INHIBITORY CONTROL OF VOLUNTARY ARM MOVEMENTS:

A DOORWAY TO FREE WON'T

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Abstract

Throughout the course of our life, we constantly have the impression of being able to act as we want. In other words, we have the strong feeling that we are able to exert volitional control over our own actions and that our conscious decisions initiate them. The conscious experience of initiating an action is at the basis of the notion of self-control and of responsibility. Surprisingly, the experimental evidence seems to show that the subjective experience of free will is something of a perceptual illusion and that unconscious brain processes begin well before we become aware of our intention to act. But if the conscious intention is a subjective corollary of an action being about to be executed, are we in control of ourselves? Are we morally responsible for our actions? The solution to this issue seems to come from our ability to inhibit prepotent actions. In fact, even though the awareness of intention follows the start of an action it still precedes the physical execution of a movement by several hundred milliseconds, allowing a subject enough time to withhold the upcoming action whenever the expected outcome does not seem any more valuable in terms of biological fitness. Therefore it is likely that the basis of our decisions is not "free will" but "free won't". Despite the key role of inhibitory control, the way it is implemented and its neural substrates are still debated and controversial. The main aim of the present project is to shed light on this issue by interpreting the pattern of electrical activity recorded over a wide region of the lateral surface of frontotemporal lobes of pharmacoresistant epileptic patients while performing a task probing their inhibitory control (stop signal task).

KEYWORDS: **Free will; conscious intention; self-control; inhibitory control; stop signal task**

INTRODUCTION

From when we wake up in the morning until we sleep at night, we perform thousands of actions and, although we might pay little attention to most of them, we perceive a strong feeling that we have a conscious control over them. Otherwise said, we tend to believe in the existence of a "free will" as an inner causal agent of our behaviour and this belief is at the root of the concept of self-control and of moral and legal responsibility. According to a long-standing philosophical and legal tradition, if someone was not ''free'' from controlling his actions, for instance, because of a psychiatric illness, he cannot be held responsible for his deeds (Glannon, 2015). In this sense, free will is a necessary precursor of social living.

For centuries theologians and philosophers, have wondered how freedom is possible in a world ruled by physical determinism (Lavazza, 2016, Racine, 2017). The inconsistency between free will and determinism can be summarized as follows. Determinism maintains that every event is strictly dependent on previous events. This is because, under Newtonian physics, the initial conditions of any system are sufficient to predict the future behavior of that system (e.g. the planets' orbit around the sun), leaving no room for alternatives. Since our brains are composed of the same physical matter as the planets and are subjected to the same physical laws, determinists maintain that our actions are as predetermined exactly as the orbit of the planets. In the words of the philosopher Daniel Dennet: "At best one has the illusion of control. One is in fact entirely controlled by external factors, locked into a life story that was written at the dawn of creation", (Dennet, 1984).

Hitherto discussions about free will have been confined mainly to philosophy, but about the beginning of the '80s, the topic was also addressed by neuroscience with the pioneering experiment of Libet et al. (1983). Before describing the cited experiment it is noteworthy to underline briefly a few general methodological issues. First, the key difference between the philosophical and the

empirical cognitive survey methods lies in the fact that the former is based on a top-down approach, while the latter relies on a bottom-up approach. Even though experimental results are subjected to a posteriori interpretation, empirical experiments represent a much more direct approach to the problem of free will with respect to a priori conjectures. Second, the empirical approach has key pitfalls too. On the one hand, the experience of free will, i.e. of the urge to act, is evident only to the individual who experiences it. Therefore, an experimenter must rely on indirect introspective reports of the subjective experiences, which might be unreliable and/or highly variable among individuals. On the other hand, the idea of using an experiment to establish whether the human being can be said to have free will would imply to provide a context in which free choices can be performed as in real life. However, what is measured in the laboratories can be hardly thought to match exactly what is going on in the outside world because of unavoidable experimental constraints. Despite these limitations, the findings of neuroscience have shed new light on the issue of free will and opened up new, unexpected avenues of research leading in promising directions.

Libet's Experiment

In this seminal experiment, Benjamin Libet and colleagues (1983) asked subjects to make a simple voluntary action, e.g. a key press, whenever they feel like it (figure 1). Participants were asked to watch a clock hand rotating on a screen, and to report the position of the clock hand at the moment when they 'felt the urge' to move their hand (the will or 'W'). At the same time they recorded the electroencephalographic (EEG) activity from scalp electrodes detecting from the electrodes placed over the motor regions of the frontal lobe, a well-known psychophysiological correlate of movement preparation called the readiness potential (RP, Kornhuber and Deecke, 1965). As expected, the RP appeared as a ramp-like buildup of electrical activity that precedes voluntary movement by ~1 second. However, rather surprisingly the subjective experience of W

