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Transcranial direct current stimulation of SMA modulates anticipatory postural adjustments without affecting the primary movement

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Abbreviations: AD, anterior deltoid muscle ; APA, anticipatory postural adjustments ; BB, biceps brachii muscle ; EMG, electromyogram ; FDS, flexor digitorum superficialis ; SMA, supplementary motor area ; TB, triceps brachii muscle ; tDCS, transcranial direct current stimulation

Highlights

- tDCS was used for interfering with the central pathways governing intra-limb APAs
- SMA was stimulated in anodal, cathodal and sham configuration during finger tapping
- Anodal tDCS increased APAs in biceps and triceps, muscle that stabilize the elbow
- tDCS had no effect on prime mover recruitment and voluntary movement kinematics
- The postural and the voluntary commands seem already separated before entering SMA

Abstract

Recent works provide evidences that anticipatory postural adjustments (APAs) are programmed with the prime mover recruitment as a shared posturo-focal command. However the ability of the CNS to adjust APAs to changes in the postural context implies that the postural and voluntary components should take different pathways before reaching the representation of single muscles in the primary motor cortex. Here we test if such bifurcation takes place at the level of the supplementary motor area (SMA).

TDCS was applied over the SMA in 14 subjects, who produced a brisk index-finger flexion. This activity is preceded by inhibitory APAs, carved in the tonic activity of Biceps Brachii and Anterior Deltoid, and by an excitatory APA in Triceps Brachii. Subjects performed a series of 30 flexions before, during and after 20 minutes of tDCS in CATHODAL, ANODAL or SHAM configuration.

The inhibitory APA in Biceps and the excitatory APA in Triceps were both greater in ANODAL than in SHAM and CATHODAL configurations, while no difference was found among the latter two (ANODAL vs. SHAM: Biceps +26.5%, Triceps +66%; ANODAL vs. CATHODAL: Biceps +20.5%, Triceps: +63.4%; for both muscles, ANOVA $p < 0.02$, Tukey $p < 0.05$). Instead, the APA in Anterior Deltoid was unchanged in all configurations. No changes were observed in prime mover recruitment and index-finger kinematics.

Results show that the SMA is involved in modulating APAs amplitude. Moreover, the differential effect of tDCS observed on postural and voluntary commands suggests that these two components of the motor program are already separated before entering SMA.

Keywords: voluntary movement, posture, supplementary motor area, APA, tDCS

1. Introduction

One of the main topics of our recent researches regards the anticipatory postural adjustments (APAs), developing in the same limb used to perform the voluntary movement. In fact, a brisk flexion of the index finger, driven by the prime mover Flexor Digitorum Superficialis (FDS), is accompanied by an APA chain consisting of an excitatory burst in triceps brachii (TB) and in an almost contemporary inhibition in biceps brachii (BB) and anterior deltoid (AD) (Caronni & Cavallari, 2009a). These APAs are organized so as to counteract the upward perturbation that the index finger flexion causes on the metacarpophalangeal joint, so as to avoid an elbow and shoulder flexion. Although the mass involved in this movement is tiny, these intra-limb APAs behave similarly (Chabran *et al.*, 2001, Caronni & Cavallari, 2009a; Bolzoni *et al.*, 2012) to the well-known inter-limb APAs of movements involving large masses (for a review see Bouisset & Do, 2008).

Several studies suggest a superposition of neural structures governing APAs with those involved in voluntary movement. Severe APA impairments in Parkinsonian patients strengthened the role of the basal ganglia (Viallet *et al.*, 1987). Similar impairments were also associated with lesions of the primary motor cortex or of the supplementary motor area, SMA (Viallet *et al.*, 1992). An fMRI study (Schmitz *et al.*, 2005) reported that APAs were associated with activation of sensorimotor areas, SMA and the cerebellum; a finding in part confirmed by Ng *et al.* (2012), who showed anticipatory brain activity in basal ganglia, SMA and thalamus. However, little is known about the precise role of each of these structures in governing APAs. In this regard it has been shown that the cerebellum is involved in APAs timing (Diedrichsen *et al.*, 2005; Bruttini *et al.*, 2015). Moreover, both excitatory and inhibitory APAs are already shaped in the primary motor cortex, M1 (Petersen *et al.*, 2009; Caronni & Cavallari, 2009b).

