NEUROPSYCHOLOGY OF CONSCIOUSNESS

EDITED BY: Silvia Savazzi, Anna Maria Berti, Juha Silvanto and Cecilia Guariglia
PUBLISHED IN: Frontiers in Psychology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88963-099-8
DOI 10.3389/978-2-88963-099-8

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

NEUROPSYCHOLOGY OF CONSCIOUSNESS

Topic Editors:
Silvia Savazzi, University of Verona, Italy
Anna Maria Berti, University of Turin, Italy
Juha Silvanto, University of Westminster, United Kingdom
Cecilia Guariglia, Sapienza University of Rome, Italy

Citation: Savazzi, S., Berti, A. M., Silvanto, J., Guariglia, C., eds. (2019). Neuropsychology of Consciousness. Lausanne: Frontiers Media. doi: 10.3389/978-2-88963-099-8

Table of Contents

frontiers in Psychology

OPINION
published: 30 April 2019
doi: 10.3389/fpsyg.2019.00965

The Glamor of Old-Style Single-Case Studies in the Neuroimaging Era: Insights From a Patient With Hemianopia

Chiara Mazzi [1,2]* *and Silvia Savazzi* [1,2]*

[1] Perception and Awareness (PandA) Lab, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, [2] National Institute of Neuroscience, Verona, Italy

Keywords: neuropsychology, brain lesions, perceptual awareness, consciousness, hemianopia, V1, IPS

OPEN ACCESS

Edited by:
Juha Silvanto,
University of Westminster,
United Kingdom

Reviewed by:
Andreas Bartels,
University of Tübingen, Germany

***Correspondence:**
Chiara Mazzi
chiara.mazzi@univr.it
Silvia Savazzi
silvia.savazzi@univr.it

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: *22 August 2018*
Accepted: *11 April 2019*
Published: *30 April 2019*

Citation:
Mazzi C and Savazzi S (2019) The Glamor of Old-Style Single-Case Studies in the Neuroimaging Era: Insights From a Patient With Hemianopia. Front. Psychol. 10:965. doi: 10.3389/fpsyg.2019.00965

SINGLE-CASE NEUROPSYCHOLOGY AND THE ADVENT OF NEUROIMAGING

Traditionally, neuropsychology investigates the brain-behavior relationship by using a lesion-based approach. According to this approach, different brain areas subserve different cognitive processes due to the modularity of the neural system and the anatomo-functional correlation. Leaving aside the debate existing in the literature between single-case and group studies (e.g., Caramazza and McCloskey, 1988; Robertson et al., 1993), it is well-regarded that data from single-cases have proved to be very powerful in increasing our understanding on the neural correlates of cognition. In literature, there are plenty of examples of neurological patients whose unique behavior crossed the boundaries of science. This is the case of Phineas Gage whose frontal lesion led to deficits in executive functions (Damasio et al., 1994) or HM, the most thoroughly studied case of anterograde amnesia as a consequence of a temporal resection to alleviate severe epilepsy (Scoville and Milner, 1957). Other patients, though less known to the general public, had an extraordinary influence in many fields of neuropsychology. This is the case of Mr. Leborgne (known as “Tan” because that was the only word he could speak), whose behavior was fundamental for understanding language production (Broca, 1861). Further examples can be found with regards to different functions. Considering perception, for instance, we can mention studies about patients experiencing visual field defects as a consequence of occipital lesions during the First World War indicating they could complete visual forms across their blind hemifield (hemianopic completion, Poppelreuter, 1917; Riddoch, 1917), or the study of conscious and unconscious behavior while identifying objects of patient DF who developed visual agnosia following a ventral-stream damage (Goodale et al., 1991). In this context, special mention must also be made of the large body of literature on blindsight (Weiskrantz et al., 1974), with particular reference to patients FS, DB, and GY (Weiskrantz, 1986; Stoerig and Cowey, 1997; Goebel et al., 2001). The extensive study of these patients, proven to be able to unconsciously detect visual information within their blind field, contributed to uncover aspects of the visual system that cannot be highlighted under physiological conditions. All these examples have built up our knowledge not only on the correlation between the brain and its functions but also on the cognitive functions themselves, as they have been essential in the theorization of normal cognition.

The advent of neuroimaging techniques in the second half of the last century eventually resulted in a reduction of single-case studies (Chatterjee, 2005; Fellows et al., 2005; Medina and Fischer-Baum, 2017). On the one hand, the possibility to characterize brain lesions gave a strong impulse on the localization of cognitive functions in the brain, providing evidence on their anatomo-functional correlations. On the other hand, neuroimaging techniques detecting *in vivo* brain activity (e.g., PET, fMRI and more recently fNIRS) and dynamics (e.g., EEG and MEG) or interfering with normal brain processes (e.g., TMS) pushed the field toward the study of healthy participants and groups of patients. As a consequence, the number of papers on single-cases published on high-impact journals is nowadays strongly reduced (Chatterjee, 2005). At the same time, they are cited about three times less often than neuroimaging papers (Fellows et al., 2005; Medina and Fischer-Baum, 2017). Moreover, several journals previously publishing single-cases do not accept such papers any longer, except for selected cases (Medina and Fischer-Baum, 2017). Importantly, however, other high-impact scientific journals, like Cortex (Cubelli and Della Sala, 2017), have recently decided to devote a section to single case reports to counteract the reduction of single-case studies in literature given their potential value.

Here, we advocate for a renewed use of single-case studies as a valuable tool to investigate cognition by taking advantage of neuroimaging methods. The interest in single-case studies, indeed, derives from the peculiarity either of their behavior or their lesion. We trust that the combination of the lesion-based approach alongside the use of neuroimaging techniques can have a strong impact on the understanding of the brain-behavior relationship. Crucially, focal brain damages can offer the unique opportunity to test specific scientific accounts and to question theoretical models of cognition.

THE CASE OF VISUAL AWARENESS: THE CONTROVERSIAL CONTRIBUTION OF V1 AND THE ROLE OF THE DORSAL STREAM IN ACCESSING CONSCIOUSNESS

One of the greatest challenges in the field of perceptual awareness is to disentangle the role of different brain areas in generating conscious experience. A still open debate exists as to whether the activity in some specific areas correlates with the content of conscious experience. Since the first observations of patients with visual field defects (Holmes, 1945), it has become evident that lesions to the primary visual cortex (V1) result in a loss of perceptual awareness in the corresponding portion of the visual field, implying a crucial role of V1 in consciousness. However, the direct contribution of V1 in conscious visual experience still remains controversial (Barbur et al., 1993; Crick and Koch, 2003; Tong, 2003; Stoerig, 2006; Ffytche and Zeki, 2011). In this respect, an influential model (Lamme et al., 1998) states that V1 becomes crucial for consciousness when receiving feedback from other areas. This advocates for a dynamical conceptualization of cortical areas involvement in consciousness suggesting that the sole feedforward activity from V1 to higher areas does not give rise to consciousness.

Another influential model, the so-called two-streams hypothesis (Goodale and Milner, 1992), postulates that visual information processed along the dorsal stream (the "vision-for-action" system), which is devoted to the transformation of visual inputs into actions, is not available to consciousness (Milner, 2012). Conversely, activity along the ventral stream (the "vision-for-perception" system), which transforms the visual input into a coherent representation of the outer world, is suitable for conscious experience. At least in the initial conceptualization of the model, V1 represents the common origin (and the only contact point) of the two streams which then diverge with the ventral stream projecting to the inferior temporal cortex and the dorsal stream projecting to the superior parietal cortex (specifically, superior parietal lobe, SPL, and intraparietal sulcus, IPS).

Within these theoretical frameworks assuming that feedback to V1 is essential for awareness and that activity in SPL/IPS remains unconscious, studying a patient with a V1 lesion would be very informative in testing the predictions of these models.

Over the last few years, we have extensively tested one hemianopic patient, SL, using several methodologies, ranging from pure behavioral measures (Celeghin et al., 2014, 2015; Mazzi et al., 2016) to EEG/ERPs (Bollini et al., 2017; Sanchez-Lopez et al., 2017; Mazzi et al., 2018b), TMS (Mazzi et al., 2014), TMS-EEG co-registration (Bagattini et al., 2015), and, very recently, fast near-infrared optical signal (Mazzi et al., 2018a).

