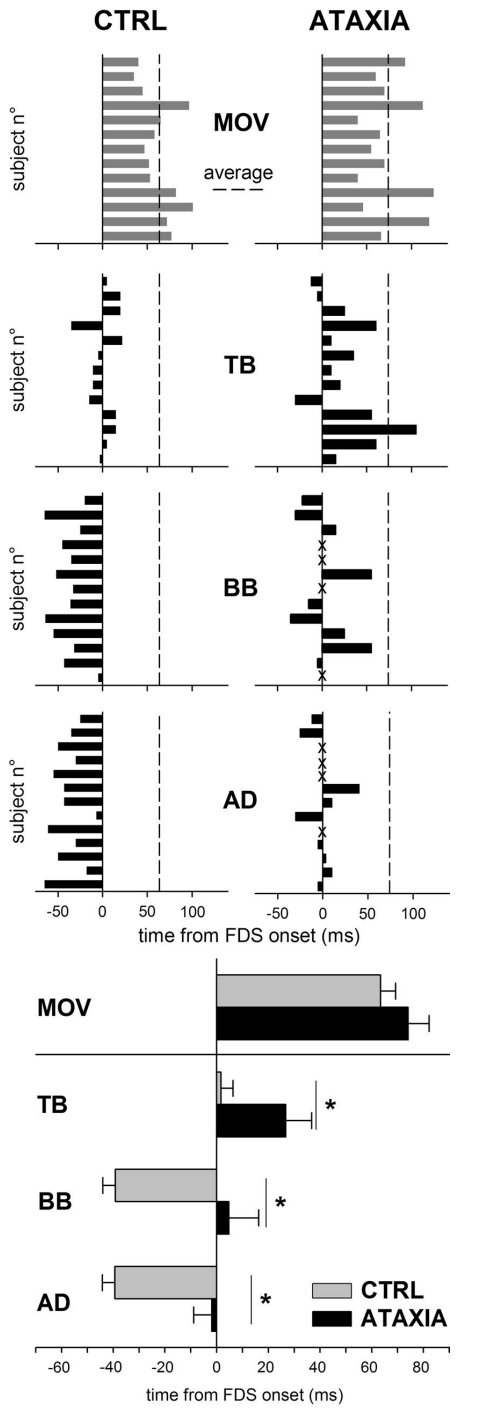

Fig. 2 Comparison of the APA chain in healthy and in cerebellar ▸ subjects. Latencies of finger flexion (MOV) and APA onsets in TB, BB and AD are plotted with respect to onset of FDS. Each single subject is represented. *Dashed line marks* the average movement latency for either group of subjects. Note 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.

Conflict of interest Research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest. This study was supported by 'F.I.R.S.T.' Grants from the Università degli Studi di Milano, Italy.

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RESEARCH ARTICLE

Intended rather than actual movement velocity determines the latency of anticipatory postural adjustments

Roberto Esposti · Carlo Bruttini · Francesco Bolzoni · Paolo Cavallari

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Abstract The literature reports that anticipatory postural adjustments (APAs) are programmed according to movement velocity. However, the linkage between APAs and velocity has been highlighted within single subjects who were asked to voluntarily change movement velocity; therefore, till now, it has been impossible to discern whether the key factor determining APA latency was the *intended* movement velocity or the *actual* one. Aim of this study was to distinguish between these two factors. We analyzed the APA chain that stabilizes the arm during a brisk index finger flexion in two groups of subjects: (1) 29 who composed our database from previous experiments and were asked to "go-as-fast-as-possible" (*go-fast*), but actually performed the movement with different speeds (238–1,180°/s), and (2) ten new subjects who performed the *go-fast* movement at more than 500°/s and were then asked to *go-slow* at about 50 % of their initial velocity, thus moving at 300–800°/s. No correlation between APA latency and actual movement speed was observed when all subjects had to *go-fast* ($p > 0.50$), while delayed APAs were found in the ten new subjects when they had to *go-slow* ($p < 0.001$). Moreover, in the speed range between 300 and 800°/s, the APA latency depended only on movement instruction: subjects *going fast* showed earlier APAs than those *going slow* ($p < 0.001$). These data suggest a stronger role of the *intended* movement velocity versus the *actual* one in modifying the timing of postural muscles recruitment with respect to the prime mover. These results also strengthen the idea of a shared postural and voluntary command within the same motor act.

R. Esposti · C. Bruttini · F. Bolzoni · P. Cavallari (✉)
Sezione di Fisiologia Umana - DePT, Università degli Studi di Milano, Via Mangiagalli 32, 20133 Milan, Italy
e-mail: paolo.cavallari@unimi.it

Keywords APA · Speed · Motor control · Posture · Voluntary movement · Human

Introduction

About 5 years ago, we started investigating the anticipatory postural adjustments (APAs) that develop in the same limb in which the voluntary movement occurs (Caronni and Cavallari 2009). In fact, a brisk finger flexion, driven by the prime mover Flexor Digitorum Superficialis (FDS), is accompanied by an APA chain in the upper limb, consisting of an excitatory burst in triceps brachii (TB) and in an almost contemporary inhibition in biceps brachii (BB) and anterior deltoid (AD). These anticipatory postural activities allow to counteract the elbow and shoulder flexion induced by the upward perturbation that the index finger flexion causes on the metacarpophalangeal joint (MP). Although resulting from the motion of a tiny mass, these intra-limb APAs behave similarly (Caronni and Cavallari 2009; Bolzoni et al. 2012; Bruttini et al. 2014) to the well-known inter-limb APAs of movements involving large masses (see Bouisset and Do 2008 for a review).

