



**HAL**  
open science

## **Perturbation-driven paradoxical facilitation of visuo-spatial function: Revisiting the ‘Sprague effect’**

Antoni Valero-Cabré, Monica N Toba, Claus C Hilgetag, R. Jarrett Jarrett Rushmore

### ► **To cite this version:**

Antoni Valero-Cabré, Monica N Toba, Claus C Hilgetag, R. Jarrett Jarrett Rushmore. Perturbation-driven paradoxical facilitation of visuo-spatial function: Revisiting the ‘Sprague effect’. *Cortex*, 2019, 122 (7), pp.10-39. 10.1016/j.cortex.2019.01.031 . hal-02415202

**HAL Id: hal-02415202**

**<https://hal.science/hal-02415202>**

Submitted on 29 Nov 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Manuscript Number: CORTEX-D-18-00588R1

Title: Perturbation-driven paradoxical facilitation of visuo-spatial function: revisiting the 'Sprague effect'.

Article Type: SI- In Honour of Dr Robert Rafal

Keywords: Sprague effect, paradoxical lesion effects, visuo-spatial attention, lesion inference, functional restoration, neglect

Corresponding Author: Dr. Monica N. Toba, PhD

Corresponding Author's Institution: University of Picardy Jules Verne

First Author: Antoni Valero-Cabre

Order of Authors: Antoni Valero-Cabre; Monica N. Toba, PhD; Claus C Hilgetag; Jarrett Rushmore

Abstract: The 'Sprague Effect' described in the seminal paper of James Sprague (Science 153:1544-1547, 1966a) is an unexpected paradoxical effect in which a second brain lesion reversed functional deficits induced by an earlier lesion. It was observed initially in the cat where severe and permanent contralateral visually guided attentional deficits generated by the ablation of large areas of the visual cortex were reversed by the subsequent removal of the superior colliculus (SC) opposite to the cortical lesion or by the splitting of the collicular commissure. Physiologically, this effect has been explained in several ways - most notably by the reduction of the functional inhibition of the ipsilateral SC by the contralateral SC, and the restoration of normal interactions between cortical and midbrain structures after ablation. In the present review, we aim at reappraising the 'Sprague Effect' by critically analyzing studies that have been conducted in the feline and human brain. Moreover, we assess applications of the 'Sprague Effect' in the rehabilitation of visually guided attentional impairments by using non-invasive therapeutic approaches such as transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS). We also review theoretical models of the effect that emphasize the inhibition and balancing between the two hemispheres and show implications for lesion inference approaches. Last, we critically review whether the resulting inter-hemispheric rivalry theories lead toward an efficient rehabilitation of stroke in humans. We conclude by emphasizing key challenges in the field of 'Sprague Effect' applications in order to design better therapies for brain-damaged patients.



## Perturbation-driven paradoxical facilitation of visuo-spatial function:

### Revisiting the ‘Sprague effect’

Antoni Valero-Cabre<sup>1,2\*#</sup>, Monica N. Toba<sup>3\*</sup>, Claus C.

Hilgetag<sup>4,5\*</sup>, R. Jarrett Rushmore<sup>2\*#</sup>

<sup>1</sup> Cerebral Dynamics, Plasticity and Rehabilitation Team, Frontlab, Brain and Spine Institute, ICM, Paris, France, Sorbonne Universités, UPMC Paris 06, Inserm UMR S 1127, CNRS UMR 7225, F-75013, & IHU-A-ICM, Paris, France

<sup>2</sup> Laboratory for Cerebral Dynamics, Plasticity & Rehabilitation, Boston University School of Medicine, Boston, MA 02118, USA

<sup>3</sup> Laboratory of Functional Neurosciences (EA 4559), University Hospital of Amiens and University of Picardy Jules Verne, Amiens, France

<sup>4</sup> Institute of Computational Neuroscience, University Medical Center Eppendorf, Hamburg University, Germany

<sup>5</sup> Department of Health Sciences, Boston University, Boston, MA 02215, USA

\*All co-authors contributed equally to this manuscript and share first and senior authorship positions.

Corresponding authors: (#) R. Jarrett Rushmore, Department of Anatomy and Neurobiology, Boston University School of Medicine, 700 Albany Street, W702, Boston, MA 02118, USA.

E-mail: [rushmore@bu.edu](mailto:rushmore@bu.edu) or (#) Antoni Valero-Cabré, CNRS UMR 7225 Office 3.028. 47

Boulevard de l'Hôpital, 75013 Paris, FRANCE. E-mail: [antoni.valerocabre@icm-institute.org](mailto:antoni.valerocabre@icm-institute.org)

/ [avalerocabre@gmail.com](mailto:avalerocabre@gmail.com)

## Abstract

1           The ‘Sprague Effect’ described in the seminal paper of James Sprague (Science  
2  
3 153:1544–1547, 1966a) is an unexpected paradoxical effect in which a second brain lesion  
4  
5 reversed functional deficits induced by an earlier lesion. It was observed initially in the cat  
6  
7 where severe and permanent contralateral visually guided attentional deficits generated by the  
8  
9 ablation of large areas of the visual cortex were reversed by the subsequent removal of the  
10  
11 superior colliculus (SC) opposite to the cortical lesion or by the splitting of the collicular  
12  
13 commissure. Physiologically, this effect has been explained in several ways - most notably by  
14  
15 the reduction of the functional inhibition of the ipsilateral SC by the contralateral SC, and the  
16  
17 restoration of normal interactions between cortical and midbrain structures after ablation. In the  
18  
19 present review, we aim at reappraising the ‘Sprague Effect’ by critically analyzing studies that  
20  
21 have been conducted in the feline and human brain. Moreover, we assess applications of the  
22  
23 ‘Sprague Effect’ in the rehabilitation of visually guided attentional impairments by using non-  
24  
25 invasive therapeutic approaches such as transcranial magnetic stimulation (TMS) and  
26  
27 transcranial direct-current stimulation (tDCS). We also review theoretical models of the effect  
28  
29 that emphasize the inhibition and balancing between the two hemispheres and show  
30  
31 implications for lesion inference approaches. Last, we critically review whether the resulting  
32  
33 inter-hemispheric rivalry theories lead toward an efficient rehabilitation of stroke in humans.  
34  
35 We conclude by emphasizing key challenges in the field of ‘Sprague Effect’ applications in  
36  
37 order to design better therapies for brain-damaged patients.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**Keywords:** Sprague effect, lesion inference, paradoxical lesion effects, interhemispheric rivalry, mutual inhibitory projections, transcallosal interactions, intercollicular commissural interactions, posterior parietal cortex, reversible cortical deactivations, thermal deactivations, non- invasive brain stimulation (NIBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), spatial attention, conscious visual perception, unilateral neglect, paradoxical functional restoration, visuo-spatial and attention rehabilitation, cat, human, focal brain damage, right hemisphere stroke.

### **Acknowledgements**

This study was funded in part by the EU project eraNET-NEURON 2009 “BEYONDVIS” to CCH and AV-C, as well as grants from the German research Council DGF HI 1286/3-1, SFB 936/A1, Z3 and TRR 169/A2 to CH. It is also supported by research grants by the IHU-A-ICM-Translationnel, ANR projet Générique “OSCILOSCOPUS”, ANR project Flag Era-JTC-HBP “CAUSALTOMICS”, PHRC Regional “NEGLECT”, PHRC National “STIM-SD”, and the Naturalia & Biologia Foundation. RJR, CCH and AV-C would also like to honor the memory of Prof. Bertram R. Payne, supervisor and mentor to us at the Boston University School of Medicine, who passed away prematurely in May 2004. His methodological expertise and intellectual guidance ignited our interest and work on the feline ‘Sprague Effect’. Without his influence, we would not have gained the ability to author the current review.

# 1 1. Introduction

2 In the Cognitive Neuroscience Summer School at Dartmouth college in July 2005, Prof.  
3 Robert Rafal stood in front of an audience of young neuroscientists united for a full week of  
4 exciting talks about brain plasticity. Across several late morning sessions and afternoon labs,  
5 he was on a mission charged to ignite the crowd about the important role of neuroanatomy,  
6 clinical neuropsychology and lesion studies as tools for understanding brain organization.  
7 Showing one of his first slides focusing on visual hemineglect, he stated: “No graduate student  
8 should be allowed to graduate if s/he does not know about the ‘Sprague Effect’ and its  
9 implications for the field of neuroscience”. Even though perhaps the majority of the audience  
10 was ignorant about this effect, the few who had heard about it were instantly captured as Dr.  
11 Rafal started unravelling the topic as if he was the main character of a ‘mystery’ movie. There  
12 is no doubt that many graduates may have successfully navigated their scientific careers while  
13 not knowing about the ‘Sprague Effect’, but it is also true that those who learned about it,  
14 particularly as taught by Dr. Rafal, rapidly felt a sense of hidden beauty and elegance subtended  
15 by the phenomenon and its neuroanatomical implications.

16 The ‘Sprague Effect’ was a serendipitous unexpected outcome than could had been  
17 easily neglected and considered a failed lesion experiment, if a fine observer and experienced  
18 neuroscientist such as James Sprague had not been present to record and analyze it. At a purely  
19 behavioral explanatory level, it showed how a contralateral brain lesion on a previously spared  
20 hemisphere could paradoxically cancel the neurological deficits generated by a first focal lesion  
21 impairing normal visuo-spatial orienting and generating visual hemineglect. At a more refined  
22 neurophysiological level, it anticipated the brain connectivity perspective, placing the focus on  
23 regional interactions as the battleground from which to better understand normal and  
24 pathological cognition. Finally, from a more applied perspective, it emphasized the  
25 particularities of mutually inhibitory, or rivalrous, interactions between brain systems, leading

1 to, at the clinical level, new theoretical perspectives to understand spontaneous recovery and  
2 drive cognitive recovery following brain lesions.

3           The current paper first presents details of the original report about the ‘Sprague Effect’  
4 published in 1966 and on that basis, we systematically review the follow-up work performed in  
5 feline models and the neuroanatomical and neurophysiological implications for the  
6 organization of visuo-spatial attention systems in animals. Second, to fully characterize the  
7 phenomena, we critically re-appraise two single clinical cases published in 1996 and 2004,  
8 paralleling and extending the observations made by Sprague in the experimental preparation to  
9 those in human neurological patients (Vuilleumier et al., 1996; Weddell, 2004) and cover work  
10 in the attention, perception and eye movements domains providing support of the Sprague  
11 model. Third, we present computational modelling work that implemented the notion of  
12 rivalrous interhemispheric systems and plausible anatomical connectivity patterns to explain  
13 known visuo-spatial behavior and make predictions about the influence of focal lesions as well  
14 as explore therapeutic solutions. Fourth, we present selected evidence which served to  
15 characterize how the mechanistic interhemispheric rivalrous model emerging from the ‘Sprague  
16 Effect’ could be experimentally manipulated with reversible invasive (thermal deactivation)  
17 and non-invasive transcranial magnetic stimulation (TMS) or transcranial direct-current  
18 stimulation (tDCS) brain modulation methods in felines and humans to ultimately affect  
19 attentional allocation to either impair or improve visual abilities. Fifth and last, we provide a  
20 critical view on how the connectivity principles originally highlighted by the ‘Sprague Effect’  
21 have been used to implement brain manipulation strategies to rehabilitate visuo-spatial  
22 attentional deficits after right hemisphere brain lesions in animal models and human stroke  
23 patients.



## 1 2. The ‘Sprague Effect’ in felines

2 In the mid-1960s, James Sprague published a short article in *Science*. The title,  
3 “Interaction of Cortex and Superior Colliculus in Mediation of Visually Guided Behavior in  
4 the Cat” did not reflect in any way the surprising results contained within (Sprague, 1966a).  
5 These results were the basis of what was later to be referred to as the ‘Sprague Effect’. The  
6 article built on previous work (Sprague and Meikle, 1965; Sprague, 1966b) that had used  
7 behavioral and neurological tests in conjunction with circumscribed brain lesions to chart the  
8 functional organization of the visual system. In these previous reports, and in the *Science* article,  
9 Sprague reported that unilateral lesion of the midbrain superior colliculus or of the visual cortex  
10 (Fig. 1) produced a florid visual deficit to targets presented anywhere in the contralateral visual  
11 hemispace (Sprague and Meikle, 1965; Sprague, 1966a).

12 After lesion of either site, the deficit was in many cases temporary, and a limited degree  
13 of recovery occurred. This recovery occurred first for targets near the vertical meridian, and  
14 extended peripherally with time, although it was typically incomplete. A complete and enduring  
15 homonymous deficit could be accomplished if all cortical visual areas were removed, including  
16 visual regions in the occipital, parietal, and temporal areas.



1 the relationship between the effects of the unilateral cortical lesion and the effects of a  
2 subsequent lesion of the contralateral superior colliculus. One may have anticipated a similar  
3 additive effect – namely a right visual field deficit would occur after a left visual cortex lesion,  
4 and a subsequent lesion of the right superior colliculus would produce a deficit to left visual  
5 targets that would superimpose on the effect of the first lesion to produce a large deficit to  
6 targets in the left and right visual fields.

7 This is not what happened. In characteristic and understated fashion, Sprague writes:  
8 *“When cortical and tectal lesions are placed sequentially on opposite sides of the brain, the*  
9 *resultant effects do not summate but instead are opposed”* (Sprague, 1966a). In other words, a  
10 complete cortical lesion on the left resulted in a long-standing inability to detect visual stimuli  
11 in the contralateral (right) visual hemispace. A subsequent lesion of the right superior colliculus  
12 did not produce additional deficits in the left visual hemispace, but instead paradoxically  
13 restored the capacity of the cat to respond to visual targets in the previously blind (right)  
14 hemifield while preserving function to targets in the left visual hemispace. This came to be  
15 known as the ‘Sprague Effect’, a paradox in which a second brain lesion improves the function  
16 lost after the first brain lesion.

17 In the original paper, Sprague presumed that the superior colliculus ipsilateral to the  
18 cortical lesion must have had the capacity to take over function but was somehow prevented  
19 from doing so. There were two possibilities to account for the inability of the ipsilateral superior  
20 colliculus to compensate. First, since a large number of cortical areas maintain excitatory  
21 projections to the superior colliculus (Segal and Beckstead, 1984; Harting et al., 1992; Wallace  
22 et al., 1993; Butler et al., 2016), removal of most of these cortical areas would produce a  
23 massive loss in excitatory input to the superior colliculus. This would result in a profound  
24 reduction in activity and a consequent inability to respond to contralateral visual stimuli  
25 (Wickelgren and Sterling, 1969; Rushmore et al., 2006). The second possibility was that the  
26 contralateral superior colliculus may exert an inhibitory influence on the ipsilateral colliculus

1 after lesion, an influence that is carried in the commissure of the superior colliculus. Removal  
2 of the contralateral superior colliculus to restore function after cortical lesion would appear to  
3 support the latter possibility. A simple test to parse between the two possibilities ensued –  
4 animals with a large cortical lesion and an intractable visual deficit received a split of the  
5 collicular commissure and displayed recovery of function, indicating that inhibitory input from  
6 the contralateral superior colliculus and traveling through the collicular commissure was  
7 responsible for preventing the superior colliculus ipsilateral to the cortical lesion from  
8 compensating for the effects of the cortical damage. Recovery occurred, therefore, when  
9 damage to the contralateral superior colliculus or section of the collicular commissure removed  
10 this inhibitory influence and restored the function of the ipsilesional superior colliculus.

11 The mechanism proposed by Sprague was powerful in its simplicity, and the  
12 experimental section of the commissure seemed to provide an appropriate confirmation.  
13 However, later work cast doubt on the idea that the superior colliculus contralateral to the visual  
14 cortex lesion was responsible for the inhibition. Sprague had found that transection of the caudal  
15 collicular commissure was sufficient to subserve recovery (Sprague, 1966a). Later anatomical  
16 results had shown, however, that most of the fibers that interconnect the colliculi did not travel  
17 in the caudal portion of the commissure – these axons originated from intermediate and deep  
18 collicular layers and crossed the midline in the rostral part of the collicular commissure  
19 (Edwards, 1977). Subsequent work confirmed that caudal transections of the collicular  
20 commissure were sufficient to produce recovery, but rostral transections were not (Wallace et  
21 al., 1989). This led to the hypothesis that the inhibitory axons crossing the midline and  
22 preventing the recovery did not originate in the superior colliculus. There was considerable  
23 evidence to suggest that such axons existed – the collicular commissure carries axons from  
24 many areas outside of the superior colliculus (Edwards, 1977; Appell and Behan, 1990; Wallace  
25 et al., 1990). To confirm that the contralateral superior colliculus was not involved in the  
26 production of intercollicular inhibitory influences that mediated the ‘Sprague Effect’, an

1 additional approach was needed. The superior colliculus opposite to a large cortical lesion was  
2 destroyed not by aspiration, which removes the neurons of the structures as well as axons  
3 passing through, but by the administration of ibotenic acid, an excitotoxic substance that  
4 destroys cells, but leaves axons of passage unaffected (Wallace et al., 1989). If the superior  
5 colliculus obtained was the origin of the inhibitory fibers, the use of ibotenic acid would restore  
6 function and produce the ‘Sprague Effect’. If inhibitory fibers whose cells of origin were  
7 outside the superior colliculus were responsible, then destruction of the collicular neurons alone  
8 would not affect performance and would not produce the ‘Sprague Effect’. The latter result was  
9 obtained, strongly suggesting that extra-collicular inhibitory influences that traveled through  
10 the commissure were responsible for inhibiting the superior colliculus after a lesion and  
11 preventing function from returning. A later paper used anatomical tracers to determine the non-  
12 collicular areas that project to the superior colliculus via the caudal portion of the collicular  
13 commissure and then ablated these areas in turn using ibotenic acid to determine which, if any,  
14 were responsible for the ‘Sprague Effect’ (Wallace et al., 1990). Surprisingly, ablation of  
15 numerous regions with contralateral projections to the superior colliculus were ineffective in  
16 reversing the visual field deficits. It was a small region of the rostro-lateral substantia nigra pars  
17 reticulata (referred to as the critical zone) that was consistently effective in producing the  
18 ‘Sprague Effect’ (Wallace et al., 1990). This region was very localized – larger lesions of the  
19 substantia nigra pars reticulata that included the critical zone did not produce the ‘Sprague  
20 Effect’, suggesting that intranuclear interactions prevented its emergence. In these latter cases,  
21 however, adding transection to the caudal commissure again produced the ‘Sprague Effect’,  
22 indicating that a structure in addition to the critical zone of the substantia nigra pars reticulata  
23 was involved in its mediation. This finding led Durmer and Rosenquist (2001) to propose the  
24 contralateral pedunclopontine nucleus as a candidate. Indeed, they found that ibotenic acid  
25 lesion of subportion of the dorsolateral pedunclopontine nucleus opposite a large cortical  
26 lesion was sufficient to produce the ‘Sprague Effect’ – this region had to be completely

1 destroyed to restore function, and cases in which portions were spared remained insensible to  
2 visual stimuli contralateral to the visual cortical lesion.

3 A series of anatomical and physiological studies further defined the role of neurons in  
4 the *substantia nigra* in modulating activity in the superior colliculus (Jiang et al., 2003, 2011).  
5 These neurons are inhibitory and have been found to be of two main types: 1) relatively  
6 common neurons that project to the ipsilateral superior colliculus, are tonically active, and  
7 display a phasic reduction of activity in response to visual stimuli, and 2) relatively rare  
8 inhibitory neurons whose axons cross the midline to reach the contralateral superior colliculus,  
9 have a lower basal activity rate, and whose activity is elevated by visual stimuli. The end result  
10 of stimulation of the substantia nigra, through both populations, is to reduce inhibition of the  
11 ipsilateral superior colliculus, and elevate inhibition of the contralateral superior colliculus.  
12 Importantly, the small number of crossed neurons exert a broad effect (Jiang et al., 2003), a  
13 finding that suggests the contralateral nigrotectal projection could have an effect over much of  
14 the superior colliculus, and is consistent with its putative role in the ‘Sprague Effect’. Moreover,  
15 the location of the crossed nigrotectal neurons fits with the location of the substantia nigra pars  
16 reticulata critical zone (Wallace et al., 1990). In contrast, the ipsilateral nigrotectal projections  
17 are likely tied to the disinhibition and detection of specific receptive field locations in the  
18 ipsilateral superior colliculus and therefore the effects are more spatially specific (Jiang et al.,  
19 2003). Accordingly, ablation of ipsilateral substantia nigra pars reticulata does not produce  
20 recovery after lesion (Ciaramitaro et al., 1997b).

21 These studies indicate that the contributions of the contralateral pedunculo-pontine and  
22 the substantia nigra pars reticulata together exert an inhibitory tone on the superior colliculus  
23 ipsilateral to a cortical lesion and prevent it from subserving visual responses. When the neurons  
24 or their axons from these regions are destroyed, the ipsilateral superior colliculus is released  
25 from inhibition and the ‘Sprague Effect’ is observed. Indeed, the substantia nigra pars reticulata  
26 and the contralateral pedunculo-pontine may be linked in a circuit designed to regulate activity

1 in the superior colliculus, and perhaps in other brain areas (Beckstead, 1983; Hall et al., 1989;  
2 Harting and Lieshout, 1991; Sprague, 1996). This line of experiments emphasizes the inhibition  
3 of the ipsilesional superior colliculus as the mechanism of the ‘Sprague Effect’.

#### 4 *2.1 Reversible thermal deactivation to understand the mechanisms underlying the ‘Sprague* 5 *Effect’*

6 For more than a decade now (1994-2006), the mechanism of the original feline ‘Sprague  
7 Effect’ has been thoroughly interrogated using reversible thermal deactivation technology.  
8 With this method, a device is placed on the surface of a cortical region of interest and, when  
9 made active, reduces the temperature and deactivates the underlying neurons without affecting  
10 activity in axons of passage (Lomber, 1999; Lomber et al., 1999). The drop-in temperature can  
11 be carefully controlled to deactivate different depths. One of the greatest advantages of this  
12 approach is that it does not produce brain damage – the device is placed on the surface of the  
13 brain and maintains the integrity of the underlying brain tissue. The use of lesions or approaches  
14 that introduce devices into the brain parenchyma initiates measures designed to reroute function  
15 such that the system can compensate for the effects of the lesion (Payne et al., 1996b). As  
16 Sprague described, lesions that included small amounts of visual cortex allowed the brain to  
17 functionally compensate for the damage and maximize function (Sprague, 1996). Evaluating  
18 the steady state effects of a lesion, therefore is a reflection of the impact of removing the brain  
19 region of interest as well as the effects of the changes in regions, circuits and networks due to  
20 functional reorganization. Thermal deactivation avoids the latter component because it is a  
21 temporary deactivation and functional recovery does not have sufficient time to occur (Lomber  
22 et al., 1999).

