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Review

Negative motor phenomena in cortical stimulation: implications for inhibitory control of human action

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ABSTRACT

Electrical stimulation of the human cortex typically elicits positive sensorimotor effects. However, many neurosurgical studies have also reported negative motor areas (NMAs) in which stimulation produces inhibition of ongoing movement. The neurocognitive implications of these studies have not been systematically explored. Here we review the neurosurgical literature on NMAs and link this to cognitive mechanisms of inhibition and their role in voluntary control of action. In particular, we discuss the functional validity of NMAs. We contest the sceptical view that negative effects following stimulation merely reflect disruption of positive motor areas. Instead, we suggest that NMAs may produce an inhibitory mechanism under ecologically valid conditions.

1. Introduction

Neurosurgical stimulation studies are an important source of information about cortical function (Penfield and Rasmussen, 1950). Patients may undergo pre-surgical implantation of subdural electrodes for functional mapping, to inform subsequent surgery. By direct electrical stimulation (DES) between specific pairs of electrodes (or by equivalent intraoperative stimulation with movable electrodes), clinicians can assess the functional role of a given cortical region, and thus guide neurosurgical interventions. Because DES can be performed in awake patients, it provides a crucial insight into the contribution of diverse cortical regions to conscious experience (Desmurget et al., 2009; Fritsch and Hitzig, 1870; Penfield and Rasmussen, 1950). In particular, the clinician can stimulate a particular cortical region and assess the impact on the patient's behaviour, and subjectively reported sensation.

Penfield and Boldrey (Penfield and Boldrey, 1937) classically mapped the human motor cortex in this way. Their work is known primarily for the 'positive' sensorimotor signs they evoked in specific muscles, leading to the famous motor homunculus.

Interestingly, stimulation of some cortical sites has 'negative' effects, causing inhibition of an ongoing movement. These sites have been termed 'negative motor areas' (NMAs) in the neurosurgical literature (Lüders et al., 1995). In his early studies, Penfield (Penfield and Boldrey, 1937; Penfield and Jasper, 1954; Penfield and Rasmussen, 1950) had already

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described speech arrest following stimulation at some sites within the supplementary motor area (SMA). However, this aspect of Penfield's data has been neglected, in comparison to the attention paid to the positive motor homunculus. Typical negative motor responses include speech arrest and arrest of movements of the hand, leg and foot.

Previous discussion of NMAs has been largely confined to the neurosurgical literature. The general interpretation in that literature suggests that the normal function of NMAs is the fine regulation of motor output (Ikeda et al., 2009). Here we propose an alternative interpretation, that NMAs reflect a functional system for inhibition of action. Given the widespread neuropsychological consensus that inhibition of action is a crucial aspect of both cognitive control of behaviour, this interpretation would make NMA data highly relevant to cognitive neuropsychology. We review the NMA literature with a specific emphasis on the possible contribution of NMAs to inhibitory processing (i.e., processing of external stimuli signalling the need for motor inhibition), and cognitive control of action (i.e., the mechanisms taking place to allow for the stopping of ongoing action).

Psychologists have often studied inhibition in the context of cognitive tasks such as the stop-signal task. In this task participants make motor responses to a designated target, but must withhold the motor response when a stop signal appears (Verbruggen and Logan, 2008). The derived stop-signal reaction time is a measure of a participant's ability to withhold action. Neuropsychological theory has long pointed to the importance of inhibitory control in the frontal lobes (Fulton and Jacobsen, 1935). The cortical and subcortical neural circuits supporting inhibitory function in the context of a stop-signal task have been extensively explored (Aron et al., 2007; Chikazoe, 2010; Nambu et al., 2002). Neuroimaging studies of the stop-signal task suggest that both the inferior frontal gyrus (IFG) and the pre-supplementary motor area (pre-SMA) contribute to inhibiting ongoing actions in response to stop signals (Aron and Poldrack, 2006; Chambers et al., 2009; Chikazoe et al., 2009; Swick et al., 2011). The precise division of labour between these areas remains unclear. On the one hand, transcranial magnetic stimulation (TMS) over the IFG has been shown to selectively impair inhibitory function in a stop-signal task (Chambers et al., 2006), without affecting general arousal. In addition, group neuropsychological studies confirmed a correlation between performance in a stop-signal task and the extent of damage to the IFG (Aron et al., 2003).

On the other hand, when a traditional stop signal task is compared with another task that controls for attentional demands BOLD activity differs only in the pre-SMA, but not in the IFG (Sharp et al., 2010; Tabu et al., 2011). Therefore it has been suggested that IFG may be involved in attending to the external stop signal, while the pre-SMA may provide the active process of inhibition (Duann et al., 2009; Hampshire et al., 2010; Mostofsky and Simmonds, 2008). In turn, this view has been disputed. Recently, Neubert and Rushworth and colleagues (Neubert et al., 2010) have suggested that pre-SMA mediates an inhibitory effect of IFG over the primary motor cortex. In our view, NMA data may be pertinent to such questions.

