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Cortex Special Issue: *The Contribution of TMS to Structure-Function Mapping in the Human Brain. Action, Perception and Higher Functions.*

Editorial: On Tickling Brains to Investigate Minds

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Stimulating the brain by either direct or eddy electrical currents for medical and research purposes has a long history. One of the first records dates back to 43AD and is attributed to Scribonius Largus, physician of the Roman Empire, who reported the treatment of migraines and headache through application of electrical currents with the torpedo fish. In the 15th century, Paracelsus suggested that magnetic forces can promote self-healing, and in the 18th century French physician Charles Le Roy started to experiment with electricity as a means to influence psychological function. Although he did not succeed in restoring vision to a blind patient by winding conducting wires around the patient's head, he did manage to make him perceive vivid flashes of light (phosphenes). Non-invasive electrical stimulation, however, was associated with painful sensations and continued to be the main stimulation device for experimental and medical treatments even after the discovery, in the first half of the 19th century by Michael Faraday, that a changing magnetic field can induce an electric current in a conducting means. It was only with Jacques-Arsène d'Arsonval, at the end of the 19th century, and Silvanus Thompson at the beginning of the 20th, that the idea of using magnetic stimulation to induce eddy currents in the brain came to light, its majestic progression made possible by Anthony Barker and collaborators who, in 1976, developed the first reliable magnetic stimulator. In 1985 it was formally introduced as a modulator of brain function. Magnetic stimulators have now become widely available in both clinical as well as research institutions. Transient side-effects may include headache, neck ache and mild discomfort, but these are secondary effects not directly related to the cortical stimulation itself. A more serious concern is the possible induction of seizures. However, based on the available empirical data, the use of TMS for studies of cognition in healthy humans is safe, with concern only for stimulation protocols outside currently available safety guidelines.

The burgeoning interest in the technique is perhaps best reflected in the close to 5000 articles¹ that have been published in peer-reviewed scientific journals over the past 20 years (with more than 2800 published only in the last 5 years).

Transcranial Magnetic Fascination

This scientific success has been mirrored in a strong fascination about brain stimulation by the general public. Stimulating the brain with TMS has not only become a popular and valuable research tool, it furthermore has become the panacea for treating, curing, and manipulating diverse clinical conditions, such as depression, migraine, tinnitus, or stroke. TMS has consequently started to penetrate the mind of the public, and more and more people have heard about the ever-increasing number of pathologies that TMS can potentially treat and the attractive prospects of the technique for studying brain-mind relationships.

This enthusiasm for the technique and the impressive possibilities evidently suggested by it, however, often goes together with a perhaps overly optimistic view of what is possible. Take for example the popular TV series whose protagonist is a sociopathic MD, who only considers medical cases that nobody else would be able to solve. In one episode, a doctor moves a caricature TMS coil over a patient's head that is expected to cure what seems like an otherwise untreatable case of cluster headaches. In fact, the patient's symptoms do not disappear after the treatment thus disconfirming the initial diagnosis of cluster headaches (*The Jerk*, 23rd episode, 3rd

¹ Based on a PubMed search restricted to human studies and having 'Transcranial Magnetic Stimulation' as keyword

series of *House*). When TMS is operated over the left fronto-temporal cortex of a human, there is a good chance that you may turn someone into a savant-like nitwit (e.g. Osborne, 2003). And even better, install a TMS machine in a fighter plane in such a way that the stimulation coil rests over the pilots back of the brain. When the pilot gets tired and drowsy, exhausted from a good days worth of combat action, tickling the pilot's brain with some TMS may wake him up again. This would make him more effective a combatant, and indeed the US Defense Advanced Research Projects Agency (DARPA) (e.g. Nelson, 2007) is currently pursuing a programme aimed to test the feasibility of such TMS application. Much more wondrous yet is the recent claim that a man who had been in a coma for almost a year was successfully awoken by employing TMS

[\(http://www.redorbit.com/news/health/1589242/experimental_brain_treatment_used_to_wake_man_from_coma/\)](http://www.redorbit.com/news/health/1589242/experimental_brain_treatment_used_to_wake_man_from_coma/). And again, TMS may be used for evoking an eclectic range of physical and mental states, from mystical thoughts to a general feeling of well-being, sexual arousal, and extra-sensory experiences (e.g. Persinger, 1995). Perhaps the common theme in these examples is the fascination to control mental states and behaviour, in addition to reinstating health where illness is otherwise not treatable.