23 The use of this technology allowed Lomber and Payne to produce a result very similar  
24 to the ‘Sprague Effect’ (Payne et al., 1996a, Lomber and Payne, 1996). Unilateral deactivation  
25 of the parietal cortex in the posterior aspect of the Middle Suprasylvian Sulcus (pMS cortex)

1 produced a syndrome in which moving targets were not detected when introduced in the  
2 contralateral visual hemispace. Performance for targets in the ipsilateral hemispace remained  
3 normal. A subsequent study showed that the initial visual deficit produced by unilateral  
4 deactivation of the pMS cortex could be reversed by reversible deactivation of the same brain  
5 region on the other side of the brain (Lomber and Payne, 1996). Visual deficits produced by  
6 unilateral deactivation of the superior colliculus could also be reversed by adding deactivation  
7 of the contralateral superior colliculus. The pMS region had previously been identified as  
8 having a profound importance in the detection of contralateral visual stimuli and as an area that  
9 exerted a powerful influence on the activity of the ipsilateral superior colliculus (Ogasawara et  
10 al., 1984; Hardy and Stein, 1988).

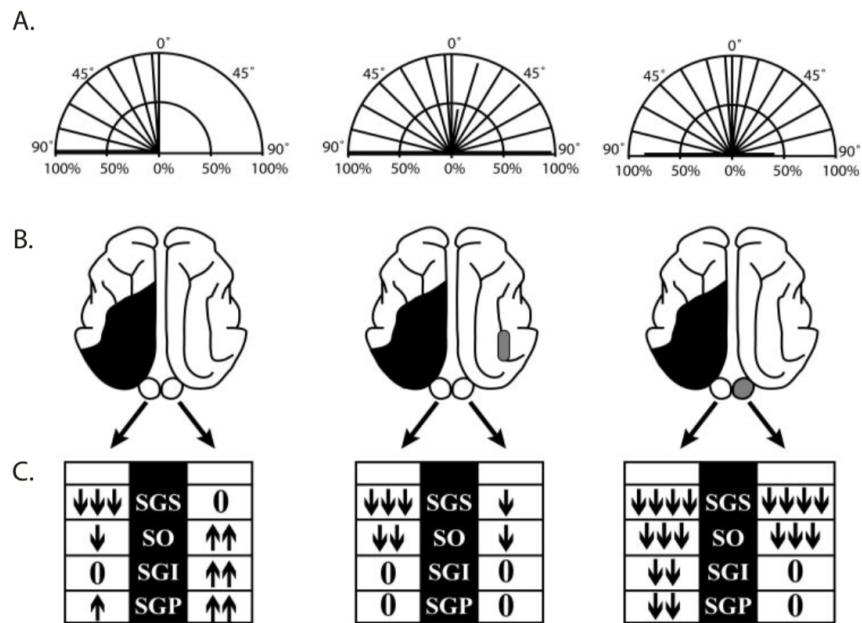
11         These data suggested that this region of the parietal cortex and the superior colliculus  
12 were foundational units in a bilateral cortico-subcortical circuit characterized by a mutual  
13 inhibitory influence at both the cortical and subcortical levels (Payne and Rushmore, 2004).  
14 The two parietal cortices were conceived to be in balance during fixation of a central stimulus,  
15 but when a visual stimulus appeared in one visual hemifield, this interhemispheric balance  
16 would be disturbed – activity would increase in visual circuits and areas in the contralateral  
17 areas and would decrease in regions of the ipsilateral hemisphere by virtue of the absence of  
18 stimulus-linked activity in the latter. This imbalance, initially produced at cortical levels would  
19 be enhanced by functionally-inhibitory interhemispheric connections between the pMS cortex  
20 and between the two superior colliculi, either directly or indirectly through the substantia nigra  
21 (Payne and Rushmore, 2004).

22         Subsequent work linked the paradoxical findings from restricted bilateral thermal  
23 deactivation experiments to those that underpinned the ‘Sprague Effect’. Lomber placed  
24 deactivation probes in either the superior colliculus or the pMS cortex opposite a large cortical  
25 lesion (Lomber et al., 2002). Animals at baseline exhibited a profound visual deficit and did  
26 not respond to stimuli presented in the visual hemifield opposite the lesion. Temporary thermal



1 deactivation of the pMS cortex opposite to the lesion reversed the deficit. During the  
2 deactivation, animals responded briskly to stimuli to which they were insensible a few minutes  
3 prior and when the deactivation ceased, the florid visual deficit returned. The same pattern of  
4 results happened after deactivation of the superior colliculus opposite the lesion, wherein  
5 collicular deactivation temporarily restored function in the previously blind hemifield.  
6 Subsequent metabolic imaging work found that a large cortical lesion produced an imbalance  
7 in activity at the level of the colliculus but not the cortex (Rushmore et al., 2006). The colliculus  
8 opposite the lesion had a level of activity that was greater than normal, and the colliculus  
9 ipsilateral to the lesion displayed a decreased level of activity. Deactivating the contralateral  
10 structures reduced this heightened activity, either directly in the case of the superior colliculus  
11 deactivation, or indirectly via corticotectal projections in the case of the pMS cortex  
12 deactivation (see Fig. 2). This line of experimentation focused on reducing excitability in the  
13 pMS cortex or the superior colliculus opposite lesion as a putative mechanism underlying the  
14 ‘Sprague Effect’.

15         The results from the deactivation experiments that emphasized reduction of  
16 contralesional excitability as important for the induction of the ‘Sprague Effect’ differ from the  
17 results of experiments that focused on the elevated inhibition of the ipsilateral colliculus as the  
18 underlying mechanism. More specifically, outcomes after direct deactivation of the  
19 contralesional superior colliculus are at odds with the identification of the substantia nigra pars  
20 reticulata and pedunculo-pontine nucleus as the regions that mediate the inhibition of the  
21 ipsilesional superior colliculus (Wallace et al., 1989, 1990; Durmer & Rosenquist, 2001).  
22 Deactivation does not impair fibers of passage at the temperatures used in the study (Lomber,  
23 1999; Lomber et al., 1999), and therefore the crossed inhibitory axons from the substantia nigra  
24 pars reticulata and the pedunculo-pontine nucleus should have been unaffected.



**FIGURE 2. Impaired and restored orienting behavior after hemispherically imbalanced and rebalanced activity. (A) Representation of orienting behavior in cats with a large lesion of visual cortical areas (left), cats with lesion and contralateral pMS deactivation (middle) and cats with lesion and contralateral superior colliculus deactivation (right). The semicircle represents visual field location with the 0° mark denoting fixation and the length of the line representing percent correct. (B) The experimental preparation of each of the three groups—black represents resected cortex and grey indicates thermal deactivation. (C) Impact of the different conditions on the activity of the layers of the superior colliculus. One arrow represents between a 5 and 10% change from intact values, two arrows represents a 10–20% change, three arrows represents a 20–30% change, four arrows represents >30% change from intact values; 0 represents no change. Abbreviations: SGS-stratum griseum superficiale, SO-stratum opticum, SGI-stratum griseum intermediale, SGP-stratum griseum profundum. Reproduced with permission from Rushmore et al. (2006).**

Several possibilities exist to resolve this discrepancy. The first is that both mechanisms may contribute to the ‘Sprague Effect’ in an independent or overlapping way such that either is sufficient, but both are not necessary. This is supported by a chemical deactivation study in which an antagonist of GABA<sub>A</sub> receptor was injected to the superior ipsilateral superior colliculus to test the hypothesis that disinhibition of the superior colliculus ipsilateral to the lesion is required to elicit the ‘Sprague Effect’ (Ciaramitaro et al., 1997a). In this study, recovery was found to occur in only 37% of the cases, suggesting additional mechanisms may be at play. A second possibility is that the deactivation of the contralateral superior colliculus may directly or indirectly reduce the excitability of the substantia nigra pars reticulata /

1 pendunculo-pontine nucleus in a way that has not yet been discovered. The superior colliculus  
2 projects to the substantia nigra pars compacta and subserves the short latency visual responses  
3 in this structure, but direct projections to the pars reticulata have not been demonstrated  
4 (McHaffie et al., 2006).

5         There is evidence in the rat that ascending collicular projections may influence basal  
6 ganglia circuitry through transthalamic routes (Watson and Alloway, 2018), but more work  
7 needs to be performed to determine whether such a pathway would reduce activity in the pars  
8 reticulata. A final possibility relates to a re-evaluation of the pathway between the two superior  
9 colliculi. Interpretations of the ‘Sprague Effect’ have invoked inhibitory interactions between  
10 the colliculi (and the cerebral cortex) as a foundational mechanism subserving hemispheric  
11 rivalry, that is, when one hemisphere is activated by exogenous attentional or motor  
12 mechanisms, the other one is depressed so as not to create a conflicting behavior (Sprague,  
13 1966a; Payne and Rushmore, 2004). While initial studies emphasized the prevalence of  
14 inhibitory projections, later studies found that intercollicular projections contain both excitatory  
15 and inhibitory axons (Sprague, 1966a; Olivier et al., 2000; Takahashi et al., 2005, 2007, 2010).

16         A more recent study has added to this literature by charting the relationship of excitatory  
17 and inhibitory neurons with respect to the premotor maps (Takahashi et al., 2010). This study  
18 showed that neurons in the medial aspect of one colliculus (corresponding to saccade  
19 production to the upper visual field) sent excitatory projections to the medial aspect of the  
20 contralateral superior colliculus, and inhibitory projections to the lateral aspect of the  
21 contralateral superior colliculus (which codes for lower visual field). This result led the authors  
22 to propose that this organization allowed for synergistic saccadic motor programs between the  
23 superior colliculi, while preventing conflicting motor programs. In addition, Takahashi et al.  
24 (2010) found that superior colliculus neurons sending premotor signals coding for movement  
25 along the horizontal meridian inhibited superior colliculus neurons coding for movement to the  
26 representation of the horizontal meridian in the opposite superior colliculus, again to prevent

1 the joint production of antagonistic motor programs. This level of specificity in intercollicular  
2 projections confirms previous theoretical treatments of the intercollicular interactions after  
3 deactivation or lesion (Hilgetag et al., 2002) in which representations along the horizontal  
4 meridian were presumed to inhibit the mirror image representation in the contralateral superior  
5 colliculus.

6 Such a complex pattern of excitatory and inhibitory intercollicular projections also  
7 suggests that the mechanisms underlying the ‘Sprague Effect’ may be more sophisticated than  
8 a result of disrupting interhemispheric inhibition. Since the ‘Sprague Effect’ may serve a  
9 mechanistic basis to drive or contribute to functional recovery in humans, an increased  
10 understanding of circuit-level mechanisms could allow for better targeted rehabilitative  
11 treatment after brain injury or neurological disease. But what is the neurological evidence from  
12 clinical cases that supports the ‘Sprague Effect’ in the human brain? And to what extent do  
13 similar anatomical, functional processes, and interactions as those described by Sprague in  
14 felines underlie analogous phenomena in humans?

### 16 **3. The ‘Sprague Effect’ in human lesion studies: the single case patient evidence**

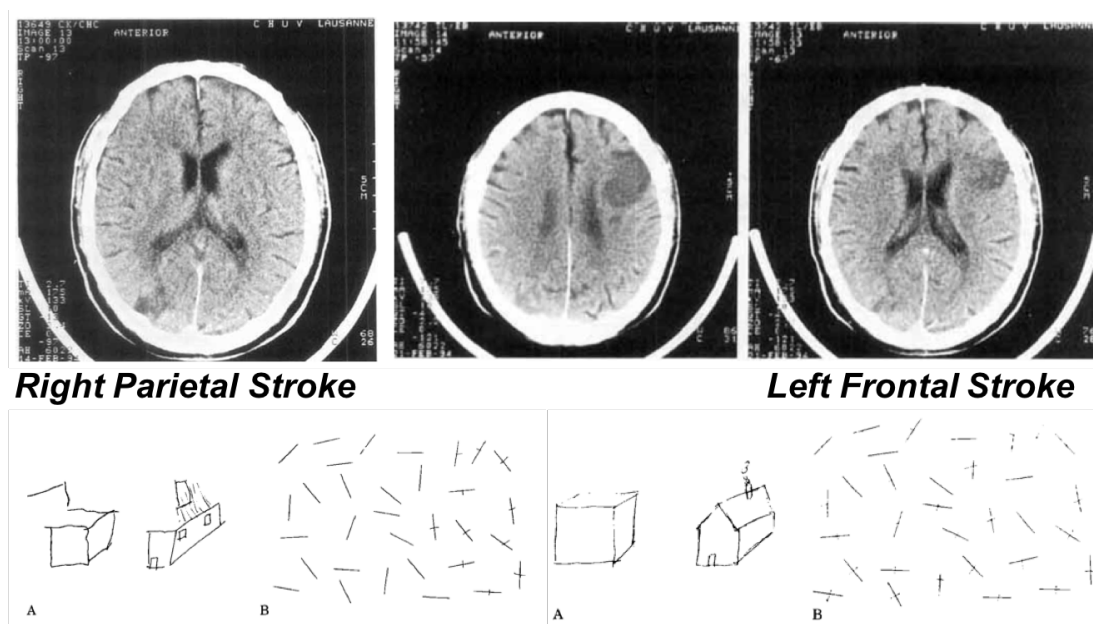
17 Dynamic interactions between structures in the cerebral cortex and also the brainstem,  
18 including the ‘Sprague Effect’, are nicely illustrated in the visual hemineglect phenomenon.  
19 Hemineglect patients fail to orient toward and respond to stimuli presented in the left part of  
20 the space in the absence of primary sensory or motor deficits. However, if hemineglect informs  
21 about how visuo-spatial attention can be disturbed after a unilateral right or left hemispheric  
22 lesion and, thus, facilitates the comprehension of the distribution of attentional networks in the  
23 human brain, the ‘Sprague Effect’ teaches us even more interesting things, particularly on how  
24 to ‘fix’ or rehabilitate post-stroke hemineglect (Rafal, 2006). In support of this idea, several  
25 studies investigating spatial attention in animals and humans have reported a paradoxical  
26 cancelation of visuo-spatial orienting deficits resulting from earlier lesions following the

1 permanent or reversible deactivation of spared cortical or subcortical regions (Sprague, 1966a;  
2 Vuilleumier et al., 1996; Rushmore et al., 2006). Moreover, the ‘Sprague Effect’ can also  
3 explain the induction of better than normal visual detection performance (Hilgetag et al., 2001b,  
4 Thut et al., 2005).

5 In what has come to become the first « classical » single case account in support of a  
6 human ‘Sprague Effect’, Vuilleumier et al. (1996) reported the case of a neurological patient  
7 from the Centre Hospitalier Universitaire Vaudois in Lausanne (Switzerland) who recovered  
8 from hemineglect after sequential strokes in opposite hemispheres. The patient, a 74-year-old  
9 right-handed male, presented with a first parieto-occipital infarct in the right hemisphere located  
10 in the junctional territory between the middle and the posterior cerebral arteries. His lesion  
11 assessed by a CT scan involved mainly the caudal part of the right angular gyrus (Brodmann  
12 area 39) (Fig. 3). Neuropsychological testing revealed hemineglect with pathological scores in  
13 line and letter cancellation, drawing copy and overlapping figures. The patient also presented  
14 neglect dyslexia and was unable to use his left upper limb when executing bimanual ideomotor  
15 actions in the evaluation of praxic abilities. However, no motor neglect was documented in the  
16 spontaneous use of his left hand in everyday activities and in bilateral movements to verbal  
17 command and bilateral tactile stimulation. No signs of hemianopia were documented either.  
18 The patient also presented a left-ear extinction on bilateral auditory stimulation, but no tactile  
19 extinction. Additionally, he was able to recognize a geographical map, but was not able to orient  
20 himself on the map. Hemineglect was severe and obvious in daily life activities.

21 Ten days after the first stroke, the patient suffered a second stroke which was hosted,  
22 according to a CT scan, in the left dorsolateral frontal lobe, at the level of the left frontal eye  
23 field (Brodmann area 8) and the surrounding areas (Brodmann areas 6, 9, 44 and 45) (Fig. 3).  
24 After this stroke, the patient presented transient head and eye deviation, but paradoxically, he  
25 spontaneously recovered from his former hemineglect. The neuropsychological assessment  
26 after the second stroke (12 days after the first neuropsychological evaluation) signaled a

1 transcortical aphasia with a moderate alteration of comprehension. However, no sign of  
 2 hemineglect were noticed with previously employed visuo-spatial attention tasks neither with  
 3 new experimental tasks implemented *ad hoc*. In the same vein, clinical improvement was also  
 4 observed in drawing a map, as well as in Benton's line orientation judgement test (the latter  
 5 being still deficient at the time of the examination). Vuilleumier et al. (1996) suggested that this  
 6 very unusual and abrupt evolution of hemineglect could be best interpreted in the framework  
 7 of the 'Sprague Effect'. More specifically, on the basis of the work published by Kinsbourne  
 8 (1977), they argued out that in the physiological normal state there is a balance between the  
 9 orienting attentional bias of each hemisphere toward the contralateral hemispace. Thus,  
 10 hemineglect observed after the first stroke could be the result of an imbalance between opposing  
 11 systems for lateral orientation. On the one hand, the first stroke provoked a suppression of the  
 12 interhemispheric imbalance generated by a functional depression of a cortical-subcortical  
 13 attentional system, whereas on the other hand, the second stroke restored the attentional  
 14 orienting balance in a way similar that the removal of the superior colliculus did in the original  
 15 experiment by Sprague (1966a).



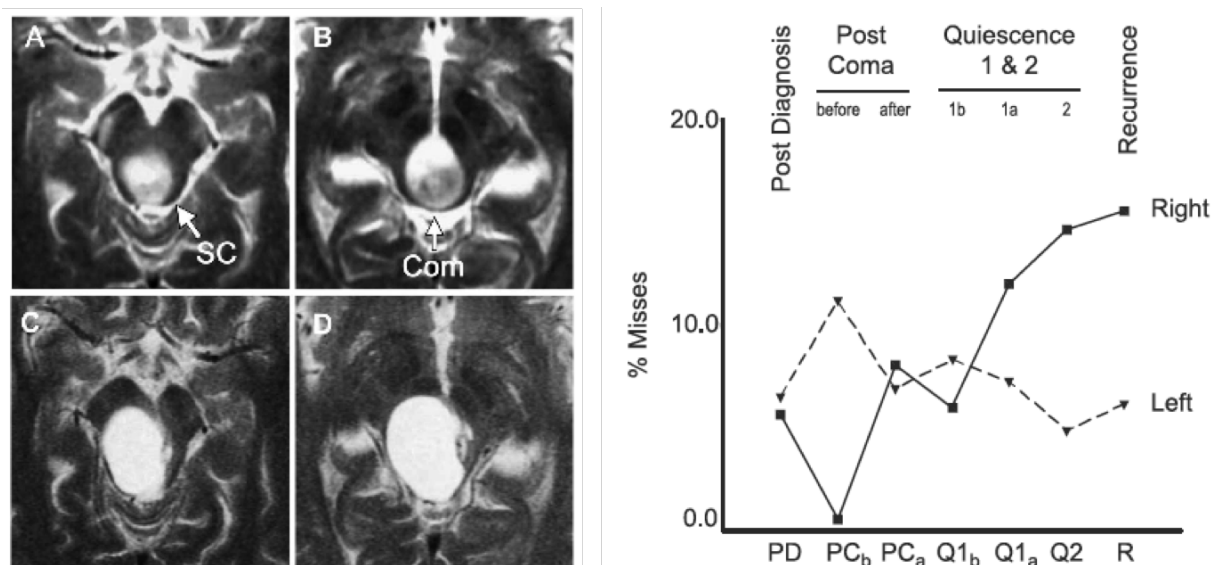
17  
 18 **FIGURE 3. Successive brain lesions generating the 'Sprague Effect' in human. Brain CT**  
 19 **acquired 7 days after the first stroke onset (right parietal stroke) and 4 days after the**

1 **second stroke onset (left frontal stroke). Neuropsychological assessment after the first**  
2 **(left) and the second (right) stroke showing the resolution of hemineglect. A. Drawing of**  
3 **a cube and a house. B. Line cancellation test. Reproduced with permission from**  
4 **Vuilleumier et al. (1996).**  
5

6 In brief, the first stroke produced a functional inhibition of the superior colliculus  
7 ipsilateral to the cortical lesion and, thus, affected the interhemispheric interactions between  
8 cortical and midbrain levels which are important in directing visual attention. The second stroke  
9 restored this imbalance by inhibiting the superior colliculus contralateral to the first cortical  
10 lesion.

11 Eight years later, a second single patient report (Weddell, 2004) revealed an even more  
12 specific likely emulation of the ‘Sprague Effect’ in a human neurological patient. Roger  
13 Weddell reported the case of a 34-year-old right-handed male patient from the Morriston  
14 Hospital, in Swansea (Wales, UK) with a midbrain grade  $\frac{3}{4}$  glioma (infiltrating the dorsal meso-  
15 pontine midline surface but sparing the intertectal commissure and preserving superficial layers  
16 of the superior colliculi, lateral superior colliculi, lateral left subadjacent tegmentum and ventral  
17 midbrain areas) (Fig. 4). After a period under coma, the patient presented florid signs of left  
18 hemineglect after right frontal damage that occurred during the management of hydrocephalus  
19 by an obstruction of the midbrain aqueduct caused by a growing glioma. Paradoxically  
20 however, hemineglect suddenly disappeared 7 months later coinciding with the appearance of  
21 a right peripheral visual disturbance affecting both eyes and suggesting the extension of the  
22 tumor related cyst at the level of the left superior colliculus. Seventeen months later, the patient  
23 reported a transient left quadratic scotoma while MRI recordings showed the presence of a new  
24 cyst under the lateral right superior colliculus (hosting the representation of the left lower visual  
25 hemifield quadrant), extending to the right, through the dorsal wall of the superior colliculus,  
26 and signs of right hemineglect later. At the neuropsychological level, general standardized  
27 assessments in different clinical stages showed relatively normal scores. A visual search test  
28 (number search) revealed that the patient employed a left-to-right visual search strategy. Of

1 note, search times were longer for missed numbers than for absent numbers. The authors also  
 2 report speed-accuracy trade-offs with more rapid leftward scanning during the clinical presence  
 3 of left hemineglect and over-compensatory left-sided scanning coinciding with clinical signs of  
 4 right hemineglect at later stages, following right-brain attentional dysfunction (Fig. 4). As in  
 5 the original report of the ‘Sprague Effect’ (Sprague 1966a), these observations support a role  
 6 for lesions of the tectal commissure (or the contralesional superior colliculus) in restoring visual  
 7 orientation in patients with hemineglect. However, specific to this particular case, the growing  
 8 superior collicular damage generated by a new cyst, this time under the right superior colliculus,  
 9 impaired left-right balance.