We present data from the key NMA studies in a way that highlights their relevance to inhibitory cognitive control. We first consider the general method for identifying NMAs. Then we analyze the specificity for inhibiting different effector systems (speech, manual action etc). Then, we consider NMA localization and the features of the stimulation threshold required to elicit a negative motor response. We next consider subjective experience generated by NMA stimulation. Finally, the discussion section considers how NMA data may constrain cognitive and neurophysiological accounts of cognitive control.

2. Limitations of direct stimulation data

An introductory word of caution is important here. Effects of DES are typically more focal than those of non-invasive brain stimulation methods, such as TMS or transcranial direct current stimulation (tDCS). The spatial resolution of DES is typically .5 cm (Mandonnet et al., 2009). TDCS has a typical current spread of the order of 2 cm (but it varies with different electrode parameters, see Faria et al., 2011), while TMS has a typical spatial resolution 1–2 cm, though this value is possibly improved for primary motor cortex mapping (Foltys et al., 2001). Nevertheless, although DES may be more local, it still targets a large and heterogeneous cluster of neurons, and a larger set of axons. The effects of DES may be mediated by stimulation or inhibition of neurons, including neurons relatively distant from the electrode site. In fact, remote effects of DES can be explained by active synaptic activation, rather than by passive current spread. Therefore, care is needed drawing conclusions about function of a stimulated area from DES results. Accordingly, we emphasise here that convergent evidence from other methods is particularly important in understanding the functional significance of NMAs. It is beyond the scope of this review to describe the possible and complex physiological effects of DES (see Borchers et al., 2012 for a critical review).

3. NMA screening method

A pioneering NMA study is that of Lüders et al. (1987), who studied 42 patients. They stimulated each of a set of subdural electrodes with progressively increasing current. When an electrode did not produce any positive motor signs, it was next tested for negative motor responses. Patients were asked to perform rapid alternating eye, tongue, hand or foot movements. NMAs were defined as areas that when stimulated produced cessation/arrest or decrease of the ongoing voluntary movement, without loss of consciousness. Cases in which movement arrest is a secondary consequence of otherwise positive effects, such as muscular co-contraction, were excluded from the NMA definition.

Twenty-four studies reporting NMAs were identified in the literature and form the basis of this review. They are summarised in Table 1. Reporting of NMAs depends strongly on sampling and stimulation protocols. Van Buren and Fedio (1976) applied DES in 60 Hz pulses with a total duration of 2.5 msec, with a current of 1 mA. Lüders et al. (1987) applied pulses of .3 msec duration in 50 Hz trains of 5–10 sec. For each electrode, the applied current was increased in .5 or 1 mA

Table 1 – Summary of studies reviewed. The site of arrest responses was determined on the basis of the authors' description, plus inspection of the figures where available. The total number of sites investigated refers to the number of implanted electrodes, pooled across patients. The total number of NMAs is also pooled across patients. N/A indicates that the information was not reported.

	Reference	Main site of arrest responses	Total number of patients	Number of patients with at least one NMA/NMR	Total number of sites investigated	Number of NMAs
1	Penfield and Rasmussen, 1949	IFG and along Rolandic line	N/A	3	26	6
2	Penfield and Rasmussen, 1950	SMA	10	1	N/A	3
3	Penfield and Welch, 1951	SMA	N/A	N/A	N/A	N/A
4	Penfield and Jasper, 1954	SMA	N/A	18	N/A	40
5	Van Buren and Fedio, 1976	Middle part SMA	7	1	N/A	1
6	Lee et al., 1986	IFG (corresponding approximately to Broca's area on the dominant side)	3	1	192	3
7	Fried et al., 1991	Left or right SMA	13	3	299	6
8	Sakamoto et al., 1991	SMA	4	1	~220	1
9	Lüders et al., 1992	IFG, Premotor cortex, immediately adjacent to the face motor area or middle frontal gyrus	42	18	N/A	42
10	Uematsu et al., 1992	PFC, "far frontal to the Rolandic line"	35	N/A	1381	18
11	Ikeda et al., 1992	SMA	2	1	50	2
12	Ikeda et al., 1993	SMA	30	3	3	1
13	Lim et al., 1994	Mostly mesial portion of superior frontal gyrus. Also cingulated gyrus and lower half of the paracentral lobule	15	N/A	232	17
14	Ikeda et al., 1995a	SMA	3	1	215	1
15	Ikeda et al., 1995b	Around the Rolandic line	7	4	~326	5
16	Nii et al., 1996	Premotor and primary motor and sensory cortices	55	N/A	736	46
17	Chauvel et al., 1996	SMA	140	N/A	225	N/A
18	Yazawa et al., 1998	Rostral to pre-sma	2	1	38	1
19	Ikeda et al., 1999	Left IFG, pre-sma, SMA	5	3	200	4
20	Yazawa et al., 2000	SNMA-plus (anterior to SMA: between PFC and SMA, "greatly overlapping with pre-sma")	2	2	26	4
21	Hanakawa et al., 2001	Posterior part of pre-SMA	3	2	102	2
22	Yamamoto et al., 2004	pre-sma, SMA	4	2	241	5
23	Mikuni et al., 2006	Medial brain surface: immediately anterior to hand motor region of SMA Lateral brain surface: premotor cortex	30	15	N/A	30
24	Chassagnon et al., 2008	pre-SMA and more anterior part of SMA, in the vicinity of the vertical line passing through the anterior comissure	52	N/A	94	1