Patient SL is a young woman suffering homonymous hemianopia on her right visual field as a result of an ischemic stroke. Structural MRI evidenced complete destruction of her left V1 (Mazzi et al., 2014). Moreover, full-field visual stimulation using fMRI did not show any activities in V1 (Celeghin et al., 2015). Accordingly, TMS at supra-threshold intensities of different portions of her lesioned occipital cortex did not result in any conscious visual percepts (Bagattini et al., 2015), thus excluding the presence of residual activity within her lesioned V1.

Having assessed that SL's V1 lesion was complete and circumscribed, we were in the privileged position to test these models. If V1 and feedback to it are necessary for awareness to emerge, as stated in Lamme's model, a complete lesion to V1 should prevent SL from having perceptual awareness in her blind field. In this respect, SL, tested with a broad variety of stimulus features (Mazzi et al., 2016; Bollini et al., 2017) reported some visual conscious experience of all kind of stimuli presented contralaterally to her lesion in a considerable number of trials (see Mazzi et al., 2017b for a review of older pieces of evidence on conscious experience within the "blind" field of hemianopic patients). Importantly, she could grade conscious visual experience within her "blind" field and the corresponding ERPs revealed differential neural activity with respect to when stimuli remained undetected (Bollini et al., 2017; Sanchez-Lopez et al., 2017; Mazzi et al., 2018b)[1]. Moreover, her electrophysiological data were similar, both in latency and topography, to those observed with healthy participants using stimuli at detection threshold level (Tagliabue et al., 2016), thus suggesting a normal pattern of neural activity even in the absence of a functioning V1.

These results show that a complete V1 lesion does not prevent from generating conscious visual experience. Instead, perceptual awareness is still possible against the predictions of Lamme's model. These data point out that V1 and feedback to it cannot be considered part of the network constituting the proper correlates of awareness (Silvanto, 2015), thus positing for a re-consideration

---

[1] In some papers data are shown as a group but the effects are present at single subject level also.

of Lamme's model. Importantly, these data do not exclude the importance of recurrent processing among visual areas (e.g., extrastriate visual areas V2/V3 as shown by Horton and Hoyt, 1991 and Slotnick and Moo, 2003), in line with other accounts postulating the importance of synchronous activity between visual areas (Pollen, 1999; Silvanto, 2015).

With respect to the preclusion to reach consciousness for activity along the dorsal stream, it may be predicted that direct stimulation of IPS should not result in conscious visual experience. A reliable way to induce conscious visual percepts is to apply TMS over visually responsive areas in order to obtain the so-called phosphenes, i.e., conscious experience of light in the absence of light entering the eyes. To test whether the dorsal stream is part of the neural correlates of awareness, we stimulated SL ipsilesional IPS. Results showed that SL could experience reliable phosphenes rating their perceptual qualities in a manner similar to that of controls and that her conscious reports fitted well with a psychophysical detection function similar to that observed in healthy participants (Mazzi et al., 2014). Moreover, in a TMS-EEG study (Bagattini et al., 2015), we observed that SL's visual percepts induced by IPS-TMS correlated with early activity within IPS. This suggests that IPS itself can be part of the neural correlates of consciousness, at least under these conditions. Importantly, these results cannot, again, be explained by feedback activity reaching V1, as V1 is lacking in SL. Notably, analogous findings have been found with both healthy participants (Bagattini et al., 2015) and another brain-damaged patient, AM, presenting with altitudinal hemianopia on his upper visual field as a result of an ischemic stroke involving V1 (Mazzi et al., 2017a), thus suggesting a possible generalization of the results. Conversely, other authors argue for an involvement of the intact hemisphere in generating aware experience as a consequence of an ipsilesional stimulation. This is the case of patient GY since the stimulation of his ipsilesional hMT+/V5 (which is part of the dorsal stream) did not result in phosphenes perception unless accompanied by the concomitant stimulation of the homologous area in his intact hemisphere (Silvanto et al., 2007, see Bagattini et al., 2015 for a possible explanation of these contrasting results).

In sum, these results advocate for a re-consideration about the dorsal stream properties of Milner and Goodale's model. Indeed, the prediction that activity in IPS is not accompanied with perceptual experience has proved not to be satisfactory in all respects, such as when a verbal conscious report is requested, there is no time pressure in executing the command or no complex or stereotyped actions are required. However, it remains highly plausible that visuo-motor transformations need to be performed in a fast and automatic manner, thus advocating for unconscious processing. As it has recently been suggested (Milner, 2017), the two streams would not be totally segregated but the ventral and dorsal streams would communicate at higher hierarchical levels. This possibility suggests that conscious experience correlating with stimulation of IPS results from the activation of the ventral stream. This possible explanation, though, contrasts with the results on both healthy participants (Bagattini et al., 2015) and brain-damaged patients (Bagattini et al., 2015; Mazzi et al., 2017a) showing that the most likely generators of IPS-phosphenes are, indeed, IPS and not the temporal cortex. It must, however, be said that the technique used, i.e., TMS-EEG co-registration, does not possess the spatial resolution needed to conclusively localize neural activity. Future research should address this question by applying TMS over SL's IPS while concurrently recording fast near-infrared optical signal (Parks et al., 2015). This technique, indeed, is characterized by the adequate spatial and temporal resolution to record fast changes of neural activity and to assess the exact neural source of it while the patient experiences conscious percepts within her/his "blind" visual field.

Taken together, results obtained with patient SL on the involvement of both V1 and IPS in the emergence of awareness are important in the context of consciousness research. Indeed, a debate exists on the identification of which brain areas are crucial for consciousness (Dehaene and Changeux, 2011; Boly et al., 2017). The results presented here provide additional pieces of evidence in favor of the existence of a posterior cortical "hot zone," comprising temporal, occipital and parietal cortices, as the content-specific neural correlates of awareness (Koch et al., 2016), that is the neural correlates of the subjective, phenomenal, conscious experience of the external world.

An important note of caution with respect to the role of V1 and IPS in awareness relates to the variety of results present in literature obtained with other extensively studied hemianopic patients, such as FS, GY, and DB, both across patients and across testing conditions within the same patient. With the exception of DB, which lesion extension cannot be ascertained with fMRI, FS, and GY (Stoerig et al., 1998; Goebel et al., 2001) showed no activity in V1 but only in extrastriate areas (i.e., hMT+/V5, LO, and V4/V8). These blindsight patients almost never reported conscious experience within their blind field, suggesting that activity in V1 might be essential for conscious vision whereas activity within ventral and dorsal streams is not sufficient for awareness to emerge. Importantly though, the fact that, under certain testing conditions, these patients could experience conscious percepts (Stoerig and Barth, 2001; Stoerig, 2006; Mazzi et al., 2017b) makes it essential, for future research, to deeply investigate hemianopic patients, with a variety of visual stimulation conditions and neuroimaging methods to understand how and which areas, among those thought to contribute to conscious vision, show overlapping results and which ones, instead, show only condition-specific results (Weiskrantz et al., 1995; Kleiser et al., 2001; Stoerig, 2001, Stoerig, 2006).

CONCLUSIONS

As aptly stated by Chatterjee (2005) "a paradigmatic advance in methods is being taken for a paradigmatic shift in understanding." The undoubtable advantages brought into the field of cognitive neuroscience by neuroimaging techniques somehow obscured the importance of extensively studying single neurological patients. However, the example of perceptual awareness given in this opinion paper with patient SL shows that results from single-case studies can bring new evidence by testing the predictions of well-regarded theoretical models. In our opinion, since this approach has proven to be helpful in one specific field, it might be helpful in general and it would make valuable advancements in scientific knowledge. We, thus, stress the need for a renaissance of the use of lesion studies, together with modern imaging techniques, as a primary tool to investigate the brain-behavior relationship.

AUTHOR CONTRIBUTIONS

CM and SS equally contributed to drafting and revising the final version of the manuscript.

FUNDING

This research was partially supported by ERC Grant 339939 Perceptual Awareness and by MIUR PRIN 2015NA4S55_002 grant Visual awareness lost and found: neural and cognitive mechanisms.

ACKNOWLEDGMENTS

We thank SL for her patience in following our (sometimes weird) requests, to have always been available to undergo our experiments and, in some cases, for having given herself the inspiration for new studies. We would like to dedicate this paper to Brenda Milner, who turned 100 in 2018. She is a pillar and a role model for the study of single patients in neuropsychology.