13 **FIGURE 4. Evolution of a brain tumor resulting in the ‘Sprague Effect’ in human. Brain**  
 14 **MRI presenting the tumor in the lower (A, C) and the upper midbrain (B, D). Patient**  
 15 **visual search misses by day and period. PD: post-diagnosis, PC: post-coma before (PCb)**  
 16 **and after (PCa) transient right peripheral impairment, Q: quiescence before (Qb) and**  
 17 **after (Qa) left lower field scotoma, R: recurrence. SC: superior colliculus, Com:**  
 18 **intertectal commissure. Reproduced with permission from Weddell (2004).**

20 Given the low occurrence of sequential lesions in such specific posterior parietal, frontal  
 21 or midbrain locations, hence the very limited number of lesion human studies able to illustrate  
 22 and provide support for an extension of the ‘Sprague Effect’ to humans, it is particularly



1 difficult to obtain neurological evidence for this phenomenon. However, other pathological  
2 frameworks can be suited to explore hemispheric interactions when appropriate experimental  
3 paradigms are used. At the anatomical level, the mammalian superior colliculus is highly  
4 integrated with oculomotor cortical system spanning across the frontal and parietal cortices,  
5 conforming a circuit important in both voluntary and reflex orienting of the gaze toward salient  
6 events occurring in the visual periphery (i.e., the visual grasp reflex, VGR). As a result,  
7 oculomotor behavior can also be used to reveal the dynamic interactions between these brain  
8 regions. By taking advantage of this fact, Henik et al. (1994) measured the effect of chronic  
9 unilateral lesions of the frontal eye field (with well-known oculomotor saccadic contributions)  
10 on the latencies of the saccadic eye movements in stroke patients. By testing both, visually  
11 guided and voluntary saccades, these authors reported that the latency of voluntary saccades for  
12 patients (vs control healthy individuals) were longer when directed to the contralesional field,  
13 whereas visually-guided saccades showed longer latencies when directed to targets in the  
14 ipsilesional field. This loss of reflexive ipsilesional behavior was explained as caused by a  
15 reorganization of the fronto-tectal circuitry and a hypo-reactivity of the contralesional superior  
16 colliculus. A complementary study conducted this time in healthy human participants used  
17 TMS to temporarily deactivate the frontal eye field (Ro et al., 1997, 1999). These authors  
18 showed that voluntary saccades latencies were longer to the contralesional field, whereas  
19 visually-guided saccades were not affected. This finding supports a reorganization of cortico-  
20 subcortical circuits, interpreted and referred to as *a reverse 'Sprague Effect'*. The explanatory  
21 mechanism proposed by the authors was that lesions of the frontal eye field disinhibit the  
22 ipsilesional substantia nigra pars reticulata; as a result, the superior colliculus opposite to the  
23 frontal eye field lesion became inhibited. In another series of experiments, Machado and Rafal  
24 (2004a, 2004b) compared in antisaccades and prosaccades performance stroke patients with  
25 frontal eye field lesions vs. patients with unilateral intraparietal lesions. Whereas frontal eye  
26 field lesions resulted in a disinhibited VGR toward contralesional signals, the opposite pattern

1 was observed for the parietal lesions. Reduced VGR toward contralesional signals is consistent  
2 with the ‘Sprague Effect’ because parietal lesions generate hyporeactivity in the ipsilesional  
3 superior colliculus.

4 In sum, a few well-characterized neurological cases (Vuilleumier et al. 1996; Weddell  
5 2004) strongly suggest the existence of an architecture of interhemispheric and intercollicular  
6 connections in the human brain able to subtend rivalrous interactions, and provides proof of  
7 concept for the ‘Sprague Effect’ in humans. Unfortunately, the lesion features (localization and  
8 size) that might need to converge so that such an effect is clinically detectable are very stringent,  
9 and the possibility to explore its mechanism, temporal dynamics and interindividual  
10 reproducibility through clinical cases remains limited. In this context, simulations in  
11 anatomically- and physiologically-inspired computational models and experimental reversible  
12 brain manipulations have provided additional test benches with which to further assess rivalrous  
13 processes and envision how they could be therapeutically applied.

#### 14

#### 15 **4. Computational models of the ‘Sprague Effect’**

16 The ‘Sprague Effect’ did not only inspire decades of experimental work, it also  
17 stimulated the development of theoretical concepts of brain function as well as concrete  
18 computational models. Such models aimed to implement a realistic scheme of structural  
19 connectivity together with the net excitatory or inhibitory influences of the interactions  
20 conveyed by the structural projections, in order to, first, simulate and mechanistically explain  
21 the surprising effect of functional restoration, and, second, explore the effect as a model for  
22 distributed brain functions and functional connectivity. Giving an indication of the significance  
23 of the effect in theoretical studies, one of the first books on the then still novel subject of  
24 Computational Neuroscience included the ‘Sprague Effect’ as a challenge to be explained  
25 (Grobstein, 1993).

#### 1 *4.1 Computational modelling of mechanisms underlying the ‘Sprague Effect’*

2 A plausible biological mechanism that can explain the reversal of visuo-attentional  
3 deficits was already suggested in the original paper of Sprague (1966a). Long-range inhibitory  
4 fibers in the superior colliculus commissure may mutually inhibit the two halves of the tectum,  
5 providing a gain amplification mechanism in the intact system as well as a basis for the  
6 restoration of function in the bilaterally impaired system. While the biological basis of this  
7 explanation was further explored in the subsequent decades, and the exact physiological  
8 underpinnings of the effects may still be debated (see sections 2 and 5 on the ‘Sprague Effect’  
9 for further details), a key feature of the effect appears to be the mutual inter-hemispheric  
10 competition played out at the level of the midbrain which is involving particularly the  
11 intermediate layers of the superior colliculus.

12 In order to assess the contribution of different structural aspects of brain organization to  
13 attentional function, several anatomical and physiological features underlying intact, impaired  
14 and restored orienting behavior in the cat were represented in a detailed computational model  
15 by Hilgetag et al. (1999). The study reviewed anatomo-physiological networks of cortical and  
16 midbrain stages that may be involved in orienting behavior and focused particularly on  
17 fundamental features of the bilateral superior colliculi and their connections in the cat that may  
18 help to explain observed aspects of the ‘Sprague Effect’ (Fig 5A). Specifically, the model  
19 description accounted for the retinotopically organized contralateral and ipsilateral spatial maps  
20 of the left and right superior colliculi and included cortical as well as extra-cortical (particularly,  
21 retino-tectal) inputs into these maps. The inputs were scaled by magnification factors in the  
22 representation of the visual field, such that central eccentricities received stronger inputs than  
23 peripheral eccentricities (approximated by a skewed Gaussian distribution). Moreover, and  
24 essentially, mirror-eccentric representations of the visual space in the left- and right superior  
25 colliculi mutually inhibited each other via long-range inhibitory fibers (Behan & Kime, 1996).

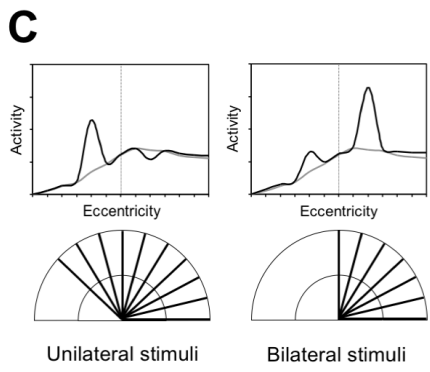
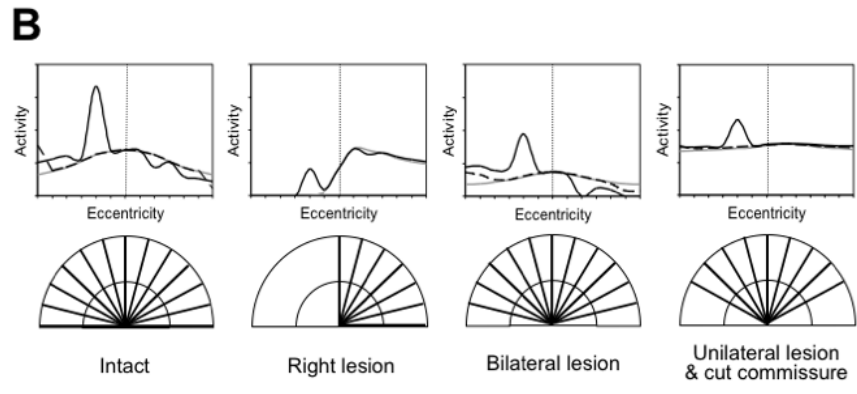
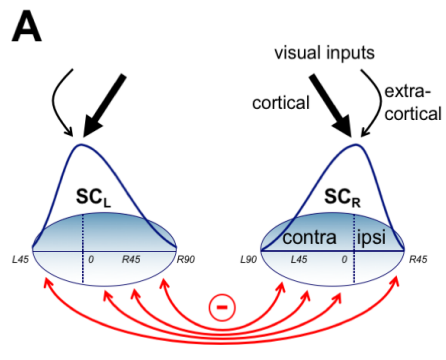
1 This model was able to account for a large variety of empirically observed behaviors in  
2 the cat (Fig. 5B). It predicted the tendency of intact animals to direct their attention towards the  
3 midline in the absence of particular stimuli. Further, it explained the redirecting of attention to  
4 stimuli presented throughout the left or right visual fields (eccentricities from the midline to  
5 90° left or right) in intact animals, as well as the failure to orient to stimuli presented in the field  
6 contralateral to a severe unilateral cortical lesion or cortical deactivation (e.g., of the feline  
7 posterior parietal area, pMS cortex).

8 In these cases of contralateral *hemineglect*, in line with clinical observations (Karnath  
9 et al., 1998), the model also predicted a shift of the focus of attention into the intact, ipsilesional  
10 field (Hilgetag, 2000). Moreover, the model explained the restoration of orienting for stimuli  
11 presented at most eccentricities for animals with bilateral severe lesions of cortical areas  
12 sending inputs to the superior colliculus. Such a restoration would also occur when transecting  
13 the commissural fibers linking the left and the right superior colliculi. In agreement with the  
14 empirical observations (Lomber & Payne, 1996), an exception from the restoration would be  
15 eccentricities at the far periphery (90° left and right). Due to the incorporated magnification  
16 factors, during increasing (homogeneous, non-topographic) deactivation of the contralateral  
17 superior colliculi, visual hemifield restoration would also proceed in a topographic manner  
18 (Hilgetag et al., 2002), as it had been observed experimentally previously in felines (Lomber et  
19 al., 2002).

20 Further, the model showed phenomena akin to *extinction* when simulating unilateral  
21 cortical lesions of more moderate impact (Fig. 5C). In these cases, unilateral stimuli presented  
22 in the contralesional space would still be able to elicit an orienting response, while bilateral  
23 stimuli presented at mirror-eccentric locations in the visual field would compete with each other  
24 in the collicular representation of the visual field, such that the activity of the ipsilesional  
25 location would win and the animal would no longer attend to the contralateral stimulus.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



**FIGURE 5. Detailed model of intact, impaired and restored orienting grounded in the anatomy and physiology of the visual midbrain, particularly the superior colliculus, in the cat. (A) Key features of the computational model. The model reflects the representation of the external visual space at the level of the left and right superior colliculi. It incorporates indirect cortical as well as direct cortical visual inputs, which are weighted by magnification factors leading to a stronger representation of the central field. Midbrain representations of mirror-symmetric eccentricities in the visual field (e.g., left and right 30° eccentricity) inhibit each other, as indicated by bidirectional red arrows. (B) Simulation of intact, severely impaired orienting resembling hemineglect, and restored orienting behavior. Top panels represent the modeled distribution of the activity-based representation of external space in the midbrain (computed by averaging the activities in the left and right midbrain maps), and bottom panels, the resulting behavioral response in a simulated orienting paradigm. Eccentricities reach from left 90° to right 90° (at 15° increments), with the dashed line representing midline. Grey curves in the top panels represent spontaneous baseline activity, in the absence of external stimulation. Solid black lines stand for stimulus-related activity for a stimulus presented at 30° eccentricity,**

1 **broken black curves indicate midbrain activity related to a 90° eccentricity stimulus. (C)**  
2 **Simulation of moderately impaired orienting resembling extinction. SC: superior**  
3 **colliculus, L: left, R: right. Figure is based on Hilgetag et al. (1999, 2001a).**  
4

5 The details of the operation of the model can be discerned from the subpanels of Fig. 5.  
6 Specifically, Fig. 5B shows that, in the *intact* system, external stimulation produces narrow  
7 activity peaks rising above the baseline, corresponding to the location of the presented stimulus.  
8 This activity profile accounts for normal orienting behavior. For a strong unilateral impairment  
9 of the attentional network, such as by a cortical *right lesion* (simulated by setting the strength  
10 of the right input pathways to 10% of their intact strength), baseline activity representing the  
11 contralesional field is severely depressed, and the baseline peak shifted into the ipsilesional  
12 field by 15°-20°. Stimuli presented in the contralesional field, unless very close to the midline,  
13 cannot produce neural activity higher than at the baseline peak. Consequently, hemineglect is  
14 displayed for stimuli in the contralesional field.

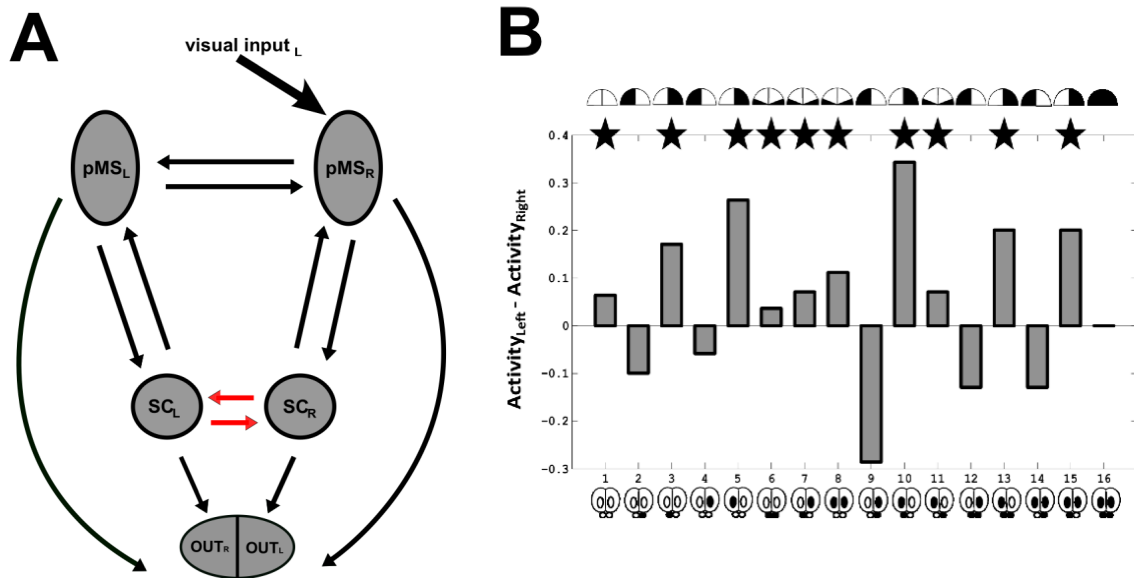
15 Matched severe *bilateral lesions* (reducing both left and right inputs to 10% of their  
16 intact strength) result in an activity baseline of similar shape, but on a lower activity level  
17 compared to the intact baseline. Stimulation at 30° eccentricity still produces a peak rising  
18 above baseline; however, stimulation at 90° eccentricity no longer does. This activity profile  
19 accounts for the empirically observed restoration of orienting to all but the most peripheral  
20 eccentricities (Lomber & Payne, 1996).

21 Finally, severe unilateral deactivation combined with elimination of the reciprocal  
22 inhibitory connection between the midbrain structures (*unilateral lesion & cut commissure*)  
23 produces a flattened baseline, albeit on higher level than in the intact state. Such an activity  
24 distribution may result in higher distractibility of the animal and difficulties in focusing  
25 attention. Stimuli presented not too far from the midline (as shown here for stimulation at 30°)  
26 result in activity rising above baseline; not, however, stimuli presented further in the periphery  
27 (e.g., at 90° eccentricity). This activity profile predicts a likely restoration of orienting for  
28 central but not peripheral eccentricities.

1 In addition, Fig. 5C shows a simulation of moderately impaired orienting resembling  
2 extinction. Note that for more moderate unilateral deactivation of the network than used in Fig.  
3 5B, leaving 30% of the input pathways intact, *unilateral stimulation* (e.g., at 30° eccentricity)  
4 produces an activity-related peak rising above the baseline, resulting in neural activity that  
5 allows orienting responses in contralesional space not too far from the midline. Moreover,  
6 bilateral stimulation at matching eccentricities (e.g., left 30° and right 30° eccentricity), on the  
7 other hand, depresses the activity peak related to the contralesional stimulus below the level of  
8 the baseline peak, and makes it likely that only the ipsilesional stimulus will be attended.  
9 Activity profiles produced under the condition of a more moderate unilateral impairment, thus,  
10 result in hemi-extinction.

11 The detailed model of Hilgetag et al. (1999) used biologically inspired parameter  
12 settings for the strengths of inputs and path weights; however, it did not show how much the  
13 simulation outcome depended on the specific settings. Nonetheless, the basic effects of  
14 contralateral functional deficits after unilateral damage, and the reversal of these deficits after  
15 bilateral deactivations, could also be demonstrated in simpler, less detailed models of the  
16 orienting network (Hilgetag et al., 1999; Zavaglia & Hilgetag, 2016; Fig. 6), suggesting that  
17 the basic mechanism of intact, impaired and restored orienting was robust with respect to the  
18 specific mechanism of its *in silico* implementation. In particular, the principal mechanism by  
19 which the different computational models achieved these phenomena was a balancing of  
20 activity between the left and right midbrain, such that stimulus-related input activity could elicit  
21 sufficiently strong activity in the map of the superior colliculus that could then serve as a signal  
22 for orienting to the location indicated by the map activity. Importantly, models such as these  
23 can be used to predict ‘Sprague Effect’-like paradoxical functional effects in the human brain  
24 observed through non-invasive functional perturbations by repetitive TMS (Hilgetag et al.,  
25 2001b, 2003, see Section 5 for further details). Incorporating the bilateral balancing mechanism  
26 into models of spatial attention may also be an attractive option for the strengthening of

1 theoretical models of attentional function and dysfunction that focus on additional dimensions  
 2 of attention such as object-centered attention (e.g., Pouget & Sejnowski, 1997; Pouget et al.,  
 3 1999; Deneve & Pouget, 2003) or attention in multisensory integration (e.g., Bauer et al., 2015),  
 4 as well as others reviewed in Fabius (2013).



6  
 7  
 8 **FIGURE 6. Simple network model of orienting behavior and the ‘Sprague Effect’ in the**  
 9 **cat. (A) Simplified representation of the attention network of the cat. The network**  
 10 **includes cortical stages, specifically left and right pMS, the left and right superior colliculi,**  
 11 **as well as motor output structures that act as effectors. Importantly, competition by**  
 12 **mutual inhibition (indicated by red arrows) is acted out between the two colliculi. (B)**  
 13 **Simulated orienting into the left visual field for all possible combinations of intact and**  
 14 **deactivated cortical and midbrain structures, based on the steady state behavior of the**  
 15 **network model shown in (A). Stars indicate the correctly predicted orienting into the left**  
 16 **field, including the scenarios corresponding to the ‘Sprague Effect’ (for bilateral,**  
 17 **balanced deactivations of cortical and midbrain elements). In particular, indicated at the**  
 18 **bottom of the diagram are all 16 possible states of the system, ranging from all 4 cortical**  
 19 **and midbrain regions being intact (structures in white) to all regions being deactivated**  
 20 **(structures in black). Displayed at the top of the diagram are the empirically observed or**  
 21 **predicted behaviors, with white fields indicating intact orienting and black fields**  
 22 **indicating impaired orienting. The simple network model perfectly reproduces the**  
 23 **empirically observed behaviors of deactivation studies, under the assumption that the**  
 24 **animal orients to the left whenever the activity in the right-hemispheric output structure**  
 25 **is larger than that in the left-hemispheric output (i.e., bars > 0). pMS: posterior aspect of**  
 26 **the Middle Suprasylvian Sulcus, SC: superior colliculus, L: left, R: right. Figures adapted**  
 27 **from Zavaglia and Hilgetag (2016).**



## 1 4.2. The ‘Sprague Effect’ in theoretical concepts of distributed brain function

2 In addition to finding a mechanistic explanation for the surprising phenomenon of  
3 functional restoration by additional brain perturbation, the ‘Sprague Effect’ poses more general  
4 challenges to theoretical concepts of brain function and lesion inferences. Young et al. (2000)  
5 used the ‘Sprague Effect’ as an example for distinguishing different aspects of brain function,  
6 to demonstrate shortcomings of traditional approaches for lesion inference. For example,  
7 applying the conventional lesion inference of double dissociation to separately performed  
8 perturbations of right- or left-hemispheric cortical or midbrain structures involved in orienting  
9 behavior in the cat, one would assume that right-hemispheric structures are responsible for  
10 orienting to the left field and left structures for orienting to the right field, and that they function  
11 independently. Particularly the latter conclusion is upset by the ‘Sprague Effect’, which makes  
12 it evident that the brain is not just a box of accumulated specialized units that act independently.  
13 Rather, the brain forms a network of specialized processors that interact in manifold ways to  
14 produce brain function. Importantly, there is also a linkage between brain structures provided  
15 by physical interactions such as vasculature, necessitating the use of multivariate approaches  
16 for lesion inferences (Mah et al., 2014; Xu et al., 2018).

17 Paradoxical lesion effects (Kapur, 1996, 2011) such as the ‘Sprague Effect’ demonstrate  
18 that different neural elements are functionally linked, and imply that the causal contributions to  
19 different functions of the brain cannot be reliably revealed by perturbation or deactivation of  
20 individual processors, or simple combinations of processors. Instead, what is required for  
21 obtaining an exact and reliable picture of functional contributions is the analysis of the complete  
22 set of all combinations of perturbations (from single, double, triple on so on perturbations, to  
23 the deactivation of all relevant structures) together with their associated performance scores.  
24 The exhaustive functional characterization of this set of all possible combinations of intact and  
25 deactivated elements (comprising  $2^N$  states for  $N$  system elements) provides complete  
26 information on the functional contribution of all elements across all functional states.

1 One way to derive these contributions quantitatively and mathematically exactly is  
2 provided by the Shapley value (Shapley, 1953; Keinan et al., 2004b, 2006). Applying this  
3 approach to the orienting network of the cat yields the expected positive and negative  
4 contributions of contra- and ipsilateral structures to contralateral orienting, respectively. It also  
5 allows to compute interactions between structures, which can be used to make inferences about  
6 redundant functional contributions as well as synergistic interactions of neural elements, for  
7 instance in the attention network of the cat (Zavaglia & Hilgetag, 2016), and to express formally  
8 the relations underlying paradoxical lesion effects (Keinan et al., 2004a). These considerations  
9 have wider impact for the analysis of functional deficits of patients after pathological  
10 impairments, for instance by strokes (e.g., Zavaglia et al., 2015; Toba et al., 2017), and may  
11 help to identify targets for rehabilitation (particularly, structures possessing negative functional  
12 contributions after earlier impairments, which suggests that a perturbation of such structures  
13 would improve functional performance (Keinan et al., 2004a).