Our recent works provided evidence that APAs are programmed with the prime mover recruitment as a shared motor command (Caronni *et al.*, 2013; Bruttini *et al.*, 2014; Esposti *et al.*, 2015). However the ability of the CNS to selectively adjust the APA to changes in the postural context, like adding or removing a fixation point, without affecting the prime mover recruitment (e.g. Cordo & Nashner, 1982; Dietz & Colombo, 1996; Hall *et al.*, 2010) implies that the postural and voluntary components of such shared posturo-focal command should take different pathways before reaching the representation of the single muscles in M1.

The present study aims to test whether that bifurcation takes place at the SMA level. Indeed the latter area seems to be deeply involved in movement preparation (for a review: Nachev *et al.*, 2008). Direct SMA stimulation has been shown to evoke several motor and non-motor responses (Green *et al.*, 1980; Mitz & Wise, 1987; Hyland *et al.*, 1989). Stimulation could also induce a

subjective experience of movement without any overt motor activity, an “urge” to move (Fried *et al.*, 1991) or the inhibition of an action (Henry *et al.*, 2004). The fictive sensation of movement (as if a motor program was generated and its efferent copy routed to the sensory system), the urge to move (as if a motor program was ready to be executed) and the inhibition of the ongoing action (as if a resetting of motor action occurred), might all be attributed to an involvement of SMA in movement preparation. This view is also supported by the occurrence of *bereitschaft* potentials over SMA (Deecke & Kornhuber, 1978), as well as changes in SMA neuronal activity before movement execution (Brinkman & Porter, 1979; Tanji & Shima, 1994). Moreover, from a methodological perspective, SMA can be reliably identified, by means of neuronavigation and its excitability can be selectively modulated by tDCS (Vollman *et al.*, 2013). The relative distance between SMA and the M1 representation of arm muscles helps enhance the selectivity of stimulation.

In order to answer the question of whether the posturo-focal command bifurcates before or after SMA, anodal, cathodal and sham tDCS were applied on that area, looking for effects on the intra-limb APAs and/or prime mover recruitment. A parallel modification of APAs and prime mover recruitment would indicate that the SMA processes the posturo-focal command before it splits in the two components, separately routed to the primary motor cortex. On the contrary a differential effect on the two components would indicate that they are already bifurcated before the SMA.

2. Materials & Methods

Fourteen healthy volunteers (7 males, mean age: 24 ± 2 years ; 7 females, mean age: 22 ± 2 years) participated to the study. All of them were right-handed, according to the Oldfield questionnaire. Exclusion criteria were any history of neurological or orthopaedic disease, and of intake of drugs acting on the Central Nervous System. Naïve participants gave their informed consent, but were kept completely unaware of the stimulation condition. The experiments were conducted in conformance with the policies and principles contained in the Declaration of Helsinki and were approved by the local ethical committee.

2.1 Experimental design

Participants were sitting on a chair with the left arm supported by an armrest and the right upper-arm lying along the body, elbow flexed at 90° and prone hand lined-up with the forearm. Right index-finger was kept aligned with the hand and in contact with a proximity switch (CJ10-30GK-E2, Pepperl and Fuchs®, Mannheim, Germany), all other fingers hanging (Fig. 1A). Subjects were

asked to keep their back supported and both feet on the ground throughout the experiment. The height of the chair was adjusted to each participant and the proximity switch screwed on an articulated arm (143 MAGIC ARM + 035 Superclamp Kit, Manfrotto®, Cassola, Italy). The set-up was adapted to the body size.

