

Elsevier Editorial System(tm) for CORTEX
Manuscript Draft

Manuscript Number: CORTEX-D-08-00266R2

Title: Does TMS need functional imaging?

Article Type: Commentary

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Response to Reviewers: To be published as a commentary following the Rusconi and Bestmann
Special Issue

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Maastricht, 02.12.2008

Dear Dr. Rusconi and Dr. Della Sala,

Please find enclosed my invited commentary "*Does TMS need functional imaging?*" regarding the review article by Ruff et al. entitled "*Combining TMS and fMRI: From virtual lesions to functional-network accounts of cognition*", to be published in the Cortex Special Issue "*The Contribution of TMS to Structure-Function Mapping in the Human Brain - Action, Perception and Higher Functions*"; guest editors Elena Rusconi and Sven Bestmann.

In my commentary I highlight the importance and the particular scientific value of concurrent TMS & fMRI studies, but also argue that despite the recent evidence derived from simultaneous TMS & fMRI regarding the functional relevance of its indirect neural effects, a valuable and conclusive TMS study does by no means depend on functional imaging.

Yours sincerely,

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Does TMS need functional imaging?

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For centuries, scientists have aimed to establish causal relationships between neural activity in a discrete region of the brain and a particular behavioural or cognitive function. The possibility of TMS to transiently disrupt local neural activity non-invasively in healthy conscious human volunteers and reveal a subsequent inability to perform a particular behaviour has led to its rise as a unique research tool for revealing such causal brain-behaviour relationships. The simultaneous combination of TMS with functional magnetic resonance imaging (fMRI) promises to be of particular great value for our understanding of the human brain, as it provides the opportunity to stimulate a particular brain region while simultaneously monitoring whole-brain changes in brain activity, thereby allowing for causal brain-behaviour inferences across the entire brain. Following the pioneering work of Bohning et al. (1998), a small number of research groups have continued to establish the technical feasibility of applying TMS inside the MR scanner. Since such simultaneous combinations impose great technical challenges, until today only few research groups worldwide have been able to routinely realize concurrent TMS and fMRI studies.

In the special issue of Cortex on “*The Contribution of TMS to Structure-Function Mapping in the Human Brain: Action, Perception and Higher Functions*”, one of the most productive and influential of these research groups provides a timely and

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informative review article entitled “*Combining TMS and fMRI: From 'virtual lesions' to functional network accounts of cognition*”. In their review, Ruff et al. (2009) focus on simultaneous TMS and fMRI studies with the specific aim to investigate inter-regional interactions in the human brain and their possible functional consequences for perception and cognition. The authors’ outline of these TMS and fMRI studies seems to converge to the following three main conclusions: i) focal TMS applied to a particular brain region has both local and remote neural effects in the brain; ii) these local and remote neural effects of TMS are state-dependent, and iii) the state-dependent remote neural effects of TMS may be functionally relevant for behaviour.

Especially the last conclusion seems to pose severe limitations for the interpretation of behavioural TMS studies, i.e. TMS without imaging. In essence, it questions the notion that TMS effects on perception and cognition solely reflect local cortical effects below the TMS coil. Indeed, empirical evidence for the functional relevance of the indirect neural effects of TMS stems, e.g., from an elegant study conducted by Ruff et al. (2006). The authors applied TMS over right FEF inside the MR scanner and revealed remote BOLD effects in two bilateral sets of occipital brain regions within retinotopic visual areas V1-V4. Right FEF-TMS led to BOLD increases for peripheral visual field representations but BOLD decreases for the central visual field. Assuming that higher BOLD signals equal higher contrast sensitivity, the authors concluded that FEF-TMS may enhance peripheral relative to central vision, and in fact confirmed this prediction in a subsequent psychophysical experiment where perceived contrast was enhanced for peripheral relative to central Gabor gratings during right-FEF TMS. This study not only demonstrates how TMS may lead to spatially-specific remote neural effects which are functionally relevant for perception and cognition, but exemplifies how these remote neural consequences of

