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REVIEW

The uses and interpretations of the motor-evoked potential for understanding behaviour

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Abstract The motor-evoked potential (MEP) elicited in peripheral muscles by transcranial magnetic stimulation (TMS) over human motor cortex is one of the hallmark measures for non-invasive quantification of cortical and spinal excitability in cognitive and clinical neuroscience. In the present article, we distinguish three main uses for MEPs in studies of behaviour: for understanding execution and performance of actions, as markers of physiological change in the motor system, and as read-out of upstream processes influencing the motor system. Common to all three approaches is the assumption that different experimental manipulations act on the balance of excitatory and inhibitory pre-synaptic (inter)neurons at the stimulation site; this in turn contributes to levels of (post-synaptic) excitability of cortico-spinal output projections, which ultimately determines the size of MEPs recorded from peripheral muscles. We discuss the types of inference one can draw from human MEP measures given that the detailed physiological underpinnings of MEPs elicited by TMS are complex and remain incompletely understood. Awareness of the different mechanistic assumptions underlying different uses of MEPs can help inform both study design and interpretation of results obtained from human MEP studies of behaviour.

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Introduction

The motor-evoked potential (MEP), elicited by transcranial magnetic stimulation (TMS) over human motor cortex, provides a quantification of cortico-spinal excitability at the time of stimulation (Rothwell 1997; Chen et al. 2008; Bestmann 2012; Di Lazzaro et al. 2004; Rothwell et al. 1999; Terao et al. 1995). The soundness of conclusions drawn from human MEP measurements relies on an appropriate understanding of the complex nature of their physiological underpinnings. Here, we discuss three main ways in which MEPs have been used and interpreted, each dependent on distinct assumptions with regard to cortico-spinal, intra- and trans-cortical contributions to MEPs, respectively.

First, MEPs are interpreted in relation to the execution and performance of actions. This assumes that the quality and integrity of motor output to the spinal cord can be quantified with TMS and directly relates to movement quality itself. Seen in this way, MEPs provide insight into the mechanisms controlling motor output. TMS, however, targets both pre-synaptic inputs and post-synaptic elements of cortico-spinal neurons, which may not always be the same as the ones activated by volitional motor commands, thus complicating making a direct link between the two.

Second, changes in MEPs are used to probe the physiology of motor cortex, by providing a read-out of the state of post-synaptic cortical excitability and pre-synaptic intracortical processes. Such measures may be quantitative physiological markers of change, but may have no causal relevance to actual motor behaviour.

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Third, changes in the amplitude of MEPs can disclose physiological processes that occur outside primary motor cortex (M1) but induce measurable state-changes there. A significant proportion of MEP changes is directly or indirectly conveyed by afferent inputs into motor cortex that represent decision-making and other cognitive processes transmitted to M1. Viewed in this way, MEPs not only reveal the excitability of elements controlling motor output, but also serve as a read-out of upstream processes that are not themselves necessarily related to movement production. That is to say, MEPs might have functional relevance but could also just be an epiphenomenal marker of processes taking place elsewhere that happen to impinge upon M1 because of anatomy.

Motor-evoked potentials elicited by TMS over human motor cortex

When applied over M1, TMS can elicit contraction in contralateral muscles. The amplitude of evoked potentials detected with surface electromyography (EMG) quantifies the level of cortico-spinal excitability (Barker et al. 1985; Rothwell et al. 1987a, b; Mills et al. 1987; Day et al. 1987). In humans, TMS can therefore non-invasively assess changes in the state of excitability in the cortico-spinal system.

Briefly, TMS induces an electrical current in underlying cortical tissue, which is short-lived (~200 μs) and of similar amplitude to that produced by a conventional stimulator applied directly to the surface of the brain. At appropriate stimulation intensities, these currents can elicit contralateral muscle responses, most readily in intrinsic hand muscles. These evoked responses consist of both cortical and spinal-segmental contributions, which can be difficult to dissociate. The amplitude of the MEP is therefore a compound signal, which results from a series of descending cortico-spinal volleys with different generators. How these volleys contribute to MEP amplitude depends on a variety of processes, including temporal dispersion and spinal mechanisms.