steps. Stimulation was stopped when i) a response was obtained, ii) after discharges were observed or iii) the arbitrary limit of 15 mA was reached. Most subsequent studies used similar stimulation parameters, with the exceptions of Fried et al. (1991), who applied .1 msec pulses; and Chauvel et al. (1996), who applied pulses of 1 msec duration. The final stimulation current is rarely reported.

NMAs will only be found if the electrode of interest is stimulated during an ongoing action of the appropriate musculature. Moreover, NMAs were not the main interest of many of these studies. In some cases, they are reported anecdotally, as incidental findings. Accordingly, the probability of finding an NMA depends on how many alternative movements the experimenter tries to arrest. Since many of the reported NMAs involve inhibition of a single type of motor response, it seems likely that many possible NMAs may be missed, due to sparse sampling (see Effector specificity, below). Nevertheless, NMAs are surprisingly common, and 3% (Chassagnon et al., 2008) to 35% (Nii et al., 1996) of stimulation sites have been classified as NMAs.

4. Effector-specificity of NMAs

A typical procedure involves asking the patient to read a text out loud and then serially stimulating all electrodes (Lüders et al., 1988; Lüders et al., 1992; Penfield and Jasper, 1954). If and only if speech arrest effects are found, inhibition of other motor actions from the same site is then evaluated. Unsurprisingly therefore, speech arrest is the most frequently reported negative motor response, while NMAs for non-speech movement are relatively rare. This may represent an artefact of the sampling procedure, rather than a fundamental feature of neural organisation of action inhibition. The

screening protocol based on reading aloud also over-emphasises the overlap between speech and non-speech NMAs, and thus underestimates any actual effector specificity of NMAs.

Stimulation at a given cortical site generally produces negative motor responses in a restricted set of muscles only, without affecting the ability to make other voluntary movements (Chassagnon et al., 2008; Hanakawa et al., 2001; Ikeda et al., 1999; Lim et al., 1994; Mikuni et al., 2006; Penfield and Rasmussen, 1950). That is, NMAs can sometimes be effector-specific. Negative motor effects are predominantly contralateral. Further, negative motor responses were in some cases stronger and more frequent for distal muscles than for proximal ones, and for fingers as opposed to toes (Lüders et al., 1992). This suggests an effector-specific organisation of motor inhibition. On the other hand, the arrangement of effector-specific NMAs within the cortex seems to lack the clear somatotopic spatial arrangement of the classical motor homunculus (see Localisation). Some authors (Chassagnon et al., 2008; Ikeda et al., 1992; Nii et al., 1996; Uematsu et al., 1992) report sites producing both inhibition of ongoing hand movements and also excitation of facial musculature. In one case, stimulation of SMA caused a negative motor response affecting all parts of the body (Ikeda et al., 1992). In summary, although NMAs often show some degree of somatotopical specificity, this is not always the case.

5. Localisation in the brain

The localisation data in the NMA literature is not systematic, and lacks a consistent coordinate system. All the reported sites are found in the frontal lobes. Clearly, this could reflect a sampling bias based on clinical requirements for electrode placement, or on scientific assumptions about localisation of inhibition. However, in a study with 35 patients, 21 of which had electrode grids placed over the frontal-parietal-temporal cortex, all NMAs were found anterior to the Rolandic line (Uematsu et al., 1992). Penfield (Penfield and Rasmussen, 1950) reported hand, leg and jaw and tongue arrest "in the lower sensorimotor strip, just above the fissure of Sylvius". Lüders et al. (1987, 1992) found NMAs most consistently in the IFG 'immediately in front of the face motor area'. Several studies reported NMAs in the SMA (Chassagnon et al., 2008; Chauvel et al., 1996; Fried et al., 1991; Hanakawa et al., 2001; Lüders et al., 1988; Penfield and Rasmussen, 1950) and around the Rolandic fissure (Nii et al., 1996; Uematsu et al., 1992). Mikuni (Mikuni et al., 2006) recently added the dorsal premotor cortex to this list. Fig. 1 shows the NMAs from the studies in Table 1, positioned as precisely as possible using the information from the original papers. Some of the studies reporting NMA sites on the lateral cortex do not report the hemisphere in which they were found (Nii et al., 1996; Penfield and Rasmussen, 1949). Nii et al report that NMAs were found "in similar numbers in the left and right hemispheres". Therefore, half of the reported sites were arbitrarily assigned to the left and half to the right hemisphere. In the case of Penfield and Rasmussen, the sites are shown on the right hemisphere.