occurred much later, only ~200 ms before the movement onset. Put simply, this finding indicates that the subject's conscious decision to press the button followed and not preceded the onset of brain electrical activity. This suggests that the motor system generates a movement and, subsequently, some brain regions read out the neural activity of this network producing the subjective experience of willing to execute that action, which is perceived as being freely chosen (Hallet, 2007). Clearly, this interpretation runs directly contrary to the classical conception of free will.
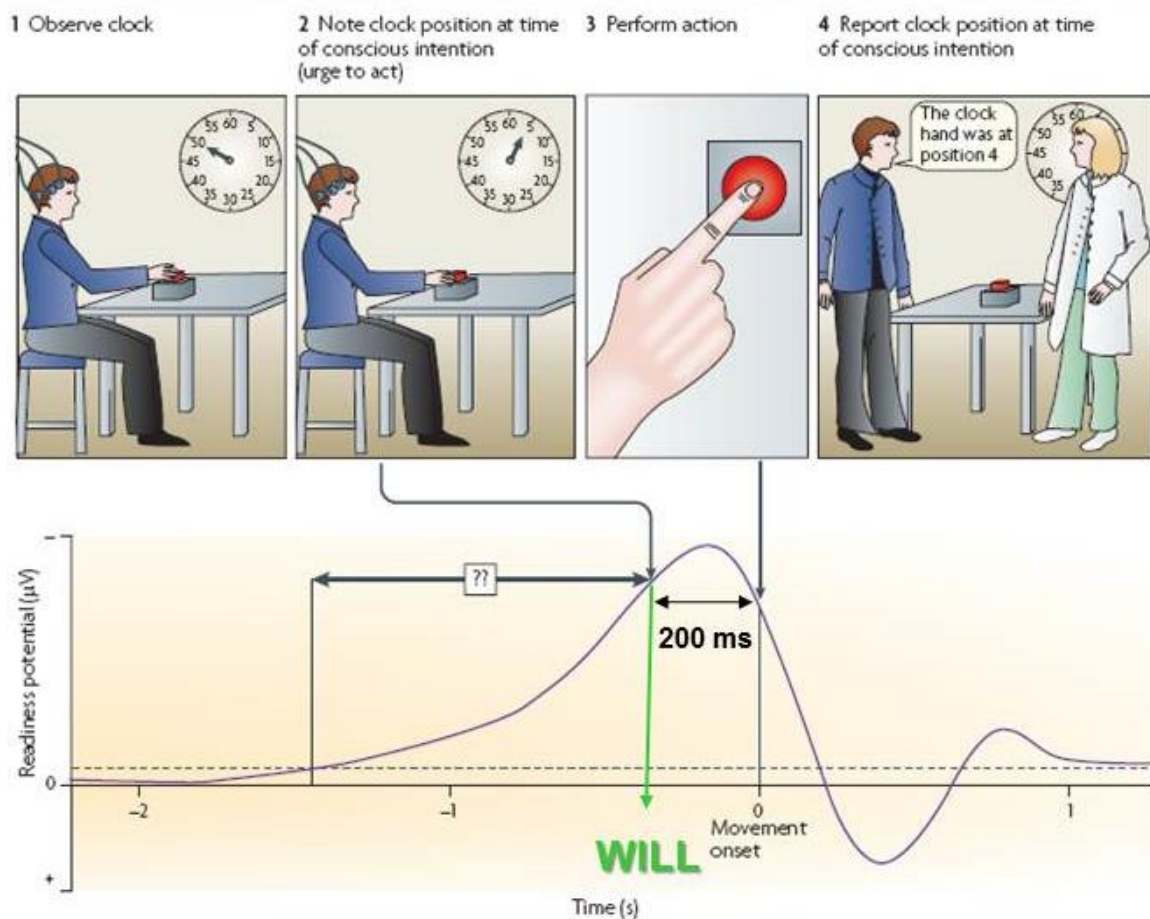

Figure 1. Libet's experiment. Participants watch a virtual clock on a computer monitor that completes a revolution in 2.56 seconds and voluntarily press a button. Later, after the action is made, they are asked to report when they felt the urge to move their hand ('Will'). From electrodes placed on the scalp, the investigators measured the so-called readiness potential which is thought to

be generated by the motor areas of the medial frontal cortex. On average, participants reported the conscious intention to act ~200 ms before the movement onset. However, preparatory brain activity begins ~1 s before movement onset.

Libet's experiment has been extensively criticized. The main objection is that subjective estimates of when conscious experiences of will occur are unreliable and might depend upon the way participants divide attention between the clock and their own motor preparation. Another objection is about the role of RP in the generation of conscious willing. Alexander et al. (2015) have argued that as the RP occurs also when healthy subjects perform endogenously-initiated movements under post-hypnotic suggestion, i.e. in a context in which they are not supposed to experience a conscious feeling of having willed those movements, then neural activity indexed by RP are unlikely to represent the underpinnings of conscious wiliness.