14 In sum, anatomically-plausible computational models of inter-hemispheric and inter-  
15 collicular interactions in the feline brain have been used to model the impact of lesions and  
16 mimic the behavioral consequences of the ‘Sprague Effect’. By doing so, they helped pinpoint  
17 some of the necessary conditions for achieving restoration of attentional orienting. The use of  
18 multivariate inferential methods, such as the game-theoretical Shapley analysis, has provided  
19 models that better account for the complexity of functional and physical interactions present in  
20 visuo-spatial systems, and has led to better predictions of how hemineglect deficits can be  
21 overcome. However, experimental evidence on manipulating interhemispheric rivalry in  
22 reversible perturbation experiments continues to be paramount, to either validate models or  
23 implement their therapeutic predictions. Therefore, in the context of the ‘Sprague Effect’, we  
24 proceed by comprehensively reviewing causal evidence from felines and humans that has  
25 developed our knowledge on visuo-spatial attentional systems, its disorders and our ability to  
26 modulate them non- invasively with brain stimulation.

## 5. Non-invasive manipulation of interhemispheric rivalry in humans and animal models

Non-invasive brain stimulation technologies (NIBS) play a major role in the study of causal brain-behavior associations in cognitive neuroanatomy. Additionally, they provide a unique opportunity to modulate abnormal brain activity patterns subtending neuropsychiatric pathology and provide new promise of recovery. To date, two main technologies are being used to stimulate brain systems in neurorehabilitation: Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). Both have been used to manipulate human visuo-spatial attentional systems and their disorders in experiments reminiscent of the feline 'Sprague Effect'

TMS is based on a focal induction of an electrical current transported intracranially via a short-lasting magnetic pulse (~150-250  $\mu$ s), able to depolarize exposed neurons. Used in repetitive patterns of pulses for periods between 10 to 30 minutes, the so called repetitive TMS (rTMS) has the ability to modulate brain activity during (*online*) but also beyond the duration of the pulses (*offline* impact of *aftereffects*) and drive increases or decreases of excitability. Such effects can be prolonged and become therapeutically meaningful by accruing daily stimulation sessions with less than 24 hours interval. The direction of rTMS modulations depends on the spatiotemporal organization of its pulses within a short burst or a long pattern. Generally speaking, low rTMS frequencies (notably 1 Hz continuous patterns) have shown suppressive effects, whereas high frequencies (trains of 5 Hz rTMS or higher, i.e., generally 10 Hz and 20 Hz trains with interleaved pauses) increase local activity. Complex mixed-frequency rTMS patterns, known as Theta Burst Stimulation (TBS) delivering 50 Hz rTMS triplets (3 pulses) at a 5 Hz frequency (i.e., every 200 ms) are also widely used to transiently modulate brain activity and either inhibit (continuous TBS or cTBS, for only 40 seconds) or excite (intermittent TBS, iTBS for only 110 seconds) brain excitability. Even if rTMS is delivered focally (with a spatial resolution of ~12-15 mm radius), it can also generate effects in distant

1 regions interconnected with the initial target as a function of the richness of structural  
2 connectivity and the type and number of synaptic steps between (Valero-Cabr  et al., 2017).

3 Non-invasive stimulation with tDCS is based on the modulation of resting membrane  
4 potential of a large area of neurons (at least 5 to 7 cm) by passing a weak constant current (1-2  
5 mA) between an active electrode (either the anode or a cathode) placed on a scalp region  
6 overlying a cortical target and a reference electrode. It has been shown that anodal stimulation  
7 tends to increase the probability of neuronal firing across the targeted region, whereas cathodal  
8 stimulation exerts the opposite effect. Such modulations lasting between 10 to 20 minutes are  
9 very intense while the field is on (online effects) but can also outlast their duration (offline  
10 effects or aftereffects). As for rTMS, the accumulation of daily tDCS sessions is thought to  
11 achieve longer-lasting modulatory effects, which can become therapeutically useful. Unlike  
12 rTMS, tDCS does not increase epileptogenic risk, hence it is easier to use and safer. It also can  
13 be easily made portable, or wireless and it is therefore more suited for clinical settings or home-  
14 delivered treatments. Unfortunately, large regions of the cortical surface between the active and  
15 reference electrodes are influenced by the generated electric fields and this lack of focality  
16 makes it less suited than TMS for the exploration of brain-behavioral causal inferences (Valero-  
17 Cabr  et al., 2017).

18 Since 2001, both non-invasive stimulation approaches, initially TMS but more recently  
19 also tDCS, are being used to manipulate mutually rivalrous interhemispheric interactions  
20 involved in the allocation of visuo-spatial attention. These approaches have aimed to  
21 experimentally validate the models and hypotheses of Sprague (1966a), and Kinsbourne (1977)  
22 and test hemispheric contributions in human attentional allocation systems hypothesized by  
23 Heilman (1980) and Mesulam (1981, 1990, 2002).

24 Pioneering efforts were initially developed mainly with TMS in healthy human  
25 participants or even stroke patients. Work in feline experimental models addressing similar  
26 questions was performed in parallel, with little awareness and interaction with experiments in

1 the human domain. Explorations in both human and feline studies employed lateralized visual,  
2 tactile or auditory detection/discrimination paradigms based on unilateral or bilateral targets.  
3 Effects were recorded by means of computer-controlled tasks in which animals or humans were  
4 required to acknowledge and localize visual stimuli or report some of their features (spatial  
5 frequency, orientation, color etc.), during the impact of TMS delivered at specific time windows  
6 or while under the influence of tDCS fields (*online designs*). Studies, also employed designs  
7 based on evaluating effects on visuo-spatial and perceptual abilities outlasting the delivery of  
8 magnetic field or electrical currents (*offline designs*) to a specific cortical region (Valero-Cabré  
9 et al., 2017). Specific stimulation parameters or montages in *online* and *offline designs* (e.g.,  
10 low vs high frequency rTMS or cTBS vs iTBS or anodal vs cathodal tDCS) aimed to either  
11 increase or decrease local (and network excitability), generate transient reversible unbalances  
12 of inter-hemispheric interactions, and by doing so, test the functional malleability (suppression  
13 vs facilitation) of visuo-spatial performance (see Valero-Cabré et al., 2017 for a recent review).

### 14 15 *5.1 Non-invasive manipulation of interhemispheric rivalry principles in humans*

16 The earliest pioneering study on this topic matter was performed in healthy human  
17 participants by Pascual-Leone et al. (1994). Paradoxically, this occurred years before reversible  
18 invasive (Payne and Lomber, 1996) and non-invasive (Valero-Cabré et al., 2006a) manipulation  
19 methods were tested in feline models to emulate Sprague's work. Following rapid rate rTMS  
20 trains (25 Hz bursts) delivered just prior to target onset on the right posterior parietal cortex  
21 (EEG 10-20 system site P4), these authors reported *extinction-like* behavior for left lateralized  
22 visual targets when competing with the simultaneous presence of a target in the right hemifield.  
23 Also, interestingly, left posterior parietal stimulation (EEG 10-20 system site P3) induced  
24 'hemineglect-like' effects but this time for right targets.

25 Paralleling this experience in the somatosensory domain, a study supervised by Robert  
26 Rafal applied double TMS pulses (50 ms interval) over two ill-defined parietal regions and

1 observed paradoxical increases of sensitivity to cutaneous finger stimulation delivered  
2 ipsilateral to the stimulation, compared to sensorimotor or frontal stimulation (Seyal et al.,  
3 1995). These authors related this result to a transient dysfunction of the ipsilateral parietal  
4 cortex resulting in the disinhibition of the contralateral parietal cortex.

5 To further explore the multimodal nature of parietal contributions on attentional  
6 orienting in space, Oliveri et al. (2000a) explored the *online* impact of short (1 ms) inhibitory  
7 inter-stimulus intervals (ISI) vs. long excitatory ISI intervals (5 ms) of paired pulse stimulation  
8 on the human right posterior parietal cortex. These authors reported higher levels of *extinction-*  
9 *like* effect for left hand tactile stimulation during bilateral tactile presentations with the former,  
10 and facilitatory tactile detection effects in these same types of trials, at the latter interval.

11 A year thereafter, a highly influential study (see editorial discussion by Rafal, 2001)  
12 used a visual detection task titrated for difficulty in healthy participants (Hilgetag et al., 2001).  
13 Authors demonstrated for the first time lasting ‘*hemineglect-like*’ effects (5–10 minutes  
14 duration) after a single session of inhibitory repetitive TMS patterns (1 Hz, 10 minutes 600  
15 pulses) to the right and left posterior parietal cortex (10-20 EEG sites P4 and P3 respectively).  
16 They showed improvement for left-sided targets during bilateral presentations and for unilateral  
17 right-sided target, respectively (Hilgetag et al., 2001). Importantly, the study also showed that  
18 following right posterior parietal cortex suppression via rTMS, the attended ‘*extinction-like*’  
19 effects for left visual targets (hence classically observed in visual hemineglect syndromes and  
20 also reported in Pascual-Leone et al., 1994) were accompanied by improvement of detection  
21 for ipsilateral targets. This outcome provided causal support for models of interhemispheric  
22 competition in distributed brain networks for spatial attention, anticipated by Sprague (1966a)  
23 and later translated to humans by Kinsbourne (1977).

24 Subsequently, a study by Thut et al. (2005) using the same *offline* rTMS design  
25 employed by Hilgetag et al. (2001) extended this observation to the allocation of voluntary -  
26 endogenous- attention. These authors presented sound cues with different pitches, predictive of

1 the hemifield in which a contrast-titrated visual target would appear (right or left vs no cue  
2 neutral condition). Irrespective of the presentation side, 600 pulses of inhibitory 1 Hz rTMS on  
3 the right posterior parietal cortex (EEG site P4) preserved the overall benefit of cuing. However,  
4 it interfered with the spatial information carried by leftward cues (i.e., sound predictive of a left  
5 target onset) and with the detection of left targets. Importantly, inhibitory 1 Hz rTMS enhanced  
6 ipsilateral right target detection after valid rightward cuing. This result further substantiated the  
7 notion of interhemispheric rivalry for spatial attentional orienting pioneered by Hilgetag et al.  
8 (2001). Moreover, according to Sprague's original observations, it supported the ability of focal  
9 cortical inhibition to paradoxically result in visual performance enhancements.

10 Additional support in favor of interhemispheric rivalry interactions and Sprague's  
11 model was published in 2006 by Dambeck et al.. These authors first demonstrated *hemineglect-*  
12 *and extinction-like* effects generated *online* with a time-locked single TMS pulse (150 ms but  
13 not 250 ms, pre-target onset) to the right posterior parietal cortex (EEG site P4). Most  
14 interestingly however, the former effect did not occur during bilateral single pulse stimulation  
15 (Dambeck et al., 2006) of the right and the left posterior parietal cortex (P4 and P3)  
16 simultaneously. Indeed, building on the latter study, we combined lasting rTMS to a hemisphere  
17 (suppressive or excitatory) with a second rTMS pattern with opposite or identical effects on the  
18 opposite hemisphere (Hilgetag, Valero-Cabré and Rushmore, personal communication).  
19 Nonetheless, all our attempts provided inconclusive results, warning about the  
20 oversimplification of conceiving inter-hemispheric interactions and their modulation as purely  
21 additive/subtractive processes.

22 A majority of the above-reported studies that set the field exploited the concept of  
23 'virtual lesion' and used inhibitory rTMS patterns to transiently take a region *offline*, and  
24 emulate classical post-stroke visual hemineglect. Nonetheless, a study in healthy participants  
25 by Kim et al. (2005) tested the impact of excitatory rTMS (10 Hz) on a line bisection judgment  
26 task. Opposite to prior and by now well-proven *hemineglect-like* and/or *extinction-like* effects

1 of low frequency rTMS, these authors reported for the first-time increased allocation of  
2 attention in the contralateral visual hemifield following right (EEG site P4) and also left (EEG  
3 site P3) posterior parietal stimulation.

4 Due to its low spatial resolution and lower modulatory power, the manipulation of  
5 interhemispheric interactions tied to attentional allocation with tDCS has received less  
6 attention. Nonetheless a contribution (see Sparing et al., 2009, Experiment 1) in healthy  
7 participants provided first time evidence that anodal (hence likely excitatory) tDCS to right and  
8 left posterior parietal cortices (EEG sites P4 and P3), facilitated the detection of contralateral  
9 targets, whereas showed no effects for ipsilateral targets. Additionally, in this same experiment,  
10 cathodal (likely inhibitory) tDCS decreased detection for contralateral (*hemineglect-like*) and  
11 bilateral (*extinction-like*) targets but it paradoxically increased detection performance for  
12 ipsilateral targets. These outcomes provided tDCS support of Sprague’s postulates as extended  
13 to humans and showed once more (Hilgetag et al., 2001; Thut et al., 2005) the ability of  
14 suppressive neurostimulation patterns to paradoxically facilitate visuo-spatial function in the  
15 healthy brain. Most importantly, it opened the door to a safer, less expensive and portable  
16 technology better suited for therapy such as tDCS, for rehabilitation of visuo-spatial disorders.

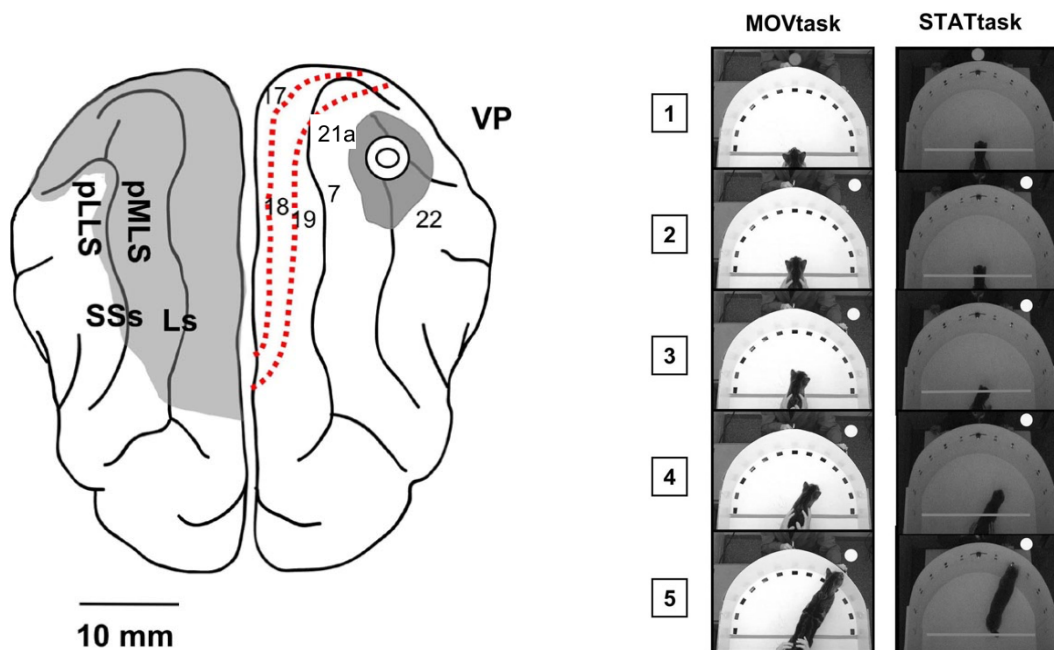
17 Since 2006, therapeutic approaches for the rehabilitation of post-stroke hemineglect in  
18 humans intend to capitalize on paradoxical improvements driven by neurostimulation. They  
19 built their rational on ‘Sprague Effect’ principles and the ability of TMS/tDCS technologies to  
20 modulate activity in opposite directions (see Section 6 for further details). Nonetheless, the  
21 relation between excitatory and inhibitory rTMS/tDCS patterns and increases and decreases of  
22 performance remains dubious. At least two studies (Jin and Hilgetag, 2008, Dombrowe et al.,  
23 2015) have failed to report significant differences between high vs low rTMS offline patterns  
24 delivered to the right or left posterior parietal cortex (posterior portion of the intraparietal sulcus  
25 overlying the angular gyrus) in visuo-spatial attention tasks.



1 These outcomes impose to any neurostimulation strategy aiming to reverse hemineglect  
2 based on the ‘Sprague Effect’ a careful choice of stimulation parameters and ideally, the  
3 evaluation in pre-therapeutic stages of suppressive or facilitatory interventions over the same  
4 targets. The use of neuroimaging or neurophysiological methods to document the modulatory  
5 changes induced by the intervention, considering the targeted area and its status following  
6 damage is also highly recommended. In an attempt to minimize uncertainty when facing human  
7 clinical trials, the same feline model of visuo-spatial attention that led to the ‘Sprague Effect’  
8 has been used as a test bench to evaluate therapeutic strategies.

## 10 *5.2 Non-invasive manipulation of interhemispheric rivalry principles in felines*

11 To date, a handful of studies experimented with the non-invasive manipulation of  
12 interhemispheric rivalrous interactions in the same feline model that was originally employed  
13 to report paradoxical visual function recovery following sequential brain lesions. The ideas  
14 behind such explorations built upon studies by Bertram Payne and collaborators using  
15 reversible local thermal deactivations (also referred as cooling) with unilateral or bilaterally  
16 (cortical or subcortical) implanted probes in the cat extrastriate visual cortex (Lomber et al.,  
17 1999).



**FIGURE 7.** Left Panel. Dorsal view of the cat's brain. Location of the visuo-parietal (VP) cortex is identified (shading) with the target area of rTMS stimulation (⊙). The medial (pMLS) and lateral (pLLS) banks of the posterior suprasylvian sulcus (pMS cortex), located on the sides of the suprasylvian sulcus (SSs) are indicated. The primary visual areas 17, 18 and 19, extrastriate visual regions 7, 21a and 22, and the lateral sulcus (Ls), are also labeled. Notice the extent of the ablated striate and extrastriate visual cortex in the injured subjects (light gray shading), which is delimited by cingulate sulcus in the midline (not shown), and the lateral bank of the suprasylvian cortex in the lateral region of the parietal lobe. Scale=10 mm. Right Panel Serial snapshots of a representative cat performing a trial in the moving stimulus task (MOVtask; first column) or the static stimulus task (STATtask; second column). In the former, cats are taught to respond to the detection of a scoop with wet food on the top. In the latter, animals need to respond as quickly as possible to the appearance of a LED in different peripheral locations. When the target is correctly detected and approached, they are given wet food as a reward. For both tasks, cats are trained to fixate to a 0° fixation stimulus for a variable period (1). Then, as soon as a peripheral stimulus appears (2) and only if they become aware of it, detect and locate it correctly, they orient the head to that specific eccentricity (3), and they move towards it (4), reaching the target (5) in a straight radial trajectory. The MOVtask uses highly salient moving stimulus with high background illumination, whereas the STATtask is performed with static stimulus at very low background intensity, thus high contrast.

The area responsible for allocation of attention in space and hemineglect in the feline model (hence a sort of 'homologue' of the human posterior parietal cortex areas often referred as visuo-parietal, VP cortex) is the pMS area (see section 2.1, for further details). Four seminal papers using reversible thermal deactivation - two of them communicated to the journal Proceedings of National Academy of Science by James Sprague himself - laid the groundwork

1 to optimize the methods and causally pinpoint the networks encompassing mutually inhibitory  
2 interactions predicted by Sprague (1966a) (Lomber et al., 1994; Payne et al., 1996; Vanduffel  
3 et al., 1997; Lomber et al., 1996).

4 In 1994, Lomber and Payne showed during reversible thermal inactivation of the feline  
5 visuo-parietal cortex, a blockade of local neuronal firing and impaired figure-ground  
6 segregation, with moving but not static masks. Two years later, these same authors deactivated  
7 either the visuo-parietal cortex or the ipsilateral superior colliculus, and showed reversible signs  
8 of hemineglect in the contralateral visual hemifield (Payne et al., 1996). In 1997, a third study  
9 by the same group used metabolic labeling with radioactive  $^{14}\text{C}$ -2DG (2-deoxyglucose) of  
10 the pMS cortex area during unilateral cooling deactivation of this area combined with  $^3\text{H}$   
11 proline and  $^3\text{H}$  leucine tracer injections. They revealed local but also distant deactivations in  
12 a network of richly interconnected cortical and subcortical nodes, hosted in the ipsilateral visual  
13 cortex, the superficial layers of the superior colliculus and some nuclei of the posterior visual  
14 thalamus (Vanduffel et al., 1997). Most importantly, emulating for the first time a reversible  
15 version of Sprague's original experiment (see Payne et al., 1996 for a review), Lomber and  
16 Payne revealed how task-specific hemineglect for moving targets induced by unilateral  
17 deactivation of the cat's pMS cortex or the superior colliculus could be reversed with a  
18 combined bilateral cortical (or collicular) deactivation, in both hemispheres (Lomber and  
19 Payne, 1996; Lomber and Payne, 2001). In their own words, they wrote: "*removing both halves*  
20 *restored the whole*". Of note, task-specific hemineglect for static stimuli was not reversed with  
21 bilateral deactivations.

22 Completing a long step-by-step experimental process to further develop the feline model  
23 of visuo-spatial attention (from 1994 to 2002, see Payne and Rushmore, 2004 for a systematic  
24 review), the exact conditions and outcomes of Sprague's original experiment (1966a) were re-  
25 tested. Importantly, this re-evaluation confirmed that visual hemineglect for moving stimuli  
26 following a unilateral ablation of the visuo-parietal cortex could be offset by a focal

1 deactivation of the contralesional pMS cortex or the superior colliculus. The latter set of  
2 observations opened the stage to explore the restoration of attentional orienting in feline  
3 hemineglect by means of invasive (thermal deactivation by cooling probes) and non-invasive  
4 (TMS, tDCS) deactivation methods applied to the healthy contralesional hemisphere, which  
5 unfolded during the following decade (2005-2014, see Section 6 for full details).

6 Building on solid ground, intact felines have been used as test bench to evaluate the  
7 manipulation with NIBS technologies (TMS and tDCS) of attentional orienting systems and  
8 their subtending interhemispheric rivalrous interactions, previously exclusively used in  
9 humans.

10 In their first TMS feline studies, Valero-Cabr e et al. (2005) confirmed the ability to  
11 achieve spatially selective unilateral TMS stimulation and obtained motor evoked responses  
12 from the cat's primary motor (M1) region by using the edge of a small circular coil. Then, these  
13 authors injected radioactively labelled 2-deoxy-glucose ( $^{14}\text{C}$ -2DG) to anesthetized cats  
14 during the delivery of high frequency rTMS (20 Hz, in 2 second-trains with a 28 seconds  
15 intertrain interval, total of 2240 pulses) lasting for 28 minutes to the right pMS area. Active or  
16 sham stimulation of the frontal cortex (around the location of M1) and sham stimulation on the  
17 pMS were used as active and placebo controls, respectively. Similar to Vanduffel et al. (1997),  
18  $^{14}\text{C}$ -2DG findings revealed local *online* decreases of glucose uptake (i.e., during the delivery  
19 of rTMS). Surprisingly, reductions of  $^{14}\text{C}$ -2DG uptake were also noticed in an extended and  
20 richly interconnected set of regions (e.g., the primary and splenial visual cortex, the superficial  
21 layers of the superior colliculus and specific posterior thalamic nuclei) known to subtend  
22 connectivity with the former. Importantly, the impact of distant stimulation correlated with the  
23 richness of anatomical connectivity and the number of synaptic steps. The study visualized for  
24 the first time the network distributed impact of focal rTMS stimulation.