REFERENCES

Bagattini, C., Mazzi, C., and Savazzi, S. (2015). Waves of awareness for occipital and parietal phosphenes perception. *Neuropsychologia* 70, 114–125. doi: 10.1016/j.neuropsychologia.2015.02.021

Barbur, J. L., Watson, J. D., Frackowiak, R. S., and Zeki, S. (1993). Conscious visual perception without V1. *Brain* 116 (Pt 6), 1293–1302. doi: 10.1093/brain/116.6.1293

Bollini, A., Sanchez-Lopez, J., Savazzi, S., and Marzi, C. A. (2017). Lights from the dark: neural responses from a blind visual hemifield. *Front. Neurosci.* 11:290. doi: 10.3389/fnins.2017.00290

Boly, M., Massimini, M., Tsuchiya, N., Postle, B. R., Koch, C., and Tononi, G. (2017). Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence. *J. Neurosci.* 37, 9603–9613. doi: 10.1523/JNEUROSCI.3218-16.2017

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé suivies d'une observation d'aphemie. *Bull. Soc. Anthr.* 6, 330–357. doi: 10.1038/nature12077

Caramazza, A., and McCloskey, M. (1988). The case for single-patient studies. *Cogn. Neuropsychol.* 5, 517–527. doi: 10.1080/02643298808253271

Celeghin, A., Barabas, M., Mancini, F., Bendini, M., Pedrotti, E., Prior, M., et al. (2014). Speeded manual responses to unseen visual stimuli in hemianopic patients: what kind of blindsight? *Conscious. Cogn.* 32, 6–14.doi: 10.1016/j.concog.2014.07.010

Celeghin, A., Savazzi, S., Barabas, M., Bendini, M., and Marzi, C. A. (2015). Blindsight is sensitive to stimulus numerosity and configuration: evidence from the redundant signal effect. *Exp. Brain Res.* 233, 1617–1623. doi: 10.1007/s00221-015-4236-6

Chatterjee, A. (2005). A madness to the methods in cognitive neuroscience? *J. Cogn. Neurosci.* 17, 847–849. doi: 10.1162/0898929054021085

Crick, F., and Koch, C. (2003). A framework for consciousness. *Nat. Neurosci.* 6, 119–126. doi: 10.1038/nn0203-119

Cubelli, R., and Della Sala, S. (2017). Looking back to go forward: promoting single case studies. *Cortex* 97, A1–A3. doi: 10.1016/J.CORTEX.2017.09.023

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., and Damasio, A. R. (1994). The return of phineas gage: clues about the brain from the skull of a famous patient. *Science* 264, 1102–1105. doi: 10.1126/SCIENCE.8178168

Dehaene, S., and Changeux, J. P. (2011). Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227. doi: 10.1016/j.neuron.2011.03.018

Fellows, L. K., Heberlein, A. S., Morales, D. A., Shivde, G., Waller, S., and Wu, D. H. (2005). Method matters: an empirical study of impact in cognitive neuroscience. *J. Cogn. Neurosci.* 17, 850–858. doi: 10.1162/0898929054021139

Ffytche, D. H., and Zeki, S. (2011). The primary visual cortex, and feedback to it, are not necessary for conscious vision. *Brain* 134, 247–257. doi: 10.1093/brain/awq305

Goebel, R., Muckli, L., Zanella, F. E., Singer, W., and Stoerig, P. (2001). Sustained extrastriate cortical activation without visual awareness revealed by fMRI studies of hemianopic patients. *Vision Res.* 41, 1459–1474.

Goodale, M. A., and Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends Neurosci.* 15, 20–25.

Goodale, M. A., Milner, A. D., Jakobson, L. S., and Carey, D. P. (1991). A neurological dissociation between perceiving objects and grasping them. *Nature* 349, 154–156. doi: 10.1038/349154a0

Holmes, G. (1945). Ferrier Lecture: the organization of the visual cortex in man. *Proc. R. Soc. London. Ser. B* 361, 2239–2259. doi: 10.1098/rstb.2006.1832

Horton, J., and Hoyt, W. (1991). Quadrantic visual field defects. *Brain* 14(Pt 4), 1703–1718. doi: 10.1093/brain/114.4.1703

Kleiser, R., Wittsack, J., Niedeggen, M., Goebel, R., and Stoerig, P. (2001). Is V1 necessary for conscious vision in areas of relative cortical blindness? *Neuroimage* 13, 654–661. doi: 10.1006/nimg.2000.0720

Koch, C., Massimini, M., Boly, M., and Tononi, G. (2016). Neural correlates of consciousness: progress and problems. *Nat. Rev. Neurosci.* 17, 307–321. doi: 10.1038/nrn.2016.22

Lamme, V. A. F., Supèr, H., and Spekreijse, H. (1998). Feedforward, horizontal, and feedback processing in the visual cortex. *Curr. Opin. Neurobiol.* 8, 529–535. doi: 10.1016/S0959-4388(98)80042-1

Mazzi, C., Bagattini, C., and Savazzi, S. (2016). Blind-sight vs. degraded-sight: different measures tell a different story. *Front. Psychol.* 7:901. doi: 10.3389/fpsyg.2016.00901

Mazzi, C., Mancini, F., and Savazzi, S. (2014). Can IPS reach visual awareness without V1? Evidence from TMS in healthy subjects and hemianopic patients. *Neuropsychologia* 64, 134–144. doi: 10.1016/j.neuropsychologia.2014.09.026

Mazzi, C., Mazzeo, G., and Savazzi, S. (2017a). Markers of TMS-evoked visual conscious experience in a patient with altitudinal hemianopia. *Conscious. Cogn.* 54, 143–154. doi: 10.1016/j.concog.2017.01.022

Mazzi, C., Parisi, G., Colombari, E., Metzger, B., Marzi, C. A., and Savazzi, S. (2018a). Spatiotemporal dynamics of attentional cueing in healthy participants and a hemianopic patient. A fast optical imaging study. *Front. Comput. Neurosci.*

Mazzi, C., Savazzi, S., and Silvanto, J. (2017b). On the "blindness" of blindsight: what is the evidence for phenomenal awareness in the absence of primary visual cortex (V1)? *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.10.029. [Epub ahead of print].

Mazzi, C., Tagliabue, C. F., Mazzeo, G., and Savazzi, S. (2018b). Reliability in reporting perceptual experience: behaviour and electrophysiology in hemianopic patients. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2018.01.017. [Epub ahead of print].

Medina, J., and Fischer-Baum, S. (2017). Single-case cognitive neuropsychology in the age of big data. *Cogn. Neuropsychol.* 34, 440–448. doi: 10.1080/02643294.2017.1321537

Milner, A. D. (2012). Is visual processing in the dorsal stream accessible to consciousness? *Proc. Biol. Sci.* 279, 2289–98. doi: 10.1098/rspb.2011.2663

Milner, A. D. (2017). How do the two visual streams interact with each other? *Exp. Brain Res.* 235, 1297–1308. doi: 10.1007/s00221-017-4917-4

Parks, N. A., Mazzi, C., Tapia, E., Savazzi, S., Fabiani, M., Gratton, G., et al. (2015). The influence of posterior parietal cortex on extrastriate visual activity: a concurrent TMS and fast optical imaging study. *Neuropsychologia* 78, 153–158. doi: 10.1016/j.neuropsychologia.2015.10.002

Pollen, D. A. (1999). On the neural correlates of visual perception. *Cereb. Cortex* 9, 4–19. doi: 10.1093/cercor/9.1.4

Poppelreuter, W. (1917). *Die Psychischen Schädigungen Durch Kopfschuss im Kriege 1914-1916 (Die Storungen der Niederen und Hoheren Sehleistungen durch Verotsungen des Okzipitalhirns)*. Liepzig: Verlag von Leopold Voss.

Riddoch, G. (1917). Dissociation of visual perceptions due to occipital injuries, with especial reference to appreciation of movement. *Brain* 40, 15–57. doi: 10.1093/brain/40.1.15

Robertson, L. C., Knight, R. T., Rafal, R., and Shimamura, A. P. (1993). Cognitive neuropsychology is more than single-case studies. *J. Exp. Psychol. Learn. Mem. Cogn.* 19, 710–717; discussion 718–34.

Sanchez-Lopez, J., Pedersini, C. A., Di Russo, F., Cardobi, N., Fonte, C., Varalta, V., et al. (2017). Visually evoked responses from the blind field of hemianopic patients. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.10.008. [Epub ahead of print].