However, Libet's results have been replicated several times. For instance, Soon et al. (2008) using functional magnetic resonance imaging, showed that the outcome of a decision process could be encoded in brain activity of prefrontal and parietal cortex as early as 7 s before the subject became aware of it. In this sense, the findings of Fried et al (2011) are of particular relevance. They took advantage of the rare opportunity to record the discharge of single cells in the human supplementary motor cortex (SMA) and pre-SMA, i.e. the brain areas thought to generate the scalp RP (see figure 2). This opportunity stems from the fact that in some cases of intractable pharmacoresistant epilepsy, intracranial electrodes are used for localizing the epileptic focus, before surgically removing it. Under those circumstances, it was possible to record the firing rates of single neurons while subjects were performing the Libet's experiment and reporting their intentions.
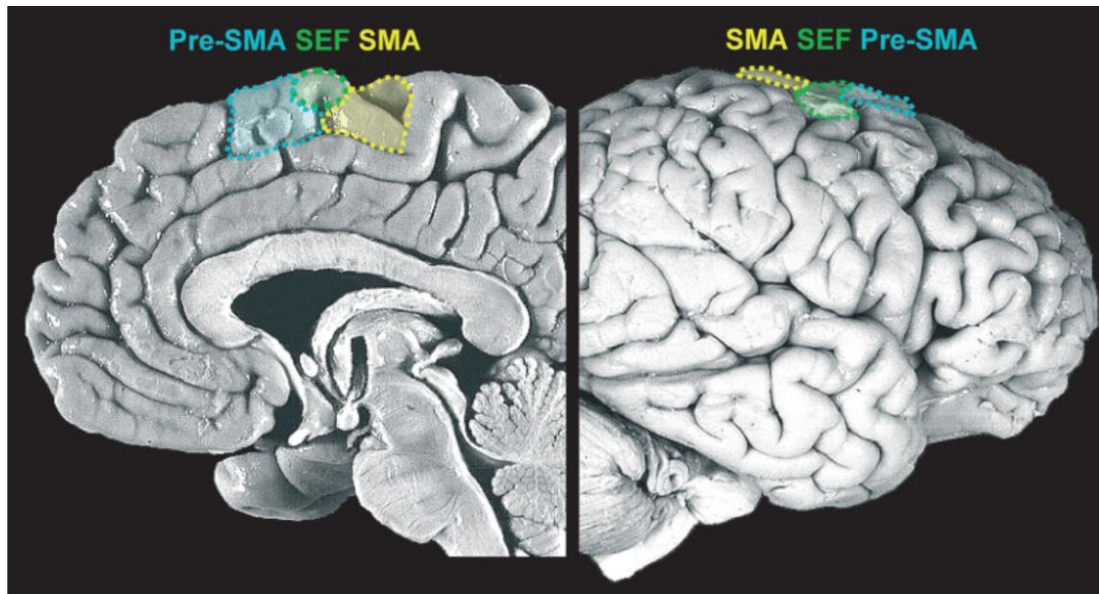
Figure 2. Medial frontal cortex (details of the medial portion of Brodmann areas 6 and 8). Midsagittal view of the medial wall (left) and lateral prefrontal cortex surface (right), delineating the main the supplementary motor area (SMA), supplementary eye field (SEF) and pre-supplementary motor area (pre-SMA).

They found a relatively small subset of neurons, mainly located in SMA, which showed a gradual ramp-like increase or decrease in firing rate starting about 1 s prior to subjects' conscious decision to act. Furthermore, Fried a colleagues (2011), using an integrate-and-fire computational model, demonstrated that the time of 'will' could be predicted from small subpopulations of these neurons, well before the time that participants reported it.

The origin of preparatory signals in the motor system

Given the above described results, a question naturally arises: what does it trigger the activation of the motor system? Is there a ghost in the machine? A plausible answer to this question comes from the concept of 'affordance' put forward by Gibson (1979). According to this idea features of the objects in the surrounding environment are automatically translated into potential

actions. Thus, even if a person encounters a particular car door handle for the first time, he is able to use it correctly without thinking thanks to its particular features (figure 3).

Figure 3. According to the concept of affordance, the features of a car door handle are intrinsically linked to the potential actions that allow interacting with this object. Thus, even if a person encounters a new type of car door handle, he is able to use it correctly.

In line with this idea, Grafton et al (1997) demonstrated that the mere observation of pictures of manipulable objects elicits the activity of motor brain regions that control the body part involved in the potential action, even when the person isn't planning to move. In particular, it has been shown that SMA is involved in this process (Grezes & Decety 2002). Therefore, cues in our environment may inadvertently trigger potential actions. These stimulus-driven activations are rapid, involuntary and unconscious. Clearly, if we would have been compelled to act upon each object we encounter, we would not survive to a walk around a kitchen. This is the sad condition of two rare

neuropsychological disorders, the alien hand syndrome, and the utilization behaviour. Both diseases are characterized by the fact that patients cannot resist objects affordance, and they are automatically forced to perform stimulus-driven motor responses even when they do not need those objects (Humphreys & Riddoch 2000). Patients exhibiting utilization behavior compulsively grasp and use objects placed within their reach, even when the object is not specifically drawn to their attention (figure 4). This syndrome has been linked to bilateral damage to the medial frontal region involving the SMA, pre-SMA and cingulate motor areas (Boccardi et al., 2002).