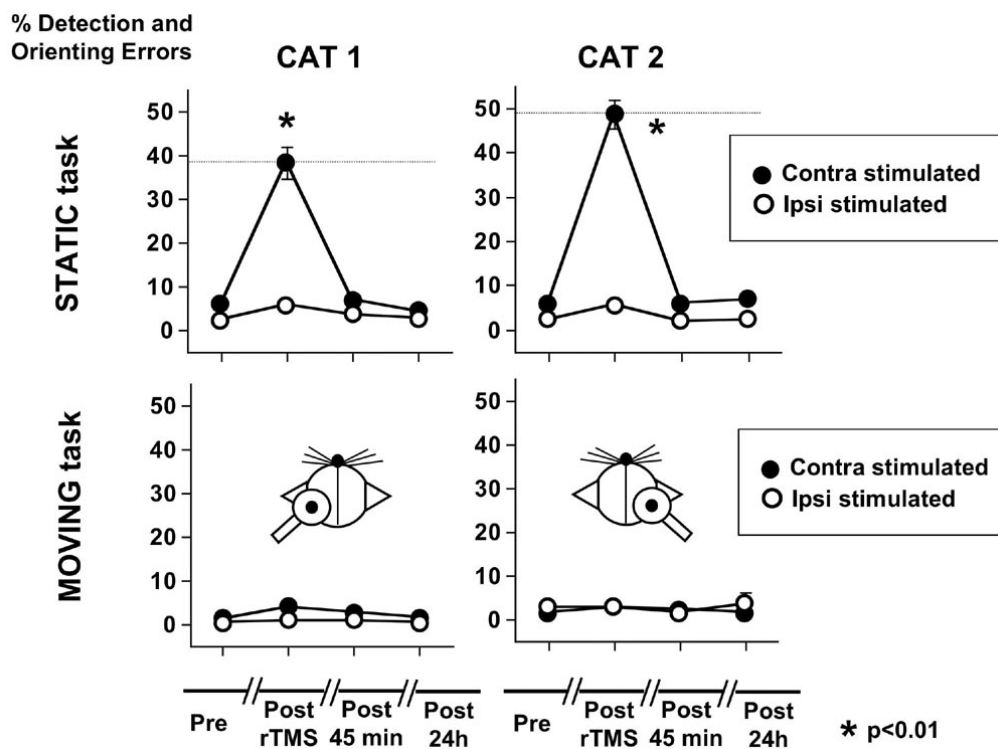
25 In a second  $^{14}\text{C}$ -2DG feline metabolic labelling experiment, Valero-Cabr e et al.  
26 (2007) reproduced the same *online* metabolic effects reported in 2005, and extended their

1 observations to the *offline* metabolic impact (i.e., following the delivery of a 28 minutes rTMS  
2 pattern) of active vs sham high frequency rTMS (20 Hz bursts, 2240 pulses) vs. low frequency  
3 rTMS (continuous 1 Hz, 1800 pulses) rTMS. The study revealed, increases of local and distant  
4 - hence network distributed - metabolic impact following active 20 Hz rTMS compared to sham,  
5 whereas opposite, 1 Hz rTMS showed local decreases. These local modulatory effects, proved  
6 weaker than those generated online, and in any case transient and rather short-lasting, wearing  
7 off 30 minutes after the end of the stimulation (Valero-Cabr e et al., 2007). Also, importantly,  
8 no significant transynaptic effects were observed during such local aftereffects.

9 Building on such *offline* rTMS effects, parallel experiments to those undergone with  
10 thermal deactivation a decade before (Payne et al., 1997), Valero-Cabr e et al. (2006a) showed  
11 reversible impairments of visuo-spatial orienting to static targets this time in awake intact cats,  
12 lasting for 15 minutes after the unilateral delivery of 1Hz rTMS (20 minutes, 1200 pulses) on  
13 the pMS cortex (Fig. 8). Importantly, such reversible ‘hemineglect-like effects’ only impacted  
14 the localization of targets displayed in the contra-stimulated visual hemifield, following a  
15 peripheral-to-pericentral eccentricity gradient (Valero-Cabr e et al., 2006a).

16 In agreement with ‘Sprague Effect’s predictions verified in humans by Hilgetag et al.  
17 (2001), a combined behavioral and metabolic labeling feline experiment showed that 1 Hz  
18 inhibitory rTMS to the right pMS cortex induced contralateral ‘*hemineglect-like*’ effects but  
19 also paradoxical detection improvements for ipsilateral static targets. These effects were visible  
20 when a well-titrated task, with performance rates equidistant from floor and ceiling levels was  
21 used as read-out. In this same experiment, a comparison of unilaterally applied high-frequency  
22 (10 Hz, 1 second trains, 5 second intertrain interval, for 20 minutes) vs. low-frequency (1 Hz,  
23 600 pulses, 20 minutes) stimulation on the right pMS cortex revealed similar behavioral  
24 outcomes, consisting of contralateral (‘hemineglect-like’ effects) and ipsilateral (‘paradoxical’  
25 detection improvements) performance outcomes for rTMS patterns. As attended, 14[C]-2DG  
26 labeling revealed opposite modulations of local pMS metabolism (as reported in Valero-Cabr e

et al., 2007). However, unexpectedly, we found identical transynaptic network effects on metabolism with decreases of activity in cortical, collicular and posterior thalamic transynaptic targets (Valero-Cabr e et al., 2008b). These results suggested that both, inhibitory and excitatory modulations of local activity by high and low frequency rTMS, induce a common network impact on transynaptic targets, which translate into similar patterns of behavioral outcomes. On this basis, we hypothesized that irrespective of the direction of the net modulatory effect, the local impact of rTMS induces a pMS ‘disconnection’ from nodes of its own network, hence that is the latter effect rather than the local impact what is ultimately responsible from changes in visuo-spatial performance.



**FIGURE 8.** Percentage of errors ([number of errors/Total number of trials]\*100) in the detection and location of static (first row, STATtask), or moving (second row, MOVtask) stimuli, displayed on the ipsi-stimulated (same side as the TMS coil, white dots), or contra-stimulated (opposite side as the TMS coil, black dots) visual hemifield (Valero-Cabr e et al. 2006a). Data correspond to the 2 intact animals (cats 1 & 2) evaluated before, immediately after, and 45 minutes and 24 hours after the end of a 20 minutes 1 Hz rTMS stimulation period. They represent the average of 8 different experiments per cat. Notice the dramatic but reversible increase in the percentage of errors detecting and responding

1 **to static (STATtask) contralateral targets but not moving (MOVtask) targets, after real**  
2 **rTMS. \*: p<0.01 vs. pre-real rTMS.**

3  
4  
5 More recently, some feline behavioral correlates of attentional orienting have been also  
6 probed with tDCS. Similar to rTMS, ‘hemineglect-like’ effects for contralateral targets have  
7 also been found in cats during or following cathodal (but not sham) tDCS delivered to the right  
8 pMS cortex (Schweid et al., 2008). As shown later on for humans by Sparing et al. (2009), this  
9 evidence corroborated the use of transcranial Electrical current (tECS) technologies in the  
10 modulation of visuo-spatial systems and their place as a potential therapy for hemineglect.

11 Any of these prior feline thermal deactivation or non-stimulation studies used single  
12 session perturbations, hence fully reversible. However, in a unique attempt to support the  
13 therapeutic promise for neuromodulation (e.g., overcoming obvious ethical limitations to  
14 perform such an experiment in humans), Valero-Cabré et al. (2008) tested in the intact feline  
15 brain the long-lasting impact of consecutive rTMS sessions. Across 4 weeks of daily low  
16 frequency rTMS (continuous 1Hz, for 20 minutes, 600 pulses, 30 daily sessions Monday to  
17 Sunday) to the right pMS cortex, our study showed progressive magnitude increases of *offline*  
18 ‘hemineglect-like’ of intact cat effects, as those reported previously (Valero-Cabré et al., 2006a)  
19 for static visual targets. Interestingly the behavioral effects induced by each individual session  
20 were found worn off 1 hour and 24 also hours following each rTMS session (Valero-Cabré et  
21 al., 2008). However, the facility to evoke these daily ‘hemineglect-like’ transient effects  
22 increased progressively and remained so for at least a whole week after the last rTMS session.  
23 Importantly these results strongly supported the possibility of inducing long-lasting visuo-  
24 spatial effects and to use them therapeutically to reverse hemineglect in injured brains.

25 In sum, intact human and feline experiments developed for the last 20 years reversibly  
26 manipulating (via thermal deactivation, or TMS and tDCS) visuo-spatial networks have been  
27 instrumental for deepening our understanding on the role played by interhemispheric rivalrous  
28 interactions in attentional orienting. Moreover, they also contributed significantly in providing

evidence on our ability to modulate such systems, hence paving the way for further testing that could result into effective therapies based on ‘Sprague Effect’ principles. Nonetheless, efficient translation of such knowledge into clinical applications still requires evidence on punctual or longer lasting manipulations in hemineglect animal models or post-stroke hemineglect patients. The following section will comprehensively review feline and human patient studies intended to reverse hemineglect with non-invasive stimulation after brain damage.

## **6. The ‘Sprague Effect’ as a therapeutic model for noninvasive stimulation in hemineglect**

The ‘Sprague Effect’ is a fascinating example of seemingly paradoxical and unpredictable interactions between brain structures. It occurs when a unilateral lesion encompassing systems in the right or left hemisphere involved in attentional allocation (fronto-parietal nodes and networks) unbalances a delicate equilibrium of excitability between the two hemispheres. It operates on the basis of mutually opposing inhibitory interactions driven by the fibers of the corpus callosum or the midbrain’s intercollicular commissure. Most specifically, the initial damage (hence the attentional systems herein, including right or left cortical, subcortical and brainstem structures) will decrease the strength of the inhibition exerted towards the opposite hemisphere. As a result, relevant attentional systems within the spared hemisphere experience increases of excitability, which will inhibit even further damaged contralateral regions (cortical or collicular) preventing remapping of function and spontaneous recovery.

From a clinical perspective, rebalancing brain activity between the two hemispheres by targeting and modulating specific brain areas may have the ability to uncover functions that do not appear spontaneously after brain damage. This principle has provided recovery of visuo-spatial dysfunctions and particularly of the so called hemineglect in animal models and human right hemisphere stroke patients. Importantly, the rebalance of mutually inhibitory visuo-spatial networks hosted in opposite hemispheres allowing the recovery of sound spatial allocation of attention could be achieved: 1) by increasing activity in lesional and perilesional regions within



1 the damaged hemisphere likely to remap lost function or alternatively, 2) by suppressing an  
2 excess of inhibition from the spared hemisphere, allowing such process to occur naturally. We  
3 will now review evidence showing how the ‘Sprague Effect’ not only was at the forefront of a  
4 renewed view on how to conceptualize the relation between brain interactions and neurological  
5 conditions, but also instigated new ways to treat them, which crystalized with the advent of  
6 brain stimulation technologies.

### 7 8 *6.1 Non-invasive manipulation of visual hemineglect in felines*

9 In feline models, the effects of unilateral damage to visuo-spatial systems have been  
10 reversibly modulated by means of invasive (thermal deactivation probes) and also non-invasive  
11 (rTMS and tDCS) approaches. Given that at difference to humans, the feline attentional system  
12 is not right-lateralized, experiments interventions have indistinctively tried to compensate right  
13 posterior parietal damage with left pMS cortex (i.e., homologue of the human posterior parietal  
14 cortex) or with left collicular deactivations, and vice-versa.

15 The very first study on this matter tested the impact of an invasive thermal deactivation  
16 by local cooling of the pMS or the superior colliculus contralateral to an extensive occipito-  
17 parietal cortical lesion encompassing the pMS cortex. Data clearly showed the induction of an  
18 enduring hemineglect for moving visual targets in the contralesional visual hemispace and its  
19 reversible cancellation when either the spared pMS or the superior colliculus were inactivated  
20 (Lomber et al., 2002). In an attempt to overcome the limitations of invasive cryoloop probes,  
21 Valero-Cabr e and Rushmore developed the application of rTMS and tDCS methods in this same  
22 feline model. As for thermal deactivation of cats with hemineglect, the goal of these  
23 interventions was to re-enact the ‘Sprague Effect’ this time by reducing brain excitability in the  
24 hemisphere opposite to the damage with inhibitory rTMS (low frequency stimulation) or tDCS  
25 (cathodal stimulation) patterns.

1 In the first pilot experimental therapeutic trial in feline enduring hemineglect following  
2 a large ablation of the visuo-parietal cortex, we tested a daily regime (40 consecutive sessions,  
3 5 sessions a week, Monday to Friday, for 2 months) of active vs sham inhibitory rTMS  
4 (continuous 1 Hz, 20 minutes, 1200 pulses/session) delivered to the spared contralesional pMS  
5 cortex. It was already known that large occipito-parietal ablations (also referred to as visuo-  
6 parietal or VP damage) induced a florid and complete (from 0° to 90°) hemineglect contralateral  
7 to the lesion, that at difference to what is usually observed in human stroke patients, did not  
8 show any level of spontaneous recovery. Nonetheless, prior to rTMS treatment, animals were  
9 followed for 3.5 months to verify this complete lack of spontaneous recovery. Based on what  
10 had been learned in prior studies about rTMS targeting and parameters (see Valero-Cabr e et al.,  
11 2005 & 2007, but particularly Valero-Cabr e et al., 2006a and later published Valero-Cabr e et  
12 al., 2008a), animals were stimulated daily for 8 weeks. Such active rTMS intensive regime (but  
13 not sham rTMS) induced a progressive amelioration of orienting and visual detection skills for  
14 moving targets (Valero-Cabr e et al., 2006b) (see Fig. 9 for details). Interestingly, we observed  
15 that coinciding with the highest rate of recovery for contralateral targets, cats showed slight  
16 transient impairments for ipsilateral targets. In coherence with ‘Sprague Effect’ principles, this  
17 observation suggests a ‘push and pull’ phenomenon between right and left posterior parietal  
18 contributions to control their respective attentional hemispaces. Analysis of behavioral  
19 improvements and metabolic impact of up to 3.5 months under daily rTMS and further follow  
20 for up to 3 months after discontinuing treatment is currently ongoing.

21 A subsequent study evaluated the impact of rTMS stimulation in a feline model of  
22 unilateral pMS neurotoxicity damage with local injections of ibotenic acid (Afifi et al., 2013).  
23 This lesion model attacks neuronal bodies, inducing a loss of neurons, leaving passing white  
24 matter fibers from neuronal bodies outside the injected zone, intact. As normally observed in  
25 human stroke patients, these lesions, which were highly circumscribed to the banks of the pMS,  
26 do allow for a certain level of spontaneous recovery in subsequent post injury months.

1 Importantly, it was already known that performance remains impaired and far from complete,  
2 particularly for static visual targets, hence providing however significant leverage for further  
3 improvements.

4 Our study showed that the accrual of 70 daily sessions (Monday to Friday, during 3.5  
5 months) of excitatory rTMS (10 Hz, 1 second long bursts, 5 seconds inter-burst time, for 20  
6 minutes, total of 2400 pulses/ session) on the perilesional area of the injured hemisphere  
7 induced significant hemineglect recovery at least in half of the animals. Importantly, recovery  
8 remained for up to 6 weeks after discontinuing periodical rTMS. Interestingly, the only  
9 predictor of final recovery was the level of improvement achieved spontaneously prior to the  
10 onset of the rTMS treatment (Afifi et al., 2013). This result puts forward the notion that in lesion  
11 models allowing a degree of recovery, rTMS acts by boosting further forward plasticity  
12 mechanisms which engaged spontaneously reach a glass-ceiling. In order to provide further  
13 insights on effects and mechanism leading to therapeutic failure or success, an ongoing analysis  
14 is currently focusing on the  $^{14}\text{C}$ -2DG metabolic impact in these cat populations.

15 A final and last published attempt extended our therapeutic trials on feline hemineglect  
16 to uses of tDCS. On the basis of prior studies in intact cats (see Schweid et al., 2008), a daily  
17 regime of tDCS (20 minutes of cathodal stimulation, 5 sessions a week, Monday to Friday, for  
18 3.5 months) was used to non-invasively reduce activity in the pMS cortex opposite to the same  
19 type of visuo-parietal ablation well characterized previously (Lomber et al., 2002; Valero-Cabré  
20 et al., 2006b). The treatment was sustained for 14 weeks in an attempt to train the circuits  
21 (Rushmore et al., 2013). Animals exhibited a progressive recovery of function that lasted after  
22 cessation of the tDCS treatment, which to the extent it could be compared to the one achieved  
23 by rTMS, proved slower and less complete.

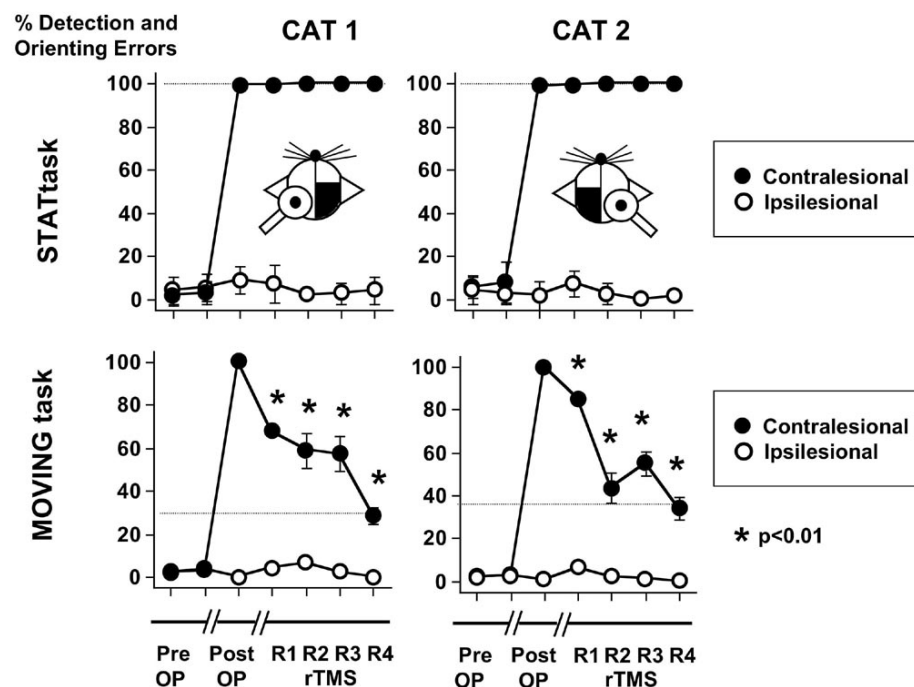
24 Even if here we focused attention on focal top-down brain manipulations via non-  
25 invasive electromagnetic technologies, visuo-spatial attentional systems could be also  
26 modulated by means of sensory (visual, auditory, tactile or combinations thereof) inputs

1 conveyed bottom-up physiologically. A good example of a completely different approach in  
2 manipulating excitability and producing the ‘Sprague Effect’ in felines has been recently  
3 carried out by Jiang et al. (2015). This group took advantage of the fact that many neurons in  
4 the superior colliculus receive multisensory input. On that basis, they trained animals with large  
5 visual cortical lesions using a regime of coincident visual and auditory stimuli (5 days a week  
6 for 4 weeks). While auditory stimulation in the blind hemifield was insufficient to produce  
7 recovery, pairing visual and auditory stimulation induced a complete recovery, suggesting that  
8 increasing excitability in collicular neurons through multisensory stimulation sources was  
9 sufficient to overcome ipsilesional inhibitory signals and restore levels of excitability in the  
10 ipsilateral superior colliculus (Jiang et al., 2015). This venue instigates future interest in  
11 combining *top-down* (brain stimulation) with *bottom-up* (sensory stimulation) strategies to  
12 enhance even further potential therapeutic effects.

13 In the current section, we comprehensively presented evidence in models of feline  
14 hemineglect and showed how punctual or periodical perilesional or contralesional  
15 manipulations of activity could reverse its effects. The isolated or combined long-term clinical  
16 effectiveness of rTMS, tDCS or multisensory inputs remain to be further explored. Nonetheless,  
17 their impact on the ‘Sprague Effect’ should already be taken as an indication that the effects of  
18 brain damage can be reversed, provided one knows how to adequately manipulate the circuit.  
19 The main task for which effects have been reported is an orienting task, one in which the  
20 superior colliculus and the cortex can both independently subservise. However, animal models  
21 displaying the ‘Sprague Effect’ are unable to easily perform most other visual tasks associated  
22 with cortical processing, such as pattern recognition, discrimination (Loop & Sherman, 1977)  
23 or more difficult orientation tasks (Rushmore et al., 2013). This leads to the conclusion that  
24 paradoxical improvement of this type only takes place when functions are parallel and  
25 symmetrically distributed between the two hemispheres. That all being said, the foundation of

1 the ‘Sprague Effect’ does predict that re-modulating connected systems may improve function  
 2 if the circuits and the interactions between them are known.

3 Paradoxically, many of the above-mentioned feline hemineglect studies that used  
 4 reversible interventions to re-enact the ‘Sprague Effect’ followed -instead of preceded- in time  
 5 the first pre-therapeutic and therapeutic rTMS studies in post-stroke hemineglect patients.  
 6 Indeed, human rTMS applications, rather than being first tested in humans to be later translated  
 7 clinically, blatantly ignored animal research and progressed on their own. Regardless, animal  
 8 models have served to reassure the NIBS community about the safety of intensive rTMS  
 9 regimes while providing some unique interesting insights on the potential and limitations of  
 10 rTMS/tDCS methods. The most important ones are that enduring recovery of hemineglect that  
 11 engages adaptive plasticity is task dependent, and only possible if stimulation regimes are  
 12 periodical (less than 24 h intervals in between stimulation) and long duration (at least several  
 13 months).