Scoville, W. B., and Milner, B. (1957). Loss of recentmemory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21. doi: 10.1136/jnnp.20.1.11

Silvanto, J. (2015). Why is "blindsight" blind? A new perspective on primary visual cortex, recurrent activity and visual awareness. *Conscious. Cogn.* 32, 15–32. doi: 10.1016/j.concog.2014.08.001

Silvanto, J., Cowey, A., Lavie, N., and Walsh, V. (2007). Making the blindsighted see. *Neuropsychologia* 45, 3346–3350. doi: 10.1016/j.neuropsychologia.2007.06.008

Slotnick, S. D., and Moo, L. R. (2003). Retinotopic mapping reveals extrastriate cortical basis of homonymous quadrantanopia. *Neuroreport.* 14, 1209–1213.doi: 10.1097/00001756-200307010-00004

Stoerig, P. (2001). The neuroanatomy of phenomenal vision: a psychological perspective. *Ann. N. Y. Acad. Sci.* 929, 176–194. doi: 10.1111/j.1749-6632.2001.tb05716.x

Stoerig, P. (2006). Blindsight, conscious vision, and the role of primary visual cortex. *Prog. Brain Res.* 155, 217–234. doi: 10.1016/S0079-6123(06)55012-5

Stoerig, P., and Barth, E. (2001). Low-level phenomenal vision despite unilateral destruction of primary visual cortex. *Conscious. Cogn.* 10, 574–587. doi: 10.1006/ccog.2001.0526

Stoerig, P., and Cowey, A. (1997). Blindsight in man and monkey. Brain 120 (Pt 3), 535–559.

Stoerig, P., Kleinschmidt, A., and Frahm, J. (1998). No visual responses in denervated V1: high-resolution functional magnetic resonance imaging of a blindsight patient. *Neuroreport* 9, 21–25.

Tagliabue, C. F., Mazzi, C., Bagattini, C., and Savazzi, S. (2016). Early local activity in temporal areas reflects graded content of visual perception. *Front. Psychol.* 7:572. doi: 10.3389/fpsyg.2016.00572

Tong, F. (2003). Primary visual cortex and visual awareness. *Nat. Rev. Neurosci.* 4, 219–229. doi: 10.1038/nrn1055

Weiskrantz, L. (1986). *Blindsight: A Case Study and Implications.* Available online at: https://philpapers.org/rec/WEIBAC (accessed November 29, 2018).

Weiskrantz, L., Barbur, J. L., and Sahraie, A. (1995). Parameters affecting conscious versus unconscious visual discrimination with damage to the visual cortex (V1). *Proc. Natl. Acad. Sci. U.S.A.* 92, 6122–6126.

Weiskrantz, L., Warrington, E. K., Sanders, M. D., and Marshall, J. (1974). Visual capacity in the hemianopic fiels following a restricted occipital ablation. *Brain* 97, 709–728. doi: 10.1093/brain/97.1.709

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 09 April 2019
doi: 10.3389/fpsyg.2019.00697

Ipsilesional Impairments of Visual Awareness After Right-Hemispheric Stroke

Mario Bonato[1*†], **Zaira Romeo**[2†], **Elvio Blini**[3], **Marco Pitteri**[4], **Eugenia Durgoni**[2], **Laura Passarini**[2], **Francesca Meneghello**[2] **and Marco Zorzi**[1,2*]

[1] *Department of General Psychology and Padova Neuroscience Center, University of Padua, Padua, Italy,* [2] *IRCCS San Camillo Hospital, Venice, Italy,* [3] *Integrative Multisensory Perception Action and Cognition Team, University Claude Bernard of Lyon, Lyon, France,* [4] *Neurology Section, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*

Unilateral brain damage following stroke frequently hampers the processing of contralesional space. Whether and how it also affects the processing of stimuli appearing on the same side of the lesion is still poorly understood. Three main alternative hypotheses have been proposed, namely that ipsilesional processing is functionally (i) hyperefficient, (ii) impaired, or (iii) spared. Here, we investigated ipsilesional space awareness through a computerized paradigm that exploits a manipulation of concurrent information processing demands (i.e., multitasking). Twelve chronic right-hemisphere stroke patients with a total lack of awareness for the contralesional side of space were administered a task that required the spatial monitoring of two locations within the ipsilesional hemispace. Targets were presented immediately to the right of a central fixation point (3° eccentricity), or farther to the right toward the screen edge (17° eccentricity), or on both locations. Response to target position occurred either in isolation or while performing a concurrent visual or auditory task. Results showed that most errors occurred when two targets were simultaneously presented and patients were faced with additional task demands (in the visual or auditory modalities). In the context of concurrent visual load, ipsilesional targets presented at the rightmost location were omitted more frequently than those presented closer to fixation. This pattern qualifies ipsilesional processing in right-hemisphere stroke patients as functionally impaired, arguing against the notion of ipsilesional hyperperformance, especially when under visual load.

Keywords: spatial processing, spatial awareness, consciousness, stroke, hemianopia, neglect, ipsilesional

Edited by:
Silvia Savazzi,
University of Verona, Italy

Reviewed by:
Marco Neppi-Modona,
University of Turin, Italy
Britt Anderson,
University of Waterloo, Canada

****Correspondence:***
Mario Bonato
mario.bonato@unipd.it
Marco Zorzi
marco.zorzi@unipd.it

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: *30 November 2018*
Accepted: *13 March 2019*
Published: *09 April 2019*

Citation:
Bonato M, Romeo Z, Blini E, Pitteri M, Durgoni E, Passarini L, Meneghello F and Zorzi M (2019) Ipsilesional Impairments of Visual Awareness After Right-Hemispheric Stroke. Front. Psychol. 10:697. doi: 10.3389/fpsyg.2019.00697

INTRODUCTION

Lesions of the right hemisphere often result in visuospatial deficits, such as the widely known hemispatial neglect and extinction. The pathognomonic clinical feature common to most of these disorders consists in impaired conscious processing for stimuli appearing in the side of space opposite to the damaged hemisphere (Driver and Vuilleumier, 2001; Corbetta and Shulman, 2011; Bartolomeo et al., 2012; Vuilleumier, 2013; Cubelli, 2017). Within the context of impairment of contralesional space processing, whether processing of ipsilesional space is intact, or just comparatively less affected, is a question that has not been often addressed. It is known that the presence and the severity of contralesional space impairment changes according to a wealth of factors including, for instance, the type of test (e.g., cancellation tasks vs. line bisection tasks, see Ferber and Karnath (2001), the level of motor involvement, and nature of the spatial domain investigated (e.g., peripersonal vs. extrapersonal space (Halligan and Marshall, 1991). On the top of that, mounting evidence suggests that the presence and severity of contralesional awareness deficits is strongly modulated by task demands. For instance, when multiple spatial locations are to be processed, an increased attentional engagement enlarges the neglected portion of contralesional space (Russell et al., 2004; Sarri et al., 2009). Moreover, when target position is kept constant, higher task demands result in increased omission rates (Bonato, 2012). Whether the same phenomena can be found within the ipsilesional side of space is largely unknown. Still, if we assume that neglect is task-dependent, the extent of space that is affected – and therefore the relationship between contra- and ipsilesional disorders – has to be considered direct. Let us consider, for instance, the performance of a neglect patient in a typical cancellation task: if the extent of the neglected space depends on task difficulty, a very difficult task might result in omissions extending from the contralesional toward the less lateralized portions of the ipsilesional side of space.

The dependency of contralesional space deficits on task difficulty clearly depicts neglect as a continuous disorder, not only when considering the extent of space neglected, but also when, more importantly, a diagnosis has to be made. Many patients with non-pathological scores might, in fact, simply present subclinical impairments which go undetected by standard methods (Pitteri et al., 2018). Similarly, patients with minor deficits might present severe patterns of omissions when tested with other methods. In order to better address the task-dependency issue, Bonato et al. (2010) devised a computer-based task with constant stimuli and varying attentional demands. In their approach, the detection rate of briefly presented, lateralized targets is compared across different conditions, allowing the patient either to focus on target stimuli only or requiring them to process additional, visual/auditory concurrently-presented stimuli (dual-tasking). Chronic stroke patients, under these more challenging conditions, show deficits for the contralesional space which are much more severe than those detected by standard, paper-and-pencil neuropsychological evaluation. Across a number of studies (Bonato et al., 2010) interpreted the emergence of contralesional omissions under multitasking as due to the impossibility to compensate for a spatial deficit which was present in a latent form. This approach also allowed us to characterize two possible core neglect features – namely its low frequency after left-hemisphere damage (Blini et al., 2016), and its putative stabilization in the chronic phases (Bonato, 2015) – as being task-dependent and, therefore, ascribed to the low sensitivity of standard clinical assessment methods. It should also be noted that brain damage can directly hamper contralesional visual perception by causing a pure visual deficit (i.e., homonymous hemianopia), which very often cannot be easily disentangled from severe neglect (Müller-Oehring et al., 2003).

