

Hemispheric asymmetries in fronto-parietal networks underlying attentional control

Citation for published version (APA):

Duecker, F. (2013). *Hemispheric asymmetries in fronto-parietal networks underlying attentional control*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20131122fd>

Document status and date:

Published: 01/01/2013

DOI:

[10.26481/dis.20131122fd](https://doi.org/10.26481/dis.20131122fd)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Chapter 7

Summary and Conclusions

The work described in this thesis is subdivided into two parts. In the first part, we used transcranial magnetic stimulation (TMS) to investigate hemispheric asymmetries in fronto-parietal networks underlying attentional control. In the second part, we focused on methodological aspects of TMS that are of particular importance in attention research but also have a bearing on TMS methodologies in general. In the following, we summarize the main findings of this thesis and discuss the implications of our work.

Hemispheric Asymmetries in Fronto-Parietal Networks

The simple fact that spatial neglect is more common and severe after damage to the right hemisphere has led to a long-standing debate in cognitive neuroscience regarding the mechanisms underlying attentional control (Corbetta & Shulman, 2011; Heilman & Abell, 1980; Kinsbourne, 1977; Mesulam, 1981). Today, this discussion is as lively as ever and there are three competing theories offering very different explanatory approaches. A detailed overview of these theories is provided in the general introduction of this thesis. Most importantly, they all predict hemispheric asymmetries in either dorsal or ventral fronto-parietal networks. While neuroimaging studies deserve all the credit for identifying these networks and their general functions (Corbetta & Shulman, 2002), it has been proven difficult to assess the precise functional roles of the brain areas constituting these networks (Corbetta & Shulman, 2011). In particular, hemispheric asymmetries have been rarely reported making it difficult to decide between competing theories of attentional control. In the last decade, TMS has provided a new perspective on hemispheric asymmetries especially in posterior parietal brain regions. The vast majority of studies report evidence in favor of Kinsbourne's "opponent processor" model (Kinsbourne, 1977) with impaired task performance commonly found only in the visual field contralateral to the hemisphere that was disrupted by TMS (Dambeck et al., 2006; Hilgetag, Theoret, & Pascual-Leone, 2001; Silvanto, Muggleton, Lavie, & Walsh, 2009). Moreover, there are indications for inter-hemispheric competition, e.g., with bilateral TMS having no effect instead of the combined effects one could expect based on unilateral stimulation (Dambeck et al., 2006). However, frontal brain areas

have received far less attention and the existing work only confirmed their general involvement in attentional control but failed to reveal hemispheric asymmetries specific to shifts of spatial attention (Grosbras & Paus, 2002; Muggleton, Juan, Cowey, & Walsh, 2003; Silvanto, Lavie, & Walsh, 2006; Smith, Jackson, & Rorden, 2005).

In *Chapter 2*, we show for the first time that right and left frontal eye field (FEF) have functional properties that are in agreement with Heilman's "hemispacial" theory (Heilman & Abell, 1980). Using a "virtual lesion" approach, we demonstrate that the right FEF mediates attention shifts to both hemifields whereas the left FEF only mediates attention shifts to the right hemifield. It therefore appears that the two models of attentional control as proposed by Kinsbourne and Heilman are not mutually exclusive. Instead, Kinsbourne's "opponent processor" model seems to apply to parietal cortex whereas Heilman's "hemispacial" theory seems to apply to frontal cortex. This finding is of direct relevance for current functional-anatomical models of attentional control.

In *Chapter 3*, we set out to extend our work over frontal cortex to posterior regions of the dorsal and ventral fronto-parietal network. Applying the same experimental design that has shown to be successful in our previous study, we aimed to investigate whether the above mentioned functional difference between frontal and parietal cortex indeed reflect general hemispheric asymmetries within the dorsal network or can be explained by other experimental factors such as task or TMS parameters. Moreover, we also applied TMS over the ventral network in order to examine its right-lateralization and interactions with the dorsal network as recently put forward by Corbetta and Shulman (Corbetta & Shulman, 2011). Unfortunately, a suboptimal TMS coil positioning approach based on Talairach coordinates and high within-subject variability severely compromised the experiment leading to a null result. Despite this disappointing outcome, the research questions addressed here remain highly relevant and we are currently planning follow-up studies.

Taken together, the main finding of these content-driven chapters is that Heilman's "hemispacial" theory should not be discarded despite the strong evidence in favor of Kinsbourne's "opponent processor" model in parietal cortex. The existing evidence clearly suggests that different hemispheric asymmetries coexist

within the dorsal network. Potentially the most important implication of this finding is that understanding spatial neglect is more complex than one might have initially thought. With Kinsbourne's "opponent processor" model receiving so much support, the last years have seen a strong interest to apply TMS not only as a research tool but also as a possible way to promote recovery in neglect patients after stroke (Alonso-Alonso, Fregni, & Pascual-Leone, 2007; Bashir, Mizrahi, Weaver, Fregni, & Pascual-Leone, 2010; Koch et al., 2012; Miniussi et al., 2008). Based on the principle of inter-hemispheric competition, the potential of non-invasive brain stimulation techniques has been explored by either directly "boosting" the lesioned hemisphere or by suppressing the contralesional hemisphere thereby reducing its inhibitory effect creating room for recovery. Obviously, the latter approach only makes sense in the context of Kinsbourne's "opponent processor" model. Thus far, clinical TMS studies have only applied this rationale to parietal cortex, matching the empirically discovered hemispheric asymmetries. Our results indicate that a simple transfer of these principles to frontal cortex might be ineffective because the underlying functional organization is different from parietal cortex. As a consequence, the present findings contribute to creating an evidence base for proper TMS interventions that are tailored to the specific functional network and brain area.