On the other hand, one may criticise TMS as being a blunt instrument; as imprecise because it has a comparatively poor spatial resolution; or even as pretty much useless because its precise mechanism of action remains to be determined, and because it causes a maelstrom of activity in the human brain (Jones, 2007). While, based on the available empirical data, the use of TMS for studies of cognition within currently available safety guidelines in healthy humans is safe, the (admittedly rare) occurrence of medically relevant side-effects and a certain media taste

for the sensational have also initiated renewed discussion about the possible ethical concerns of TMS (see e.g. Steven and Pascual-Leone, 2005, Knoch et al., 2007).

Both the dreamy possibilities as well as sometimes vitriolic rejections of TMS are extremes that fail to properly acknowledge and integrate what is known about how the technique interacts with cortical function. It is easy to dismiss the outright outrageous: Few researchers using TMS will seriously believe that TMS can transform humans into supermen (or nitwits), and one could think about countless better (and cheaper) ways to keep someone awake. As far as we know, TMS is certainly no better than drugs for treating comatose patients, and complex cognitive abilities or behaviours are unlikely to reside in a single node on a patch of cortical surface. Nevertheless, examples such as the ones above often capture the limelight and grab the public's attention. In most cases, such examples are met with broad reservation, even among people unfamiliar with the technique or research in general. Time will tell if these are foolish dreams or whether we, the editors, have simply failed to grasp the full potential of the technique. Perhaps, if the latter were the case, many more studies would have succeeded in manipulating minds beyond the subtle behavioural changes reported by the majority of cognitive TMS studies?

A more pressing concern pertains to the lacunae in our knowledge about how TMS affects brain activity, and the interpretational limitations this may bring about for cognitive TMS studies. Again, few researchers familiar with the technique will deny that the technique has limitations and that a lot of ground needs to be paved in order to fully understand its mechanism of action. It is important, however, to stress that currently it is the best method we have for investigating causal brain-behaviour relationships in the healthy human brain. And in our view,

powerful inferences about brain-behaviour relationships may not require a model about the cellular changes to TMS, however desirable such knowledge might be. A well-controlled double dissociation in a behavioural TMS experiment can often provide powerful inferences about the function of a tested brain region and about the architecture of mental processes. In some cases, however, the interpretation of dissociations between mental processes may be misled by a failure in understanding physiological effects.

The link between a change in behaviour (most commonly observed as a change in reaction times or error rates), and the corresponding physiological changes at the site of stimulation is often complex. A lot of detail is known about how TMS changes intracortical (or corticospinal) inhibition and excitation. But this knowledge may not be directly applicable to the interpretation of behavioural changes elicited by TMS. Our intuition is that a relationship between physiological and behavioural changes induced by TMS is often made because of a semantic fallacy. It seems tempting to connect an “inhibition” of behaviour with an inhibition in intracortical excitability. Vice versa, it may initially seem appealing to link an increase in excitability with an “increase”, or improvement, in performance. Yet very little is known about how these two observations relate to one another. It may be wrong to infer such relationships, and is perhaps even unnecessary. Knowing about the neural circuits that are targeted by TMS may not tell us that much more about cognition at a systems level, unless we know precisely how a change in behaviour relates to changes in neuronal inhibition and excitation. The behavioural consequences impinging from TMS to a cortical region are most likely a mixture of both inhibition and excitation: for example, the initial synchronisation of large swaths of neurons may be followed by a prolonged period of ongoing inhibitory post-synaptic potentials (IPSPs). When

it is intriguing to speculate about the link between the physiological effects of a TMS protocol and its behavioural consequences, several alternative possibilities should be considered. In some cases, the advent of combined TMS and neuroimaging or electrophysiological techniques can provide one way of directly testing the different ways in which TMS may interact with cortical processing, and hence behaviour (Bestmann et al., 2008; Sack and Linden, 2003; Taylor et al., 2008; Thut and Miniussi, 2009).

Another important aspect about the physiological underpinnings of TMS that has recently re-entered the focus of attention regards the state-dependence of TMS-induced neural activity, and how these relate to behaviour (Silvanto et al., 2009; Bestmann et al., 2007). The relative activation level of the targeted neural populations will shape the effects of TMS. This may provide a useful framework for studying cognitive functions using TMS (see also Sandrini and Rusconi, 2009), even though some of the physiological underpinnings of the state-dependence of TMS remain to be determined.