In contrast, the latency of the MEP reflects the conduction time for neural impulses from the cortex to peripheral muscles, which is determined by the conduction velocity of the fastest cortico-spinal projections, the summation of descending volleys at the spinal motoneuron level, and the conduction time along peripheral motoneurons. State-changes at each of these stages can significantly influence the latency of MEPs.

One can in principle distinguish between stimulation of cortico-spinal, intra-cortical, and trans-cortical elements, but single TMS pulses are unlikely to selectively activate any of these elements but instead target all three to varying degrees. Direct stimulation of cortico-spinal neurons or their axons contrasts with the stimulation of intra-cortical and trans-cortical elements; their contributions to MEP size likely is complex and can result from stimulation of apical or basal dendrites on cortico-spinal neurons, of the cell body, and of intra-cortical and trans-cortical inputs onto M1 interneurons. Several excellent reviews provide in-depth discussion and detailed overview of the physiology of motor-evoked potentials (Di Lazzaro et al. 2008, 2012; Di Lazzaro and Ziemann 2013; Chen 2004; Cash et al. 2011; Ziemann and Rothwell 2000; Rusu et al. 2014).

In what follows, we briefly describe some of the properties of different descending waves elicited by TMS in so much as they pertain to examples in this review.

D- and I-waves in motor cortex

Suprathreshold TMS pulses evoke a series of descending cortico-spinal volleys that make up different components of the MEP. The first volley is termed the direct (D-) wave (Patton and Amassian 1954) and is evoked from the initial axonal segments of fast-conducting pyramidal tract neurons. D-wave latency and duration depend on the direction and intensity of TMS-induced currents. This direction dependence suggests that either slightly different populations of neurons or axons are being stimulated, or the population causing D-wave activity can be activated at slightly different sites such as the cell body versus first internode. D-waves with the shortest latency are relatively resistant to changes in cortical excitability, suggesting activation of cortico-spinal axons in the subcortical white matter.

Subsequent volleys are termed indirect (I-) waves (Day et al. 1987; Patton and Amassian 1954; Kaneko et al. 1996; Nakamura et al. 1997) and have a frequency of about 600 Hz. The relevant point here is that different descending volleys have distinct generators. I-waves are thought to result from trans-synaptic (intra- and trans-cortical) activation of pyramidal tract neurons. The first I-wave following the D-wave (termed I_1) reflects direct synaptic input onto cortico-spinal pyramidal tract neurons (Fisher et al. 2002). Later I-waves, by contrast, occur at latencies between 2.4 and 7 ms after the D-wave, and include contributions from cortico-cortical afferents, such as connections from PMd and SMA (Groppa et al. 2011; Ziemann and Rothwell 2000). For example, direct stimulation of premotor areas elicits repetitive I-wave discharges, which disappear following ablation or inactivation of motor cortex (Patton and Amassian 1954; Shimazu et al. 2004). TMS pulses could act on I-wave generators in several ways: (a) segregated types of interneuron may provide independent input onto cortico-spinal tract neurons, (b) reverberating circuits of activated interneurons may generate successive I-waves, (c) chains of interneurons may become activated, or (d) changes in the membrane properties of cortico-spinal

tract neurons occur, possibly through differential effects on inputs to distal versus proximal synapses (Rusu et al. 2014).

Collectively, I-waves are generated through a mixture of activation of intra-cortical afferents to pyramidal tract neurons within M1, as well as long-range cortico-cortical afferents projecting to M1 pyramidal tract neurons (Di Lazzaro et al. 2011). These distinct generators perhaps also explain the inherent trial-by-trial variability in evoked cortico-spinal volleys (Burke et al. 1995) and thus MEPs (Kiers et al. 1993; Schmidt et al. 2009; Goetz et al. 2014; Klein-Flugge et al. 2013).