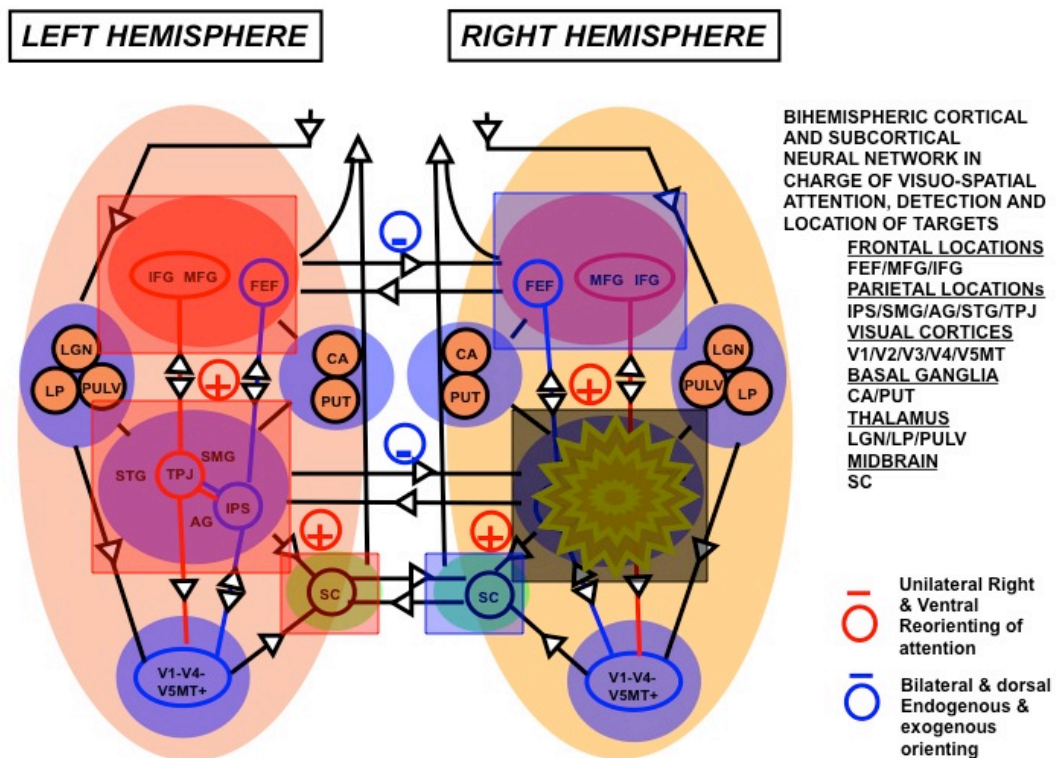


15  
 16 **FIGURE 9.** Percentage of errors in the detection and orienting towards static (first row, STATtask), or moving (second row, MOVtask), stimuli, appearing on the ipsi-lesioned (same side as lesion white circles), or contra-lesioned (opposite side as visuo-parietal lesion, black circles) visual hemifield. Data correspond to the 2 individual animals (cats

1 **1 & 2) at the end of training and right before the surgical unilateral ablation of visuo-**  
2 **parietal cortex (pre-OP), 3.5 months after the injury (post-OP), 1 week after the end of 1**  
3 **(R1), 2 (R2), 3 (R3) and 4 (R4) rounds of 10 days of daily 1 Hz rTMS. Data represent the**  
4 **average  $\pm$  SD of 15 blocks (recorded in 3 training sessions), per time set per cat. Cats**  
5 **performed with minimal % of errors before the surgery (pre-OP). Unilateral removal of**  
6 **visuo-parietal cortex resulted into a complete hemineglect to either moving or static**  
7 **targets appearing in the contralesional visual hemifield, and had no impact on ipsilateral**  
8 **targets. Notice across the 4 rTMS rounds (R1-R4) the progressive decrease in the**  
9 **percentage of errors detecting and orienting to moving (MOVtask) contralateral targets**  
10 **but not static (STATtask) targets. \*:  $p < 0.05$  vs. post OP data.**  
11

## 12 *6.2 'Sprague Effect'-based therapies for visual hemineglect in human stroke patients*

13 Similar to animal models, the 'Sprague Effect' has been particularly put to test and  
14 manipulated during the rehabilitation of left hemisphere stroke human patients suffering  
15 enduring visual hemineglect (Fig. 10). Indeed, for the last 15 years (from the seminal  
16 publication of Oliveri et al. (1999) to those of Koch et al. (2012) and Cazzoli et al. (2012)),  
17 non-invasive stimulation methods -but most notably rTMS- have been tested pre-  
18 therapeutically (single session TMS/tDCS intervention) or therapeutically (multiday periodical  
19 regimes) either in single case patient reports, un-controlled small cohort non-blinded studies or  
20 randomized, single blind phase II monocentric clinical trials. Nonetheless, an effective  
21 translation of feline evidence to human neurological patients calls for clarification of several  
22 relevant questions. Most importantly, what are the characteristics of human hemineglect? What  
23 makes the former similar or different to the feline hemineglect syndrome? And last but not  
24 least, to what extent do the clinical symptoms of the 'Sprague Effect' apply to human right  
25 hemisphere stroke patients?



**FIGURE 10.** Schematic drawing representing the wide spread impact resulting from a focal lesion of the posterior parietal cortex in the right hemisphere. As networks are highly interconnected ensembles, damage in a specific location would produce mainly a local insult by which neural tissue will be directly destroyed or killed. Nonetheless, the neurological symptoms derived from such insult (see yellow star) are to be explained not only by these local effects but also on the basis of *diaschetic* effects conveyed by patterns of white matter connectivity to distant regions of either the same or the opposite hemisphere. In this case, a posterior parietal cortex lesion resulting in signs of visual hemineglect will induce a reduction of activity (see blue shaded areas) in ipsilesional right hemisphere structures such as the frontal cortex and the superior colliculus in the midbrain caused by the lack of excitatory input to these areas from the damaged region. For similar reasons, we would also observe a process of disinhibition in structures of the contralateral spared left hemisphere, mediated by failing inhibitory right to left transcallosal inhibitory projections. Such increases in left hemisphere activity (see red shaded areas) will in turn induce an abnormal level of over inhibition from spared left hemisphere areas to right perilesional tissue that in normal circumstances would be unable to overtake visuo-spatial orienting function. Lesions have local and widespread connectivity mediated effects that explain neurological deficits. Similarly, on this same basis, one could easily envision different approaches to ameliorate hemineglect symptoms by operating on these abnormal mechanisms of transcallosal inhibition that prevent effective spontaneous recovery by plasticity and remapping.

Hemineglect (or also denominated visual hemineglect or visuo-spatial neglect) is a clinically complex deficit that manifests itself with disturbances of perception, attention and action performed in the contralesional space. Those translate into a difficulty or inability to

1 explore the left hemi-space, and as a result, patients may behave as if half of the space has  
2 ceased to exist (Urbanski et al., 2007). Visual hemineglect is most commonly observed in  
3 humans after lesions of the temporo-parietal junction, inferior parietal lobe and ventral posterior  
4 parietal cortex, inferior and middle frontal gyri and the anterior cingulate cortex.

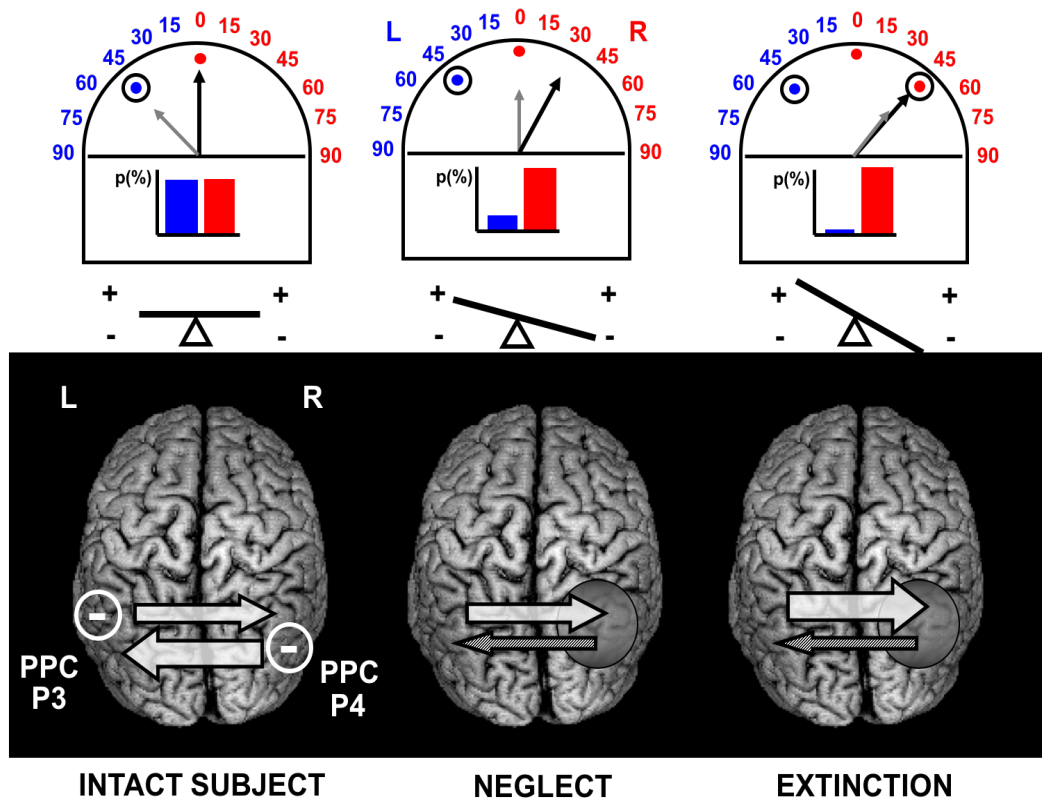
5         Functional MRI (fMRI) studies have hypothesized the existence of two different fronto-  
6 parietal circuits in the orienting of attention and its malfunction in hemineglect. These involve  
7 several ventral and dorsal subregions of the frontal gyri and posterior parietal cortex. More  
8 specifically, according to influential fMRI-based research, a bilaterally distributed *dorsal*  
9 *fronto-parietal attentional network* (linking the dorsal intraparietal sulcus and the frontal eye  
10 fields) has been found specifically in charge of ‘bottom-up’ and ‘top-down’ orienting of  
11 attention. In parallel, a strongly right lateralized *ventral fronto-parietal attentional network*  
12 (encompassing the ventrally located right temporo-parietal junction and right inferior/middle  
13 frontal regions) is in charge of attentional re-orienting (Corbetta et al., 2005; Chica et al., 2011).

14         Models strongly inspired in the feline ‘Sprague Effect’ conceived human hemineglect  
15 as a lateralized left attentional and representational spatial deficit caused by an excitability  
16 imbalance between the two cerebral hemispheres. Following right hemisphere damage,  
17 Kinsbourne’s interhemispheric rivalry hypothesis (Fig. 11) proposes that each hemisphere  
18 directs attention to the contralesional field and balance between hemispheres is exerted through  
19 reciprocal mutual inhibition of homologous structures (Kinsbourne, 1977). Therefore, under  
20 normal circumstances and at rest, the right and left hemisphere are in a sort of ‘equilibrium’ of  
21 mutual inhibition. If a stimulus was to appear in the left visual hemispace, the right hemisphere  
22 would become more excited, thus would inhibit the left hemisphere further.

23         At difference to animal species like cats, this theory suggests also a stronger orienting  
24 bias in the left than the right hemisphere. In others words, in humans at rest, the left cerebral  
25 hemisphere has a slightly larger vector of attention directed to the right visual field than the  
26 right hemisphere’s vector onto the left visual field (Kinsbourne, 1987). Therefore, when the



1 right hemisphere is damaged, the bias of the left hemisphere becomes exaggerated and  
 2 consequently hemineglect is more severe and pervasive. In contrast, left hemisphere parietal  
 3 damage produces mild right visual hemineglect because the unopposed orienting bias generated  
 4 by the right hemisphere is weaker in comparison.



6  
 7 **FIGURE 11.** Schematic illustration of the *Interhemispheric Rivalry Hypothesis* and its  
 8 application to visuo-spatial attention and hemineglect. This hypothesis poses  
 9 interhemispheric inhibitory projections between both posterior parietal regions (see white  
 10 arrows). (Left) In humans, transcallosal inhibitory projections from the right hemisphere  
 11 (10/20 International EEG System P4) are stronger (see white arrows on the brain) than  
 12 those originated in the left posterior parietal cortex (scalp position P3). This results into a  
 13 fixed balance of inhibition that ensures an equally distributed vector of attention (thick  
 14 black arrow on the perimetry area) and equal probability to respond to left or right  
 15 stimuli which would be detected, so that, as shown in the example, if a target appears at a  
 16 left location (45°), the subjects directs to it (see grey arrow). (Middle column) When  
 17 systems for orienting attention in the right hemisphere are damaged) (notice grey area on  
 18 right posterior parietal cortex), homologous regions in the left hemisphere are dis-  
 19 inhibited, so the balance of interhemispheric inhibition shifts to the right. Under those  
 20 circumstances (i.e., hemineglect), the vector of attention (black arrow) is shifted to the  
 21 right and the probability of detecting a single stimulus in the left decreases, whereas for  
 22 those in the right increases. Under these circumstances, left targets are ignored by the  
 23 subject (grey arrow). (Right) When bilateral stimulation is presented, the right visual

1 **stimulus activates the left cortex increasing further left to right inhibition, causing**  
2 **extinction of the left target.**  
3

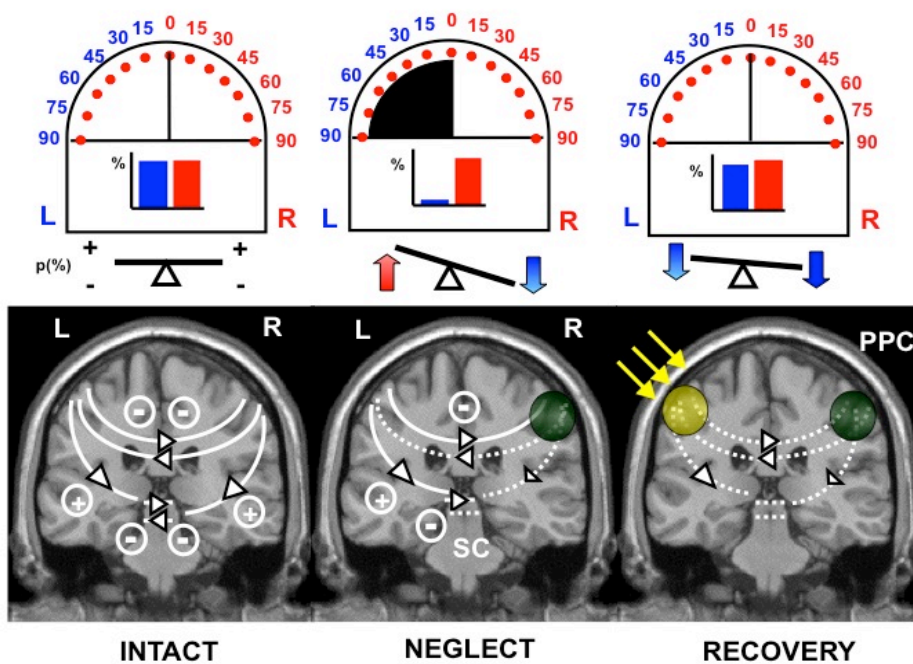
4           Very similarly, according to the model proposed by Heilman and Van den Abell (1980)  
5 and further developed by Mesulam (Mesulam, 1981; Daffner et al., 1990; Gitelman et al., 2002)  
6 on the basis of the works of Sprague (1966a) and Kinsbourne (1977), the right hemisphere  
7 could control the right and the left attentional hemispaces, while the left hemisphere would only  
8 control the right attentional hemisphere (Fig. 11). Therefore, a right hemisphere injury leads to  
9 a phenomenon of attention excessively directed to the right side (Fig. 10), that Gainotti et al.  
10 (1991) compared to a ‘*magnetic attraction*’ to the ipsilesional side, making impossible any  
11 attempt to laboriously capture the contralesional attentional hemisphere. This explanation is  
12 supported by fMRI studies showing higher activation in the right parietal hemisphere of healthy  
13 subjects when performing visuo-spatial tasks (Gitelman et al., 1999; Nobre et al., 1997).

14           However, other authors have reported that in hemineglect, both hemispheres could be  
15 dysfunctional. Using fMRI, Corbetta et al. (2005) observed that acute hemineglect was linked  
16 to a relative hyperactivity of the left undamaged hemisphere. Later studies suggested that  
17 recovery of acute hemineglect was associated to an improvement of interhemispheric  
18 correlations between the left and right posterior parietal cortices (He et al., 2007).

19           Nonetheless, complementary to Mesulam’s model and Kinsbourne theory attributing  
20 hemineglect to a disruption of inter-hemispheric rivalry by disconnection, more recent views  
21 have also emphasized the role of intra-hemispheric interactions. Supporting this alternative  
22 model, visuo-spatial attention has proven a highly specialized function relying on right  
23 lateralized intra-hemispheric networks. More particularly, disruptions of the superior  
24 longitudinal fasciculus connecting the inferior and the superior parietal lobules with the middle  
25 and superior frontal gyri have been highlighted as potential causes for hemineglect (Thiebaut  
26 de Schotten et al., 2005). Hence suggesting that not only cortical gray matter damage but also  
27 that disconnection of white matter tracts connecting right frontal to right parietal regions might

1 be most relevant to cause hemineglect (Bartolomeo, 2006; Doricchi et al., 2008; Toba et al.,  
2 2018). In an attempt to reconcile the roles of both intra-hemispheric and interhemispheric  
3 connections, a recent study by Lunven et al. (2015) concluded on a role for both, intra-  
4 hemispheric fronto-parietal disconnection (superior longitudinal fasciculus II/ III branches) in  
5 the emergence and persistence of visual hemineglect, but also emphasized inter-hemispheric  
6 caudal disconnection (splenium of the corpus callosum) in pervasive hemineglect (Lunven et  
7 al., 2015). Said otherwise, intact posterior callosal fibers allow left fronto-parietal attentional  
8 networks to compensate for the failure of right hemisphere homologues, hence increasing the  
9 ability of the left hemisphere to take into account information from the right hemispace and  
10 compensate hemineglect (Lunven et al., 2015).

11         The impact of hemineglect in the life of stroke patients can be dramatical. It for example  
12 is widely accepted that the presence of this syndrome is a poor prognostic factor for recovering  
13 from neurological impairments (Denes et al., 1992; Kinsella & Ford, 1980) and regain an  
14 independent life after a stroke (Cherney et al., 2001; Katz et al., 1999). Moreover, according to  
15 a meta-analysis involving 23 studies with a total of 628 participants, published by the Cochrane  
16 Institute (Bowen et al., 2013), none of the multiple sensory or cognitive rehabilitation  
17 approaches for hemineglect show a consistent effect, suggesting the need for additional  
18 rehabilitation approaches. It is in this context that operating on therapeutic principles and  
19 guided by the feline ‘Sprague Effect’, non-invasive stimulation technologies are being tested to  
20 modulate inter-hemispheric disbalance of excitability and ameliorate hemineglect.



**FIGURE 12.** Left. After a right parietal lesion resulting into left hemineglect (see visual field representation on top), the balance of inter hemispheric parietal inhibition is biased towards the right, resulting into an increase of inhibition in the right posterior parietal cortex, accompanied by a disinhibition in the left hemisphere. The probability to detect stimuli in the left attentional field is low or null (see blind area in black and 0% detection probability in the histograms). According to the *Interhemispheric Rivalry Hypothesis*, interventions that decrease left disinhibition should result into rebalance of inter-inhibition, and a recovery of performance on both sides. Middle. rTMS at 1Hz applied on the left posterior parietal cortex (PPC) at the dorsal intraparietal sulcus (IPS 10-20 EEG site system scalp position P3) – which is known to result into a long-lasting cortical inhibition- resulted into a short (Brighina et al., 2003) or long lasting (Valero-Cabr e et al., 2006b) cancellation of hemineglect symptoms. Right. Similar effects were observed after rTMS on the inferior/medial frontal gyrus at scalp location (10-20 EEG site F3 (Oliveri et al., 1999) in a tactile detection task, probably through the ipsilateral decrease in left-to-right inhibition induced by ipsilateral left frontal eye field – posterior parietal cortex (Paus et al., 1996). The hypothesis that this is generated through direct activation of right PPC (Paus et al., 1997) or mediated through subcortical structures cannot be ruled out, and actually has been strongly considered during cancellation of visual hemineglect. PPC: posterior parietal cortex, SC: superior colliculus.

To date, only 15 studies in post-stroke patients have been devoted to evaluate rTMS/tDCS on human visuo-spatial disorders such as hemineglect. This is a fairly modest number, compared to peer-reviewed published research on rTMS/tDCS rehabilitation of motor function in brain-injured patients, accounting now for several hundred of articles. Moreover, methodological disparities (e.g., population characterization and patient number, hemineglect severity, delays post-stroke, targeted anatomical sites, stimulation frequency, intensity,

1 periodicity, regime duration and evaluation tests etc.) make those few studies difficult to  
2 compare. Consequently, the use of rTMS/tDCS in the rehabilitation of hemineglect remains an  
3 experimental off-label clinical procedure in attendance of further evidence. To weigh the  
4 promise of rTMS/tDCS therapeutic indications, we will comprehensively review published  
5 human clinical studies of rTMS/tDCS in post/stroke hemineglect. Readers should keep in mind  
6 that the strong bias towards studies with positive results in the peer-reviewed clinical literature,  
7 might project an image of success that is still to be fully proven or work in progress.

8 Three pioneering exploratory studies of Oliveri et al. published nearly two decades ago  
9 were the first to test the therapeutic impact of rTMS in hemineglect. Relying in ‘Sprague Effect’  
10 principles, they further characterized the ability to modulate hemineglect signs in subacute or  
11 chronic right hemisphere stroke patients suffering hemineglect by manipulating spared left  
12 hemisphere regions. Interventions were performed with either single-pulse (Oliveri et al.,  
13 1999), double pulse (Oliveri et al., 2000b), or single sessions of rTMS (Oliveri et al., 2001) in  
14 frontal/parietal sites.

15 In a pioneering study conducted in 28 subacute stroke patients presenting tactile  
16 extinction, Oliveri et al. (1999) delivered single TMS pulses to right and left prefrontal (EEG  
17 10-20 system Fp1, Fp2), frontal (F3, F4) or parietal (P3, P4) scalp locations prior to unilateral  
18 or bilateral finger electrical stimulation. Outcomes showed a reduction of tactile extinction rate  
19 generated by simultaneous finger stimuli when time-locked single TMS pulse were delivered  
20 40 ms after finger stimuli onset, to the left frontal region (but not in any left prefrontal, parietal  
21 or any right region) of the uninjured hemisphere.

22 A year later, a similar article by these same authors used paired pulse TMS at short (2  
23 ms) and long (20 ms) inter-pulse intervals, resulting in local intracortical GABA mediated  
24 inhibition or Glutamate facilitation, respectively. The team delivered these patterns to the  
25 spared left hemisphere in 8 subacute post-stroke hemineglect patients suffering tactile  
26 extinction (Oliveri et al., 2000a). Similar to their prior study, they showed a trial-by-trial

1 modulation of tactile extinction severity rate, which decreased with the use of short TMS  
2 intervals and increased with long ones, influenced by the delivery time with regard to tactile  
3 input onset.

4         Shortly thereafter, in the very first pre-therapeutic attempt to demonstrate effects  
5 outlasting the duration of the rTMS pulses, Oliveri et al. (2001) reported a series of 7 subacute  
6 and chronic stroke patients with parietal or frontal injuries in the right (n = 4) or left (n = 3)  
7 hemisphere treated with a single session of real/sham 1 Hz rTMS delivered to the left or right  
8 parietal intact cortex (10-20 EEG system sites P5 and P6). The results showed a significant  
9 reduction or an abolition of the rightward bias in line bisection, occurring only after active left  
10 parietal stimulation (but not sham rTMS or right parietal rTMS).

11         The quest for longer lasting clinically relevant effects was first tested by the study of  
12 Brighina et al. (2003). In a very short uncontrolled report, these authors applied 7 sessions of  
13 active low frequency rTMS (1 Hz, 15 minutes, 900 pulses) on the left posterior parietal cortex  
14 (10-20 EEG site P5) every day for 2 weeks in 3 subacute or chronic stroke patients with right  
15 temporo-parietal (n = 2) or temporo-frontal (n = 1) injuries. The results revealed a reduction of  
16 rightward bias in bisected line length judgment, persisting 15 days after the rTMS regime in all  
17 3 cases (Brighina et al., 2003).