Figure 4. This patient, affected by utilization behaviour, is putting on three pairs of glasses simply because they were placed in front of him.

Patients with the alien hand syndrome perform involuntary actions with the upper limb contralateral to a focal brain lesion most frequently located in the medial frontal cortex, usually involving the SMA and/or the pre-SMA (Biran & Chatterjee 2004). These patients are particularly sensitive to objects' affordances so that, even when these patients are instructed to perform a

specific motor task, movements of their affected hand are captured by competing tasks, such as reaching for distractors (Kritikos et al 2005). To some extent, the sites of the lesions causing those two syndromes are largely overlapping, with the difference that in the latter case it is located just in one hemisphere whereas in the former case it affects both hemispheres.

Fortunately, in healthy subjects, stimulus-driven activations do not necessarily lead to action execution. According to a recent hypothesis, affordances might increase the motivation to act, but to execute an action they have to be coupled with an internal state congruent with the primed action (e.g. the sight of a glass of water will prime the action if and only if an individual is thirsty; Mirabella 2014). In other words, our brain would evaluate whether stimulus-driven activations would match with our internal needs and, if this is not the case, it would suppress it. Even though the neural underpinnings of this process are still a matter of debate, several lines of evidence indicate that the fate of these activations might be decided in pre-SMA, which would act as a gate through which the available action affordances might be translated into actual actions (Ridderinkhof et al., 2011). The details of this process are beyond the scope of the present paper, however talking about this topic allowed to introduce two key concepts that might provide part of the explanation for how we could maintain our freedom: the evaluation and the inhibition of actions.

The role of inhibitory control in shaping our voluntary behavior

Libet was not a determinist, and even though his discoveries seem to point in that direction, he himself put forward a way out. He reasoned that although awareness of intention appears after the start of an action-related thought process, it still precedes the physical execution of a movement, allowing a person just enough time to withhold the upcoming action if the expected outcome might be inappropriate. This veto power, or "free won't", would, therefore, be the basis of our free will. It is a common experience that, at least to some extent, we can consciously exert control over our

actions and inhibit those that we believe are not appropriate. For instance, we can prevent ourselves from hitting our noisy neighbor, thus if we do not refrain from doing it, we are fully responsible.

However, this might represent just a part of the story as it is very unlikely that we consciously withhold all inappropriate actions. This would require an excessive and inappropriate exploitation of brain computational resources. The number of times in which consciousness has to be involved during inhibitory control has to be necessarily very limited. In addition, what are the elements that lead an agent to leave an action or stopping it?

Modern theories of behavioral control converge onto the idea that goal-directed/voluntary behaviors are intimately tied to the evaluation of resources. According to this idea, all moving animals select those actions that, on the basis of a subjective value assigned to them, are most likely to lead to the greatest reward. In other words, critical for all forms of decision making is the ability to accurately predict future outcomes. However, as animals live in a world where events cannot be fully predicted, they have to take many decisions with only limited information about their consequences, i.e. they often have to take risky decisions. Thus, the opportunity of executing an action must be evaluated continuously, not only during the genesis of an action but also during the planning of an already selected action, as changes in environmental conditions or in our internal states can make the selected action inappropriate for achieving the desired goal. In all these instances, movements must be suppressed (Mirabella, 2014). Therefore, inhibitory control represents a hinge of behavioral flexibility and, possibly in humans of free won't. Despite its key role, the way inhibition is implemented and its neural substrates are still unclear and hotly debated.

Their uncovering is the aim of the work that my team is doing at the University of Rome "La Sapienza" and the core of the project I will develop here at the Italian Academy.