Mechanisms for the control of I-waves

Different descending waves can selectively activated with different experimental manipulations. For example, the neural elements within M1 with a low threshold for stimulation are gamma-aminobutyric type (GABA) inhibitory interneurons, which influence motor output by suppressing I-waves (though it is also possible that GABA-ergic interneurons are trans-synaptically excited). In contrast, axonal elements of pyramidal tract neurons have higher stimulation thresholds. Paired-pulse protocols (Kujirai et al. 1993) make use of this by applying a low-intensity conditioning pulse that can activate low-threshold interneurons, which then suppress specific I-waves elicited by a subsequent higher intensity test pulse. Thus, paired-pulse protocols can be used to preferentially probe different I-waves (Di Lazzaro et al. 1999a, b; Tokimura et al. 2000). Relatedly, different directions of induced current flow influence the latency of surface EMG responses (Werhahn et al. 1994; Di Lazzaro et al. 1998, 2001) by differentially activating D-waves, and early versus late I-waves (Hamada et al. 2007; Hanajima et al. 2001, 2003). Successive I-waves can furthermore be distinguished by their pharmacological fingerprints. For example, late I-waves, but not the I_1, are depressed by enhancement of neurotransmission through the inhibitory GABA-A (Di Lazzaro et al. 2000; Kujirai et al. 1993; Ziemann et al. 1996a). This selective recruitment and modification of different I-waves provides further evidence for independent neural generators (Di Lazzaro and Ziemann 2013). The ability to independently manipulate different I-waves potentially allows for testing hypotheses about the processes acting on these distinct neural elements.

In summary, descending volleys are influenced by activation of multiple intra-cortical excitatory and inhibitory neurons with axons of varying size, location, orientation, and functional properties; their relative contribution likely depends on the specific stimulation protocol and experimental intervention. The differential I-wave composition of MEPs means that they do not reflect a straightforward read-out of changes from a homogeneous group of neural elements within M1. Several mechanisms underpinning MEP generation have been proposed (Cash et al. 2009; Ni et al. 2011; Chen 2004; Di Lazzaro et al. 2004; Rothwell et al. 1990; Ziemann et al. 1996b; Thickbroom 2011; Ziemann and Rothwell 2000), with recent work in computational neurostimulation (de Berker et al. 2013) shedding further light on the circuitry for I-wave generation (Di Lazzaro et al. 2008; Rusu et al. 2014; Di Lazzaro and Ziemann 2013). It is important at this stage, however, to point out that the precise origin and nature of I-waves, and therefore MEPs, remains incompletely understood (Di Lazzaro et al. 2008; Rusu et al. 2014; Di Lazzaro and Ziemann 2013).

Spinal contributions to MEPs

In addition to supraspinal mechanisms, the size of the MEP is also determined by the excitability of the spinal motoneuron pool (Taylor 2006; Groppa et al. 2012). Without control of spinal motoneuron excitability, MEPs may provide an inaccurate estimate of cortico-spinal integrity. For example, the known facilitation of MEPs obtained during ongoing EMG activity is thought to largely depend on an excitability increase at the spinal level. Moreover, MEP amplitude is influenced by phase cancellation arising from temporal dispersion of cortico-spinal volleys (Groppa et al. 2012). As a consequence, changes in MEP amplitude can arise even though the number of descending volleys remains constant. These caveats do not diminish the usefulness of using MEPs for quantifying state-changes in the human motor system during behaviour; they just caution against conclusions about absolute excitability levels in motor cortex without explicit assessment of changes occurring at the spinal level.

Using MEPs to assess the quality and integrity of motor output to the spinal cord

MEPs have been used for the assessment and quantification of the quality and integrity of motor output to the spinal cord. A central assumption with this approach is that the magnitude (and latency) of MEPs are directly correlated with motor performance itself, such as the force (Barthelemy et al. 2012; Oathes and Ray 2006; Baud-Bovy et al. 2008; Perez and Cohen 2009b), speed (Uehara et al. 2011), or accuracy of movement (Davare et al. 2006; Pearce and Kidgell 2009; Classen et al. 1998). In other words, such approaches assume that the amplitude of MEPs correlates with "how" actions are executed.