18         A similar uncontrolled brief study was carried out by Shindo et al. (2006) in 2 chronic  
19 stroke patients (~6 months post-stroke) with hemineglect, who underwent 6 sessions (3 sessions  
20 a week on alternate days, for 2 weeks) of low frequency rTMS (0.9 Hz, ~10, minutes, 900  
21 pulses) on the left posterior parietal cortex (10-20 EEG site P5) contralateral to injuries in right  
22 parieto-frontal and parieto-occipital regions, respectively. Outcomes showed an increase of the  
23 Behavioral Inattention Test (BIT) scores following stimulation that kept progressing 2 to 4  
24 weeks after treatment.

25         Six years elapsed between these uncontrolled therapeutic single case studies and the  
26 first fully randomized and sham controlled rTMS trial published by Koch et al. (2012). In this

1 study (lacking however pre-registration in *clinicaltrials.gov* or similar), either active or sham  
2 stimulation was performed in a varied population of 20 subacute right post-stroke visual  
3 hemineglect patients (~1 to 3 months post-stroke), who in parallel followed classical  
4 hemineglect rehabilitation (including computer based visuo-spatial scanning, attentional and  
5 concentration training). The clinical trial tested the impact of 10 consecutive rTMS sessions  
6 (twice a day from Monday to Friday, for 1 week) of continuous theta burst (cTBS) inhibition  
7 (two 600 pulses cTBS blocks/day, interleaved by 15 minutes break), on the left posterior  
8 parietal cortex. For the first time, individual MRI or CT scan-based neuronavigation systems  
9 were used to accurately position the coil in the posterior portion of the intraparietal sulcus  
10 overlying the angular gyrus. In addition to improvements of the BIT score, authors used paired  
11 pulse to test for changes in left hemisphere parieto-frontal (left intraparietal sulcus to M1)  
12 excitability generated by the potential release of transcallosal inhibition. The study showed  
13 significant increases of the BIT score in the active but not sham cTBS group and also decreases  
14 of left parieto-frontal excitability, both lasting for 2 weeks post treatment. It claimed Class III  
15 evidence that left posterior parietal cTBS stimulation might improve hemineglect for two weeks  
16 post treatment.

17 Implementing a similar rTMS strategy as Koch et al. (2012), a double-blind sham  
18 controlled cross-over randomized study (active rTMS and sham rTMS or vice-versa) by Cazzoli  
19 et al. (2012) tested the impact of 2 consecutive daily sessions of a modified cTBS active vs  
20 sham protocol (4 x cTBS trains made of 30 Hz triple pulses repeated at 6 Hz, for a total of 801  
21 pulses delivered for 44 seconds at times 0 (1<sup>st</sup> train), 15 min (2<sup>nd</sup> train), 60 min (3<sup>rd</sup> train) and  
22 75 (4<sup>th</sup> train) min post 1<sup>st</sup> train) on hemineglect. A cohort of 24 subacute (~1-month post injury)  
23 post-stroke hemineglect patients were recruited for the study and randomly assigned to 3 groups  
24 (n = 8 patients each): Sham cTBS followed by active cTBS, active cTBS followed by sham  
25 cTBS and a no-stimulation group. Patients remained eyes-closed during the stimulation that  
26 targeted their left posterior parietal cortex according to 10-20 EEG coordinate systems (P3).

1 All patients followed in parallel a full neurorehabilitation therapy, including visuo-spatial  
2 exploration and attention and concentration therapy. Authors reported more accurate detection  
3 and faster responses for left-sided targets following active but not sham cTBS 2-days treatment.  
4 Most importantly, stimulation showed for the first time significant improvements in a daily life  
5 activity score (Catherine Bergego Scale), which remained ameliorated at least up to 3 weeks  
6 post-treatment, hence claiming Class I evidence of cTBS as a viable add-on therapy in  
7 hemineglect rehabilitation.

8 To date, a single study in human hemineglect by Kim et al. (2013) has systematically  
9 studied the effects of excitatory rTMS (> 5 Hz or iTBS) delivered to perilesional regions of the  
10 right posterior parietal cortex, and compared it to inhibitory stimulation (1 Hz rTMS or cTBS)  
11 of spared left hemisphere areas. Compared to the suppression of the spared contralesional  
12 hemisphere (Koch et al., 2012, Cazzoli et al., 2012), the former rTMS strategy has been  
13 considered of higher epileptogenic risk as it directly delivers fast and synchronous electrical  
14 patterns to stroke-injured tissue that might be prone to seize. The study recruited 27 subacute  
15 stroke patients who were randomly assigned to three groups (n = 9 patients each): 1 Hz rTMS  
16 on the intact left posterior parietal cortex, 10 Hz rTMS in the perilesional right posterior parietal  
17 cortex area or sham rTMS stimulation, was delivered daily during 10 days. Line bisection and  
18 a Korean Modified Barthel Index (KM-BI) were the only tests that showed significant effects  
19 for both active rTMS modalities (ipsilesional right 10 Hz and contralesional left 1 Hz rTMS)  
20 compared to sham. The study also concluded that both strategies, left inhibitory and right  
21 excitatory proved equally beneficial for visual hemineglect (Kim et al., 2013).

22 In spite of the increasing popularity of tDCS (favored as compared to rTMS by its easy  
23 use, high portability, safe profile of side effects and perfectly concealed sham), this technique  
24 has been scarcely evaluated in human hemineglect, particularly in randomized controlled trials  
25 and multiday stimulation regimes.



1 The pioneering proof-of-principle tDCS study by Ko et al. (2008) was the first to show  
2 line bisection improvements in 15 right stroke hemineglect patients following a single session  
3 of anodal -excitatory- tDCS delivered on the ipsilesional right posterior parietal cortex.

4 A year later, a pre-therapeutic study by Sparing et al. (2009) tested the impact of a single  
5 20 minutes session of 4 stimulation conditions: active left cathodal tDCS, active right anodal  
6 tDCS, active left anodal tDCS or active right sham tDCS. Stimulation was delivered on the  
7 posterior parietal areas (10-20 EEG sites P3 and P4 for left and right respectively) in a mixed  
8 group of 10 post-stroke hemineglect patients in acute, subacute or chronic stages (from 15 days  
9 to 12 months post-stroke). Patients tested 2 of 4 conditions a day with a 3 hours wash-out period,  
10 in two separate days. Supporting the notion of inter-hemispheric rivalrous balance based on  
11 Sprague's principles, active right anodal and left cathodal tDCS decreased reaction times for  
12 the 'hemineglect subtest' of the Test of Attentional Performance (TAP). Importantly, neither  
13 right anodal sham tDCS nor left anodal active tDCS modulated hemineglect, attested the  
14 specificity of the effects. This study set the stage for further clinical work with a regime of  
15 consecutive tDCS sessions in human hemineglect (Sparing et al., 2009 see Experiment 2).

16 Further tDCS work based on similar principles, compared a single session of the so-  
17 called dual tDCS (i.e., left posterior parietal cathodal inhibitory tDCS combined with right  
18 posterior parietal anodal tDCS) to left posterior parietal cathodal inhibitory tDCS and sham  
19 stimulation (Sunwoo et al., 2013). To this end, 10 right subacute stroke hemineglect patients  
20 were tested using a cross-over design with 3 conditions. These authors reported a superiority of  
21 the dual tDCS approach, which most optimally facilitated a rebalance towards normal levels of  
22 interhemispheric rivalry in right hemisphere stroke hemineglect.

23 Given its easy use in clinical settings, a handful of studies in small and selected cohorts  
24 of stroke patients have combined tDCS strategies with other classical or experimental  
25 hemineglect rehabilitation interventions, such as prism adaptation (Ladavas et al., 2015),  
26 optokinetic drift (Turgut et al., 2016), or visual feedback training (Bong et al., 2015) with

1 interesting outcomes. At difference with rTMS, tDCS is particularly suited to combined  
2 interventions, since the presence of a mild electrical constant field can be completely concealed  
3 and induces no distractive or potentially bothering side-effects on patients while performing  
4 rehabilitation. Nonetheless, it should be noted that quite often, patients recruited for both rTMS/  
5 tDCS hemineglect trials do follow in parallel -although not concomitantly- intensive visuo-  
6 spatial and attentional rehabilitation (see for example Koch et al., 2012 and Cazzoli et. al.,  
7 2012). Hence, a potential facilitatory effect of neurostimulation over visuo-spatial training or  
8 vice-versa cannot be ruled out as taking part as necessary but not sufficient cause in clinical  
9 recovery achieved by neurostimulation. Further work ruling out first the clinical impact of  
10 isolated intervention, followed by a study of their combined effects are needed to gauge the  
11 importance of concomitant visuo-spatial training in rTMS/tDCS driven rehabilitation.

12 In sum, the clinical niche for rTMS/ tDCS methods in the manipulation of the ‘Sprague  
13 Effect’ to improve human hemineglect has been studied, for two decades. In spite of the  
14 interests and promises that neurostimulation generates, the number of randomized double-blind  
15 studies able to provide clear support remains low and indications in post-stroke hemineglect  
16 are still far from becoming clinically mainstream. To make progress, further innovation able to  
17 boost efficacy and strengthen evidence requires further knowledge on the circuits mechanisms  
18 by which the ‘Sprague Effect’ occurs and can be manipulated in human patients. Innovation  
19 could in part be found in considering in more details the interactive contribution of intra-  
20 hemispheric and inter-hemispheric commissural matter tracts and the coding role of oscillations  
21 and network synchrony in attentional allocation and its disorders.

22 To this regard, a recent white matter lesion study in 45 stroke patients suggested  
23 dynamically evolving interactions from the subacute to the chronic phase, between intra-  
24 hemispheric interactions (right fronto-parietal systems via the superior longitudinal fasciculus)  
25 considered crucial for the emergence of hemineglect and inter-hemispheric interactions  
26 (splenial trascallosal anatomical projections) deemed paramount to explain its enduring

1 character and influence spontaneous left-hemisphere compensations (Lunven et al., 2015). This  
2 evidence points at the need to design patient-customized and stage-specific therapeutic  
3 strategies of focal neurostimulation that target at the right timing intra-hemispheric and inter-  
4 hemispheric mechanisms.

5 Also, interesting and innovative for the field, a recent magnetoencephalography (MEG)  
6 study in 5 post-stroke hemineglect patients has strongly pointed at alterations of left hemisphere  
7 synchrony and showed pre-target onset, increases of low-beta (~14 Hz) rhythms in a left pre-  
8 frontal region as significantly associated to visual target omissions (Rastelli et al., 2013). More  
9 recently, an EEG study in 9 stroke patients with hemineglect has further characterized this  
10 condition as an oscillopathy, and reported significant correlation between awareness and  
11 attentional deficits and decreases in beta (15-25 Hz) and theta (4-8 Hz) fronto-parietal rhythms  
12 in the right hemisphere (Yordanova et al. 2016). This evidence also calls for the development  
13 of novel neuromodulation strategies that beyond -or in addition to- operating on local  
14 excitability aims to suppress deleterious rhythms or to entrain adaptive episodic oscillations,  
15 favoring synchrony states that facilitate attentional orienting.

16 These two novel directions place the spotlight to the study of visuo-spatial attention and  
17 hemineglect in a wide-network perspective, which structured on the basis of white matter  
18 connectivity relies on oscillatory and synchrony mechanisms to efficiently process information  
19 and engage cognitive operations. Moreover, therapy-wise, these hodological and oscillatory  
20 perspectives call for new targets and non-invasive stimulation parameters to achieve restoration  
21 of normal visuo-spatial attention via neurostimulation. Only a better comprehension of  
22 anatomical networks, their interactions and neurophysiological basis, integrating oscillatory  
23 mechanisms and their manipulation, might inspire the design of novel causal *evidence-based*  
24 therapies that replace current *effect* or *symptom-based* treatments.

25 Last but not least, further and more effective neurostimulation therapies will also require  
26 technological innovations in brain neuromodulation TMS/ tDCS procedures. These should be

1 better tailored to develop and operate in the above-mentioned frameworks, allowing precise  
2 targeting, higher focality, multi-site stimulation schemes, oscillation-tailored patterns,  
3 neuroimaging (PET or MRI) and/ or neurophysiological (EEG or MEG) monitoring and  
4 patient-customized strategies considering individual anatomy and neurophysiology correlates.

## 6 **7. Concluding remarks**

7 We here presented a comprehensive review of the ‘Sprague Effect’ phenomenon since  
8 its first publication in 1966, and followed its history along 40 years of studies in felines, human  
9 healthy subjects and stroke patients. We showed how what could have been considered a  
10 curious feline post-lesion phenomenon, has served to put forward very influential ideas on how  
11 anatomical systems interact to generate behaviors or cause pathology. Moreover, simulated via  
12 computation models or manipulated experimentally with invasive and non-invasive methods,  
13 the ‘Sprague Effect’ has significantly increased our mechanistic comprehension of human  
14 visuo-spatial attentional systems and how their disorders could be reversibly enacted, cancelled  
15 or long-lastingly treated. Finally, the animal models and human enacting the ‘Sprague Effect’  
16 have allowed to evaluate the safety, efficacy and applications of TMS and tDCS methods, and  
17 contribute to the development and popularization of non-invasive brain stimulation in  
18 neurology.

19 Nonetheless, even after extensive study, the ‘Sprague Effect’ and analogous processes  
20 is a work in progress. Complex structural and functional network interactions, and how damage  
21 and recovery might re-shape them is not yet entirely-described and comprehended. A better  
22 understanding of the behavior of any circuit in the intact and damaged hemisphere can lead to  
23 more accurate predictions on how the system changes, and how it can be rehabilitated after  
24 lesion to optimize functional recovery. The charting of network interactions requires a joint  
25 effort of neural circuits analysis in animals, rigorous and careful computational approaches, and

1 confirmatory experiments in healthy humans and patients. More complete mechanistic  
2 understanding will lead to better treatment.

3 The simplicity and elegance of the rules leading to the ‘Sprague Effect’ and its  
4 paradoxical behavioral effects will keep capturing scientific audiences. It does it so efficiently  
5 because it provides a simple and reassuring mechanistic framework in which to understand and  
6 experience how the anatomy and physiology of cerebral networks bring behavior to life and  
7 explain specific neurological symptoms. It is also highly attractive, because it demonstrates the  
8 unpredictable and often ‘paradoxical’ nature of brain interactions and the surprising outcomes  
9 that such may unexpectedly produce. Finally, personality profiles with a pure applied outlook  
10 on research can also be captured by a phenomenon that coupled with non-invasive brain  
11 stimulation techniques provides innovative therapeutic concepts and directions.

12 By collaborating in the exploration of the ‘Sprague Effect’ and also by disseminating  
13 knowledge and educating audiences on its conceptual and practical relevance, the contribution  
14 of Robert Rafal to the neuropsychology and neuroscience of attention has been invaluable. As  
15 a new scientific era unfolds and the frantic search for constant novelty, fast turn-over of ideas  
16 and short-lasting memories of past achievements continues, we are all very thankful to scientists  
17 like Bob Rafal for keeping the memory of past relevant scientific phenomenon alive and pass  
18 it generously to new generations of neuroscientists. Indeed, all the data, and models that are  
19 built on them and all their applications justify why “No neuroscience master student should be  
20 allowed to graduate if s/he does not know about the ‘Sprague Effect’ and its implications for  
21 the field of neuroscience”. Nonetheless, we should add that no neuroscientist should activate in  
22 the field without being aware of the applications and implications of the ‘Sprague Effect’.

## 1 **References**

- 2
- 3 Appell PP, Behan M (1990) Sources of subcortical GABAergic projections to the superior  
4 colliculus in the cat. *J Comp Neurol* 302:143–158.
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
- 61
- 62
- 63
- 64
- 65
- 5 Afifi L, Rushmore RJ, Valero-Cabré A (2013) Benefit of multiple sessions of perilesional  
6 repetitive transcranial magnetic stimulation for an effective rehabilitation of visuospatial  
7 function. *Eur J Neurosci* 37(3):441-54.
- 8 Bang DH, Bong SY (2015) Effect of combination of transcranial direct current stimulation and  
9 feedback training on visuospatial neglect in patients with subacute stroke: a pilot  
10 randomized controlled trial. *J Phys Ther Sci.* 27(9):2759-61.
- 11 Bartolomeo P (2006) A parieto-frontal network for spatial awareness in the right hemisphere  
12 of the human brain. *Archives of Neurology* 63:1238-1241.
- 13 Bauer J, Magg S, Wermter S (2015) Attention modeled as information in learning multisensory  
14 integration. *Neural Netw* 65: 44-52.
- 15 Beckstead RM (1983) Long collateral branches of substantia nigra pars reticulata axons to  
16 thalamus, superior colliculus and reticular formation in monkey and cat. Multiple  
17 retrograde neuronal labeling with fluorescent dyes. *Neuroscience* 10:767–779.
- 18 Behan M, Kime NM (1996) Spatial distribution of tectotectal connections in the cat. *Prog. Brain*  
19 *Res.* 112: 131-142.
- 20 Brighina F, Bisiach E, Oliveri M, et al (2003) 1 Hz repetitive transcranial magnetic stimulation  
21 of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans.  
22 *Neurosci Lett* 336:131–133.
- 23 Butler BE, Chabot N, Lomber SG (2016) A quantitative comparison of the hemispheric, areal,  
24 and laminar origins of sensory and motor cortical projections to the superior colliculus of  
25 the cat. *J Comp Neurol* 524:2623–2642.

- 1 Cazzoli D, Muri RM, Schumacher R, von Arx S, Chaves S, Gutbrod K, Bohlhalter S, Bauer D,  
2 Vanbellingen T, Bertschi M, Kipfer S, Rosenthal CR, Kennard C, Bassetti CL, Nyffeler  
3 T (2012) Theta burst stimulation reduces disability during the activities of daily living in  
4 spatial neglect. *Brain* 135(Pt 11):3426-39.
- 5 Cherney LR, Halper AS (2001) Unilateral visual neglect in right-hemisphere stroke: a  
6 longitudinal study. *Brain Inj* 15, 585-92.
- 7 Chica AB, Bartolomeo P, Valero-Cabré A (2011) Dorsal and ventral parietal contributions to  
8 spatial orienting in the human brain. *J Neurosci.* 1;31(22):8143-9.
- 9 Ciaramitaro VM, Todd WE, Rosenquist AC (1997a) Disinhibition of the superior colliculus  
10 restores orienting to visual stimuli in the hemianopic field of the cat. *J Comp Neurol*  
11 387:568–587.
- 12 Ciaramitaro VM, Wallace SF, Rosenquist AC (1997b) Ibotenic acid lesions of the substantia  
13 nigra pars reticulata ipsilateral to a visual cortical lesion fail to restore visual orienting  
14 responses in the cat. *J Comp Neurol* 377:596–610.
- 15 Bowen A, Hazelton C, Pollock A, Lincoln NB (2013) Cognitive rehabilitation for spatial neglect  
16 following stroke. *Cochrane database of systematic reviews.* Doi:  
17 10.1002/14651858.CD003586.pub3
- 18 Corbetta M, Kincade MJ, Lewis C, Snyder AZ & Sapir A (2005) Neural basis and recovery of  
19 spatial attention deficits in spatial neglect. *Nat Neurosci* 8, 1603-10.
- 20 Daffner KR, Ahern GL, Weintraub S, Mesulam MM (1990) Dissociated neglect behavior  
21 following sequential strokes in the right hemisphere. *Annals of neurology.* 1990 28(1):  
22 97-101.
- 23 Dambeck N, Sparing R, Meister IG, Wienemann M, Weidemann J, Topper R, Boroojerdi B  
24 (2006) Interhemispheric imbalance during visuospatial attention investigated by  
25 unilateral and bilateral TMS over human parietal cortices. *Brain Res.* 9;1072(1):194-9.

- 1 Denes G, Semenza C, Stoppa E, Lis A (1982) Unilateral spatial neglect and recovery from  
2 hemiplegia: a follow-up study. *Brain* 105 (Pt 3): 543.
- 3 Deneve S, Pouget A (2003) Basis functions for object-centered representations. *Neuron* 37:347-  
4 59.
- 5 Dombrowe I, Juravle G, Alavash M, Gießing C, Hilgetag CC (2015) The effect of 10 Hz  
6 repetitive transcranial magnetic stimulation of posterior parietal cortex on visual  
7 attention. *PLoS One* 13;10(5): e0126802.
- 8 Doricchi F, Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P (2008) White matter  
9 (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into  
10 the brain networks of spatial awareness. *Cortex* 44(8):983-95.
- 11 Durmer JS, Rosenquist AC (2001) Ibotenic acid lesions in the pedunculo-pontine region result  
12 in recovery of visual orienting in the hemianopic cat. *Neuroscience* 106:765–781.
- 13 Edwards SB (1977) The commissural projection of the superior colliculus in the cat. *J Comp*  
14 *Neurol* 173:23–40.
- 15 Fabius JH (2013) The value of connectionist models in neuropsychology: A case study of  
16 neglect, Master thesis, Faculty of Medicine, University Utrecht.
- 17 Gainotti G, D'Erme P, Bartolomeo P (1991) Early orientation of attention toward the half space  
18 ipsilateral to the lesion in patients with unilateral brain damage. *Journal of Neurology,*  
19 *Neurosurgery and Psychiatry* 54: 1082-1089.
- 20 Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, Meyer JR, Mesulam M (1999) A  
21 large-scale distributed network for covert spatial attention: further anatomical delineation  
22 based on stringent behavioural and cognitive controls. *Brain*. 122 ( Pt 6):1093-106.
- 23 Gitelman DR, Parrish TB, Friston KJ, Mesulam MM (2002) Functional anatomy of visual  
24 search: Regional segregations within the frontal eye fields and effective connectivity of  
25 the superior colliculus. *Neuroimage* 15(4): 970-982.



1 Grobstein P (1993) Strategies for analyzing complex organization in the nervous system. I.  
2 Lesion Experiments. In: Computational Neuroscience, ed: Schwartz EL, MIT Press  
3 Cambridge, MA, USA.  
4 Hall WC, Fitzpatrick D, Klatt LL, Raczkowski D (1989) Cholinergic innervation of the superior  
5 colliculus in the cat. *Journal of Comparative Neurology* 287:495–514.  
6 Hardy SC, Stein BE (1988) Small lateral suprasylvian cortex lesions produce visual neglect and  
7 decreased visual activity in the superior colliculus. *J Comp Neurol* 273:527–542.  
8 Harting JK, Lieshout DPV (1991) Spatial relationships of axons arising from the substantia  
9 nigra, spinal trigeminal nucleus, and pedunculo-pontine tegmental nucleus within the  
10 intermediate gray of the cat superior colliculus. *Journal of Comparative Neurology*  
11 305:543–558.  
12 Harting JK, Updyke BV, Van Lieshout DP (1992) Corticotectal projections in the cat:  
13 anterograde transport studies of twenty-five cortical areas. *J Comp Neurol* 324:379–414.  
14 He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M (2007) Breakdown of  
15 functional connectivity in frontoparietal networks underlies behavioral deficits in spatial  
16 neglect. *Neuron* 53: 905–18.  
17 Heilman KM, Van Den Abell T (1980) Right hemisphere dominance for attention: the  
18 mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology*  
19 30(3):327-30.  
20 Henik A, Rafal RD and Rhodes D. (1994) Endogenously generated and visually guided  
21 saccades after lesions of the human frontal eye fields. *Journal of Cognitive Neuroscience*  
22 6: 400-411.  
23 Hilgetag CC, Kötter R, Young MP (1999) Inter-hemispheric competition of sub-cortical  
24 structures is a crucial mechanism in paradoxical lesion effects and spatial neglect. *Prog*  
25 *Brain Res* 121:121-141.