The APAs originate from a feed-forward command (Belen'kii et al. 1967; Friedli et al. 1984; Aruin and Latash 1995; Massion et al. 1997), and therefore, APAs are tuned depending on several kinematic aspects of the primary movement. Of particular interest for the understanding of APA programming is the dependence of their latency from movement velocity, illustrated by Horak et al. (1984), Lee et al. (1987), and also appreciable in figure 2a of Shiratori and Aruin (2007). In those papers, information about the linkage between APAs and speed of voluntary movement was obtained within single subjects, by comparing their behavior when instructed to change the movement velocity;

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therefore, it was impossible to discern whether the key factor determining the modification of APA latency was the change of the *intended* or the *actual* movement speed. The aim of this study was to distinguish between these two factors.

To address this issue, we analyzed the well-known intra-limb APA chain that stabilizes the arm during a brisk index finger flexion, in two groups of subjects: 29 composing our database of previous experiments, who received the same "go-as-fast-as-possible" (*go-fast*) instruction but actually performed the movement at different velocities (238–1,371°/s) and 10 new subjects who performed the *go-fast* flexion at more than 500°/s and were then asked to *go-slow* at about 50 % of their initial speed, so that they moved faster than 250°/s. Assuming that all subjects actually obeyed the *go-fast* and *go-slow* instructions by planning a movement at 100 and 50 % of their maximal speed, respectively. The change of movement *instruction* should have been reflected into a parallel change of the *intended* movement speed.

In the *go-fast* population, we tested the correlation between APA latency and *actual* movement speed, while the *go-fast* versus *go-slow* behavior of the 10 new subjects allowed us to assess the effect of the *intended* movement speed. Moreover, a last comparison was drawn between subjects moving at the same speed but obeying the two different instructions, i.e., planning two different speeds. Results from these experiments allowed us to properly distinguish whether APA latency depends on *actual* or *intended* movement velocity, or on both.

Materials and methods

Two groups of subjects were analyzed. The first group was composed by our database of 29 subjects (12 females), recorded in previous studies. All of them performed experiments in which they were asked to briskly flex the index finger as fast as possible (*go-fast* instruction). The actual velocity of their movements ranged from 238 to 1,180°/s. Their mean (±SD) anthropometric characteristics were: age 26.2 ± 8.9 years, weight 65.8 ± 11.6 kg, height 172 ± 16 cm, index finger length 8.7 ± 0.8 cm and upper limb length 70.4 ± 6.4 cm.

The second group was obtained by collecting ten new subjects (four females) who were able to perform the *go-fast* finger flexion at more than 500°/s. These subjects were then asked to *go-slow,* at about 50 % of their initial speed. Their mean (±SD) anthropometric characteristics were: age 28.1 ± 5.7 years, weight 68.4 ± 13.4 kg, height 174 ± 13 cm, index finger length 9.2 ± 0.9 cm and upper limb length 72.3 ± 5.8 cm.

In both groups, no subject had any history of orthopedic or neurological disease and all of them gave written consent to the procedure, after being informed about the nature of the experiments. The procedure was approved by the local Ethics Committee in accordance to the 1964 Declaration of Helsinki.

Experimental procedure

The ten new subjects underwent the same experimental procedure described in Caronni and Cavallari (2009): they sat on a chair with both arms along the body, the right elbow flexed at 90°, the right hand prone and in axis with the forearm. The right index finger was kept extended and in contact with a proximity switch (Pepperl and Fuchs, CJ10-30GK-E2), so that the MP joint angle was about 180°, all other fingers hanging. Subjects were explicitly asked to keep their back supported, the arm and forearm 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 position of the subject was always visually controlled by the experimenter.

Subjects were asked first to flex their index finger at the MP joint. Each movement was self-paced and performed after an acoustic signal delivered every 7 s. The time interval between the beep and the movement onset varied according to the will of the subject. This procedure was adopted to exclude any reaction time. Subjects performed two sequences of 30 finger flexions in which they were instructed to *go-fast*, followed by two more sequences in which they were instructed to *go-slow*, i.e., to reduce their speed to about 50 % of the fast value. A rest time of about 5 min was allowed between each session. Subjects never complained about fatigue. Movement speed was monitored by the experimenter, who alerted the subjects to speed-up or slow-down when necessary.

Movement and EMG recordings

The onset of the fingertip movement was monitored by the proximity switch. Flexion of the right MP 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, Rhode Island, 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 prime mover FDS and from some of the ipsilateral postural muscles: BB, TB and AD. A good selectivity of the EMG recordings was achieved both by a careful positioning of the electrodes and by checking that the activity from the recorded muscle,

during its phasic contraction, was not contaminated by signals from other sources. EMG was AC amplified (IP511, Grass Technologies®, West Warwick, Rhode Island, USA; gain 2–10 k) and band-pass filtered (30–1,000 Hz, to minimize both movement artifacts and high-frequency noise). Goniometric and EMG signals were A/D converted at 2 kHz with 12-bit resolution (PCI-6024E, National Instruments®, Austin, Texas, USA), visualized online, and stored for further analysis.

Data analysis

On each sequence, the 30 EMG traces of the prime mover and those simultaneously recorded from the postural muscles were digitally rectified and integrated (time constant: 25 ms). Traces collected from each muscle were then averaged in a fixed temporal window: from −1,000 to +300 ms with respect to the onset of the FDS EMG, identified by a software threshold set at +2 SD of the reference signal level (from 1,000 to 500 ms prior to movement onset). On each experiment, latency of the postural activity was measured off-line on the averaged traces. The EMG onset in each postural muscle was identified by a software threshold set at ±2 SD of the reference signal level, and visually validated. Latency of the APA was referred to the FDS EMG onset, with negative values indicating a time advance.

Statistics

Pearson's product-moment correlations was used to assess the relationship between APA latency and actual movement speed in BB, TB and AD muscles, in all subjects who were instructed to *go-fast* or to *go-slow*.

Two-way repeated measures ANOVA was employed to test the effect of *instruction* (*go-fast* vs. *go-slow*) and *muscle* (BB vs. TB vs. AD) on APA latency, in the 10 new subjects.

Two-way mixed ANOVA was used to test the effect of *instruction* (between-groups factor) and *muscle* (within-subjects factor) in the 10 new subjects when they had to *go-slow* versus those from our database who had to *go-fast* but actually moved in the same speed range. Movement speed was compared by an unpaired *t* test.