Overall, NMAs appear to be intermixed with sites where positive sensory or positive motor effects are found. This is not compatible with Lüders suggestion of a 'negative motor homunculus' (Lüders et al., 1995). Instead, it goes in line with recent views (Farrell et al., 2007) suggesting that the cortex presents a mosaic of functional organization, rather than the classic somatotopical sensory and motor organisations that Penfield described (Mazzola et al., 2009).

6. Effects of varying current intensity

There has been little systematic analysis of stimulation levels required for eliciting negative motor responses. Chauvel et al. (1996) showed that current levels that elicited positive motor signs on some sites could also elicit negative motor effects at other sites. Mikuni et al. (2006), on the other hand, reported four sites where stimulation initially elicited a negative response, but increasing stimulation generated a positive effect.

7. Physiological characteristics

The readiness potential (RP) is an established neurophysiological signal classically recorded in the second or so preceding voluntary movements (Shibasaki and Hallett, 2006). RPs are often recorded in subdural electrodes generating positive motor signs (Ikeda et al., 1995a, 1995b; Ikeda et al., 1992; Lee et al., 1986; Neshige et al., 1988; Rektor et al., 1994; Sakamoto et al., 1991) and are generally interpreted as positive preparation of skilled movement. RPs were occasionally reported within NMAs, (Ikeda et al., 1993; Kunieda et al., 2004; Yazawa et al., 2000). Ikeda reported RPs from one electrode, within the SMA, that qualified as an NMA on the basis of stimulation testing. This potential occurred in association with both ipsi- and contralateral single or repetitive finger movements. Yazawa et al. also found RPs in two NMAs situated within the SMA. Again, these RPs were not strongly selective for specific movements. Finally, Kunieda found one NMA site that showed a RP preceding both foot and shoulder movement. Kunieda et al. report the existence of 'omni-RPs', i.e., RPs associated with several movement effectors. They further noted that these are often found in electrodes adjacent to NMAs.

The existence of RPs in NMAs might appear incompatible with the concept that NMAs have a role in inhibitory control of action. However, Yazawa et al. (1998) reported RPs from several electrodes (including both NMAs and electrodes eliciting positive responses) prior to *stopping* a voluntary muscle contraction, as well as contracting the muscle. Nonivasive recordings confirm this finding. Electroencephalographic (EEG) recordings before the end of prolonged muscle contractions show RPs before muscle relaxation of both hand (Terada et al., 1995) and foot (Terada et al., 1999). Similarly, neuroimaging studies showed greater activations (Toma et al., 1999) in SMA and pre-SMA before muscle relaxation than before muscle contraction. This suggests that the cortical outflow from areas such as SMA, premotor cortex and M1 may recruit inhibitory interneurons in the spinal cord to inhibit muscle activity (Shibasaki and Hallett, 2006).