METHODS

The neural representation of pending action suppression has been studied using the stop-signal task (Logan et al. 1984). This paradigm probes a subject's ability to withhold a planned movement triggered by a go signal when an infrequent stop signal is presented after a variable delay. In the implementation of the task I have made, subjects are asked to perform a reaching arm movement (e.g. Mirabella et al 2008; 2011; 2017; Figure 5). This is not an irrelevant detail as these movements are more complex and have a different ecological relevance with respect to key-presses or saccades used in almost all the other labs. In fact, reaching arm movement are the only ones which allow physical interactions with the environment outside neurophysiology laboratories. The use of such paradigm allowed some new findings (see Mirabella et al 2008; 2013)
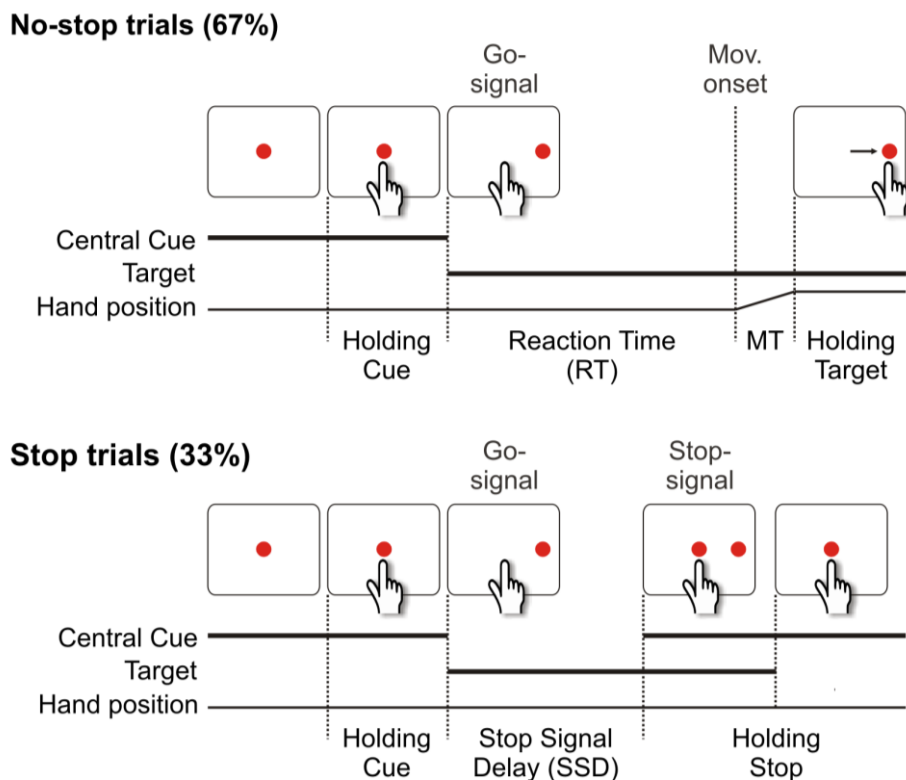

Figure 5. Temporal sequence of the visual displays for no-stop and stop trials in the reaching version of the stop signal task. Subjects were seated in front of a touchscreen. All trials began with the presentation of a central stimulus. After a variable holding delay (500-800 ms) it disappeared

and simultaneously a target appeared to the right, acting as a go-signal. In the no-stop trials subjects had to start a speeded reaching movement toward the peripheral target. Randomly, on a fraction of interleaved trials (33%), the central stimulus reappeared after variable delays (SSDs), instructing subjects to inhibit movement initiation. In these stop trials, if subjects countermanded the planned movement keeping the arm on the central stimulus the trial was scored as a stop-success trial. Otherwise, if subjects executed the reaching movement the trial was scored as a stop-failure trial (not shown).

Starting from the behavioral performance during the stop signal task it is possible to yield an estimate of the duration of the suppression process (stop-signal reaction time, SSRT; Band et al. 2003; Logan et al, 1984). The SSRT is a key behavioral parameter for uncovering the neural substrates of inhibition. In fact, those brain regions showing a change in activity when a movement is produced with respect to when it is suppressed, and where the onset of this shift precedes the end of the SSRT, can be assumed to be causally related to the suppression process.

RESULTS

Historically inhibitory control has been ascribed among the highest executive function, and as such it has been thought that it must be implemented by some prefrontal regions. This view is still held by many researchers, for instance, it has been claimed that "such inhibition depends on the rIFC (uniquely among PFC regions) and that, rIFC could implement its function is via the rSTN" (Aron et al, 2014). However, it is becoming increasingly clear that a large network of brain regions, including both cortical and subcortical structures, is involved in this process (e.g. Mirabella 2014).

In order to check whether the motor cortices could take part in this process, we recorded the activity of single units in the dorsal premotor cortex (PMd) of monkeys trained in a stop signal task (Mirabella et al, 2011). We found that about 33% of PMd cells changed their discharge before the

end of the SSRT when the monkey had to stop a reaching movement. Thus these neurons exhibit a

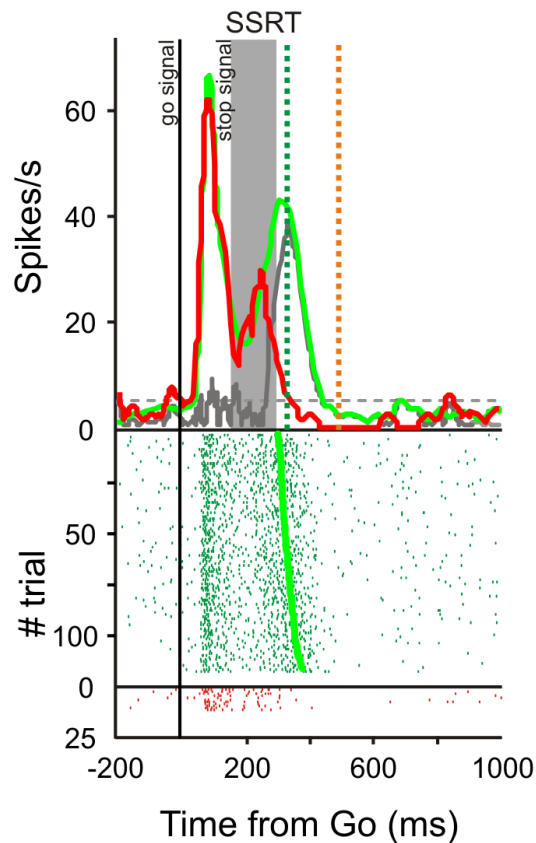pattern of activity suggesting that PMd is causally involved in reactive inhibition (see Figure 6).