For all tests, significance threshold was set at 0.05.

Results

Anticipatory postural adjustments prior to a fast index finger flexion

Despite the large range of their actual movement speeds (from 238 to 1,371°/s), both the 29 subjects from our database and the new 10 subjects, who were instructed to *go-fast*, showed no correlation between APA latency and actual movement velocity (BB: $r^2 = 0.0001$, $p = 0.95$; TB: $r^2 = 0.0122$, $p = 0.50$; and AD: $r^2 = 0.0030$, $p = 0.74$, see Fig. 1). On average, the TB muscle activation was almost synchronous (mean ± SE −0.3 ± 2.2 ms) to prime mover FDS, while inhibition of BB and AD clearly preceded it (−37.5 ± 2.9 and −34.2 ± 3.2 ms, respectively).

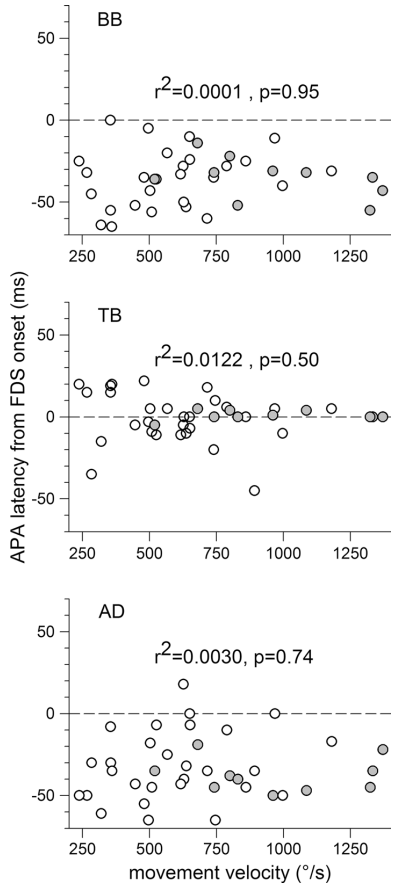

Fig. 1 Relation between the APA latency in the three postural muscles (biceps brachii, BB; triceps brachii, TB; and anterior deltoid, AD) and the actual movement velocity. Data from subjects from our database (*white circles*) and from the new ten subjects (*gray circles*) are plotted. Time 0 (*dashed line*) refers to prime mover EMG onset. No correlation between APA latency and movement velocity was found in the whole population

Anticipatory postural adjustments prior to a slow index finger flexion

The different behavior between the *go-fast* and *go-slow* instruction is depicted in Fig. 2 for a representative subject.

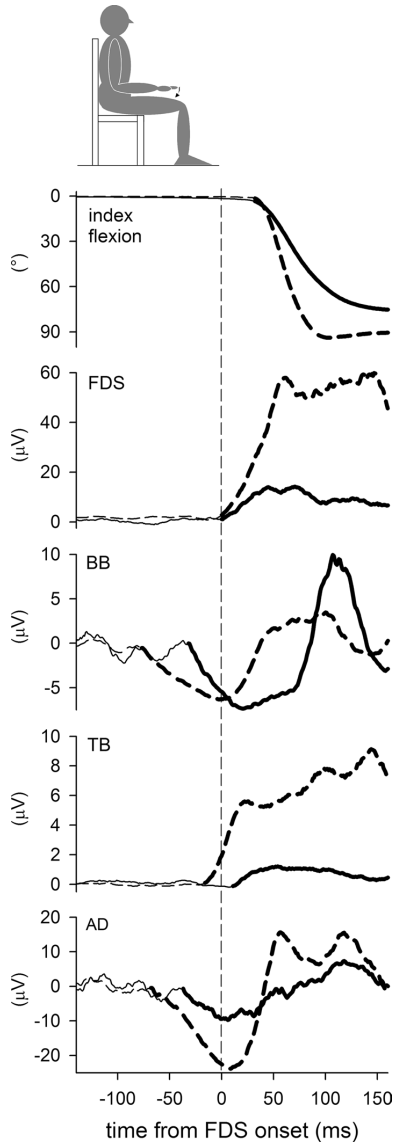

Fig. 2 Go-fast and go-slow movements in a representative subject. The *inset* depicts the position of the subject in the experimental setup. Goniometric recording of the index finger flexion (*top panel*) and rectified and integrated (25 ms) EMG from the prime mover FDS and from BB, TB and AD. *Note* that when going fast (*dashed traces*) the prime mover onset was preceded by APAs in BB, TB and AD. APAs (embolded) were instead clearly delayed when going slow (*solid traces*). Time 0 (*vertical dashed line*) refers to prime mover EMG onset

The latency lag during *go-slow* movement may be easily appreciated by matching the bolded lines in the three postural muscles. When *going slow*, the movement speed was reduced from 1,324 to 590°/s, i.e., to about 50 % of its maximal value.

The APA latencies obtained in *go-fast* and *go-slow* movements of the 10 new subjects are shown in Fig. 3. On the left, latency is plotted against actual movement speed. Note that the range of the *go-slow* movements (from 309 to 794°/s) fell within the range of the *less fast* subjects plotted in Fig. 1. In this case too, no correlation was found between APA latency and movement velocity (BB: $r^2 = 0.0063$, $p = 0.83$; TB: $r^2 = 0.00001$, $p = 0.99$; and AD: $r^2 = 0.013$, $p = 0.75$). Mean latencies and individual values are plotted in the right panels, showing that when instructed to *go-slow* subjects clearly delayed their postural activities of about 20–25 ms.

A two-way repeated measures ANOVA showed a significant effect of movement *instruction* (*go-fast* vs. *go-slow*, $F_{1,9} = 38.6$, $p = 0.0002$) and *muscle* ($F_{2,18} = 33.9$, $p < 0.0001$), while interaction was not significant ($F_{2,18} = 1.2$, $p = 0.32$), i.e., the change in latency was similar in the three muscles.