1 TMS as revealed by concurrent fMRI can be used to generate new predictions for
2 behavioural TMS studies outside the MR scanner. In a similar vein, our own group
3 recently showed that simultaneous TMS and fMRI during active task execution may
4 hold the potential for an in-vivo imaging of the neural network effects underlying
5 TMS-induced behavioural changes. We applied TMS over respectively right and left
6 parietal cortex inside the MR scanner during whole-brain BOLD fMRI of spatial
7 cognition performances in order to concurrently observe its behavioural and neural
8 effects in the active human brain. Our results show that right, but not left, parietal
9 TMS (1) behaviourally impairs spatial cognition, (2) induces neural activity changes
10 in a larger right-hemispheric network of fronto-parietal regions, and (3) shows
11 significant correlations between TMS-induced behavioural impairments and neural
12 activity changes in both the directly stimulated parietal and ipsilateral frontal brain
13 regions. Our findings thus strongly suggest that neural activity in both the stimulated
14 right superior parietal lobule (SPL), but also the remote ipsilateral middle frontal
15 gyrus (MFG) were influenced by right parietal TMS, and contributed to the reduction
16 in spatial cognition performance (Sack et al., 2007).
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39 Behavioural TMS studies without imaging often seem to neglect such possible
40 TMS-induced processing changes in remote brain regions. As a consequence, they do
41 not consider that the perceptual and behavioural effects of TMS may be caused by
42 TMS-induced influences on remote interconnected brain regions rather than solely on
43 the stimulated region itself. Alternatively, neither local nor remote activity changes
44 may per se be exclusively relevant for successful task execution, but instead the
45 disruption of effective connectivity, i.e., task-specific cross-talk between different
46 nodes of the network sustaining the task may cause the behavioural effect. In any
47 event, it appears that the conclusions derived from concurrent TMS and fMRI studies
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1 indicate a new conceptualization of TMS that goes beyond strictly modular views of
2 brain function towards new perspectives on how functional interactions between
3 remote but interconnected brain regions may support perception and cognition.
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7 Consequently, one may critically ask whether behavioural TMS studies without
8 imaging can still be considered as valid empirical tools for revealing the functional
9 necessity of the stimulated brain region. The simple answer is: Yes! Although it
10 seems intuitive to interpret the revealed remote neural effects of TMS as functionally
11 relevant, none of the above mentioned concurrent TMS and fMRI studies provide the
12 necessary conclusive evidence that would justify such an interpretation. Regarding
13 our own study, although parietal TMS affected neural activity in remote frontal
14 regions in a task-specific manner and although these remote effects were significantly
15 correlated to the TMS-induced task impairments, any causal interpretation of this
16 relationship would make the same epistemological faux pas of mixing up correlation
17 with causality which brought us from imaging to TMS in the first place. In fact, there
18 are several alternative interpretations for the described relation between TMS-induced
19 remote neural activity changes and affected behaviour, ranging from remote changes
20 being the consequence of altered behaviour rather than its driving cause to incidental
21 co-variations driven by different physiological processes. In essence, we are left with
22 the problem we started out with, i.e. to empirically disentangle those neural activity
23 changes that are causally related to the behavioural effect from those neural activity
24 changes that are not functionally involved in causing changes in behaviour. A related
25 limitation refers to the study by Ruff et al. (2006). Although it seems intuitive to
26 conclude that the changes in peripheral contrast perception following right FEF-TMS
27 are caused by the FEF-TMS-induced remote activity changes in early visual areas,
28 there is no direct evidence for this interpretation of affected perception to be due to
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1 changes in low-level vision. In essence, the only way to empirically address the
2 question whether the revealed remote brain activity changes are indeed functionally
3 relevant for perception or cognition would be to target these remote brain regions
4 directly by TMS in order to disrupt the underlying neural activity and measure
5 respective changes in behavioural performances. This can “easily” be done in a
6 classical behavioural TMS study outside the MR scanner. For our own study this
7 means that if we wanted to make any claim regarding the functional role of right MFG
8 for spatial cognition, there would be no way around using TMS over MFG and
9 measure the behavioural consequences. No concurrent TMS and fMRI design and no
10 sophisticated analytical framework of identifying the neural network connectivity
11 effects of TMS can ever replace or overcome this simple epistemological theorem.
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27 In this sense, I agree with the authors and want to strongly emphasize their notion
28 that simultaneous TMS and fMRI should be regarded as a complementary approach to
29 behavioural TMS studies, helping to refine the causal topography of structure-
30 function relationships across the entire brain by identifying new potential candidate
31 target areas for TMS within a functionally relevant brain connectivity network. The
32 scientific value and capability of TMS to reveal functional brain-behaviour
33 relationships in the absence of functional imaging has, however, been demonstrated in
34 countless well-conducted behavioural TMS studies. Ellison et al. (2007), for example,
35 applied TMS over posterior parietal cortex (PPC) and/or V5 during the execution of
36 two visual search tasks: color/orientation conjunction versus motion/orientation
37 conjunction. The two TMS stimulations sites, PPC and V5, were identified without
38 functional imaging by using a functional hunting procedure during which several
39 trials of TMS are applied to each site of a pre-defined grid of target points on the
40 participant’s scalp with the hotspot being identified as the site where the stimulation
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1 leads to respective behavioural changes in an appropriate diagnostic task (e.g., PPC =
2 TMS-induced reaction time increase in a hard conjunction task; V5 = TMS-induced
3 moving phosphenes). The authors revealed a clear functional double dissociation in
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5 which right PPC-TMS significantly impairs processing of the colour/orientation
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7 conjunction but not the motion/orientation conjunction search task, whereas the
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9 opposite pattern is seen with TMS over V5. In addition, by revealing that stimulating
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11 both sites with a dual-site TMS approach leads to an super additive effect on
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13 performance in the motion/orientation conjunction task, this study nicely exemplifies
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15 how dual-site TMS can go beyond the identification of crucial brain areas and help to
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17 uncover the interaction and the specific roles of different areas within a functional
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19 network.
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27 In conclusion, there is no question that it is sensible to combine TMS with fMRI,
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29 and that it is highly valuable to visualize and measure exactly where we stimulate and
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31 what local and remote neural activity changes we induce by applying TMS to a
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33 certain brain region. In fact, the ability to measure and relate these local and remote
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35 neural effects of TMS and their task-specific effective brain connectivity pattern to
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37 changes in perception and cognition, may indeed refine our conclusions how
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39 interactions between components of extended networks may support cognition,
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41 perception and behaviour. However, it is just as important to emphasize that although
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43 the combination of TMS with fMRI has great scientific value, conducting a valuable
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45 and conclusive TMS study to reveal functional brain-behaviour relationships does by
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47 no means depend on it.
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