Figure 6. **Changes of activity driven by the stop-signal onset in one PMd neuron**. This neuron
discharge differently when a movement is executed (green line represents the average neural
activity during no-stop trials) with respect to when it is stopped (red line represents the average
neural activity during stop-success trials). Importantly, the differential activity occurs after the
presentation of the stop signal and before the end of the SSRT (gray band), that is before the end of
the behavioral estimate of the stop process duration. The upper graph represents the average spike
density function while the lower graph shows the raster plots of neural activity in no-stop trials
(green tick-marks) and stop-success trials (red tick-marks). Neural activity was always aligned to
the go-signal onset (first vertical line). The grey band represents the estimated duration of the SSRT
in that session. The grey line represents the differential spike density function while the dashed grey
line represents the threshold value for significant divergence. The green and the orange vertical
dotted lines in the top panels indicate the average reaction time (RT) and the average end of
movement time (MT), respectively. The green dots in the raster represent the end of the RTs.

In this cell, (red line) initially resembles that of no-stop trials (green line) but, with a delay after the stop signal presentation, it suddenly starts to decrease and the differential spike density function crosses the threshold 34.4 ms before the end of the SSRT.

As it is very well established that PMd is critically involved in limb movement preparation and initiation (e.g. Cheney and Fetz 1980; Churchland and Shenoy 2007), our findings seem to suggest that acting and stopping could be functions emerging from the same or partially overlapping brain regions. However, using this technique we could sample the activity from a very small region of the brain. Therefore, we could not disentangle whether inhibitory commands are generated in PMd (and in other motor regions) or whether the modulation of neural activity was a reflection of inhibitory commands generated in other brain regions.

To overcome this limitation, we recorded the electrocorticographic (ECoG) activity from subdural electrode grids placed over the entire lateral surface of the frontotemporal lobes of one hemisphere for the localization of seizure foci prior to surgical resection (figure 7) of 10 pharmacoresistant epileptic patients performing a reaching version of the stop signal task (Mattia et al 2012). The great advantage of this technique lied in the fact that it enabled us to record from a vast brain region, having at the same time a very high spatiotemporal resolution. For the first time, we used an analytical approach different from what was done previously (e.g. Swann et al, 2009) as we did not select a priori any electrode but, after discarding those contacts with a high noise level, we analyzed the activity of all the remaining ones. This is a key detail because we have observed that the inter-electrode variability is huge and there is no way to select what could be defined a 'representative' electrode for any given cortical area.
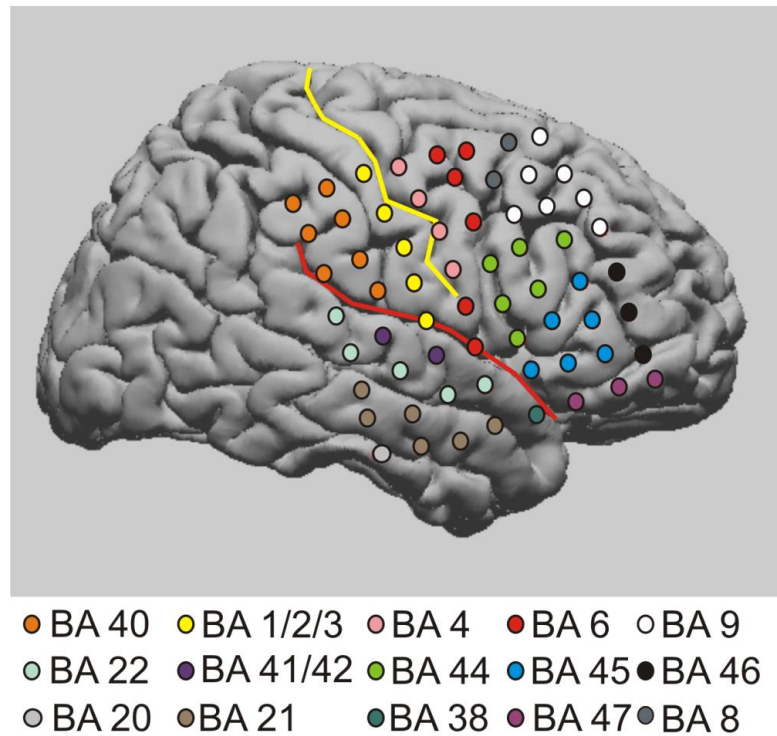
Figure 7. Localization of electrodes over the right fronto-temporal lobe in a representative subject. Electrodes are projected onto the MRI brain template used by the software package for the co-registration between the electrodes and the Talairach space (i.e. ''Location on Cortex'', Miller et al., 2007). The colors of the electrodes code different Brodmann areas (BA).