Knowing about how the activity of a region, or its state, determines the efficacy of a stimulation protocol may in principle also inform us about better experimental protocols and designs. Behavioural TMS experiments can suffer from a lack of degrees of freedom in the dependent variables and an inflation of possible independent variables (just think about the various stimulation parameters one can choose from). One can easily measure reaction times or error rates, or both, but compared to the seemingly endless possibilities of stimulation parameters, it is easy to imagine that many effects will simply go undetected. However, in many cases more powerful experiments may be designed by carefully controlling for differences in the

activation state of the stimulated brain region. One interesting proposal is to borrow concepts from other experimental approaches such as psychophysics. For example, signal-detection theory can in principle provide an interpretational framework for cognitive TMS studies, with the advantage of a well-described theoretical basis that may not always require substantial physiological data for linking behavioural to neural effects at the population level (Harris et al., 2009).

Sometimes experimenters may be asking questions that the technique simply cannot address. A thorough understanding about what is known the physical underpinnings and limitations of TMS is therefore imperative. For example, direct stimulation of subcortical structures is unlikely to be achieved or could only be done by stimulating everything above as well. On the other hand, more and more realistic head models provide more and more detailed information about the precise site of stimulation, and accurate targeting can now be guaranteed by the various ways of using frameless stereotaxy for neuronavigation. The implementation of Diffusion Tensor and Spectrum Imaging (DTI and DSI) data into neuronavigation systems will probably enable researchers to determine the optimal coil placement and orientation (therefore, induced current spread and direction) for each participant and improve stimulation effectiveness in a not so far future. The results from neuroimaging studies provide additional information about the candidate regions involved in a cognitive task – and TMS together with neuronavigation can now be used to accurately target these functional regions one by one to test for their relevance and necessity. How and if TMS does affect remote, and putatively interconnected brain regions, including subcortical structures, can now be tested through the combination of TMS with neuroimaging. Combinations with neuroimaging may help to explain

the effects of stimulation on entire networks in the brain, and how these relate to behaviour; but they may also reveal why sometimes stimulation of a region does not alter behaviour in cases when other regions show compensatory activity changes.

In the attempt to uncover the functions of the healthy human brain by testing causal models in healthy individuals TMS is currently unrivalled, and the only non-invasive technique available for cortical stimulation in man. However, it is increasingly becoming clear that some of the limitations of TMS need to be overcome in order to tap its full potential. In particular recent technical developments such as multi-coil arrangements (e.g. Koch et al., 2007), realistic head-models to estimate the induced currents in the brain (e.g. Wagner et al., 2004), and the combination of TMS with neuroimaging techniques (e.g. Bestmann et al., 2008) will lead towards a deeper understanding of the physiological underpinnings of TMS and the networks targeted by stimulation of a cortical region. Such developments will help to secure a significant role for TMS in the cognitive neurosciences, in providing more fine-grained inferences about the functional specialisation of different brain regions, but also in enabling us to go beyond modular accounts of cognition by considering causal interactions within cortical networks.

This special issue and beyond

This special issue provides an overview about the current role of TMS for studies of cognition. In that, we bring together several key researchers that have explored the neural underpinnings of TMS as well as used the technique for obtaining unique insights into cognitive processing of the human brain. A specific aim was to have several methodological and physiological reviews, with a specific focus on implications for cognitive TMS studies, and on highlighting some of the important limitations of the technique for studies of cognition (Wagner

et al., this issue; Siebner et al., this issue; Ruff et al., this issue). These articles precede and complement the topical reviews and empirical contributions showing the various facets in which TMS can be used for studying cognition in the healthy human brain. Clearly, one special issue cannot embrace the variety of questions that have been addressed with TMS. This issue therefore focuses on some of the domains in which TMS has had a particularly prosperous contribution: sensorimotor systems (Perez et al., this issue; Romei et al., this issue; Davare et al., this issue; Avenanti et al., this issue), language (Stoeckel et al., this issue; Harpaz et al., this issue; Pobric et al., this issue; Schuhmann et al., this issue), and visuo-spatial attention (Kalla et al., this issue). We also felt that within these domains of cognitive TMS studies it was overdue to have a comprehensive review on the use of TMS for studying somatosensory processing and body representation (Azañon and Haggard, this issue).