Finally, the results from the 10 subjects who had to *go-slow* were matched with those who performed the *go-fast* task at a similar velocity, i.e., 300–800°/s. The mean APA latency was clearly different in the two groups, witnessing that movement instruction, not actual movement speed, was the most significant factor in determining the APA timing.

Table 1 reports the movement speed and the mean APA latencies in the two groups. Despite similar velocities, it is apparent that the jump of latency is due to the different instruction. Unpaired *t* test showed no difference in movement velocity between the two groups ($t_{29} = 1.05$, $p = 0.30$); instead, a two-way mixed ANOVA showed a significant effect of movement *instruction* (*go-fast* vs. *go-slow*: $F_{1,29} = 18.1$, $p = 0.0002$) and *muscle* (BB vs. TB vs. AD: $F_{2,58} = 35.4$, $p < 0.0001$), while the interaction was not significant ($F_{2,58} = 1.8$, $p = 0.17$).

Discussion

This study showed that the key factor determining the modification in APA latency when performing a voluntary movement was the change in the movement *instruction (go-fast* vs. "go slow"), not the *actual* movement velocity. This conclusion stemmed from three observations: (1) There was no correlation between APA latency and movement speed when all subjects *had to* follow a *go-fast* instruction, as shown in Fig. 1, (2) APAs were delayed when subjects reduced their movement velocity because they *had to* follow a *go-slow* instruction (Fig. 3), and (3) in a large range of speeds, the APA latency depended exclusively on movement instruction: subjects *going fast* showed earlier APAs than those *going slow* (Table 1). Under the assumption

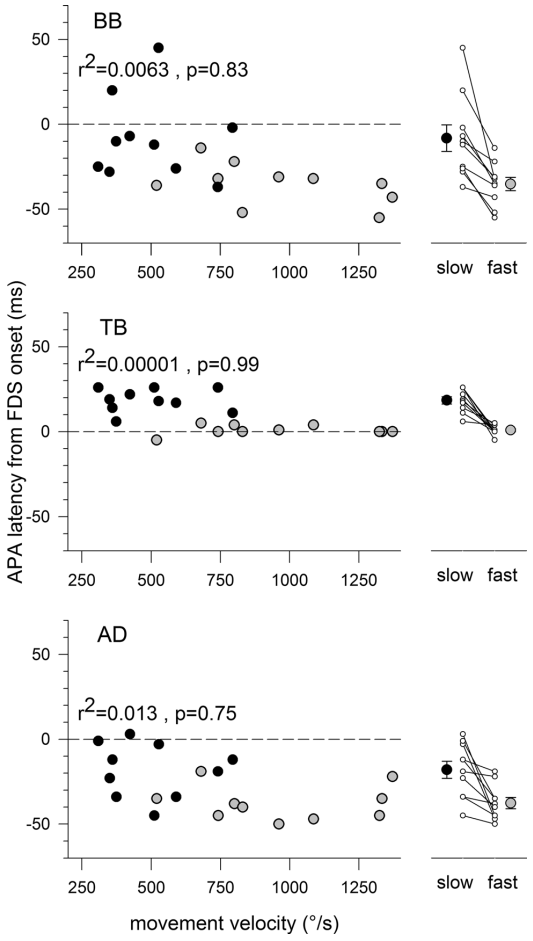

Fig. 3 Go-fast and go-slow APA latency in the ten new subjects. The *left panel* illustrates the relation between movement velocity and mean latencies of the three postural muscles when subjects were asked to go-fast (*gray circles*) or to go-slow (*black circles*). Time 0 (*dashed line*) refers to prime mover onset. No correlation between APA latency and movement velocity was found when subjects were asked to go-slow. *Right panel* compares individual and mean (±SE) APA latency in fast and slow movements

Table 1 Effect of movement instructions on APA latency

	Speed (°/s)	BB (ms)	TB (ms)	AD (ms)
Go-fast	558 ± 30	−39.4 ± 4.5	1.1 ± 2.7	−32.4 ± 5.3
Go-slow	498 ± 53	−8.2 ± 7.8	18.5 ± 2.1	−18.0 ± 5.0

Mean APA latency ± SE in biceps brachii (BB), triceps brachii (TB) and anterior deltoid (AD) in two groups of subjects who were instructed to *go-slow* or *go-fast*, but actually performed index finger flexion at 300–800°/s. First column shows that they actually moved at similar velocities. Statistics (see text) found no difference in movement speed, but a significant effect of instruction on all muscles

that all subjects actually obeyed the *go-fast* and *go-slow* instructions by planning a movement at 100 and 50 % of their maximal speed, respectively, the change in movement *instruction* was paralleled by a change in the *intended* movement speed; hence, the latter should have been the key factor for determining the APA latency.

The previous literature considers APAs as pre-programmed according to several task parameters, such as velocity, load and direction (for a review, see Bouisset and Do 2008). In particular, for what concerns the relationship between APA latency and movement velocity, several studies (Horak et al. 1984; Lee et al. 1987; Ito et al. 2003, see also in figure 2a of Shiratori and Aruin 2007) found delayed APAs when the subjects voluntarily slowed their movement, in agreement with the second of our above observations. It might appear strange that Ito et al. (2003) found no change in APA latency between fast and slow movements. However, these authors measured latency with respect to movement onset, not to prime mover recruitment, and since, in general, the delay between prime mover activation (EMG) and movement onset increases when slowing the movement, and this could have compensated the reduction in APA latency with respect to prime mover onset. Note also that in all the above studies, the latency–speed relation was observed within single subjects who were explicitly compelled to change the speed of their movement. Such an approach, i.e., studying subjects who planned different movement speeds, did not allow to distinguish whether the APA latency changed in function of the *intended* movement velocity or of the *actual* one. In this regard, the novelty of the present paper is to have discerned between these two factors.