In all subjects, the effect of tDCS in anodal, cathodal and sham configuration was tested on three successive days, in a random order. On each day, subjects were required to perform three sequences of 30 brisk flexion movements of the right index-finger at the metacarpophalangeal joint: one sequence immediately before tDCS (PRE), one during the last 5 minutes of full current tDCS (DUR), and one 20 minutes after ending tDCS (POST). Each movement was self-paced and performed after an acoustic signal. The time between the signal and the movement onset varied according to the subject will. This procedure was adopted to exclude any reaction time. No subjects complained about fatigue.

2.2 tDCS and neuronavigation

Figure 1B illustrates the anatomical references for SMA identification and the positions of the tDCS electrodes; stimulation was applied by using a neuroConn® DC-Stimulator Plus (model 0021) connected to two sponge electrodes, filled with saline solution (active 10.7 cm², reference 100cm² in order to be functionally inefficient, according to Vollmann *et al.* (2013). Active electrode was placed over the SMA under the guidance of an MRI-based neuronavigation system (Softaxic Optic 2.0). Target Talairach coordinates for SMA (-4, -9, 55) were obtained by converting MNI coordinates (-3, -2, 57, SMA-proper) from Vollmann *et al.* (2013), by using the algorithm proposed in Lancaster *et al.* (2007). The reference electrode was placed on the forehead over the contralateral supraorbital area and kept in contact with the scalp by elastic bands.

Anodal and cathodal stimulations started with a 30 s fade-in period, followed by 20 minutes DC at 1mA (current density 93.46 $\mu\text{A}/\text{cm}^2$) and ended with a 30 s fade-out (ANODAL and CATHODAL). In sham configuration the 30 s fade-in was immediately followed by the 30 s fade-out and then by 20 minutes without any current (SHAM). The constancy of impedance (4-10 k Ω) was monitored throughout the experiment.

2.3 Movement and EMG recordings

The onset of the right fingertip movement was monitored by the proximity switch. Flexion-extension of the right metacarpophalangeal and elbow joints was recorded by strain-gauge goniometers (mod. F35 and SG110, respectively, Biometrics Ltd®, Newport, UK) taped on the skin.

Angular displacements were DC amplified (P122, Grass Technologies[®], West Warwick, Rhode Island, USA) and gains were 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 prime mover, 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 recording was achieved both by 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. In order to maintain a steady tonic EMG activation in shoulder and elbow flexors, a weight of 0.5 kg was applied at the right wrist. 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).

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.

2.4 Data analysis

The EMG traces of the prime mover and those simultaneously recorded from the postural muscles were digitally rectified and integrated (time constant: 25 ms). For each sequence, all 30 EMG and goniometric traces were averaged in a fixed temporal window: from -1000 to +300 ms with respect to the onset of index-finger flexion. The mean EMG activity in a time window clearly free from APAs (from -1000 to -500 ms) was utilized to calculate the baseline reference level, which was subtracted from each EMG trace. On each sequence, latency and amplitude of the postural activity were measured off-line on the averaged traces. The onset of an effect in each postural muscle was identified by a software threshold set at ± 2 SD of the reference signal level, and visually validated. Latency of APA was referred to movement onset, thus assuming negative values. For each tDCS configuration, the APA amplitude in the DUR and POST sequences was measured as the mean level of the trace in the temporal window from the APA onset to the movement onset. In order to normalize the APA amplitude between days and sequences, they were expressed as a percentage of the corresponding amplitude measured in the PRE sequence of that day. The above time-window was chosen in order to avoid any effect due to re-afferentation triggered by the focal movement. The same criteria for onset detection and amplitude measurement were applied to voluntary activity in FDS.

APAs amplitude and latency, FDS amplitude and latency, movement amplitude and duration, as well as baseline BB and AD activity, were compared by two-way *time* (DUR vs. POST) \times *configuration* (ANODAL vs. CATHODAL vs. SHAM) repeated measures ANOVAs. Whenever significance was reached ($p < 0.05$), the effect size was calculated by the partial eta square (η^2_P) and Tukey HSD test was used for post-hoc comparisons.