- 1 Hilgetag C (2000) Spatial neglect and paradoxical lesion effects in the cat - A model based on  
2 midbrain connectivity. *NeuroComputing*; 32-33:793-799.
- 3 Hilgetag C, Lomber S, Payne B (2001a) Neural mechanisms of spatial attention in the cat.  
4 *NeuroComputing* 38-40:1281-1287.
- 5 Hilgetag CC, Théoret H, Pascual-Leone A (2001b) Enhanced visual spatial attention ipsilateral  
6 to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat Neurosci* 4(9):953-957.
- 7 Hilgetag C, Lomber S, Rushmore R, Payne B (2002) Topographic restoration of visual spatial  
8 attention in the cortically blind cat. *NeuroComputing* 44-46:831-835.
- 9 Hilgetag CC, Kötter R, Théoret H, Claßen J, Wolters A, Pascual-Leone A (2003) Bilateral  
10 competitive processing of visual spatial attention in the human brain, *NeuroComputing*  
11 52-54: 793-798.
- 12 Jiang H, Stein BE, McHaffie JG (2003) Opposing basal ganglia processes shape midbrain  
13 visuomotor activity bilaterally. *Nature* 423:982–986.
- 14 Jiang H, Stein BE, McHaffie JG (2011) Physiological evidence for a trans-basal ganglia  
15 pathway linking extrastriate visual cortex and the superior colliculus. *J Physiol (Lond)*  
16 589:5785–5799.
- 17 Jiang H, Stein BE, McHaffie JG (2015) Multisensory training reverses midbrain lesion-induced  
18 changes and ameliorates haemianopia. *Nat Commun* 6:7263.
- 19 Jin Y, Hilgetag CC (2008) Perturbation of visuospatial attention by high-frequency offline  
20 rTMS. *Exp Brain Res.* 189(1):121-8.
- 21 Kapur N (1996) Paradoxical functional facilitation in brain-behaviour research: A critical  
22 review. *Brain* 119: 1775–1790.
- 23 Kapur N (ed.) (2011) *The Paradoxical Brain*. Cambridge University Press.
- 24 Karnath HO, Niemeier M, Dichgans J (1998) Space exploration in neglect. *Brain* 121: 2357–  
25 2367.

1 Katz N, Hartman-Maeir A, Ring H, Soroker N (1999) Functional disability and rehabilitation  
2 outcome in right hemisphere damaged patients with and without unilateral spatial neglect.  
3 Arch Phys Med Rehabil 80, 379-84.  
4  
5  
6 4 Keinan A, Kaufman A, Sachs N, Hilgetag C, Ruppin E (2004a) Fair localization of function  
7 via multi-lesion analysis. Neuroinformatics 2(2):163-8.  
8  
9  
10 6 Keinan A, Sandbank B, Hilgetag C, Meilijson I, Ruppin E (2004b) Fair attribution of functional  
11 contribution in artificial and biological networks. Neural Computation 16(9):1887-915.  
12  
13  
14 8 Keinan A, Sandbank B, Hilgetag C, Meilijson I, Ruppin E (2006) Axiomatic scalable  
15 neurocontroller analysis via the Shapley value. Artificial Life12(3):333-52.  
16  
17  
18 10 Kim BR, Chun MH, Kim DY, Lee SJ (2013) Effect of high- and low-frequency repetitive  
19 transcranial magnetic stimulation on visuospatial neglect in patients with acute stroke: a  
20 double-blind, sham-controlled trial. Arch Phys Med Rehabil. 94(5):803-7.  
21  
22  
23 11 Kim YH, Min SJ, Ko MH, Park JW, Jang SH, Lee PKW (2005) Facilitating visuospatial  
24 attention for the contralateral hemifield by repetitive TMS on the posterior parietal cortex.  
25  
26  
27 12 Neuroscience Letters 382: 280–285.  
28  
29  
30 13 Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, Yoo WK, Hallett M (2006) Repetitive  
31 transcranial magnetic stimulation-induced corticomotor excitability and associated motor  
32 skill acquisition in chronic stroke. Stroke 37(6):1471-6.  
33  
34  
35 14 Kinsella G, Ford B (1980) Acute recovery from patterns in stroke patients: neuropsychological  
36 factors. Med J Aust. 13;2(12):663-6.  
37  
38  
39 15 Kinsbourne M (1977) Hemi-neglect and hemisphere rivalry. Adv Neurol 18:41-9.  
40  
41  
42 16 Kinsbourne M (1987) Mechanisms of unilateral neglect. In: Jeannerod M, ed.  
43 Neurophysiological and neuropsychological aspects of spatial neglect. Amsterdam:  
44 North-Holland; pp. 69 - 86.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1 Ko MH, Han SH, Park SH, Seo JH, Kim YH (2008) Improvement of visual scanning after DC  
2 brain polarization of parietal cortex in stroke patients with spatial neglect. *Neurosci.Lett.*  
3 448,171–174.  
4  
5  
6 4 Koch G, Bonni S, Giacobbe V, Bucchi G, Basile B, Lupo F, Versace V, Bozzali M, Caltagirone  
7  
8 C (2012) Theta-burst stimulation of the left hemisphere accelerates recovery of  
9 hemispatial neglect. *Neurology* 3;78(1):24-30.  
10  
11  
12 7 Làdavas E, Giulietti S, Avenanti A, Bertini C, Lorenzini E, Quinquinio C, Serino A (2015) A-  
13 tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment  
14 in neglect. *Restor Neurol Neurosci.* 33(5):647-62.  
15  
16  
17 10 Lomber SG (1999) The advantages and limitations of permanent or reversible deactivation  
18 techniques in the assessment of neural function. *J Neurosci Methods* 86:109–117.  
19  
20  
21 12 Lomber SG, Cornwell P, Sun JS, MacNeil MA, Payne BR (1994) Reversible inactivation of  
22 visual processing operations in middle suprasylvian cortex of the behaving cat. *Proc Natl*  
23 *Acad Sci U S A.* 12;91(8):2999-3003.  
24  
25  
26 15 Lomber SG, Payne BR (1996) Removal of two halves restores the whole: reversal of visual  
27 hemineglect during bilateral cortical or collicular inactivation in the cat. *Vis Neurosci*  
28 13:1143–1156.  
29  
30  
31 16 Lomber SG, Payne BR (2001) Task-specific reversal of visual hemineglect following bilateral  
32 reversible deactivation of posterior parietal cortex: a comparison with deactivation of the  
33 superior colliculus. *Vis Neurosci.* 18(3):487-99.  
34  
35  
36 18 Lomber SG, Payne BR, Cornwell P (2001) Role of the superior colliculus in analyses of space:  
37 superficial and intermediate layer contributions to visual orienting, auditory orienting,  
38 and visuospatial discriminations during unilateral and bilateral deactivations. *J Comp*  
39 *Neurol.* 3;441(1):44-57.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 Lomber SG, Payne BR, Hilgetag CC, Rushmore J (2002) Restoration of visual orienting into a  
2 cortically blind hemifield by reversible deactivation of posterior parietal cortex or the  
3 superior colliculus. *Exp Brain Res* 142:463–474.

4 Lomber SG, Payne BR, Horel JA (1999) The cryoloop: an adaptable reversible cooling  
5 deactivation method for behavioral or electrophysiological assessment of neural function.  
6 *J Neurosci Methods* 86:179–194.

7 Loop MS, Sherman SM (1977) The effect of cortical lesions upon visual discriminations in  
8 binocularly deprived cats. *J Comp Neurol* 1;174(1):89-94.

9 Lunven M et al. (2015) White matter lesional predictors of chronic visual neglect: a longitudinal  
10 study. *Brain* 138, 746–760.

11 Machado L and Rafal RD (2004a) Control of fixation and saccades during an anti-saccade task:  
12 An investigation in humans with chronic lesions of oculomotor cortex. *Experimental*  
13 *Brain Research* 156: 55-63.

14 Machado L and Rafal RD (2004b) Control of fixation and saccades in humans with chronic  
15 lesions of oculomotor cortex. *Neuropsychology* 18: 115-123.

16 Mah YH, Husain M, Rees G, Nachev P (2014) Human brain lesion-deficit inference remapped.  
17 *Brain* 137: 2522-31.

18 McHaffie JG, Jiang H, May PJ, Coizet V, Overton PG, Stein BE, Redgrave P (2006) A direct  
19 projection from superior colliculus to substantia nigra pars compacta in the cat.  
20 *Neuroscience* 138:221–234.

21 Mesulam, M. M. A cortical network for directed attention and unilateral neglect (1981) *Ann*  
22 *Neurol* 10, 309-25.

23 Nobre AC, Sebestyen GN, Gitelman DR, Mesulam MM, Frackowiak RS, Frith CD (1997)  
24 Functional localization of the system for visuospatial attention using positron emission  
25 tomography. *Brain* 120 (Pt 3), 515-33.

- 1 Ogasawara K, McHaffie JG, Stein BE (1984) Two visual corticotectal systems in cat. *J*  
2 *Neurophysiol* 52:1226–1245.
- 3 Oliveri M, Bisiach E, Brighina F, Piazza A, La Bua V, Buffa D, et al (2001) rTMS of the  
4 unaffected hemisphere transiently reduces contralesional visuospatial hemineglect.  
5 *Neurology* 57(7), 1338-1340.
- 6 Oliveri M, Caltagirone C, Filippi MM, Traversa R, Cicinelli P, Pasqualetti P, Rossini PM  
7 (2000b) Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition  
8 and facilitation in the human parietal cortex. *Journal of Physiology* 529.2, pp. 461—468.
- 9 Oliveri M, Rossini PM, Filippi MM, Traversa R, Cicinelli P, Palmieri MG, Pasqualetti P,  
10 Caltagirone C (2000a) Time-dependent activation of parieto-frontal networks for  
11 directing attention to tactile space. A study with paired transcranial magnetic stimulation  
12 pulses in right-brain-damaged patients with extinction. *Brain* 123 (Pt 9):1939-47.
- 13 Oliveri M, Rossini PM, Traversa R, Cicinelli P, Filippi MM, Pasqualetti P, et al (1999) Left  
14 frontal transcranial magnetic stimulation reduces contralesional extinction in patients with  
15 unilateral right brain damage. *Brain* 122 (Pt 9), 1731-1739.
- 16 Olivier E, Corvisier J, Pauluis Q, Hardy O (2000) Evidence for glutamatergic tectotectal  
17 neurons in the cat superior colliculus: a comparison with GABAergic tectotectal neurons.  
18 *Eur J Neurosci* 12:2354–2366.
- 19 Pascual-Leone A, Gomez-Tortosa E, Grafman J, Alway D, Nichelli P, Hallett M (1994)  
20 Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal  
21 lobe. *Neurology* 44(3 Pt 1):494-8.
- 22 Paus T (1996) Location and function of the human frontal eye field: A selective review.  
23 *Neuropsychologia* 34:475–483.
- 24 Payne BR, Lomber SG, Geeraerts S, van der Gucht E, Vandebussche E (1996a) Reversible  
25 visual hemineglect. *Proc Natl Acad Sci USA* 93:290–294.

1 Payne BR, Lomber SG, Rushmore RJ, Pascual-Leone A (2003) Cancellation of visuoparietal  
2 lesion-induced spatial neglect. *Exp Brain Res.* 150(3):395-8.  
3  
4 Payne BR, Lomber SG, Villa AE, Bullier J (1996b) Reversible deactivation of cerebral network  
5 components. *Trends Neurosci* 19:535–542.  
6  
7  
8 Payne BR, Rushmore RJ (2004) Functional circuitry underlying natural and interventional  
9 cancellation of visual neglect. *Exp Brain Res* 154:127–153.  
10  
11  
12  
13 Pouget A, Deneve S, Sejnowski TJ (1999) Frames of reference in hemineglect: a computational  
14 approach. *Prog Brain Res.* 121:81-97.  
15  
16  
17  
18 Pouget A, Sejnowski TJ (1997) A new view of hemineglect based on the response properties  
19 of parietal neurons. *Philos Trans R Soc Lond B Biol Sci.* 352:1449-59.  
20  
21  
22  
23 Rafal R (2006) Oculomotor functions of the parietal lobe: Effects of chronic lesions in humans.  
24  
25  
26  
27  
28 Rafal R. (2001) Virtual neurology. News and views. Comment on Enhanced visual spatial  
29 attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat*  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1 Rushmore RJ, DeSimone C, Valero-Cabr  A (2013) Multiple sessions of transcranial direct  
2 current stimulation to the intact hemisphere improves visual function after unilateral  
3 ablation of visual cortex. *Eur J Neurosci* 38:3799–3807.
- 4 Rushmore RJ, Valero-Cabre A, Lomber SG, Hilgetag CC, Payne BR (2006) Functional  
5 circuitry underlying visual neglect. *Brain* 129:1803–1821.
- 6 Schweid L, Rushmore RJ, Valero-Cabr  A (2008) Cathodal transcranial direct current  
7 stimulation on posterior parietal cortex disrupts visuo-spatial processing in the  
8 contralateral visual field. *Exp Brain Res.* 186(3):409-17.
- 9 Segal RL, Beckstead RM (1984) The lateral suprasylvian corticotectal projection in cats. *J*  
10 *Comp Neurol* 225:259–275.
- 11 Seyal M, Ro T, Rafal R (1995) Increased sensitivity to ipsilateral cutaneous stimuli following  
12 transcranial magnetic stimulation of the parietal lobe. *Ann. Neurol.* 38, 264–267.
- 13 Shapley LS (1953) A Value for n-person Games. In Kuhn HW, Tucker AW *Contributions to*  
14 *the Theory of Games.* *Annals of Mathematical Studies.* 28. Princeton University Press.  
15 pp. 307–317
- 16 Shindo K, Sugiyama K, Huabao L, Nishijima K, Kondo T, Izumi SI (2006) Long-term effect  
17 of low frequency repetitive transcranial magnetic stimulation over the unaffected  
18 posterior parietal cortex in patients with unilateral spatial neglect. *J Rehabil Med*  
19 38(1):65-7.
- 20 Sparing R, Thimm M, Hesse MD, Ku J, Karbe H, Fink GR (2009) Bidirectional alterations of  
21 interhemispheric parietal balance by non-invasive cortical stimulation. *Brain* 132; 3011–  
22 3020.
- 23 Sprague JM (1966a) Interaction of cortex and superior colliculus in mediation of visually  
24 guided behavior in the cat. *Science* 153:1544–1547.
- 25 Sprague JM (1966b) Visual, acoustic and somesthetic deficits in the cat after cortical and  
26 midbrain lesions. In: *The Thalamus.* New York, NY: Columbia University Press.



- 1 Sprague JM (1996) Neural mechanisms of visual orienting responses. *Prog Brain Res* 112:1–  
2 15.
- 3 Sprague JM, Meikle TH (1965) The role of the superior colliculus in visually guided behavior.  
4 *Exp Neurol* 11:115–146.
- 5 Sunwoo H, Kim YH, Chang WH, Noh S, Kim EM, Ko MH (2013) Effects of dual transcranial  
6 direct current stimulation on post-stroke unilateral visuospatial neglect. *Neurosci.Lett.*  
7 554,94–98.
- 8 Takahashi M, Sugiuchi Y, Izawa Y, Shinoda Y (2005) Commissural excitation and inhibition  
9 by the superior colliculus in tectoreticular neurons projecting to omnipause neuron and  
10 inhibitory burst neuron regions. *J Neurophysiol* 94:1707–1726.
- 11 Takahashi M, Sugiuchi Y, Shinoda Y (2007) Commissural mirror-symmetric excitation and  
12 reciprocal inhibition between the two superior colliculi and their roles in vertical and  
13 horizontal eye movements. *J Neurophysiol* 98:2664–2682.
- 14 Takahashi M, Sugiuchi Y, Shinoda Y (2010) Topographic organization of excitatory and  
15 inhibitory commissural connections in the superior colliculi and their functional roles in  
16 saccade generation. *J Neurophysiol* 104:3146–3167.
- 17 Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Levy R, Dubois B., Bartolomeo P  
18 (2005) Direct evidence for a parietal-frontal pathway subserving spatial awareness in  
19 humans. *Science* 309(5744): 2226-2228.
- 20 Thut G, Nietzel A, Pascual-Leone A (2005) Dorsal posterior parietal rTMS affects voluntary  
21 orienting of visuospatial attention. *Cereb Cortex* 15:628–638.
- 22 Toba MN, Migliaccio R, Batrancourt B, Bourlon C, Duret C, Pradat-Diehl P, Dubois  
23 B, Bartolomeo P (2018) Common brain networks for distinct deficits in visual neglect. A  
24 combined structural and tractography MRI approach. *Neuropsychologia* 115:167-178.

- 1 Toba MN, Zavaglia M, Rastelli F, Pradat-Diehl P, Valero-Cabr  A, Hilgetag CC (2017) Game  
2 theoretical mapping of causal interactions underlying visuo-spatial attention in the human  
3 brain based on stroke lesions. *Human Brain Mapping*, doi: 10.1002/hbm.23601  
4  
5 Turgut N, Miranda M, Kastrup A, Eling P, Hildebrandt H (2016) tDCS combined with  
6 optokinetic drift reduces egocentric neglect in severely impaired post-acute patients.  
7  
8 *Neuropsychol Rehabil.* 5:1-12.  
9  
10 Urbanski M, Angeli V, Bourlon C, Cristinzio C, Ponticorvo M, Rastelli F, Thiebaut de Schotten  
11 M, Bartolomeo P (2007) Unilateral spatial neglect: a dramatic but often neglected  
12 consequence of right hemisphere damage. *Rev Neurol (Paris)*. 163(3):305-22.  
13  
14 Valero-Cabr  A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA (2017) Transcranial  
15 magnetic stimulation in basic and clinical neuroscience: A comprehensive review of  
16 fundamental principles and novel insights. *Neurosci Biobehav Rev.* 83:381-404.  
17  
18 Valero-Cabr  A, Pascual-Leone A, Rushmore RJ (2008a) Cumulative sessions of repetitive  
19 transcranial magnetic stimulation (rTMS) build up facilitation to subsequent TMS-  
20 mediated behavioural disruptions. *Eur J Neurosci.* 27(3):765-74.  
21  
22 Valero-Cabr  A, Payne BR (2006b) Non-invasive induction and cancellation of visuo-spatial  
23 deficits by repetitive Transcranial Magnetic Stimulation (rTMS): Lessons on “surgery-  
24 less” manipulation of complex visuo-spatial brain networks. *Revista Brasileira de*  
25 *Neurologia. II International Congress on Neuroregeneration Proceedings* 73-83.  
26  
27 Valero-Cabr  A, Payne BR, Pascual-Leone A (2007) Opposite impact on 14C-2-deoxyglucose  
28 brain metabolism following patterns of high and low frequency repetitive transcranial  
29 magnetic stimulation in the posterior parietal cortex. *Exp Brain Res* 176:603–615.  
30  
31 Valero-Cabr  A, Payne BR, Rushmore J, Lomber SG, Pascual-Leone A (2005)  
32 Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic  
33 brain activity: a 14C-2DG tracing study in the cat. *Exp Brain Res.* 163(1):1-12.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1 Valero-Cabré A, Rushmore RJ, Payne BR (2006a) Low frequency transcranial magnetic  
2 stimulation on the posterior parietal cortex induces visuotopically specific neglect-like  
3 syndrome. *Exp Brain Res.* 172(1):14-21.
- 4 Valero-Cabré A, Afifi L, Rushmore R, Japp B, Hilgetag C, Jedd A (2008b) When opposite  
5 frequencies lead to same behavioral effects: A case for a reversible *disconnection*  
6 *syndrome* induced by rTMS on visuo-spatial networks? *Brain stimulation* 1(3):289-  
7 290.
- 8 Vanduffel W, Payne BR, Lomber SG, Orban GA (1997) Functional impact of cerebral  
9 connections. *Proc. Natl. Acad. Sci. USA* Vol. 94, pp. 7617–7620.
- 10 Vuilleumier P, Hester D, Assal G, Regli F (1996) Unilateral spatial neglect recovery after  
11 sequential strokes. *Neurology* 46:184–189.
- 12 Wallace MT, Meredith MA, Stein BE (1993) Converging influences from visual, auditory, and  
13 somatosensory cortices onto output neurons of the superior colliculus. *J Neurophysiol*  
14 69:1797–1809.
- 15 Wallace SF, Rosenquist AC, Sprague JM (1989) Recovery from cortical blindness mediated by  
16 destruction of nontectotectal fibers in the commissure of the superior colliculus in the cat.  
17 *J Comp Neurol* 284:429–450.
- 18 Wallace SF, Rosenquist AC, Sprague JM (1990) Ibotenic acid lesions of the lateral substantia  
19 nigra restore visual orientation behavior in the hemianopic cat. *J Comp Neurol* 296:222–  
20 252.
- 21 Watson GDR, Alloway KD (2018) Opposing collicular influences on the parafascicular (Pf)  
22 and posteromedial (POm) thalamic nuclei: relationship to POm-induced inhibition in the  
23 substantia nigra pars reticulata (SNR). *Brain Struct Funct* 223:535–543.
- 24 Weddell RA (2004) Subcortical modulation of spatial attention including evidence that the  
25 Sprague effect extends to man. *Brain Cog* 55(3): 497-506.

- 1 Wickelgren BG, Sterling P (1969) Influence of visual cortex on receptive fields in the superior  
2 colliculus of the cat. *J Neurophysiol* 32:16–23.
- 3 Xu T, Jha A, Nachev P (2018) The dimensionalities of lesion-deficit mapping.  
4 *Neuropsychologia* 115:134-141.
- 5 Young MP, Hilgetag CC, Scannell JW (2000) On imputing function to structure from the  
6 behavioural effects of brain lesions. *Philos Trans R Soc Lond B Biol Sci* 355(1393):147-  
7 161.
- 8 [Yordanova J, Kolev V, Verleger R Heide W, Grumbt M, Schürmann M. Synchronization of](#)  
9 [fronto-parietal beta and theta networks as a signature of visual awareness in neglect](#)  
10 [\(2017\). \*Neuroimage\* 146:341-354.](#)
- 11 Zavaglia M, Forkert ND, Cheng B, Gerloff C, Thomalla G, Hilgetag CC (2015) Mapping causal  
12 functional contributions derived from the clinical assessment of brain damage after stroke,  
13 *NeuroImage: Clinical* 9, 83–94.
- 14 Zavaglia M, Hilgetag C (2016) Causal functional contributions and interactions in the attention  
15 network of the brain: an objective multi-perturbation analysis. *Brain Structure and*  
16 *Function* 221(5):2553-2568.