It may be argued that the lack of inter-subjects correlation between APA latency and actual movement speed could have been ascribed to a subject-dependency of APAs, like the walking speed in elderly vs. young subjects (cfr. Schimpl et al. 2011). This could be true, even if in our subjects neither the APA latencies nor the maximal movement speed were correlated with age (in all cases, $r^2 < 0.044$; $p > 0.20$). However, this would not affect the main message of our study: the literature on APAs reports that their latency is scaled according to the movement speed, our study (1) showed that such relation held only within-individuals, while no significant correlation was observed between-subjects and (2) concluded that the *intended* movement speed is a key factor for determining the APA latency because it was the only factor which systematically changed within-individuals and not between-subjects.

Given that the CNS is able to adapt APAs to the postural demand of the forthcoming mechanical perturbation, one may ask whether postural control and voluntary recruitment stem from two separates control centers or they instead result from a shared motor command. In the former

case, it was expected that after few trials, APAs would have adapted their latencies according to the *actual* movement velocity, as shown, when changing the postural context (Cordo and Nashner 1982; Hall et al. 2010; Bruttini et al. 2014). In fact, the postural controller would have overcome the *intended* command because of the proprioceptive feedback. Instead, in the case of a shared motor command, the *intention* would have prevailed, so that APA latency would have always been tailored to it. Present results clearly agree with the latter view.

Such view is not new: it had been already forwarded for justifying the persistence of APAs even after a forearm ischemia, which suppressed (1) the prime mover EMG, (2) the ensuing finger movement and (3) the related mechanical perturbation (Bruttini et al. 2014). In that condition, the CNS did not adapt APAs to the absence of mechanical perturbation, seemingly because the motor command was unchanged. A result indirectly suggested that the recruitment of postural and prime mover muscles was driven by a shared motor command. The concept of a shared postural and voluntary command within the same motor act was also envisaged by Caronni et al. (2013), who showed that APAs properly tailored to the prime mover activation contribute to make the focal movement accurate by securing the position of the proximal joints. Leonard et al. (2011) reached similar conclusions showing that the CNS employs a predictive mode of postural control and consistently adapts the postural muscle activity before correcting the prime movers recruitment. These authors concluded that the postural corrections could be described as being a component of the voluntary movement, rather than being aimed to ensure the maintenance of equilibrium. Present results are also in agreement with Davidson and Wolpert (2005), who illustrated a stronger role of predictive feed-forward internal models versus sensory feedback in several aspects of human motor control, such as oculomotor and skeletomotor control, perceptual processing, mental imagery and also postural control (see also Wolpert et al. 1995, 2011).

Little is known about the neural sub-systems governing APAs, but several studies suggested a superposition of the neural structures for APAs and those for voluntary recruitment, thus indirectly supporting the above hypothesis of a shared motor command. 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). In particular, beyond their role in shaping the movement, basal ganglia may be involved in the intentional movement selection, through the pathway involving the anterior mid-circulates cortex (see Hoffstaedter et al. 2013). Anticipatory brain activity before the execution of a bimanual load-lifting task was recently localized in basal ganglia, supplementary motor area (SMA), and thalamus in the hemisphere contralateral to the load-bearing arm (Ng et al. 2012). It is worth noting that these areas are component nodes of the basal ganglia-thalamo-cortical network implicated in well-learned finger movements (Boecker et al. 1998). The possible involvement of the SMA in the APA network was suggested by several human and primate experiments (Brinkman 1984; Viallet et al. 1992; Yoshida et al. 2008; Jacobs et al. 2009). A change in firing rate, depending on speed instruction, had also been shown in the pre-motor cortex of rhesus monkey (Shenoy et al. 2003), another area involved in motor program selection (see for references Hoffstaedter et al. 2013). This result is of particular interest for us because the movement paradigm closely replicated many aspects of our task, such as the delayed movement onset with respect to the go signal, in order to avoid a reaction time movement, and the two different speed instructions.

Finally, the hypothesis of a *functionally unique motor command* deserves a brief consideration within the framework proposed by Bouisset and Do (2008) in their review on APAs. According to these authors, the voluntary movement is any motor act in which the intention of the subject is to perform a given task. These authors distinguished two aspects of the "task": First, the task to be performed, which depends on the environmental context and the category of the intended movement, such as pointing, tapping, and throwing. Second, the real task, i.e., the outcome of the motor command, which may satisfy the intended movement by a various degree of efficiency. As these authors stated: "Efficiency is measured by the actual parameter values (speed, precision, etc.) with respect to the intended ones and depends on the neural and muscular–skeletal properties of each subject. Therefore, a voluntary movement is part of a more general process, called the motor act. In other words, a voluntary movement is the mean to complete a motor task". In this perspective, the present results strengthen the idea that *APAs* belong to the same *motor act* as that of the *voluntary recruitment*. Indeed, just as voluntary movement, APAs may be considered "the mean to complete a motor task", as they provide the proper fixation chain.

Conclusion

This study showed: (1) a lack of correlation between APA latency and actual movement speed in subjects who planned the same movement, i.e., an as-fast-as-possible flexion of their index finger, despite a wide range of actual movement velocities, and (2) that APAs were delayed when 10 subjects were asked to repeat the movement at about 50 % of their maximal speed. These data suggest a stronger role of intended versus actual movement speed in modifying the timing of postural muscles recruitment with respect

to prime mover, thus strengthening the idea of a shared postural and voluntary command within the same motor act.

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Conclusions

In past literature, it has been often considered that APAs are unconscious muscular activities aimed to counteract the perturbation induced by the primary movement. This idea was born from several papers (Belenkii et al. 1967, Cordo and Nashner 1982, Zattara and Bouisset 1988) and summarized in the review from one of the giants of the APAs research, Jean Massion (1992).

The results of the present thesis do not contrast the Massion's view, but aim to refine his definition. In particular, both the demonstration of the APA role in refining movement accuracy (Caronni et al. 2013) and the persistence of the APA chain under an ischemic block (Bruttini et al. 2014), challenge Massion's definition. Indeed, it seems now feasible to define APAs as part of a voluntary motor act, or, as defined by Bouisset and Do (2008), as the "optimal biomechanical means" to initiate voluntary movement and to approach postural programming.