In order to verify the effect of SHAM tDCS, amplitude and latency data recorded in DUR session under SHAM were compared to those recorded in PRE. This was done by means of one-sample t-tests for amplitude of APA and prime mover recruitment, and paired t-tests for APA latency as well as for the amplitude and duration of movement. Given that no significant differences were found (p always ≥ 0.15), SHAM configuration was assumed as the term of comparison for ANODAL and CATHODAL effects throughout the study.

3. Results

The pattern of intra-limb APAs under tDCS is shown in Figure 2, for a representative subject. Note that the pattern was similar among SHAM, ANODAL and CATHODAL configurations: an inhibition in BB and AD EMG, paralleled by an excitation of TB, clearly preceded the brisk index-finger flexion of about 70-90 ms. Note that APAs acting on the elbow joint were greater during ANODAL than during SHAM stimulation. Indeed, a deeper BB inhibition and a higher TB excitation are clearly shaped. No effect of ANODAL stimulation could be observed on AD APAs, as well as on FDS activation and on finger flexion. CATHODAL stimulation was instead apparently unable to induce any effect with respect to SHAM. No changes in EMG latency could be appreciated.

Figure 3A shows the effects of tDCS on the amplitude and latency of BB, TB and AD APAs, in the whole population (DUR and POST sessions). Repeated measures *configuration x time* ANOVA, and Tukey post-hoc (see asterisks in Fig. 3A), found that APAs in TB and BB were significantly larger under ANODAL than under CATHODAL or SHAM (main effect of *configuration*: $F_{2,26} = 15.28$, $P < 0.0001$, $\eta^2_P = 0.54$ for TB and $F_{2,26} = 4.62$, $P = 0.019$, $\eta^2_P = 0.26$ for BB). Interestingly, neither the effects of *time* (DUR vs. POST) nor the *interactions* reached significance, indicating that ANODAL stimulation was equally effective both during its application and 20 min after it. Instead, APAs on AD were not affected by tDCS (ANOVA found no significant effects).

The increase in APA amplitude in muscles acting on the elbow should not be ascribed to a stronger recruitment of prime mover, because amplitude of FDS activation was unchanged in both

DUR and POST sessions (Fig.3B, no significant ANOVA effects). The same statistical analysis applied to EMG latencies (panels on the right) showed no significant changes of this parameter in each of the recorded muscles.

With regard to the amplitude and duration of the index-finger flexion, as well as to the tonic activity in BB and AD, substantial stability was observed throughout the experiment (Fig. 4). In fact, ANOVA showed no effect of *configuration* or *time* and no *interaction*, thus excluding possible biases due to changes in movement kinematics as well as in the baseline level of motoneuronal activity.

4. Discussion

Results show that the SMA is involved in modulating APAs amplitude and that tDCS selectively interferes with intra-limb APAs without affecting neither the prime mover recruitment nor movement kinematics. The differential effect of tDCS on postural *vs.* voluntary commands suggests that these two components of the motor program are already separated prior to entering SMA.

4.1 Some considerations about tDCS on SMA

The SMA is a particularly well-suited target for transcranial brain stimulation. Although direct transcranial stimulation of this area does not evoke overt motor responses, SMA is quite easily identified both by MRI-based neuronavigation (Vollmann *et al.*, 2013) as well as by finding the M1 hotspot of Tibialis Anterior by transcranial magnetic stimulation (TMS) and moving 2 cm in the frontal direction (Muri *et al.*, 1994). Our pilot experiments showed good agreement among these two methods. Moreover, Vollmann *et al.* (2013) demonstrated that tDCS on SMA affects visuomotor learning, while no such effect can be elicited by tDCS on the neighbour pre-SMA. All these observations made us confident that even in our set-up the tDCS specifically acted on the SMA.