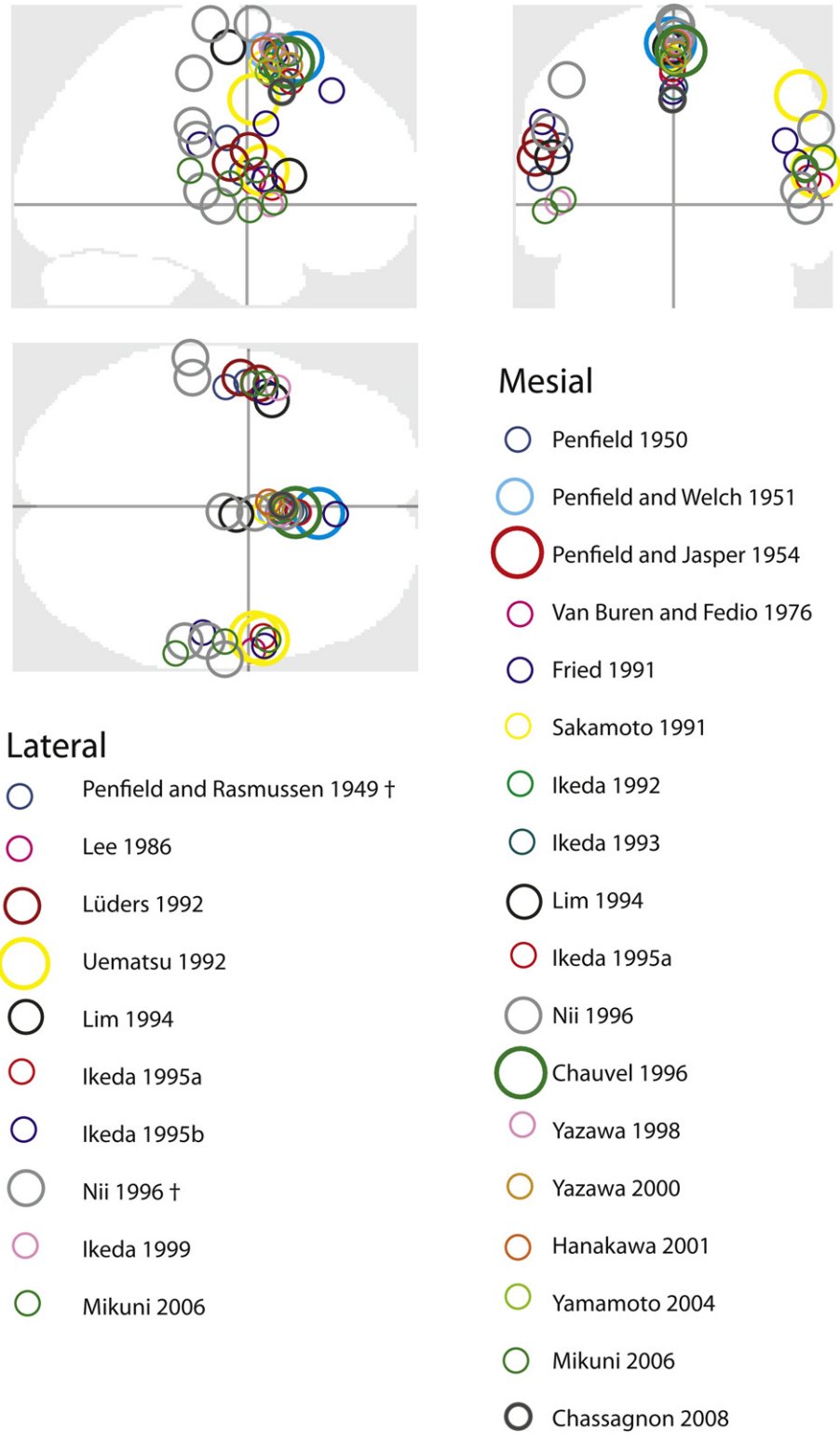

Fig. 1 – Approximate location of NMAs shown on a glass brain. Coordinates were approximated by visual inspection of the original figures. Small circles represent 1–5 NMA sites, medium circles represent 6–20 NMA sites, and the larger circles represent >20 NMA sites. Different colours represent individual studies, but colours may be repeated due to one study showing more than one NMA cluster. † indicate studies in which the lateralization on the NMAs was not reported, and was therefore inferred (Nii et al., 1996) or depicted on the right (Penfield and Rasmussen, 1949). Gray lines intersect at the anterior comissure.

In summary, the presence of RPs cannot, in itself, be taken as evidence against an inhibitory function of NMAs.

8. NMAs and negative motor seizures

Negative motor seizures are a rare epileptic condition that consists of solely motor arrest without loss of awareness (Lüders et al., 1998). If negative motor seizures originate in NMA, they may give important clues to the normal functions of NMA, since seizure activity often produces results consistent with the normal functional specialisation of the area where the seizure occurs. Recently, it has been suggested that NMAs are indeed responsible for negative motor seizures (Ikeda et al., 2009). This would support our argument that NMAs could represent a neural circuit for action inhibition, though interpretations based on ictal apraxia have also been suggested (Ikeda et al., 2009). Unfortunately, the existing data remains equivocal on this point. Although negative motor seizures were found to originate within the broad lateral and medial zones defined as NMAs, the specific electrodes within those zones showing most epileptiform activity did not necessarily produce negative motor responses when stimulated.

9. Subjective experience

A few NMA studies include subjective reports of the experience of NMA stimulation. These provide some intriguing hints about the psychological level at which NMAs contribute to the cognitive control of action:

'*…like I forgot how to wiggle*' (Lüders et al., 1992)

'*I heard you. I didn't know why I didn't do it*', (Lüders et al., 1992)

'*…Knew what I wanted to get out but would not go*' (Van Buren and Fedio, 1976).

'*Yes, it felt like paralysis going down my right leg*' Penfield and Rasmussen, 1950).