As pointed out above, this idea is not aligned with part of the previous literature that has considered the postural component and the focal movement as controlled by two separate motor commands (Hess 1943; Cordo and Nasher 1982; Brown and Frank 1987). In particular, Brown and Frank (1987) favored the idea of a distinction between posture and movement by demonstrating that the time between the activation of postural adjustments and that of focal muscles varies according to the predictability of the perturbation. In fact, when asking subjects to perform a two-choice task involving pushing or pulling on a stiff handle, and allowing them to predict the upcoming direction of responding with a 80, 50 or 20% certainty, APAs were delayed when subjects were more "confident" of the direction of the perturbation, while more anticipated in the opposite case. However, the demonstration that APAs change their latency according to the predictability the upcoming direction of the handle does not ascertain that APAs and prime mover(s) are recruited by two different motor commands. Indeed, as stressed by Andrè-Thomas (1940), the maintenance of the equilibrium against unexpected fall and the execution of a voluntary movement without falling down are controlled by different mechanisms. Moreover, the change in APA latency could reflect a safety strategy to

avoid a violent fall when uncertain about the environmental context in which one is moving, i.e. the reliability of the fixation points, since the CNS may develop earlier APAs in order to produce a more effective counter-perturbation.

Similar observations could be drawn with respect to the arm-pull experiment in standing subjects performed by Cordo and Nashner in 1982, who also sustained the hypothesis of two parallels commands for APAs and focal movement. In their experiments, subjects showed reduced APAs in the Soleus when adding a fixation point to the trunk. This result let the authors to suggest that APAs and prime mover recruitment are controlled by two different motor commands. However, in this situation, it could be argued that the oscillation caused by pulling the handle was prevented thanks to the presence of the additional support and, therefore, reduced the importance of the intervention of the posterior muscles of the lower limb. Furthermore, it is known that the length of the APA chain depends on the position of the fixing point to which it is anchored (see also Bruttini et al. 2014a). Consequently, in my opinion, the experiments performed by Cordo and Nashner in 1982 are not sufficient to demonstrated a parallel command for posture and voluntary movement.

On the other hand, in an unstable condition, i.e. when reducing the support base area, APAs are usually reduced in amplitude (Gantchev and Dimitrova 1996). In fact, since the APA themselves determine the movement (Bouisset and Do, 2008), when the support base is small, the APA themselves could cause a displacement of the CoM, potentially threatening the whole body balance. Indeed, the importance of an adequate support base to ensure a reliable fixation point for the APA chain was suggested by Dietz & Colombo (1996), who showed that no APAs in lower limbs could be observed when performing push/pull movements when the body is fully immersed in water. It is thus apparent that moving without any fixation point is not an adequate condition for the APA chain to develop. Indeed, as expressed by Gray, when the human body is considered as a whole, muscular forces are internal to the mechanical system. As such, these forces cannot determine the overall movement of the body, being thus able to provoke just segmental movements; moreover, the global center of gravity can only move if the body encounters resistance originating from the environment, usual a

support base, which offers the appropriate reaction to the internal muscular forces. This view is also in agreement with one of the findings of the present thesis. In Bruttini et al. (2014a) it was illustrated that, when performing a sequence of unilateral movements of the right index-finger, with the right forearm fixated at the wrist, intra-limb APAs in the same limb were deeply reduced. In fact, the new fixation point at the wrist, i.e. closer to the voluntary moving segment (index-finger), strongly attenuated APAs in the more proximal muscles.

Boendermaker et al. (2014) have described the neural structures in the CNS, which detect the environment in which we are moving and therefore permit to adapt the APA chain to the context. In that paper, it was demonstrated that applying a pressure on three lumbar spinous processes, a significant activation patterns in the somatosensory cortices (S1 and S2), supplementary motor area and anterior cerebellum was observable. According to these authors, the CNS should reasonably interpret the pressure as a new fixation point on the back and thus trigger a predictive APA adaptation, based on the new postural context. In other words, online sensory information about the environment in which we are moving are available early enough to tailor the APA chain.

The analysis of the general postural context in which the body is moving obviously examines both the physical properties of the support base and the interface between the body and the support. The first depends on the characteristics of the environment in which we are moving, the latter on our own body posture. The interpretation on the external environment, related to our possibility of interacting with it, represent the "support base" that permit a successful APA-voluntary movement programming and is probably stored in the sub-cortical and cortical areas described by Boendermaker.

The experiments of Caronni et al. (2013) have illustrated the role of retinal afferences and of extra-ocular muscles proprioception in adapting the APA chain to the forthcoming voluntary movement. In those experiments, a couple of prismatic lenses have produced a rightward shift of the binocular eye-field of about 11°. Therefore, the target projection on the retina was moved leftward with respect to the fovea. This induced a rightward shift of the eyeball to realign the fovea to the target. Both the initial

shift of the projection of the target on the retina and the proprioception of the following extra-ocular muscular activities made the subject to miss the target, causing a large rightward error. As shown in the paper section, the pointing error was associated to a modification of APAs, without any change of the prime mover activities, unveiling the role of the vision and the proprioception of the extra ocular muscles in the APA programming.