Methodological Aspects of TMS research

The content-driven experiments described in the first part of this thesis have also inspired work on methodological aspects of TMS research. An important prerequisite for investigating the behavioral consequences of TMS-induced brain activity changes is accurate TMS coil positioning. Only then, it is possible to reveal structure-functional relationships and to observe any TMS effect in the first place. The importance of accurate TMS coil positioning has been demonstrated empirically (Sack et al., 2009) with effect sizes being highest when using individual functional localization based on neuroimaging data. We used this approach for identifying TMS target points in chapter 2 and successfully interfered with attentional processes. In chapter 3, however, we had to rely on a suboptimal approach based on individual anatomical data in combination with Talairach coordinates from the

literature. In our view, this was a main reason for why we did not observe any TMS effect. There are many situations where individual functional data cannot be obtained and, for that reason, it is crucial to make best use of that data available. In *Chapter 4*, we presented a novel method for TMS coil position that only requires anatomical data for each participant but outperforms alternative approaches such as targeting based on Talairach coordinates. This so-called CBA-based approach relies on advanced whole-brain alignment schemes that exploit curvature information of the cortical surface in order to remove macro-anatomical variability across subjects (Fischl, Sereno, & Dale, 1999; Frost & Goebel, 2012). We show empirically that the CBA-based approach significantly improves localization of functional brain areas compared to traditional Talairach-based targeting. Given the widespread availability of cortex-based alignment schemes, the proposed procedure is easy to implement and at no additional measurement costs. Thus, our CBA-based approach for TMS coil positioning should be the method of choice either when individual functional data cannot be obtained or experimental factors argue against it (e.g. training or surprise effects).

In the final two chapters of this thesis, we explored the non-neural side effects of TMS. The clicking sound of the TMS coil and sensations on the head that accompany every TMS pulse create a strong need for appropriate control conditions in order to make sure that effects of interest are indeed the result of the intended brain activity changes. Surprisingly, there is hardly any empirical knowledge regarding the non-neural effects of TMS in the context of a given task performance. It is often assumed that these effects are unspecific, that is, they do not depend on TMS parameters such as stimulation site or time point of stimulation. In this thesis, we have challenged this assumption on empirical grounds. In *Chapter 5*, we showed that the clicking sound of a sham TMS coil can systematically influence task performance when applied prior to target appearance. Specifically, we observed facilitation of reaction times dependent on the TMS time window and TMS coil position due to a warning signal effect and exogenously triggered shifts of spatial attention, respectively. In *Chapter 6*, we showed that these facilitatory effects of pre-stimulus sham TMS generalize to a more complex task that involves higher cognitive functions and requires a more complex stimulus response mapping.

Moreover, we found non-neural effects during post-stimulus TMS time windows with reaction times being slowed down because participants seem to ‘wait’ for the TMS pulse. Finally, we observed a non-neural effect on accuracies that depended not only on TMS time window and task but was stronger when applying real TMS over vertex compared with sham TMS. This difference clearly shows that both auditory and somato-sensory effects can have an influence on task performance with sham TMS only mimicking the former but not the latter side effect of TMS. This complex interplay of several factors emphasizes that the non-neural effects of TMS need to be carefully considered when designing an experiment and interpreting the data. Our results create an empirical basis of control strategies in TMS research and point at potential pitfalls that should be avoided. Importantly, based on our results, we advise to follow one general rule that should result in a well-controlled TMS experiment: TMS control conditions should always be orthogonal to the TMS factor of interest! To give an example, when using TMS chronometrically in order to reveal when a brain area is relevant for task performance, it is insufficient to directly compare different TMS time windows because differences between them might simply result from the non-neural effects of TMS. Instead, a separate control condition is required that also applies TMS during all time windows. Since we have shown task performance depends not only on the time point of stimulation but also the position of the TMS coil, the experimental task, and the presence of both auditory and somato-sensory effects, it is strongly advised to apply this reasoning to all common control strategies in TMS research. Finally, there is an experimental dilemma because it might not always be possible to control for all these possible confounders. Specifically, current sham TMS coils fail to mimic the sensations on the head when a TMS pulse is administered whereas any control conditions that makes use of real TMS necessarily has to be applied to another brain area so that the exact TMS coil position is no longer identical across TMS conditions. In the end, these factors have to be carefully considered in the light of the specific research question and experimental paradigm. Nevertheless, the current work not only increases awareness of these issues but is a first steps towards the empirical foundations of control strategies in TMS research.

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