Despite many studies reporting that anodal stimulation enhances excitability, whereas cathodal stimulation depresses it, (for a review see Brunoni *et al.*, 2012) we did not see such a polarity-specific effect. Our cathodal tDCS did not alter any of the recorded APAs. To our knowledge, of the few studies which reported significant effects of tDCS applied on SMA, two (Kwon & Kwon, 2013; Vollmann *et al.*, 2013) applied only anodal tDCS, whilst Hayduk-Costa *et al.* (2013) tested both polarities but did not see any effect of cathodal.

With regards to the after-effects, many studies highlighted that the changes in excitability not only developed during DC stimulation, but lasted for several minutes or hours after its end. This

effect was observed on several cortical and sub-cortical areas (Polania *et al.*, 2012; Monte-Silva *et al.*, 2013; Bolzoni *et al.*, 2013a,b; Nonnekes *et al.*, 2014; Priori *et al.*, 2014) and also on the spinal cord (Cogiamanian *et al.*, 2008; Ahmed, 2013; Priori *et al.*, 2014). The after-effects are likely mediated by mechanisms of synaptic long-term potentiation and depression, which affect neuroplasticity (Nitsche *et al.*, 2002; Ahmed, 2013; Monte-Silva *et al.*, 2013). Our result of a persistent APA increase (20 minutes after the end of tDCS) fully agrees with the above literature.

For what concerns the lack of a significant effect on AD, this might be explained either by an unbalanced current distribution on the SMA and/or result from the smaller (weaker) somatotopic representation of shoulder vs. elbow movers in that area (Boudrias *et al.*, 2006).

4.2 SMA and posture

As summarized in the Introduction, SMA involvement in voluntary movement preparation suggested testing its engagement in intra-limb APAs. Our results positively concluded for such engagement and are in accordance with several other studies on both neurologic patients and healthy individuals. Indeed, it has been described that patients suffering from medial hemispheric lesions (including SMA) showed reduced APAs during the well-known barman task, i.e. when the postural forearm was voluntary unloaded (Massion *et al.*, 1989; Viallet *et al.*, 1992). Moreover, Yoshida *et al.* (2008) found that healthy individuals had larger Bereitschafts potentials when flexing the shoulder in the standing position, rather than when sitting, suggesting that SMA Bereitschafts increase with increased postural demands.

SMA stimulation might produce an effect on APAs through many different pathways. It has been shown that the SMA directly contributes to the corticospinal tract, providing about 10% of all corticospinal cells (Dum & Strick, 1991; He *et al.*, 1995; Wise, 1996) and that the pattern of synaptic projections of SMA corticospinal cells is similar to that of M1 pyramidal cells, suggesting that also SMA directly connects with spinal motoneurons (Dum & Strick, 1996). Moreover, the SMA has reciprocal connections with M1 (Luppino *et al.*, 1993) and is also a main component of the cortico - basal ganglia - thalamo - cortical loop, engaging in the “direct”, “indirect” and also “hyperdirect” pathways (Parthasarathy *et al.*, 1992; Nambu *et al.*, 1996; Inase *et al.*, 1999; Akkal *et al.*, 2007; Frank *et al.*, 2007).

It is also fruitful to consider our observation of a differential effect of tDCS on APAs vs. prime mover recruitment, within the framework of a shared posturo-focal motor command proposed by Bruttini *et al.* (2014). In fact, the tDCS selective action upon one of the two components suggests that the shared command is generated at a higher hierarchical level than SMA. Considering that SMA receives thalamic projections and that its stimulation elicits sensory effects (Nachev *et*

al., 2008), it might be inferred that the SMA receives information for APAs modulation, like the postural context in which the movement occurs (Cordo & Nashner, 1982; Dietz & Colombo, 1996; Baldissera & Esposti, 2005; Esposti & Baldissera, 2011), and tailor the APAs consequently.