It should be expected that the information about the environmental physical properties should be translated from sensory to motor areas that are involved in the APA programming. Little is known about the neural sub-systems governing APAs, but several studies suggested a superposition of the neural structures for APAs to those for voluntary motor command, thus indirectly supporting the above hypothesis of a "global command". 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 observed in patients with a lesion of the motor cortex or of the Supplementary Motor Area, SMA (Viallet et al. 1992). The possible involvement of the SMA in the APA network was indicated also by other experiments (Brinkman 1984; Yoshida et al. 2008; Jacobs et al. 2009). Anticipatory brain activity before the execution of a bimanual load-lifting task was recently localized in basal ganglia, SMA, and thalamus in the hemisphere contralateral to the load-bearing arm (Ng et al. 2012). Yakovenko and Drew (2009), who studied the discharge properties of cat pyramidal tract neurons (PTN) and their temporal linkage with APAs associated to reaching movements also support this latter view. These authors found a strong linear relationship between the onset of PTNs discharge and the APAs onset, strengthening the idea that the motor cortex contributes to generate the APAs. It is worth noting that these areas are component nodes of the basal ganglia-thalamo-cortical motor network, which is implicated in well-learned finger movements (Boecker et al. 1998). Moreover, Schepens and colleagues (Schepens and Drew 2004; Schepens et al. 2008) emphasized the role of pontomedullary reticular formation (PMRF) in the coordination of posture and movement. In particular, they suggested that PMRF is a site of integration of signals from both cortical and subcortical structures, and that these signals ensure that APAs

are appropriately scaled in time and in magnitude to the intended movement, contributing to integrate the control of posture and movement, as also illustrated by Toussaint et al (1998).

In the present thesis it has been strengthen the idea of an involvement of SMA in APA programming (Bolzoni et al. 2014) and it was also proposed, together with other previous works (Diedrichsen et al. 2005, Yamaura et al. 2013), an involvement of cerebellum in the neural networks responsible for generating and/or controlling APAs (Bruttini et al. 2014b). All these data suggest a superposition of the neural structures for both the APAs and the voluntary motor command and indirectly support the hypothesis of a global (common) command.

The oneness of the postural and voluntary commands were suggested particularly by other experiments such as Bruttini et al. (2014a), Bolzoni et al. (2012), Caronni et al. (2013) and Esposti et al. (2014). In the first paper it was illustrated the persistence of the APA chain associated to a voluntary movement in an experimental condition in which the voluntary command was normally dispatched but the prime mover was not able to contract. Given the well-known ability of the CNS to adapt APAs to changes in the postural demand of the motor task within few movement repetitions (Belen'kii et al. 1967; Cordo and Nashner 1982; Aruin and Shiratori 2004; Shiratori and Aruin 2007; see also Hall et al. 2010), one could have expected that in these conditions APAs are suppressed, since unnecessary and uneconomical. Intriguingly enough, when repeatedly trying to flex the index-finger under ischemia, significant anticipatory adjustments were still clearly visible in BB, TB and AD. In other words, when the subject was asked to flex the index-finger, he recruited several upper limb muscles which do not act on the focal segment, independently if the actual movement, and therefore the ensuing perturbation, develops or not. The question of what is "economical" when controlling the voluntary movement, therefore, arise. It could be then argued that for the CNS is more economical to use a unique motor command fast to be dispatched, according to a well-acquired pattern, rather than saving energy at the muscular level. Note that the subjects were asked to generate the same voluntary command in both conditions and any attempt to recruit FDS still resulted in a

recruitment of BB, TB and AD, without adaptation to the suppression of finger movement. The similarity of the motor command in the two conditions could not be directly assessed, but it may be inferred from the invariance of APAs amplitudes and latencies and the simultaneity and constancy of the contra-lateral index-finger flexion, visually controlled by the subject during the experiment. In this framework, as also suggested by Leonard et al. (2011), it would be difficult to keep strictly divided the control of posture from the control of the primary movement, as instead it was often proposed in previous literature (Hess 1943; Cordo and Nasher 1982; Brown and Frank 1987). The results of Bruttini et al. (2014a) suggests that the voluntary motor command recruit each muscles of the muscular chain starting from the fixation point and terminates on the focal (prime) mover.

In this regard, it is interesting to mention the studies of Gritsenko et al. (2009) and Leonard et al. (2011) showing that when correcting an ongoing arm pointing movement, the CNS employs a predictive mode of postural control and consistently adapts the postural muscles activities before spot on the prime mover recruitment. These authors concluded that the postural corrections could be described as being a component of the voluntary movement, rather than ensuring the maintenance of equilibrium. The observation that APAs remained tailored to the expected perturbation even when that perturbation did not occur supports the idea that APAs should be considered as the first part of a unique motor act starting from a fixation point, developing with the APA chain and including the prime mover activity.

The oneness of postural and voluntary command was also witnessed by the finding that the APA latency depends on the movement instruction ("go-fast" vs. "go slow"), not on its actual velocity. This conclusion stems from three observations: i) there is no correlation between APA latency and movement speed when subjects obeyed the same instruction, ii) APAs were delayed when subjects reduced their movement velocity because they obeyed to a go slow instruction, iii) given a certain speed, APA latency depend on the instruction since go fast subjects showed earlier APA than go slow. Also in this case, if the recruitment of the postural muscles had involved a separate neural mechanism with respect to that governing the prime mover(s), APAs would have been

expected to change their latencies according to the actual movement velocity. Instead, present results shows that, APAs were delayed only when changing the movement instruction. In other words, APAs seem to be tailored to the expected perturbation, much more than on the real one, strengthening the idea that the postural and prime mover muscles are driven by a functionally unique command.

Similar conclusions were reached in Caronni et al. (2013), who showed that prisms-induced pointing error specifically underlies changes in APAs amplitude with no changes in the prime mover activation, thus sustaining the hypothesis that a successful and accurate pointing movement relies upon a specific tuning between APAs and prime mover activation (see Caronni & Cavallari 2009a). In other words, "a movement never responds to detailed changes by a change in its detail; it responds as a whole to changes in each small part, such changes being particularly prominent in phases and details sometimes considerably distant both spatially and temporally from those initially encountered" (Bernstein 1967).