'*I could not do it*' (Penfield and Rasmussen, 1950).

'*You paralyzed my jaw*' (Penfield and Rasmussen, 1950).

Patients seem to report the arrest of action as being something *externally* imposed onto their ongoing stream of action. They do not report any conscious decision to inhibit. Rather, they report a failure to move despite intact volition and intention to act. Thus NMAs do not appear to cancel the intention to act, but only its actual motor implementation. Further, they do not produce a conscious experience of intentional withholding or self-control. This suggests that NMAs are part of an action suppression mechanism, rather than housing an internal decision-centre, or trigger to inhibit.

10. Results of excision

Of the studies explicitly reporting NMAs, only three additionally report the results of the surgical excision of NMAs (Mikuni et al., 2006; Penfield and Welch, 1951; Uematsu et al., 1992). Penfield and Uematsu both state that although an NMA may interfere with movement when stimulated, its resection does not greatly disrupt action. Mikuni et al. described two patients in whom an NMA was removed. In one case, excision of an NMA related to inhibition of right hand movement generated a clumsiness of the hand that lasted for not more than half an hour. In the other case, no clinical deficits were observed. However, these comments suggest results of NMA excisions were evaluated based mainly on positive motor criteria (i.e., the ability to move skilfully) rather than negative motor criteria exclusively (i.e., the ability to inhibit action). As a result, it remains unclear whether NMAs are necessary for normal inhibition of action. In the future, it would be valuable to perform established neuropsychological tests of inhibitory function before and after surgical resection of NMAs.

11. Functional relevance

NMAs suggest a mechanism for action inhibition, which can be manipulated directly in clinical experiments. Do NMAs therefore have an inhibitory function, and what light could NMAs shed on mechanisms of action inhibition?

First, there are obvious differences in the timing of inhibition between existing behavioural paradigms of inhibition and NMAs. To demonstrate these differences we will consider two tasks used to study action inhibition. Behavioural NOGO tasks involve stopping an action which is prepared but not yet in execution (Kiefer et al., 1998). In stop signal tasks, the inhibition is triggered as close as possible to the "point of no return" after which an action can no longer be inhibited (Logan, 1994). In contrast, negative motor responses are defined as stimulation-induced inhibitions of an action which is *already* being executed. Of course, the NMA mechanism that stops execution may well also serve to inhibit actions that are still under preparation, and have not yet been initiated. To our knowledge, no neurosurgical study has stimulated NMAs during action preparation, so this point remains speculative.

One recent study addressing the roles of pre-SMA and IFG has reported very interesting results concerning NMAs. In a rare patient with electrodes implanted both in the right IFG and the pre-SMA, Swann et al (Swann et al., 2011) studied the anatomical and functional connectivity between pre-SMA and IFG electrodes. Diffusion tensor imaging (DTI) analyses showed that the projections from pre-SMA to the lateral prefrontal cortex specifically target the IFG. Strikingly, the pre-SMA electrode that most closely corresponded to this anatomical connection also produced a negative motor response upon electrical stimulation. In turn, the electrode within IFG closest to the anatomical connection showed the strongest signal during performance in a stop-signal task. Furthermore, a direct functional connection was suggested by a strong and short-latency cortico-cortical evoked potential in the IFG electrode following stimulation of the NMA in pre-SMA. Together, these results from a single but rare case suggest that (a) NMAs play a functional role in motor inhibition; (b) they may do so by driving a network of several frontal cortical areas that provide a balance between excitation and inhibition.

NMAs have been found to show some degree of somatotopical specificity, although this is not the general rule. This interestingly relates to the distinction between global and selective inhibition. In a modified stop-signal task, (Aron and Verbruggen, 2008) have shown that effector-selective

stopping processes can be dissociated from global stopping processes. As an interesting possibility, we suggest that NMAs showing different degrees of effector-specificity may allow for global versus selective inhibitory mechanisms.

12. 'Natural' inhibitory function of NMAs

From a neuropsychological perspective, it is crucial to establish whether negative motor responses could be artificial activations of a cortical mechanism whose normal function is to inhibit and withhold action.

A sceptic might question the relevance of NMA to functional inhibition for three reasons. First, because DES artificially induces neural activity that bears little resemblance to normal physiological activity, NMAs could be dismissed as artificial effects without physiological relevance. A second, related view is that NMAs do indeed activate cortical inhibitory mechanisms, but these mechanisms may be purely epiphenomenal, without any causal or functional role in action control. We agree that electrical stimulation is not ecological, but we reject the radical view that its effects have no functional relevance. The RPs found in NMAs (Ikeda et al., 1993; Kunieda et al., 2004; Yazawa et al., 1998; Yazawa et al., 2000) and the study by Swann et al. (2011) strongly suggest that NMAs have some relevant links to movement control.