By looking at event-related potentials (ERP) time-locked at the stop-signal presentation, we found that an ERP complex was *selectively* expressed after the presentation of the stop signal but before the end of the SSRT in the motor cortices (M1 and premotor cortex and BA9, see Figure 8; Mattia et al 2012). These results demonstrate that, at least as far as reactive inhibition is concerned, a considerable overlap between the brain regions subserving the planning of goal-directed movements and their suppression and lead to the intriguing hypothesis that the performance of actions and their suppression are not specified by independent sets of brain regions.
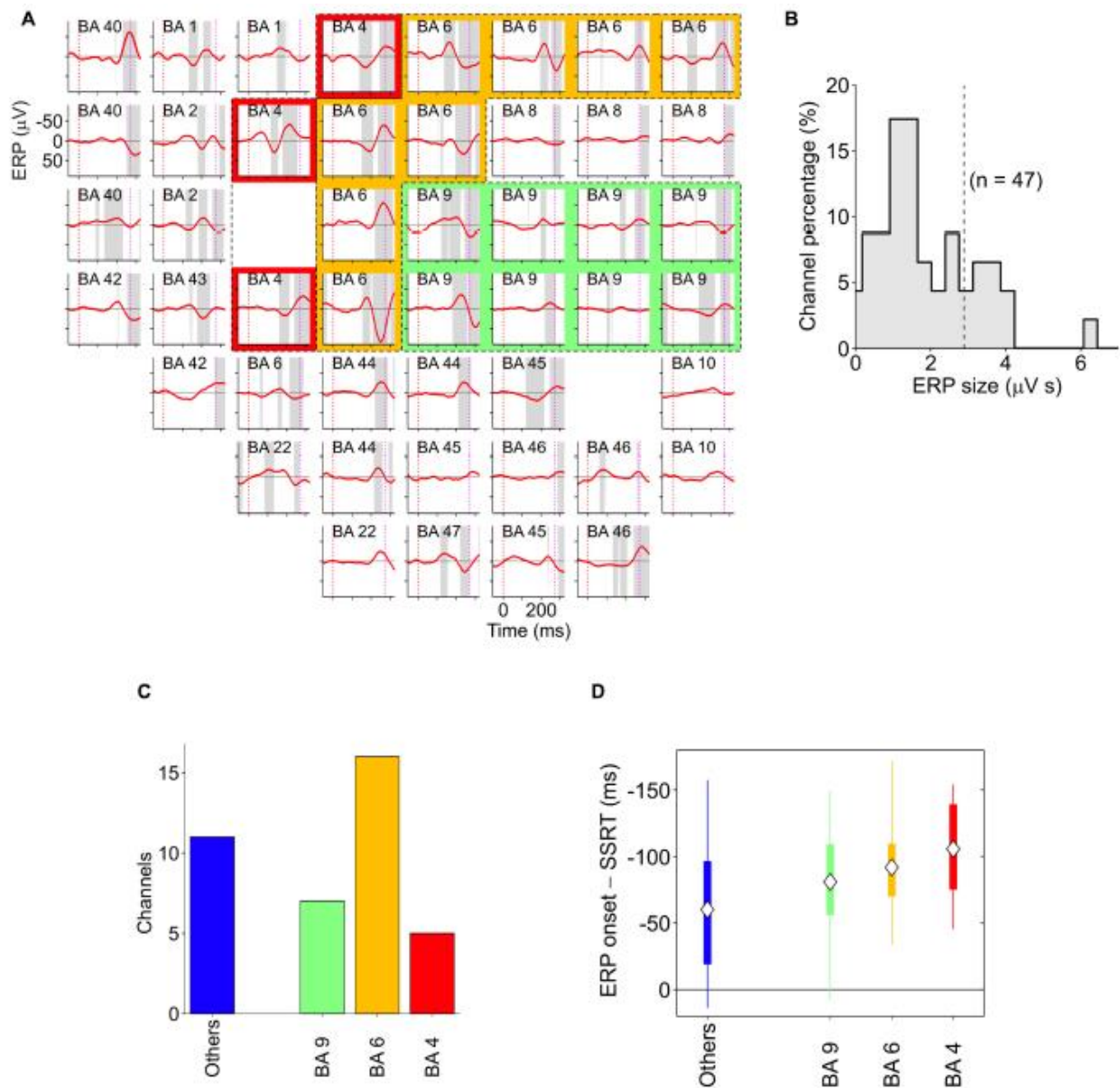
Figure 8. **Spatiotemporal distribution of stop-event-related potentials (ERPs) in successful-stop (SS) trials**. **A.** Average stop-ERPs (solid red curves) of SS trials centered on stop-signal appearance corresponding to the selected channels for one pharmacoresistant epileptic patient. Gray areas, time intervals at which the stop-ERP was significantly different from 0 (Wilcoxon signed-rank test, $P < 0.01$). Subplot labels: Broadmann's areas (BAs) over which electrodes were positioned. Colored areas: electrodes placed over the primary motor cortex (red, BA4), the premotor cortex (yellow, BA6) and the dorsolateral prefrontal cortex (green, BA9). **B.** Histogram of the stop-ERP sizes of panel A. Stop-ERP sizes were computed as the integral of absolute values of stop-ERP voltage deflections in the interval periods marked by gray areas within SSRT. Dashed line:

threshold value for selecting the subset of channels with large enough stop-ERPs used for population analyses (see text for details). **C.** Number of channels showing large enough average stop-ERPs across five patients (n=39) grouped by Brodmann area (BA). Blue bar (others) represents those areas where channels were not selected more than twice across all patients. **D.** Box plot of stop-ERP onsets measured with respect to the end of SSRT across all selected channels in all patients. Stop-ERP onset was defined as the first time that an electrode voltage was significantly different from 0. Diamonds indicate average onset times. Tick bars indicate the first and the third quartile. Vertical lines indicate the extreme time lags in the channel group

AIMS OF THE PROJECT

There are several different ways in which these data can be further analyzed in order to provide new information about the functioning of the inhibitory network. A relatively simple approach is to compute the time–frequency representations of the mean power modulations of the signals at different bands. Some evidence seems to indicate that beta band power modulations play a key role in inhibitory control both in cortical (e.g. Swann et al., 2009; Fonken et al. 2016) and subcortical brain regions (e.g. Zavala et al, 2015). However, this picture is far from being complete. *A priori* electrodes (e.g. Swann et al, 2009) or bands selection (Fonken et al. 2016) might have biased results. A more inclusive analysis is needed. In addition, ECoG activity recorded from large sectors of the cortex should allow also to assess the degree of functional coupling during the task between different regions, e.g. the premotor cortex (Mirabella et al 2011) and the inferior frontal gyrus, using standard technique as spectral coherence (e.g. Zhang et al 2014) and the estimation of directional influences between brain signals by means of Granger causality analysis (e.g. Brovelli et al 2004). By correlating these analyses of the electrical signal with the parameters computed from the participants' performance during the stop signal task, it should be possible to establish if, where and how changes in brain activity will correlate with participants' behavior. Finally, ECoG activity could be modeled either using attractor models (e.g. Mattia et al 2013; Rigotti et al., 2010) or

trajectory-based-models (e.g. Kaufman et al. 2014). Different analyses are prone to reveal many more details about the computations underlying reactive inhibition performed by multiple cortical areas.

CONCLUSIONS

The main conclusion that comes from these studies is that acting and stopping do not seem to be functions generated by single brain regions or by separate networks. Instead, they seem to be functions emerging from specific interactions between largely overlapping brain regions, whose activity is intimately linked (directly or indirectly) to the evaluations of pros and cons of an action (Mirabella, 2014). This does not come as a surprise, as we live in a complex and ever-changing environment, thus, our motor system is called on to perform a continuous evaluation of alternative actions that may become available, in order to decide whether to persist in a given activity or to stop it and switch to a different one. Given this picture, it is rather hard to assign a very specific role in computing complex cognitive functions to single brain regions. Possibly, those functions emerge from the coordinated activity of large-scale neuronal networks that are dynamically configured on fixed anatomical connections (e.g. von der Malsburg et al., 2010). This could explain why fMRI studies often found activations of the same region for very different tasks.

In addition, these studies might have practical applications. On the one hand, they could shed light on pathophysiological mechanisms underlying many neuropsychiatric disorders characterized by poor control of urges, such as Tourette Syndrome and Obsessive-Compulsive Disorder or neurological diseases such as Parkinson's disease (Mirabella et al 2012, 2013, 2017). On the other hand, a deeper knowledge of motor decision-making process could reveal to be very effective for improving the performance of brain-machine interfaces allowing them to reproduce goal-directed behaviors in a more naturalistic way (Mirabella & Lebedev, 2017).

Finally, you might wonder what the present findings could add to the issue of free won't. In my opinion, the neural mechanisms which allow us to refrain from killing a wife during a divorce are not so different in principle from those that allow us to refrain from crossing a road when we suddenly hear an ambulance just before we make the first step. In both cases, there is a computation of pro and cons and preplanned actions are, hopefully, halted in similar ways. What surely differs is the number of computations required in the former with respect to the latter case. I am fully aware that is a pure speculation given that the stop signal task I have employed relies on externally and not on internally triggered stops. In fact, as I have shown this task can be performed by monkeys as well (e.g. Mirabella et al., 2011) which are not thought to have the same level of consciousness of humans. Further experimental evidence, based on different experimental designs, has to be collected before venturing conclusions around the relationship between the veto power and willingness. Nevertheless, as Adele Roskies (2010) stated: "[these studies allow] us to formulate novel questions about the nature of voluntary behavior, and providing new ways of addressing them".

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