A critical question then is whether MEP changes are at all causal to the production of, for example, speeded movements, or just an epiphenomenon that can suitably be read-out from TMS over M1. In order to be causally related to

motor output, the pattern of neural discharge elicited by TMS would have to closely match the pattern of activity during natural movements. This seems unlikely given the artificial, widespread, and highly synchronized repetitive discharge in fast-conducting monosynaptic cortico-spinal fibres caused by TMS. Moreover, not all descending connections contributing to movement are equally excited by TMS. TMS will preferentially excite monosynaptic fast-conducting cortico-spinal projections (Lemon 2002) and possibly also slower-conducting monosynaptic connections with upper limb motoneurons (Porter and Lemon 1995), but does not usually target slow-conducting polysynaptic fibres. TMS consequently probes only a subgroup of descending motor fibres, albeit those most involved in controlling dexterous hand movement.

Finally, further complexity is added by potential contributions from direct cortico-spinal projections onto spinal motoneurons, which in the monkey have been shown to originate from premotor (Dum and Strick 1996, 2002) or parietal regions (Murray and Coulter 1981). Moreover, a proportion of the descending excitation to some muscles can travel via the propriospinal pathway (cf. Burke et al. 1994). This suggests that the amplitude of MEPs during behaviour could additionally be influenced by excitability changes of the spinal motoneuron pool caused by descending pathways from cortico-spinal projections other than those originating in M1. Thus, changes in MEPs may not capture the full extent of functional projections to the spinal cord.

The relationship of MEPs to motor output and learning

TMS has been used to track changes in cortical representations for motor output, during or after motor learning (Classen et al. 1998; Cirillo et al. 2009, 2011; Cohen et al. 1998). The potential problem with interpreting MEPs as biologically meaningful in the context of normal behaviour can be appreciated by considering an example when even for movements elicited by TMS, the actual relevance for behaviour is unclear. For example, TMS can evoke thumb movements in a consistent direction, but when participants move their thumbs repeatedly over minutes in an opposite direction, subsequent TMS pulses now also elicit thumb movements in the direction of the recently practised movement (Classen et al. 1998). This result has been taken as evidence that repeated movements lead to a change of cortical network representing preferred thumb movements, and that concomitantly, patterns that correspond to movements that have not recently been executed are weakened.

There is a puzzling point about these repetition-induced changes, which is rarely discussed: the same artificial and relatively unselective TMS pulse can evoke a novel movement following learning, but this novel movement does not occur when voluntarily selecting the original movement. In other words, when participants are asked to voluntarily make the baseline movement, their finger does not strangely move in the direction of the newly repeated movement. Thus, the changes quantifiable with TMS after movement repetition are of questionable relevance to voluntary movements. In addition, if movement representations that have not recently been executed weaken (as could be inferred by changes in TMS-evoked movement direction, or MEP size), one might expect that the speed or precision at which such a movement can be executed should also be affected. To the best of our knowledge, such a relationship has not been demonstrated, and indeed it would seem maladaptive if the repetition of very simple finger movements induces an immediate penalty of such a kind. The point here is that TMS-evoked movements in cases like this provide a read-out of physiological changes induced by a motor learning paradigm, but it does not follow in any logical sense that the changes in the evoked movement, and hence the descending volleys, are causally related to changes in movement performance after learning. Thus, whether it is either MEP or movement changes that are detected by TMS before and after any intervention, their relevance with respect to normal behaviour remains undetermined.