In the present investigation, we capitalize on the sensitivity of the previously described multitasking approach (Bonato et al., 2010; Blini et al., 2016) to test how resilient to increased attentional demands is the "seemingly unimpaired" awareness for ipsilesional targets in right-hemisphere stroke patients. In the following sections we discuss three specific hypotheses about the functionality of ipsilesional space processing: the first posits that ipsilesional attention is enhanced, as suggested by the fact that it is strongly attracted by items appearing in the ipsilesional side of space; the second posits that performance in the ipsilesional side of space is impaired; the third simply assumes that ipsilesional space processing is unimpaired, at least with respect to its more lateralized sectors. Note that the first two hypotheses are not to be considered alternative, but rather complementary in considering ipsilateral processing as influenced by brain damage. The third hypothesis, instead, predicts that processing of (the most) ipsilesional spatial positions is not affected by brain damage.

Ipsilesional Attraction

A first hypothesis is that patients with right hemisphere damage (RHD) might present a "magnetic" attraction toward ipsilesional stimuli (Gainotti et al., 1991). A landmark study (Mark et al., 1988) showed that the neglected side of space reduces when (ipsilesional) items are progressively erased after detection. This would relate the imbalance between neglected/non-neglected spatial extent to the presence of ipsilesional, non-neglected stimuli attracting attention. The study by Natale et al. (2007) showed that RHD patients with left neglect may be even faster than healthy controls in performing saccades toward ipsilesional targets. This, however, occurred only for slightly lateralized locations (within an off-centered ipsilesional sector of about 10°). When discussing about ipsilesional attraction, a different yet closely related phenomenon is the so-called disengagement deficit (for review see Losier and Klein, 2001), namely the specific difficulty in (re)orienting attention toward the contralesional space after having been (invalidly) cued toward the ipsilesional space. This bias is typically assessed using a Posner cueing task (Posner, 1980) and it strongly correlates with clinical indices of neglect (Morrow and Ratcliff, 1988). Further evidence often considered as supporting the ipsilesional 'hyperprocessing' hypothesis comes from extinction at double simultaneous stimulation, whereby ipsilesional targets are strongly prioritized, and hamper the report of simultaneously-presented contralesional ones (Vossel et al., 2011). However, the concurrent presence of ipsilesional attentional capture and contralesional omissions makes it difficult to disentangle the hyper- from the hypo-attentional component. In short, a number of heterogeneous proposals suggested that, at least in specific contexts, the processing of items appearing within the ipsilesional space appears to be facilitated.

Deficient Ipsilesional Processing

A second possibility, thoroughly reviewed and tested by Chokron et al. (2018), is that ipsilesional processing should be more appropriately considered as impaired. At odds with the idea of ipsilesional facilitation, Chokron et al. (2018) reported that left neglect patients often have difficulties when responding to right-sided stimuli. According to this hypothesis, patients' ipsilesional slowing would be strictly related to the severity of left neglect and would not – or at least not directly – reflect unspecific impairments (Bartolomeo and Chokron, 1999; Bartolomeo et al., 1999). As reported by Chokron et al. (2018), it is also possible to conceive the rightward attentional bias in left neglect patients as a paradoxical effect depending on task difficulty, which would thus manifest itself as ranging between facilitation for simple tasks and deficient performance in more complex ones (see also Bartolomeo and Chokron, 2000). According to this view, the seemingly hyperefficient ipsilesional space processing would be the consequence of a defective, and not enhanced, attention. The nature of this deficit has been attributed either to an unspecific loss of attentional capacity (see proposals by Robertson and Frasca, 1992; Robertson et al., 1998) or to a more specific selective attention impairment in filtering/prioritizing information (Snow and Mattingley, 2006).

Consistently with the idea of a left-to-right gradient in omissions, classical studies by Marshall and collaborators (Marshall and Halligan, 1989; Halligan et al., 1992), demonstrated that the modulation of neglect upon spatial processing is not dichotomous but continuous (see also Butler et al., 2004) and can extend, for some patients and tasks, to the ipsilesional space. The extent of space neglected by every single patient is strictly task-dependent (Sarri et al., 2009). At group level, a very clear spatial gradient is always present in cancellation tasks, whereby the detection of the more ipsilesional items is spared even in the most severe neglect patients. Evidence for a gradient has been extended to computer-based tasks by Smania et al. (1998). They reported that patients with RHD damage and left neglect omitted not only most of the contralesional targets, but also a significant number of those ipsilesionally presented immediately on the right of the fixation point. Interestingly, any "strong gradient" view suggests that the most ipsilesional spatial positions remain unaffected (see next paragraph).

Normal Ipsilesional Space Processing

The third hypothesis is that performance in the ipsilesional side of space might be fully, or at least relatively, unimpaired. Attentional deficits after RHD follow a left-to-right gradient (Behrmann et al., 1997). Therefore, as previously stated, considering performance for ipsilesional targets as unimpaired does not seem necessarily inappropriate from a theoretical perspective. The assumption, usually implicit, is that ipsilesional deficits are absent or negligible, and this would allow ipsilesional performance to be taken as individual baseline for each patient. All in all, this is a very common assumption about neglect patients' ipsilesional performance, at least when considering the most ipsilesional space sectors. Nevertheless, the observation of errorless performance for the most lateralized ipsilesional locations might depend on ceiling effects. Recently Machner et al. (2018) showed that the most severe neglect patients they tested were slower than controls in detecting ipsilesional targets in a Posner detection task, while in a search task they processed the most ipsilesional targets with the same accuracy as healthy controls (i.e., almost errorless).

In the present study we exploited the manipulation of concurrent information processing demands (i.e., multitasking) to investigate whether visual awareness for targets appearing within the ipsilesional side of space is hampered by RHD. Assessing the effect of multitasking can inform the above mentioned debate about the status of ipsilesional space processing in stroke patients.

MATERIALS AND METHODS

Participants

Twelve stroke patients with right hemisphere damage (RHD) took part in the study. All patients were admitted to the San Camillo Neurorehabilitation Hospital (Lido di Venezia, Italy) to undergo motor and cognitive rehabilitation programs. All patients were in the sub-acute to chronic phase (minimum time from onset: 63 days, see **Table 1**). Seven healthy participants were also included in the study (**Table 1**) as controls. Patients were on average younger than the control group (62 ± 7.4 years for RHD vs. 72 ± 6.9 years for controls; $t_{(13.48)} = -2.96$, $p = 0.01$). The two groups did not differ in terms of formal education (10.5 ± 5.5 years for RHD vs. 11.42 ± 5.3 years for controls; $t_{(12.95)} = -0.36$, $p = 0.732$).

Inclusion criteria for the clinical group were: the presence of a first-ever right-hemisphere stroke and severely impaired performance in detecting contralesional targets (accuracy below 25%) in face of a seemingly preserved performance in detecting ipsilesional ones (accuracy above 75%, see detailed

TABLE 1 | Demographic (all participants) and clinical (RHD patients only) data.

Subject/ group	Gender/ age/ education (years)	Handedness	Etiology	Lesional volume (cc)	Time from stroke (days)
1/RHD	F/63/5	R	I	172	221
2/RHD	M/60/8	R	H	684	1907
3/RHD	F/63/13	R	H	109	672
4/RHD	M/58/16	R	I	119	266
5/RHD	M/57/8	R	I	113	91
6/RHD	M/68/18	R	H	126	69
7/RHD	M/58/17	R	I	231	63
8/RHD	F/56/18	R	I	167	183
9/RHD	M/65/5	R	I	182	165
10/RHD	F/81/5	R	I	34	207
11/RHD	M/52/8	R	H	n.a.	72
12/RHD	F/63/5	R	I	292	192
1/Control	F/66/13	R			
2/Control	M/85/17	R			
3/Control	F/65/8	R			
4/Control	F/72/5	R			
5/Control	F/68/15	R			
6/Control	F/72/17	R			
7/Control	M/76/5	R			

I, ischemic; H, hemorragic.

operationalization later). Inclusion criterion for the control group was the absence of neurological disorders assessed with an extensive interview. Exclusion criteria for both groups were the presence of additional neurological/psychiatric disorders or substance abuse.