The articles in this special issue are complemented by brief Opinion papers and critical reappraisals from additional leading experts in the fields about several issues and questions that seemed important to address: the importance and limitations of neuronavigation (Sparing et al., in press), going beyond a simple virtual lesion model (Miniussi et al., in press; Ziemann, in press), the important role for causal studies in cognition (Postle and Feredoes, in press), and the contribution of TMS for understanding visual awareness (Ro, in press) and selective attention and multisensory integration (Chambers and Heinen, in press). While space constraints required publication of these articles in a separate forthcoming issue of *Cortex*, these opinion papers often directly refer to specific articles in this issue.

We hope the reader will enjoy the contributions to this special issue as much as we did, and get useful insights from them. As Guest Editors, we greatly thank all the authors and reviewers for their contribution.

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7 dissociation in a behavioural TMS experiment can often provide powerful inferences about the
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9 function of a tested brain region and about the architecture of mental processes. In some cases,
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11 however, the interpretation of dissociations between mental processes may be misled by a
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13 failure in understanding physiological effects.
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19 The link between a change in behaviour (most commonly observed as a change in
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21 reaction times or error rates), and the corresponding physiological changes at the site of
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23 stimulation is often complex. A lot of detail is known about how TMS changes intracortical (or
24
25 corticospinal) inhibition and excitation. But this knowledge may not be directly applicable to the
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27 interpretation of behavioural changes elicited by TMS. Our intuition is that a relationship
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29 between physiological and behavioural changes induced by TMS is often made because of a
30
31 semantic fallacy. It seems tempting to connect an “inhibition” of behaviour with an inhibition in
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33 intracortical excitability. Vice versa, it may initially seem appealing to link an increase in
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35 excitability with an “increase”, or improvement, in performance. Yet very little is known about
36
37 how these two observations relate to one another. It may be wrong to infer such relationships,
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39 and is perhaps even unnecessary. Knowing about the neural circuits that are targeted by TMS
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41 may not tell us that much more about cognition at a systems level, unless we know precisely how
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43 a change in behaviour relates to changes in neuronal inhibition and excitation. The behavioural
44
45 consequences impinging from TMS to a cortical region are most likely a mixture of both
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47 inhibition and excitation: for example, the initial synchronisation of large swaths of neurons may
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49 be followed by a prolonged period of ongoing inhibitory post-synaptic potentials (IPSPs). When
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3 it is intriguing to speculate about the link between the physiological effects of a TMS protocol
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5 and its behavioural consequences, several alternative possibilities should be considered. In some
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7 cases, the advent of combined TMS and neuroimaging or electrophysiological techniques can
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9 provide one way of directly testing the different ways in which TMS may interact with cortical
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11 processing, and hence behaviour (Bestmann et al., 2008; Sack and Linden, 2003; Taylor et al.,
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13 2008; Thut and Miniussi, 2009).
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19 Another important aspect about the physiological underpinnings of TMS that has recently
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21 re-entered the focus of attention regards the state-dependence of TMS-induced neural activity,
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23 and how these relate to behaviour (Silvanto et al., 2009; Bestmann et al., 2007). The relative
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25 activation level of the targeted neural populations will shape the effects of TMS. This may
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27 provide a useful framework for studying cognitive functions using TMS (see also Sandrini and
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29 Rusconi, 2009), even though some of the physiological underpinnings of the state-dependence of
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31 TMS remain to be determined.
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39 Knowing about how the activity of a region, or its state, determines the efficacy of a
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41 stimulation protocol may in principle also inform us about better experimental protocols and
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43 designs. Behavioural TMS experiments can suffer from a lack of degrees of freedom in the
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45 dependent variables and an inflation of possible independent variables (just think about the
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47 various stimulation parameters one can choose from). One can easily measure reaction times or
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49 error rates, or both, but compared to the seemingly endless possibilities of stimulation
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51 parameters, it is easy to imagine that many effects will simply go undetected. However, in many
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53 cases more powerful experiments may be designed by carefully controlling for differences in the
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3 activation state of the stimulated brain region. One interesting proposal is to borrow concepts
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5 from other experimental approaches such as psychophysics. For example, signal-detection theory
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7 can in principle provide an interpretational framework for cognitive TMS studies, with the
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9 advantage of a well-described theoretical basis that may not always require substantial
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11 physiological data for linking behavioural to neural effects at the population level (Harris et al.,
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13 2009).
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19 Sometimes experimenters may be asking questions that the technique simply cannot
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21 address. A thorough understanding about what is known the physical underpinnings and
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23 limitations of TMS is therefore imperative. For example, direct stimulation of subcortical
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25 structures is unlikely to be achieved or could only be done by stimulating everything above as
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27 well. On the other hand, more and more realistic head models provide more and more detailed
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29 information about the precise site of stimulation, and accurate targeting can now be guaranteed
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31 by the various ways of using frameless stereotaxy for neuronavigation. The implementation of
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33 Diffusion Tensor and Spectrum Imaging (DTI and DSI) data into neuronavigation systems will
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35 probably enable researchers to determine the optimal coil placement and orientation (therefore,
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37 induced current spread and direction) for each participant and improve stimulation effectiveness
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39 in a not so far future. The results from neuroimaging studies provide additional information
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41 about the candidate regions involved in a cognitive task – and TMS together with
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43 neuronavigation can now be used to accurately target these functional regions one by one to test
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45 for their relevance and necessity. How and if TMS does affect remote, and putatively
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47 interconnected brain regions, including subcortical structures, can now be tested through the
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49 combination of TMS with neuroimaging. Combinations with neuroimaging may help to explain
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3 the effects of stimulation on entire networks in the brain, and how these relate to behaviour; but
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5 they may also reveal why sometimes stimulation of a region does not alter behaviour in cases
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7 when other regions show compensatory activity changes.
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10 In the attempt to uncover the functions of the healthy human brain by testing causal
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12 models in healthy individuals TMS is currently unrivalled, and the only non-invasive technique
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14 available for cortical stimulation in man. However, it is increasingly becoming clear that some of
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16 the limitations of TMS need to be overcome in order to tap its full potential. In particular recent
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18 technical developments such as multi-coil arrangements (e.g. Koch et al., 2007), realistic head-
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20 models to estimate the induced currents in the brain (e.g. Wagner et al., 2004), and the
21
22 combination of TMS with neuroimaging techniques (e.g. Bestmann et al., 2008) will lead
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24 towards a deeper understanding of the physiological underpinnings of TMS and the networks
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26 targeted by stimulation of a cortical region. Such developments will help to secure a significant
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28 role for TMS in the cognitive neurosciences, in providing more fine-grained inferences about the
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30 functional specialisation of different brain regions, but also in enabling us to go beyond modular
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32 accounts of cognition by considering causal interactions within cortical networks.
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41 *This special issue and beyond*