In fact, some evidence suggests that there may not be a straightforward relationship between MEPs and motor output changes following learning (Bagce et al. 2013; Todd et al. 2009; Gelli et al. 2007; Muellbacher et al. 2000; McDonnell and Ridding 2006). For example, at the beginning of learning, MEPs increase in linear fashion with increases in grip force required to maintain a constant motor output. However, subsequently, while the newly acquired motor behaviour (here, maintaining a specific peak force profile) can be retained, MEPs return to baseline levels. There is therefore a mismatch in the dynamics of MEP changes and motor behaviour throughout different stages of motor learning, which suggests that there is not a one-to-one mapping between MEP amplitude and a change in motor output (Muellbacher et al. 2001). More recently, Bagce and colleagues showed that comparable increases in MEP size can occur with opposite behaviours (Bagce et al. 2013). Specifically, these authors used a gain adaptation task in which opposite finger movements were required for low versus high gains following adaptation. Changes in cortico-spinal excitability (CSE) were tracked in the same agonist muscle before and after adaptation. Critically, CSE increased after adaptation in *both* cases, despite opposite changes in movement amplitude. This strongly implies that state-changes elicited by learning-related processes in the gain adaptation experiment elicit changes in CSE (and hence MEP size), but do not directly relate to motor output. MEPs can therefore indicate that something is changing physiologically during motor learning, but the relationship

of these measures to the changing behaviour remains to be determined (cf McDonnell and Ridding 2006).

MEPs as surrogate markers for disease-related impairment in the quality of motor output

A popular position in the literature is that in pathologic conditions such as stroke, the magnitude or latency of MEPs evoked by contralateral TMS may act as a surrogate marker for motor impairment (Freund et al. 2011; Ward et al. 2006, 2007; Stinear et al. 2007; Jayaram et al. 2012; Reis et al. 2008). Assuming that MEP amplitude adequately reflects the degree of spared descending cortico-spinal projections, such an assumption would seem reasonable, and a close relationship with functional impairment expected at least in patients with relatively focal subcortical lesions. In such patients, MEP amplitude indeed closely tracks the degree of impairment (Jayaram et al. 2012; Liepert et al. 2005; Perez and Cohen 2009c; Stinear et al. 2007; Swayne et al. 2008; Ward et al. 2007). It is also possible that the degree of temporal dispersion of cortico-spinal volleys is altered after stroke (and perhaps differently so after subcortical vs cortical strokes). In such patients, the amount of cortico-spinal volleys could be unaltered despite changes in MEP amplitudes. A normalization of MEP amplitude during functional recovery may thus reflect a change in the temporal dispersion profile rather than the amount of cortico-spinal volleys.

The relationship of MEPs to recovery and response to rehabilitation is more problematic both with respect to logic and to empirical data. If MEPs relate to impairment, then how can they also relate to recovery from impairment? This would mean that there would have to be a relationship of MEPs to recovery that is independent of their relationship to impairment, which would mean in turn that initial impairment is not itself a good predictor of final impairment. How would this work? It would have to mean that there is a latent undamaged component of the cortico-spinal tract stimulated by TMS that is not contributing to current impairment but is proportional to the part that is. Moreover, several mechanisms other than those commonly associated with variance in MEP amplitudes might also mediate recovery after stroke (see Barker et al. 2012 for discussion). For example, direct descending cortical pathways originating from other regions than the directly stimulated one may additionally influence spinal motoneuron pool excitability, and hence MEP size. Rarely, discussed is the possibility of indirect influences through changes in reafference generated by the altered voluntary movement (Barker et al. 2012). Unfortunately, there is a paucity of discussion regarding these mechanisms in the current literature.

Finally, MEP changes are likely to involve altered contributions from later I-waves as much as the circuits controlling earlier I-waves. This suggests that the relevant anatomical substrates may not just be within M1 but can also include altered trans-cortical projections to M1, or disruption of cortico-fugal axons. We shall revisit this issue later on, but we note that if these contributions come from regions involved in, and required for, the planning, selection, and timing of actions and motor learning, a correlation with (impaired) motor output is not implausible. To avoid possible confusion, even if modulation of MEP amplitude around a normal mean value has no effect on output, as we have suggested, this does not preclude an effect on output in the setting of lowered mean MEP, as occurs after stroke. Correlations with impairment do not, however, indicate whether changes in MEPs are in fact causally relevant for motor output, and the complex nature of MEPs makes increases in their amplitude in response to interventional rehabilitation procedures hard to interpret.