4.3 tDCS in neuro-rehabilitation

Our finding that tDCS may affect the excitability of cortical regions involved in postural control suggests the possibility to exploit this technique as adjuvant in motor disorders. It has been demonstrated that the motor impairment following a stroke is partially due to changes in the anticipatory postural control (Slijper *et al.*, 2002; Dickstein *et al.*, 2004; Silva *et al.*, 2012; Pereira *et al.*, 2014). It should be also noted that trunk control at an early stage post stroke is one of the strongest predictors of upper-limb functional recovery (Hsieh *et al.*, 2002). Moreover, brainstem stroke patients enjoyed improved movement speed and accuracy of their ataxic upper-limb after a specific postural training (Stoykov *et al.*, 2005). Lastly, tDCS offers several advantages over other brain stimulation techniques. It is safer and cheaper than invasive brain stimulation, and less uncomfortable, easier to handle and also less expensive than repetitive TMS (Brunoni *et al.*, 2012). However, before proceeding in this perspective, extensive clinical investigation has to be performed.

4.4 Conclusions

This study demonstrates SMA involvement in modulating APAs amplitude. Moreover, the differential effect of tDCS on postural vs. voluntary commands suggests that these two components of the motor program are already separated prior to entering SMA.

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Figures

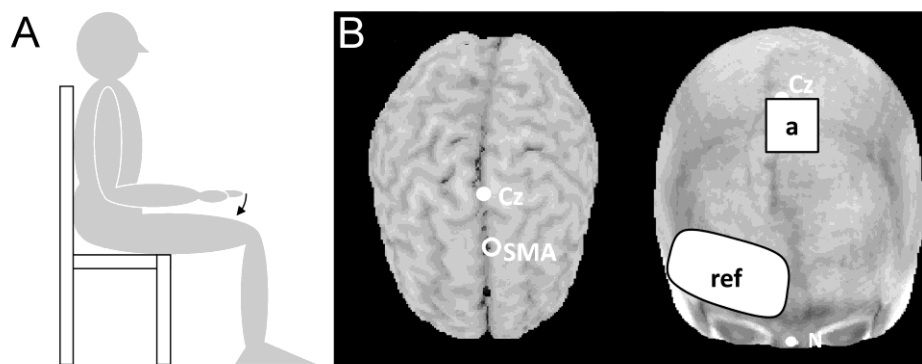


Figure 1: (A) Subject position, the arrow indicates index finger flexion with the prone hand. (B) Anatomical references for tDCS. Identification of SMA on the magnetic resonance image of a representative participant (according to Talairach coordinates, left). Active (a) and reference (ref) electrodes on the scalp. Cz and N mark vertex and nasion, respectively.