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43 This special issue provides an overview about the current role of TMS for studies of
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45 cognition. In that, we bring together several key researchers that have explored the neural
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47 underpinnings of TMS as well as used the technique for obtaining unique insights into cognitive
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49 processing of the human brain. A specific aim was to have several methodological and
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51 physiological reviews, with a specific focus on implications for cognitive TMS studies, and on
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53 highlighting some of the important limitations of the technique for studies of cognition (Wagner
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3 et al., this issue; Siebner et al., this issue; Ruff et al., this issue). These articles precede and
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5 complement the topical reviews and empirical contributions showing the various facets in which
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7 TMS can be used for studying cognition in the healthy human brain. Clearly, one special issue
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9 cannot embrace the variety of questions that have been addressed with TMS. This issue therefore
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11 focuses on some of the domains in which TMS has had a particularly prosperous contribution:
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13 sensorimotor systems (Perez et al., this issue; Romei et al., this issue; Davare et al., this issue;
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15 Avenanti et al., this issue), language (Stoeckel et al., this issue; Harpaz et al., this issue; Pobric et
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17 al., this issue; Schuhmann et al., this issue), and visuo-spatial attention (Kalla et al., this issue).
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19 We also felt that within these domains of cognitive TMS studies it was overdue to have a
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21 comprehensive review on the use of TMS for studying somatosensory processing and body
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23 representation (Azañon and Haggard, this issue).
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29 The articles in this special issue are complemented by brief Opinion papers and critical
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31 reappraisals from additional leading experts in the fields about several issues and questions that
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33 seemed important to address: the importance and limitations of neuronavigation (Sparing et al.,
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35 in press), going beyond a simple virtual lesion model (Miniussi et al, in press; Ziemann, in
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37 press), the important role for causal studies in cognition (Postle and Feredoes, in press), and the
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39 contribution of TMS for understanding visual awareness (Ro, in press) and selective attention
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41 and multisensory integration (Chambers and Heinen, in press). While space constraints required
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43 publication of these articles in a separate forthcoming issue of *Cortex*, these opinion papers often
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45 directly refer to specific articles in this issue.
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50 We hope the reader will enjoy the contributions to this special issue as much as we did,
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52 and get useful insights from them. As Guest Editors, we greatly thank all the authors and
53
54 reviewers for their contribution.
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