The pitfalls in interpreting particular sign changes in MEPs is well illustrated by turning to an influential interpretation of changes in contralesional MEP size following stroke (Murase et al. 2004; Perez and Cohen 2009a). At the core of this interpretation is the role of interhemispheric (transcallosal) inhibition (IHI) between the motor cortices for controlling movement. In healthy subjects, IHI is assessed by applying a conditioning TMS pulse to M1 in one hemisphere, and another suprathreshold pulse to the opposite hemisphere after around 5–10 ms (Ferbert et al. 1992). The common observation is that the presence of the conditioning pulse decreases the amplitude of the subsequent pulse (Kujirai et al. 1993), and in essence, it is this MEP amplitude decrease which is taken as indicative of interhemispheric inhibition. The critical observation is that IHI is abnormally maintained in patients with chronic subcortical stroke up to movement onset, whereas it decreases (or turns into facilitation) in healthy individuals (Murase et al. 2004). This result has led to the idea that abnormal interhemispheric inhibitory drive from the intact to the lesioned hemisphere plays a critical role in the paresis phenotype after stroke, and therefore reversing this inhibition may augment motor recovery.

While the basic observation of a difference in the IHI measure between patients and healthy controls is itself indicative of *something*, its mechanistic interpretation and functional relevance are both much harder to assess. Transcallosal projections are almost exclusively excitatory and glutamatergic, and therefore it would be important to know mechanistically whether the IHI effect is mediated by *decreased* excitatory drive or increased inhibition. In the latter case, IHI could be caused by an increase in contralesional intra-cortical inhibitory drive acting upon normal transcallosal glutamatergic projections, but also through an (abnormally) increased drive of excitatory transcallosal projections onto ipsilesional inhibitory interneurons.

Directly comparing the specific intra-cortical changes occurring in the ipsilesional and contralesional hemisphere, together with possible changes in transcallosal glutamatergic transmission could resolve this issue. Without such a distinction, MEP amplitude effects seen in IHI protocols in stroke patients may indeed correlate with the degree of hemiparesis but more detailed mechanistic explanation of this relationship will remain limited.

In sum, mechanistic inferences couched in the language of a balance of inhibitory and excitatory circuits, and how these may re-balance following intervention, are highly problematic and simplistic. Correlations of MEP changes with motor output do not imply that the underlying mechanism of the impairment has been revealed.

Changes in MEPs as read-out of the functional state the motor system

MEPs as read-out of the state of excitability of the stimulated motor cortex

Behaviours, such as action planning and selection (Bestmann et al. 2008; Soto et al. 2009; Tandonnet et al. 2010; Leocani et al. 2000; Hiraoka et al. 2010; Romaiguere et al. 1997; Sinclair and Hammond 2009; Hasbroucq et al. 1999; Duque and Ivry 2009; Galea et al. 2013; Klein-Flugge and Bestmann 2012; Klein-Flugge et al. 2013; Duque et al. 2014), experimental procedures, such as transcranial direct current stimulation (Nitsche et al. 2007; Nitsche and Paulus 2011) pharmacological agents (Ziemann 2004), and diseases, such as stroke (Butefisch et al. 2003; Oliviero et al. 2005), are known to change the size of the evoked EMG response, as well as its variability (Galea et al. 2013; Klein-Flugge et al. 2013).