Brain Lesions Reconstruction

Individual scans (MRI or CT) were available for 11 patients out of 12. Brain lesions were automatically reconstructed with the software Lesion Identification with Neighborhood Data Analysis – LINDA (Pustina et al., 2016). Each reconstruction was independently checked by two experimenters and, if necessary, manually corrected using MRIcron (Rorden and Brett, 2000). Individual scans were reoriented using SPM (Friston et al., 2007) and then normalized to an age-appropriate template brain by means of the SPM Clinical Toolbox (Rorden et al., 2012) using enantiomorphic normalization (Nachev et al., 2008). Lesion overlays are depicted in **Figure 1**. The maximum overlap occurred for *n* = 9 patients in the right insula (X: 31, Y: −20, Z: 17).

Neuropsychological Assessment

All patients underwent neuropsychological evaluation as per routine clinical practice (**Table 1**). The conventional part of the Behavioral Inattention Test (BIT) (Wilson et al., 1987) was administered for assessing visuo-spatial abilities. It includes six subtests: lines, letters, and stars cancellation, line bisection, figure copy, and spontaneous drawing. Each subtest was scored separately and contributed to form a global index of lateralized visuo-spatial performance. Six patients showed left neglect according to the BIT overall cut-off score (130). Scores in **Table 2** are reported separately for right- and left-sided targets.

TABLE 2 | Neuropsychological tests.

Subject/ group	MMSE cut-off: 24	RAVEN cut-off: 18.96	BIT cut-off: <130	BIT-barrage	BIT-stars	BIT-letters
				L/R	L/R	L/R
				(max 18/18)	(max 27/27)	(max 20/20)
1/RHD	n.a	22,3	119*	18/18	27/27	5/20
2/RHD	19*	n.a	133	18/18	23/27	18/18
3/RHD	25,2	26,4	140	18/18	27/27	20/18
4/RHD	23,2*	25,2	124*	18/18	24/24	14/20
5/RHD	25	27,8	66*	12/18	0/12	3/19
6/RHD	24,2	18,4*	132	18/17	23/27	20/18
7/RHD	25,2	26,2	107*	18/18	0/25	19/19
8/RHD	30	29,6	144	18/18	27/27	20/20
9/RHD	22,9*	27,9	107*	18/18	12/20	16/20
10/RHD	25,4	23	136	18/18	27/27	16/18
11/RHD	27	33,33	141	18/18	26/27	19/20
12/RHD	25,9	27	102*	18/18	15/18	14/13

*MMSE [Mini Mental State Examination (Magni et al., 1996), and Raven's progressive matrices (Carlesimo et al., 1996)]. Across all tasks, age and education corrected scores are reported. *Performance below cut-off. BIT [Behavioral Inattention Test (Wilson et al., 1987)]: scores at cancellation subtests are reported separately for left (L)/right (R) space. -: data not available. n.a.: unable to assess.*

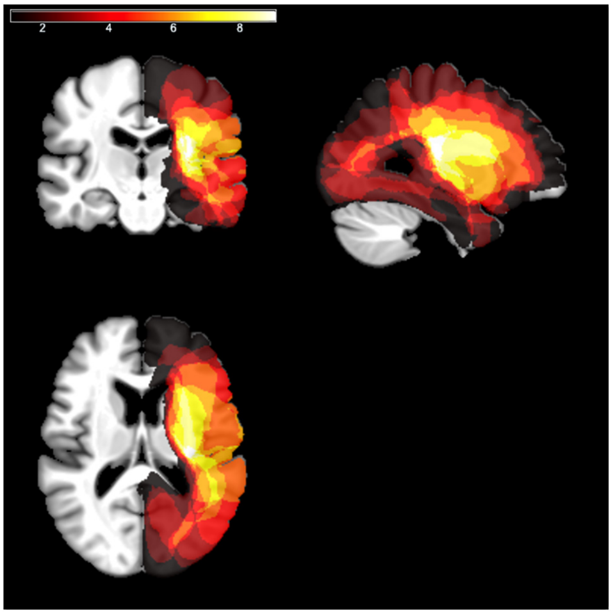


FIGURE 1 | Lesion overlays. The lesion mapping for RHD patients, normalized to a template of aged healthy individuals according to the procedure described in Rorden et al. (2012), is shown as an overlay on a standard template using MRIcron (Rorden and Brett, 2000). The different colors code for the number of overlapping lesions from dark red (minimal/no overlap) to white (maximal overlap).

Preliminary Task for Study Inclusion

Stimuli and Procedure

Patients were individually tested in a quiet room, sitting comfortably at a distance of about 60 cm from a 19-inch computer monitor. The task was adapted from Blini et al. (2016). Each trial started with a black screen (1000 ms), followed by a white fixation cross (about 1° wide) that was presented in the center of the screen for 800 ms. The lateralized visuospatial target was a white disk (diameter: 0.8°) presented against a black background for a duration of about 110 ms. The target could appear unilaterally, on the left or the right side of the display (distance from fixation: 17°), or bilaterally (both on the left- and on the right- side), simultaneously. To assess any potential response bias we included "Catch" trials, in which no target was actually displayed on the screen. The three target locations (left, right, bilateral) and the catch trials were random and equiprobable (i.e., 25% of each type). Simultaneously with the lateralized target(s), a visual shape (triangle, square, or circle) was shown at fixation, and an environmental sound (train whistle, doorbell, or hammer) was presented through binaural earphones. Once the 110 ms time window elapsed, a noisy screenshot was presented until the beginning of the following trial, as to minimize retinal after-image. Patients had to report the position of the target(s) (i.e., "no target," "right," "left," or "both" sides). In total, 36 trials were presented. Selected patients

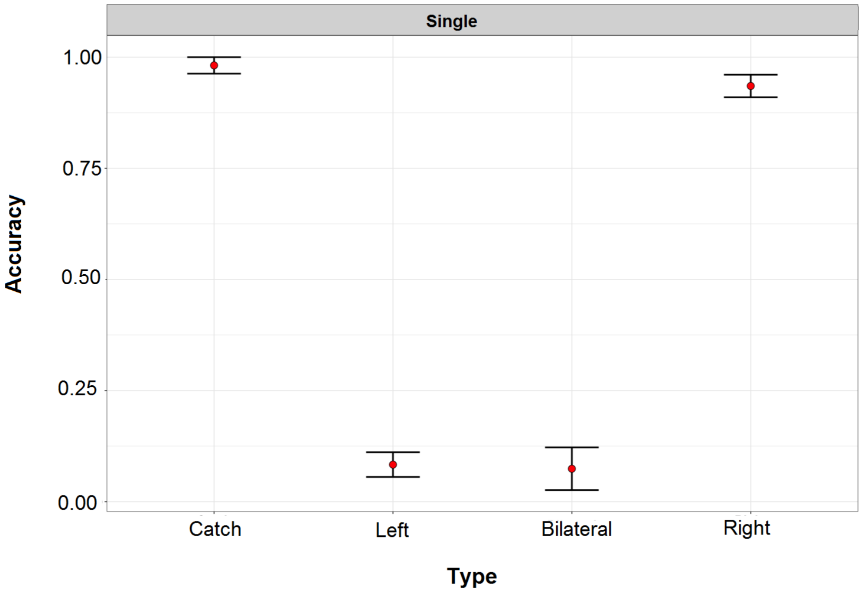


FIGURE 2 | Performance of right hemisphere damaged patients in the preliminary task for study inclusion. In this task left and right refers to the two sides of the screen. Performance for left and double target was severely compromised. Across all patients, there was no response bias and detection of targets presented within the right side of space approached ceiling performance.

correctly detected, at the group level, only 8% of left targets and 7% of bilateral ones. There was no response bias (accuracy to catch trials > 98%), and performance for right targets was highly accurate (94% of correct responses). Performance in this preliminary task is represented in **Figure 2**.

Experimental Task

Stimuli and Procedure

Patients omitting at least 75% of left, unilateral targets and less than 25% of ipsilesional targets in the preliminary task were included in the study and performed the experimental task. Task timing and stimuli were identical to those described above. Their position, instead, was different because the experimental task was specifically designed to test spatial awareness within the right side of space (see **Figure 3**). Lateralized targets were thus presented on the right of the fixation point either near right (3°), or far right (17°) (low vs. high eccentricity), or simultaneously in both locations (double target). Catch trials, in which no visual target was presented, were also administered to assess for any potential response bias. As in the screening task described above, a geometrical shape was always presented at fixation, coupled with the auditory presentation of an environmental sound (train whistle, doorbell, or hammer). There were three experimental conditions: one single-task condition, and two dual-task conditions (visual and auditory). Reporting target(s) position was the only request for the single task condition, whereas in the dual-visual or dual-auditory conditions patients also had to report, after having responded to the target, the central shape or the presented sound, respectively. The sensory stimulation was therefore kept identical across the three conditions, while the experimental manipulation was purely top–down, based on the nature and presence/absence of concurrent task demands.