Considering that a disruption of the APA chain led to movement inaccuracy, we thought it had been interesting to study the effect of a short-term immobilization on the postural control of non-immobilized segments. The effect of a cast immobilization on the prime mover are well known. Over the past few decades several authors have documented modifications in skeletal muscle properties such as atrophy (White et al. 1994; Hather et al. 1992), increasing in the intra-muscular connective tissue (Józsa et al. 1990) and reduction of the maximal voluntary contraction strength (Veldhuizen et al. 1993; Hortobàgyi et al. 2000) after cast immobilization. Moreover, Liepert et al. (1995) showed that immobilization leads to reduction of the cortical area of the inactivated muscle, while Facchini et al. (2002) demonstrated a decrease of the cortical excitability, without affecting nerve or muscle excitability, after only four days of motor restriction. Huber et al. (2006) found that these changes might even occur after twelve hours of immobilization. Finally, Moisello et al. (2008) demonstrated that short-term immobilization affect inter-joint coordination by acting on feed-forward mechanisms. Indeed, besides the well-known effects of this procedure on the pathways projecting to the prime mover and deserving inter-joint coordination, it was shown that 12-hours of

wrist and fingers immobilization effectively modify anticipatory postural adjustments of the elbow and the shoulder, i.e. those joints not immobilized within the fixation chain (Bolzoni et al. 2012). It is worth noting that, although the prime mover activation remains unchanged after the immobilization, the trajectory described by the index-finger is most likely changed after short-term immobilization due to the modification in the postural control that led to a less effective stabilization of the proximal joint (see Caronni et al. 2013). Therefore, these results may shed light on some of the mechanisms underlying the feel motor awkwardness and the reduction of the voluntary movement precision that are common experiences after the removal of a cast or a splint.

Eventually, two issues regarding the consideration of posture and voluntary movement deserve a few brief comments. First, when talking about posture we often refer as a static phenomenon, i.e. the maintenance of stance equilibrium, not dynamic and linked to the voluntary movement as we also have shown with the results of the present thesis. Moreover, in the neuro-physiological community, it was quite common to refer as *isolated* to movements that were supposed to involve only one muscle, e.g. a motor command that was supposed to be able to recruit only the biceps brachii. On the other hand, the present thesis look at the voluntary movement as a wider phenomenon, in which isolated movements do not exist. According to this view, any motor command enclose the motor program for both the postural and the focal component, in an most probably inseparable way.

Final summary and future direction

In conclusion, the ideas discussed in the present thesis could promote a new perspective in the APAs function. The characteristics of the environment and the general postural context, are able to refine the choice of the correct APA pattern. Indeed, the identification of the target position (Caronni et al. 2013) and the available fixation points, through the activation of the somatosensory cortices (S1 and S2), supplementary motor area and anterior cerebellum, trigger a predictive adaptation of APAs within the CNS (Boendermaker et al. 2014). According to the information coming from the

somatosensory and motor areas, the network composed by basal ganglia, SMA, and thalamus (Ng et al. 2010) keep tailoring the APA pattern to the movement to be made. Also other areas, involved in the execution of the voluntary movement, seem to take part in the APA programming/controlling, such as the cerebellum (Bruttini et al. 2014b) and the SMA (Bolzoni et al. 2014). The dependence of the APA latency to the intended movement velocity (Esposti et al. 2014) and the enduring development of APAs when trying to flex the index-finger under forearm ischemia (Bruttini et al. 2014a) suggests that APAs are tailored to the intended movement characteristics, much more than the measure at which they are adjustable by the sensory feed-back of the actually performed voluntary movement. Finally, the importance of a correct APA pattern in refining voluntary movement accuracy (Caronni et al. 2013) seems to confirm the oneness of APAs and primary movement, and that a functionally unique motor command drives both the prime mover and the muscles of the APA chain, connecting available support base (ground, seat, etc…), proceeding through the postural chain and then terminating on the moving segment (Bruttini et al. 2014, see for a Review Bouisset and Do, 2008). It can be thus concluded that APAs adapt to changes i) of the postural context, ii) of the intended movement, i.e. the expected perturbation, but do no adapt, despite movement repetition, to changes in the actual executed movement, i.e. to the real perturbation.

Consequently, one may wonder where is the difference between APAs and the voluntary movement. In other word, should the anticipatory muscular activities that precede the prime mover recruitment be considered as *unconscious postural* actions, aimed to counteract the primary movement perturbation and guarantee the equilibrium of the whole-body or the single segment? Or are they actually part of a unique voluntary motor command, all of them necessary in order to perform the intended movement? According to the results presented in this thesis, the second hypothesis seems the one to be preferred, i.e. that APAs and the primary movement should be considered as one within the same motor program.

Nevertheless, there are still many question to be answered. These involve, among others, a deeper description of the neural network controlling APAs, especially regarding sub-cortical structures, such as the basal ganglia. Since these structures are

the “support base” of the basal ganglia-thalamo-cortical motor network, which is implicated in well-learned finger movements (Boecker et al. 1998), it is intriguingly to imagine that these structures are also strongly correlated with the generation of the APA command. Although it is unlikely that the entire mechanism that dispatches APAs and prime mover commands would be shortly identified, continual research aimed at providing a better understanding of these mechanisms is helping for a better comprehension of the motor control and especially the relationship between postural and voluntary movement commands.

Further studies are also needed in regard of the relationship of APAs with other aspects of the sensorimotor system. In particular, it would be interesting to study how the retinal afferences and the extra ocular muscles proprioception may be able to on-line adapting the APA chain to the forthcoming intended movement. An impaired vision, such as in patients with glaucoma or Age Related Macular Degeneration, which threaten the peripheral and central visual field respectively, may cause a disruption of APAs within a voluntary movement, causing imbalance. Similarly, as recently done by Cesari et al. (2014) regarding the associations between the auditory system and action planning, also the role of the utricule and saccule in adapting APAs to the current whole body orientation may be investigated.

Eventually, a possible clinical role on these new findings may be exploited, considering the evaluation of new therapeutic approaches to achieve a successful rehabilitation of the motor act after a neurological (e.g. TIA and strokes) or orthopedical injuries (e.g. joint instabilities or bone fractures). A better knowledge of each component of the voluntary movement, and the relationship between each other, may indeed be helpful for restoring a physiological motor control in these patients.

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