Such condition-specific changes in MEPs can act as surrogate markers for physiological changes associated with different experimental manipulations or with specific disease states, but these MEP changes may not map directly onto the quality of motor output, or even map onto activity in M1 in a linear fashion. There is nothing to inform about the relevance of these MEP changes to actual motor behaviour or the quality of an ensuing action, even though there may be a correlation. In fact, this approach is agnostic about this issue, and it is not necessarily evident which underlying structures mediate the MEP change. In many cases, studies may in fact not address which specific anatomical circuits cause observed MEP changes, but solely take MEP changes as an index that the experimental manipulation has induced changes in the functional state of the motor system at the time the TMS pulse was applied. This would seem a valid conclusion and in many cases is likely to disclose relevant information, but a causal relationship to motor output is much harder to infer.

MEPs as a measure of input into rather than output from M1

Changes in MEP amplitude can reflect belief updates for forthcoming action plans that are broadcast from regions outside M1. In this view, M1 is now considered a recipient of 'pre-synaptic' decision processes occurring elsewhere (much like a 'beacon' receiving radio transmission). Processes related to action selection or decision-making occurring outside M1 exert this influence via (direct or indirect) inputs into motor and premotor cortex (Klein-Flugge and Bestmann 2012; Bestmann et al. 2008; Klein-Flugge et al. 2013). Whether such influence is meaningful or still epiphenomenal remains an open question, we also do not know which distal processes and pathways can and cannot influence MEP amplitude. A crucial question is whether changes in MEP amplitude reflect the 'what' of action selection or the "how" of action execution, i.e. parameters relating to the actual implementation of an action and its execution? But prior knowledge about anatomical connections and neural response profiles in motor and premotor cortices in principle allows for predictions about how the specific components of MEPs are influenced by different cognitive processes. If the case, then one would predict that late I-wave generating circuits are more sensitive to cognitive manipulations, whereas those generating early I-waves (and the D-wave) are less so, and possibly are more receptive to direct somatosensory inputs and motor learning-related processes occurring in M1.

Klein-Flugge and Bestmann have recently shown that MEP amplitude can indeed distinguish between chosen versus unchosen forthcoming actions some time before completion of the actual decision process driving this choice (Klein-Flugge and Bestmann 2012). In this study, the subjective values that participants assigned to the two choice options were inferred using cumulative prospect theory (cf. Klein-Flugge and Bestmann 2012, for details). This allows for estimating the parameters for subjective distortions of reward probability and reward magnitude that best explain the choice patterns made by participants. In the specific case, both excitability and reaction times varied as a function of the difference in subjective value that participants assigned to the ultimately chosen and unchosen options (i.e. how much more "worth" one option was over the other), already several 100 ms before that choice was expressed. This relationship was not observed when no value-based decision was required, and is consistent with the idea that changes in MEP size are driven by internally generated value-based decisions, already some time before the decision process is complete. This does not imply that motor cortex computes value comparisons. Instead, this is an example for MEP changes reflecting incoming evidence for one action over another, but that the computation of

this evidence or decision signal is taking place elsewhere. Additional lines of evidence furthermore suggest that transcortical pathways may be key contributors to MEP changes occurring during cognitive manipulations. MEP amplitude during action preparation and selection is influenced by cognitive processes not directly instantiated in M1, such as contextual uncertainty (Bestmann et al. 2008), value (Klein-Flugge and Bestmann 2012), or spatial attention (Mars et al. 2007).

Finally, some of the most compelling evidence for action-selection processes that occur outside of M1, but influence MEP size comes from so-called double-coil TMS experiments (Duque et al. 2012; Liuzzi et al. 2010; Civardi et al. 2001; Hasan et al. 2013; Koch et al. 2006, 2008; Buch et al. 2010; Neubert et al. 2011; Groppa et al. 2012). In these experiments, a conditioning TMS pulse is applied over a distal cortical site and its influence on MEP size assessed by a subsequent test pulse some milliseconds later. For example, using highly focal double-coil TMS with one stimulus applied over M1 and a subsequent pulse over ipsilateral PMd, Groppa, and colleagues demonstrated a task and effector-specific short-latency influence from PMd onto ipsilateral M1. More generally, double-coil studies demonstrate the influence of dorsal and ventral premotor, parietal, and prefrontal regions on M1. This influence varies as a function of the cognitive 'state' in these cortical regions, with very specific influences depending on the sites of stimulation, suggesting these areas broadcast task-relevant information to M1. This conclusion is supported by combined EEG–TMS studies, which demonstrate a close relationship between MEP amplitude and the lateralized readiness potential (Verleger et al. 2009). More generally, the use of tools such as EEG offer novel ways to study the mechanistic underpinnings of TMS-evoked responses (Bergmann et al. 2012), which can complement investigations of I-wave activity.