A third sceptical view suggests that NMAs are not truly negative, but simply reflect action disruption due to non-physiological activation of positive motor areas where the cortical control of movement is organized (Chauvel et al., 1996; Ikeda et al., 1992; Lüders et al., 1987; Mikuni et al., 2006; Yazawa et al., 2000). In other words, this view holds that the observed negative effects are not due to activation of negative areas per se, but to inactivation of positive areas.

For example, Chauvel et al. found that the same stimulation site could generate both positive vocalization and speech arrest (when stimulated during speech). They suggested that speech arrest could be a by-product of unnatural stimulation of circuits whose true function is positive fine motor control of vocal musculature.

This view faces a number of problems. First, it cannot explain why many stimulations that produce positive motor effects do not also produce negative motor responses. In fact, highly complex sequences of functional action can be evoked by some electrical stimulations (Bancaud et al., 1976), yet these positive motor effects can be readily dissociated from negative motor effects. Second, this view cannot explain why NMAs are sometimes found in quite different areas from positive motor areas (Fried et al., 1991; Uematsu et al., 1992). In particular, Lim et al. (1994) reported that NMAs were usually anterior to positive motor areas or to areas eliciting sensory signs. In the same way, Uematsu et al. (1992) elegantly showed that the distribution of NMAs is anterior to the distribution of positive motor areas. They found nearly all (94%) NMAs to be anterior to the Rolandic line. Nine of eighteen electrodes producing a negative motor response were at least 20 mm anterior to the Rolandic line. Positive motor areas, on the other hand, were most commonly found in the region within 10 mm anterior to the Rolandic line. In addition, NMA localisation matches the areas showing increased BOLD activity associated with response inhibition in stop signal tasks (see review articles by Chikazoe, 2010; Levy and Wagner, 2011; Swick et al., 2011).

Third, and crucially, this view cannot explain why NMAs are sometimes found at lower intensity than positive motor effects (Mikuni et al., 2006). Taken together these findings suggest that negative motor responses do not simply arise from disrupting normal physiological activity in excitatory areas.

For these reasons, we reject the view the NMAs merely represent unnatural disruption of actions caused by stimulating areas normally involved in positive movement generation. An alternative possibility remains open: negative motor responses might represent an artificial induction of a normal physiological process of action inhibition.

In our view, the normal organization of complex (Gerloff et al., 1997) and fine movement (Fukaya et al., 2004) involves an element of inhibition. Hierarchical control is required to regulate the balance of activation and inhibition in several motor cortical areas, so that movements are neither hyperkinetic and impulsive, nor hypokinetic and ineffective. Crucially, we suggest that there is some 'functional truth' in NMAs. We speculate that DES, albeit not ecological itself, produces negative motor responses by activating physiologically inhibitory pathways that participate in normal action control. Crucially, negative motor responses are not simply an artifactual, unnatural disruption of ongoing movement, or an overloading of positive motor effects. The interesting observations reported by Swann et al. (2012) provide clear, and perhaps the first, evidence for a possible functional relevance of NMAs in action inhibition, as an important element of action control.

The natural inhibitory function of NMAs could be important in action control for two distinct reasons. First, NMAs may reflect activation of an inhibitory mechanism for praxic control of fine details of action execution. Alternatively, NMAs may reflect artificial activation of an inhibitory mechanism for executive, decisional control over whether actions occur or not. The data reviewed here cannot conclusively distinguish between these two alternatives, and future functional studies may shed light on this interesting question. Control of praxis has been strongly linked to lateral cortical pathways linking the inferior parietal cortex and the lateral premotor cortex (Tanji and Hoshi, 2008). In contrast, executive control of action has been linked to the prefrontal and medial frontal cortices (Badre and D'Esposito, 2009; Stuss and Knight, 2002), and particular to the drive these areas receive from the basal ganglia (Heyder et al., 2003). Our review shows two clear clusters of NMAs in the lateral frontal and dorsomedian frontal cortices. By analogy with the lateral/frontal division for positive motor function, we can thus speculate that the lateral frontal cluster of NMAs reflects a praxic mechanism for fine regulation of complex action sequences, while the medial frontal cluster represents an executive mechanism for regulating whether an action is executed or inhibited.

13. Implications for normal inhibitory function

From the evidence reviewed above, we suggest that NMAs are indeed truly inhibitory. If this is true, then results of stimulating an NMA may inform about the normal physiological

processes of action control, and particularly of inhibitory action control.