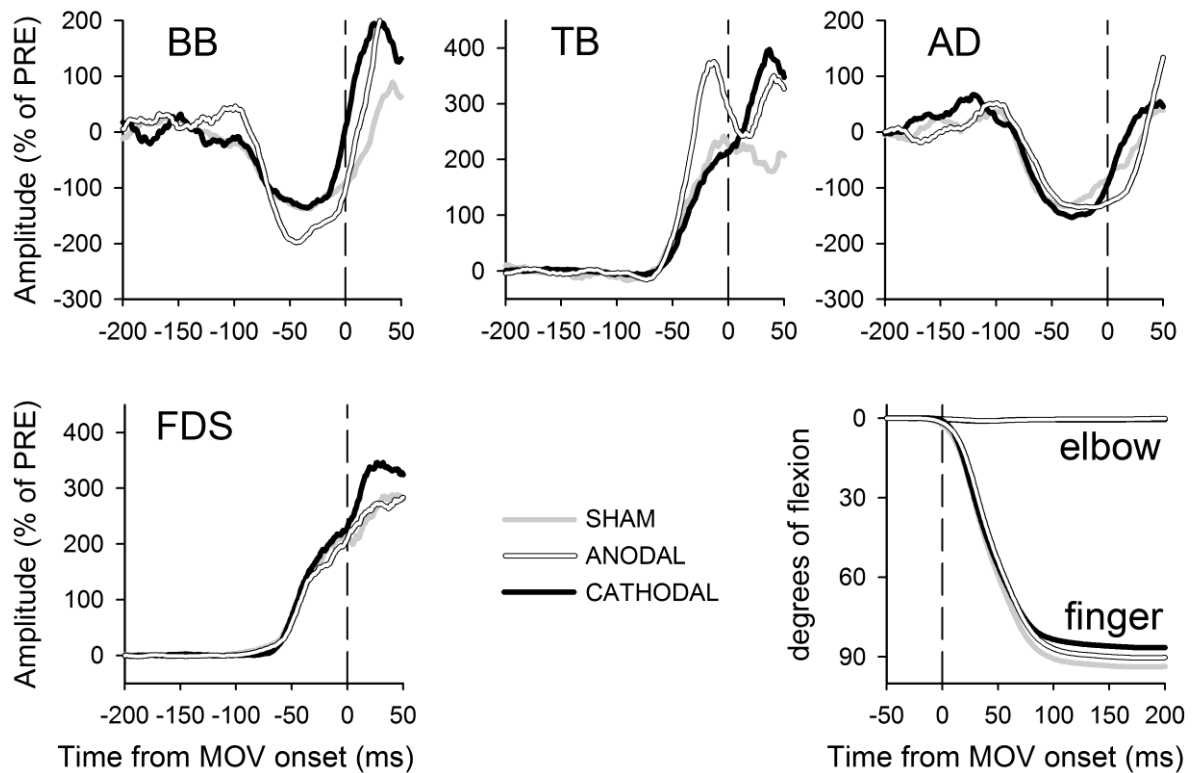


Figure 2: APAs in arm muscles associated to a brisk index-finger flexion. All recordings were taken from one representative participant, in the last 5 minutes of tDCS (DUR sequence, see Methods). EMGs were rectified, integrated and normalised to the APA amplitude recorded before tDCS (PRE sequence). Vertical dashed lines mark the onset of finger flexion. Recordings showed an inhibition of tonic activity in Biceps Brachii (BB) and Anterior Deltoid (AD), paralleled by an excitatory burst in Triceps Brachii (TB). APAs in BB and TB were larger during ANODAL tDCS than during SHAM. No CATHODAL vs. SHAM effect was appreciable. The APA in Anterior Deltoid (AD) was instead unaffected by tDCS. Note also the invariance of Flexor Digitorum Superficialis (FDS) voluntary recruitment, as well as of the kinematics.