One question arising from these studies is whether the broadcasting of action-related evidence signals is specific to situations when there is a requirement for action, as opposed to global non-specific influences that merely trickle into the motor system irrespective of the underlying ongoing cognitive process. First, such influences are generally effector specific (e.g. Groppa et al. 2012; Bestmann et al. 2008; Klein-Flugge et al. 2013), thus eschewing non-specific changes relating to arousal or undirected attention, or generalization across effector muscles as explanations. Second, when processes such as value-based decisions are tied to action, MEP size co-varies with the expected value of that decision process, whereas such effects are not observed when such processes are not tied to a subsequent action (Klein-Flugge and Bestmann 2012).

Again, we emphasize none of these upstream cognitive influences reveal a causal relationship to the action itself. There are at least four reasons why such an inference can be troublesome. First, apart from the considerations discussed above including potential spinal mechanisms, the specific type of observed relationship between MEP changes and experimental variables of interest strongly depends on baseline recordings and control conditions. A positive relationship between MEP amplitude and a process of interest can sometimes be reversed simply by using different normalization strategies. For example, CSE measures obtained at rest do not control for task-related processes such as arousal, attention, or vigilance, and relative differences between such a baseline and MEPs recorded during an active task condition likely reflect a mixture of several processes. The exact net outcome (and therefore the direction of difference) can be difficult to predict. Put simply, a relative increase in MEP amplitude, when compared to rest, may turn into a relative decrease when compared to another point in time during, for example, preparation of an action. Second, the MEP is a multicomponent signal, and it may not always possible to attribute changes in amplitude to a specific variable of interest. For example, there may be a suppressive effect on MEPs during a preparatory delay period (relative to a resting baseline period) due to inhibitory processes that prevent premature or inappropriate responses (e.g. Duque et al. 2014). But additional effector-specific changes (for example, a relatively increase in CSE for the selected versus unselected action) may "ride on top" of this inhibition (see Duque and Ivry 2009; Duque et al. 2010, 2012 for discussion). Third, effector-specific MEP changes can have time-dependent interactions during the cause of a trial (e.g. delay period): whether CSE changes during that period will be above or below resting baseline values may depend on the specific time-point of a trial at which an MEP is elicited. Finally, differential MEP excitability for one action over another may reflect differences in the weighting of two goals and not the existence of two motor plans (Wong et al. 2014). We raise these points here to highlight the issue of 'sign-matching', whereby MEP increases are seen as direct reflection of "increased" processing or computations occurring in motor cortex.

Summary

Motor-evoked potentials provide insights into state-changes in the cortical motor system, both during simple motor behaviour and complex cognitive tasks. However, the multiple circuits contributing to MEPs make interpretation of changes in MEP amplitude difficult and constrain the types of mechanistic and causal inference that can be made when they are observed. Changes in cortico-spinal tract integrity, changes within M1, and top down influences by cognitive processes on M1, all can lead to changes in the amplitude

of MEPs, with very different implications for behaviour in health and disease. That said, specific stimulation protocols, such as paired-pulse stimulation, can begin to dissect differential contributions to the MEP. Thus, muscle-specific representations of state-changes can be detected, the specific level at which these changes occur identified (e.g. intracortical, transcortical, spinal), and even neuropharmacological fingerprints obtained. A thorough appreciation of how MEPs are generated and measured allows for their optimal use in providing a unique window into physiological state-changes in the human motor system during behaviour.

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