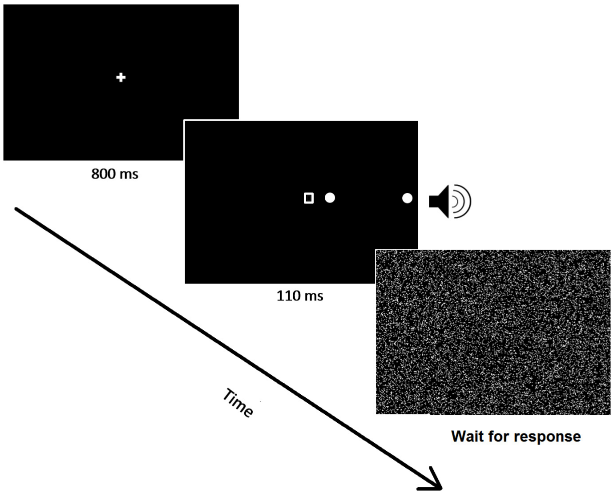


FIGURE 3 | A schematic image of a representative trial (double target) is shown. All stimuli were presented within the ipsilesional visual field.

Participants were allowed to rest after each trial, if necessary. The experimenter monitored eye movements and started each trial only when fixation was maintained. Trials affected by eye movements (<1%) were marked and discarded offline in the data analyses. The experiment was divided in 6 blocks, and each condition (single, auditory, or visual) was repeated twice (i.e., two blocks per condition). The single task condition was administered in the first and in the last block, in order to assess the potential effects of fatigue or sustained attention problems. The dual task conditions were performed in blocks 2 to 5 – with a fixed alternating order (i.e., visual-auditory-visual-auditory). A practice phase, consisting of 21 trials, was carried out before starting the experiment and allowed patients to familiarize with the task. Each experimental block comprised 36 trials. All possible combinations of shapes (3) and sounds (3) were presented within each block, balanced in frequency and with randomized order. Overall, the experiment consisted of 216 trials (3 load conditions × 4 types of target × 18 trials per cell) and could be completed in about 30 min by both patients and controls.

RESULTS

Analyses were performed using R version 3.5.1 (R Core Team, 2018). The following packages were used to implement data preprocessing and the pipeline for statistical analyses: dplyr v. 0.7.6 (Wickham et al., 2015); ggplot2 v. 3.0.0 (Wickham, 2016); afex v. 0.21-2 (Singmann et al., 2018); lme4 v. 1.1-17 (Bates et al., 2014, 2015b).

Mixed Models on Accuracy

Data have been first analyzed through *mixed-effects multiple regression models* (Baayen et al., 2008). A main advantage of mixed models is that they use single trial (rather than averaged) data; moreover, they do not assume independence amongst observations and the model fitting procedure takes into account the individual variability (random effects). This approach is particularly interesting for the analysis of clinical data because they are noisier than the data of healthy participants (for previous applications to stroke patients see, e.g., Zorzi et al., 2012; Blini et al., 2016). Models assessed detection accuracy as dependent variable through a logistic link-function, appropriate for binary variables. Prior to fixed-effect testing, the most appropriate and parsimonious (Bates et al., 2015a) matrix of random effects was chosen via an objective pipeline detailed at length in previous work (Blini et al., 2018). This pipeline for testing random effects suggested a hierarchical solution: subjects were specified as random intercepts, but nested in the respective Group, as this grouping accounted for significant variance in baseline performances. Furthermore, the random slope for stimulus Type was selected: this allows one to account, in the models, for the individual variability in performances across different configurations of stimuli. Note that the "Catch" trial Type had to be discarded from these analyses because characterized by a performance at near ceiling in both groups (see **Figure 4**), and thus yielded several convergence problems.

The testing of fixed effects found a significant main effect of Group [$\chi^2(1) = 6.55$, $p = 0.01$]. The average performance of patients was less accurate than that of controls (accuracy, excluding catch trials: 82.2 vs. 95.3%; odd ratio = 0.1, *SE* = 0.04). Furthermore, a significant main effect of Load was found [$\chi^2(2) = 32.98$, $p < 0.001$]; specifically, the Visual Dual-task impaired detection performance with respect to both the Single (odd ratio = 0.054, *SE* = 0.018, Wald $z = 3.08$, $p = 0.006$) and Auditory dual task (odd ratio = 0.039, *SE* = 0.016, Wald $z = 2.35$, $p = 0.0496$), with no differences between the latter

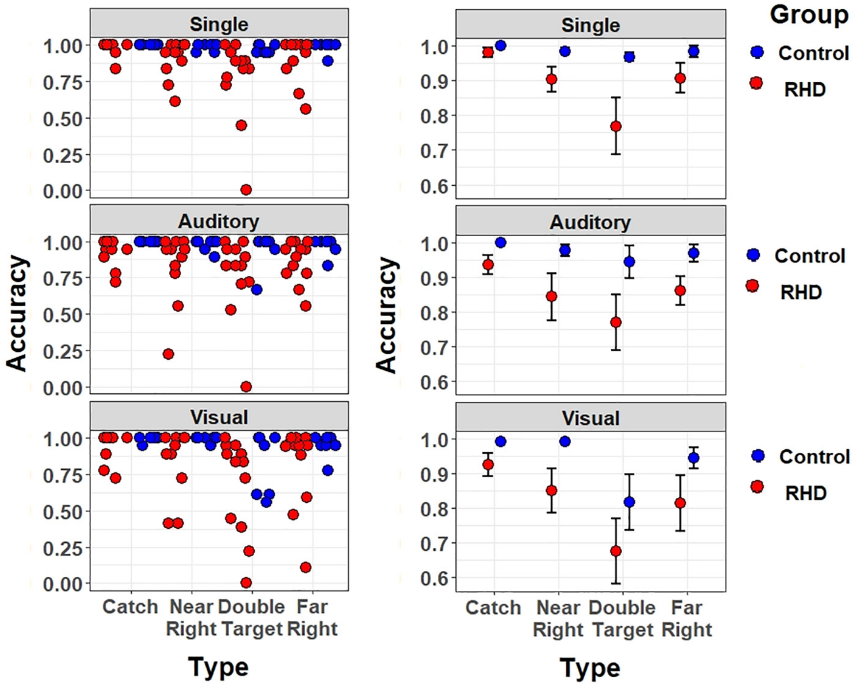


FIGURE 4 | Accuracy effect for each target type and task (top-to-bottom: single task, auditory dual-task, and visual dual task), separately for right-hemisphere damaged patients (in red) and healthy controls (in blue). Left (right) panels show individual (mean ± SEM) performance.

two. There were no other significant effects or interactions (all ps > 0.085), showing that visual multitasking-induced performance decrements were comparable across Groups. Thus, when taking into account the number of errors and not their nature, the Visual dual-task condition was found to be equally challenging in both Groups.

However, the crucial test of this study concerns potential perceptual asymmetries in detecting targets in one or another spatial location. We therefore proceeded with a fine-grained analysis of Asymmetry Indices (AIs), which better inform about the presence of *lateralized* response biases (see below). Because controls performed at near ceiling, we focus on assessing lateralized biases in patients (mean accuracy of 82.2%).

Lateralized Effects of Attentional Load on Spatial Monitoring

Asymmetry Indices summarize response asymmetries found when comparing the detection rate of ipsilesional less vs. more lateralized targets (see **Figure 5**). The AIs for double target and catch trials were (separately) computed by subtracting, for each individual, the proportion of "near right" [relative left] responses from the proportion of "far right" responses [relative right]. A negative AI indexes that "near right" responses prevailed among errors while positive AI reveals prevalence of "far right" responses. For unilateral trials, AIs were obtained by subtracting the proportion of omissions for far right targets from the proportion of omissions for near right targets. The unilateral AI is similar to the previous one, with negative values representing a leftward bias and positive values representing a rightward bias. AI values express here the asymmetry in terms of lateralized proportion of errors. That is, a value of −1 indicates that all (and only) the far right targets were missed, whereas a value of 0 indicates that an equal number of near right and far right targets were missed (or that no targets were missed). These three dependent variables were then submitted to a three-way ANOVA using Task (Single, Dual Visual, Dual Auditory) as independent variable.