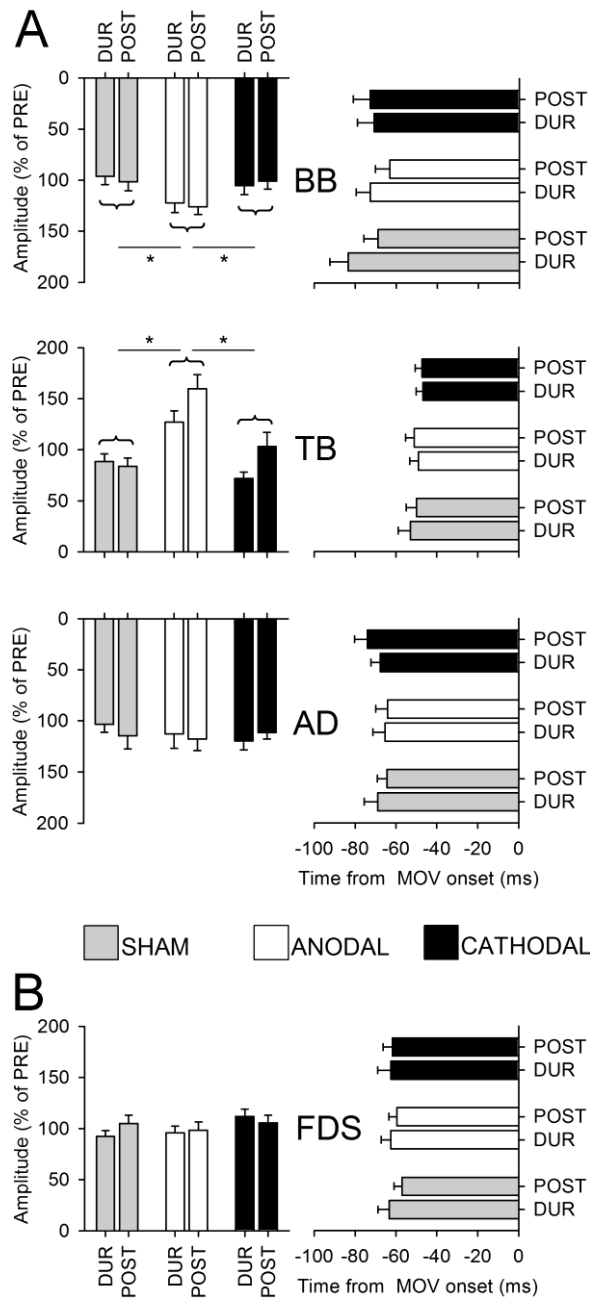


Figure 3: Amplitude and latency of BB, TB and AD APAs (A) and of FDS voluntary recruitment (B). Data was collected from the whole population, in the last 5 minutes of tDCS (DUR) and 20 minutes after its end (POST). Amplitude data are plotted on the left (expressed as percentage of the corresponding amplitude in PRE, see methods), latencies referred to movement onset on the right (mean \pm SE). Repeated measures *stimulation* \times *time* ANOVA, and Tukey post-hoc (see asterisks), found a significant increase in the amplitude of BB and TB APAs under ANODAL vs. CATHODAL & SHAM stimulation, while the APA in AD was unaffected. No effect of *time* or *interaction* was observed, thus ANODAL stimulation enhanced APAs in TB and BB with an effect lasting at least 20min. No significant changes were observed in APAs latency. Note also that tDCS had no effect on the amplitude and latency of FDS activity, witnessing that the increase in BB and TB APAs should not be ascribed to a stronger recruitment of the prime mover.

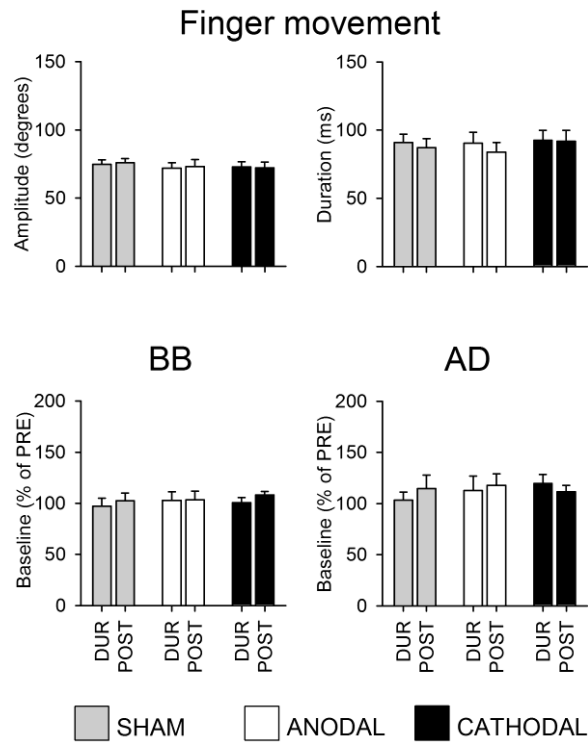


Figure 4: Control measurements. Amplitude and duration of the index-finger flexion, as well as the amplitude of tonic activity in BB and AD, showed a substantial stability throughout the experiment, with no significant effect of *configuration* or *time* and no *interaction*. This excluded possible biases due to changes in movement kinematics or in baseline motoneuronal activity.