First, the form of inhibition associated with NMAs clearly occurs late in the motor chain that leads from plan to movement. In particular, inhibition mechanisms remain available even during the execution phase, and after action initiation: negative motor responses are defined as cessation of *ongoing* movement. However, the same inhibitory process might also apply to action preparation prior to execution. Any future data on effects of NMA stimulation during action preparation would be extremely valuable. Second, NMAs seem to show a coarse somatotopy, as they are specific to particular muscular actions, rather than general cessations of all motor activity. This may relate to the finding that there are specific inhibitory mechanisms that may be distinguished from a general inhibitory function (Aron and Verbruggen, 2008; Verbruggen and Logan, 2008). Third, the inhibitory function of NMAs resembles an unconscious braking of ongoing action, rather than a conscious decision to inhibit.

Recent cognitive theories have conceptualised inhibition in two quite different ways. First, it may occur by competition between representations of alternative actions at the same representational level. The go/nogo task fits the first model, if we can accept that nogo is a form of action. Computational theories of action selection (Cisek, 2006) hold that action inhibition is the result of the competition between 'go' and 'nogo' processes. On this view there is no need to pose a hierarchical organization of inhibitory control, since response selection and response inhibition are effectively identical (Kenner et al., 2010; Mostofsky and Simmonds, 2008).

An alternative view proposes distinct 'inhibition centres', positioned hierarchically upstream of action control, and capable of globally inhibiting several motor outputs (Aron and Verbruggen, 2008). It has been argued (Aron et al., 2004) that the right inferior frontal cortex is the main brain area responsible for driving action inhibition. The IFC is thought to implement executive control by driving neural activity in subcortical and posterior cortical regions. Other, more recent data suggests that the pre-SMA also contributes to these inhibitory processes, and may play a leading role (Duann et al., 2009; Swann et al., 2012).

We may therefore ask whether evidence from NMAs is more consistent with the hierarchical or the competitive view. The hierarchical view would predict an inhibitory function to be located upstream of action control centres. Given the general anteroposterior hierarchy in the frontal cortex (Koechlin and Summerfield, 2007) this view might predict NMAs to be located anterior to positive motor areas. Further, the hierarchical view suggests that NMAs would be mostly effector-independent: since their function would be to modulate the somatotopical motor cortex, they need not show somatotopic organization themselves.

In contrast, the competitive view would predict inhibitory representations to have a similar distribution, and similar somatotopical specificity to positive motor representations. Our review suggests that NMAs are rather widely distributed across the frontal and prefrontal cortices, often anterior to positive motor areas (Uematsu et al., 1992), and show rather less somatotopical specificity than positive motor areas (See Effector-specificity of NMAs). Therefore, existing NMA evidence is more consistent with a top-down hierarchical view of action inhibition rather than a competitive view.

We have shown above that NMAs fall into two general clusters: a medial cluster focussed on the SMA, and a lateral cluster focussed on the IFG and premotor cortex, and we have speculated that these may reflect two forms of inhibitory action control for executive decision and for praxis respectively. Interestingly, the same medial-lateral gradient has also been interpreted as a distinction between systems for internally-generated and externally triggered action. This view was originally based on deficits in neurological patients (Goldberg, 1985), and primate ablation studies (Passingham, 2007), but was subsequently confirmed by electrophysiological recording studies in both medial and lateral areas (Tanji, 2001). The concept of internally generated action remains controversial (Nachev and Husain, 2010). We suggest that the medial/lateral distinction for action might be mirrored by a similar distinction between two forms of inhibition. The medial NMA cluster might be involved in stopping and regulation of so called internally generated actions, whilst lateral NMAs could be involved in the stopping of externally triggered action. Given the strong links between voluntary action and executive function on the one hand, and between object representation and praxis on the other, this distinction between internal and external processes for action inhibition can be seen as an alternative interpretation of the distinction made previously between possible NMA contributions to action decision and fine motor execution. Our review of NMA data shows support for the interesting possibility that two distinct cortical inhibitory systems might be associated with two distinct action control systems.

14. Conclusions

Neurosurgical electrical stimulation data suggests the existence of a cortical network that suppresses actions: NMAs have a clear inhibitory effect on motor output. As such, NMA data could make an important contribution to neurocognitive theories of action control. In particular, NMAs demonstrate that inhibitory mechanisms remain available until very late in the action generation chain, since NMA stimulation arrests ongoing movement after movement initiation. Further, anatomical information provided by NMAs may be relevant for neuropsychology. In particular, NMAs have been found in two main areas: medially (SMA, pre-SMA) and laterally (IFG and premotor cortex). This dissociation resembles that proposed for two distinct action systems, with medial areas being associated with internally generated actions and lateral areas with externally triggered actions. However, the normal functional role of NMAs remains unclear. Combining NMA stimulation with experimental tasks would be a valuable priority for future research. Such research might reveal whether NMAs might also be involved in suppressing intended actions at the preparation stage, prior to execution, and whether they indeed contribute to functional inhibition.

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