For the patients group, results were as follows. For catch trials, the pattern of responses was not modulated by Task ($F_{(2,22)} = 0.9$, $p = 0.42$); the average AI (collapsed across Tasks) was not lateralized [$t(11) = -0.57$, $p = 0.58$], showing no evidence of a general response bias. For unilateral trials, results were similar, with no modulation by Task ($F_{(2,22)} = 2.6$, $p = 0.097$), and no lateralized bias on average [$t(11) = -0.92$, $p = 0.38$]. For double targets, however, Task induced a significant modulation ($F_{(2,22)} = 6.11$, $p < 0.01$). Follow-up t-tests showed that the AIs were significantly lateralized and negative (i.e., biased to the left) in the Visual dual-task [$t(11) = -2.53$, $p = 0.028$]. Paired t-tests further showed that AIs differed, and were more strongly left-lateralized, for both dual tasks with respect to the single task [single vs. Dual Visual $t(11) = 2.9$, $p = 0.015$; single vs. Dual Auditory $t(11) = 2.24$, $p = 0.047$]. The two dual tasks did not differ though, $t(11) = 1.94$, $p = 0.08$. This suggests that impairments emerged in the presence of a visual or auditory load and of double targets. Finally, we performed exploratory correlations

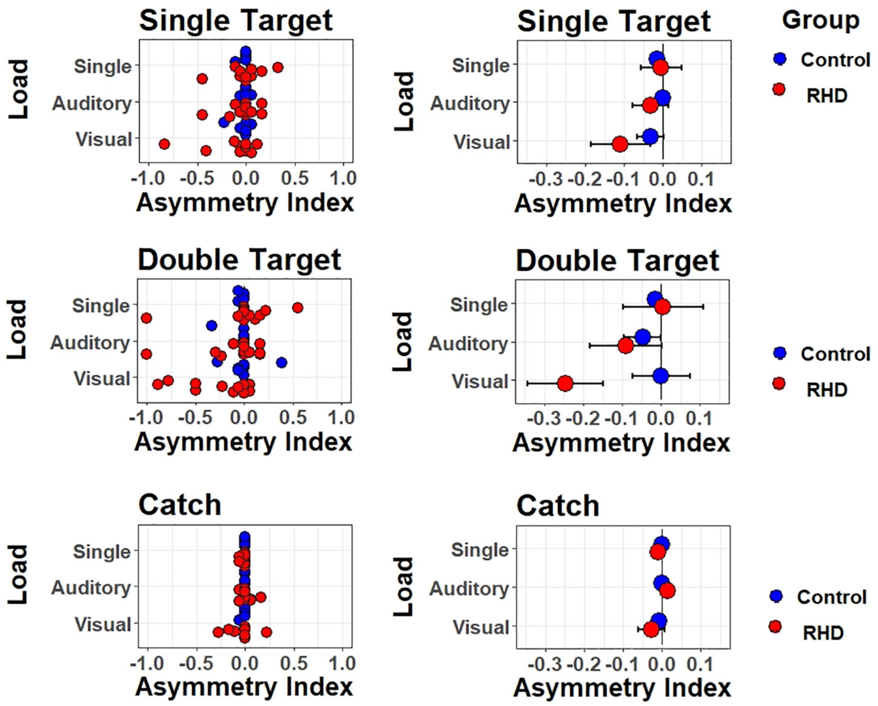


FIGURE 5 | Lateralized effects on spatial monitoring performance. Asymmetry indexes are shown for each type of trial (one target, two targets, no target) and type of task/attentional load (single task, auditory dual task, visual dual task). Left (right) panels show individual (mean ± SEM) performance.

between AI and both neuropsychological scores (i.e., BIT) and lesion volume, but no significant associations emerged.

Fatigue and Sustained Attention

A specific analysis performed at the patients' group level assessed whether fatigue, or deficient sustained attention, had an impact on performance accuracy. The single task was performed both at the beginning (i.e., first block of trials) and at the end (i.e., last block of trials) of the experiment. Therefore, a significant drop in accuracy between the first and the last block would suggest the presence of a confound due to fatigue.

A 4 (Type: catch, near right, far right, or double target) by 2 (Session: first or last) mixed model, with the same analytic precautions described above, was therefore computed. Models included a random intercept for Subject and a random by-subject slope for Type. However, the analyses did not highlight effects of Session, as either a main effect nor in interaction with Type (all $\chi^2 < 0.19$, all $ps > 0.69$) (see **Figure 6**).

DISCUSSION

We investigated whether and how multitasking affects the conscious perception of ipsilaterally-presented single and double targets. The task was performed by chronic right-hemisphere stroke patients who were specifically selected because unable to perceive items in the contralesional side of space. Targets within the right, ipsilesional space could be presented either pericentrally (near right), more laterally (far right), or in both positions. We found that patients' performance was particularly impaired for the most lateralized ipsilateral target position when the task required parallel processing of multiple stimuli, that is a double target and concurrent visual or auditory load.

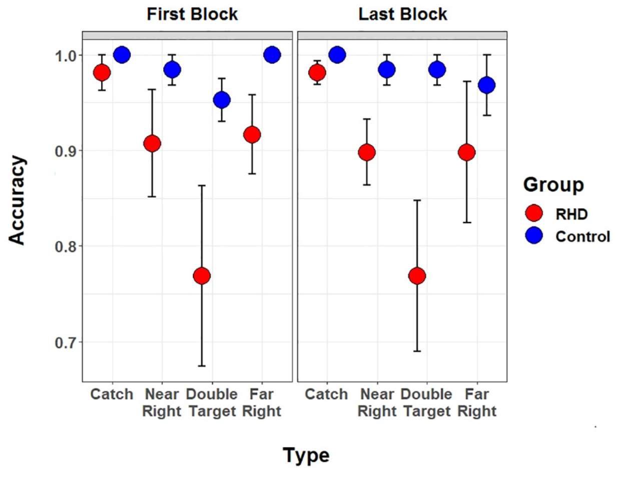


FIGURE 6 | Blockwise Task performance. Performance of right hemisphere damaged patients (in red) and controls (in blue) is shown separately for the first and the last (i.e., sixth) block of the spatial monitoring task. In both blocks the single task version was performed (participants only had to report target position).

This pattern of findings excludes the possibility that ipsilesional processing might become, after brain damage, hyperefficient due to attentional imbalance. Rather, it characterizes the performance for the ipsilesional space, or at least for the most lateralized part of the ipsilesional space, as impaired (see section "Introduction"). Strong support for this possibility comes, at individual level, from the pattern presented by Case 5. He was the only patient in the sample who presented a contralesional deficit so severe to result, in the STAR cancellation subtest, in omitting not only all targets in the left hemispace but also some on the right, ipsilesional, hemispace. In other words, this patient neglected a portion of space that extended (at least under demanding testing) to a visual angle corresponding to the position where the near-right ipsilesional targets were presented in the computer-based task. Despite this severe deficit in the cancellation task, his performance in the experimental task with double stimuli and visual load was characterized by systematic omission of the rightmost but not the leftmost target (AI: −0.77). The correct detection of targets in a spatial position that was neglected in the paper-and-pencil test occurred despite the brief duration of targets in the computer-based task.

An alternative explanation, which can only be partly ruled out here, claims that RHD patients (with neglect) may also present a severe bias favoring stimuli presented at fixation (Ptak et al., 2007). Distracters presented para-foveally severely disrupt saccade initiation irrespectively of saccade direction, leading to disproportionately increased latencies. According to Ptak et al. (2007), RHD patients with neglect not only fail to inhibit reflexive orienting toward ipsilesional items, but also exhibit a strong oculomotor bias favoring the fixated stimuli. According to this reasoning, one might claim that the impaired performance found for the rightmost targets was, at least in part, triggered by the presence of one central shape. While we cannot exclude this explanation, it seems worth pointing out that the central shape was already present under single task, when no asymmetry emerged. It rather seems that focusing attention on the central shape had to be considered a condition necessary but not sufficient for ipsilesional omissions to occur. In principle, the deficits might be ascribed to unspecific impairments. It should be also considered, however, that both alternative explanations are consistent with the presence of impaired mechanisms of visuo-spatial processing within the ipsilesional space.

Whether and how it is possible to isolate an advantage in ipsilesional processing without re-referencing performance to the contralesional side of space remains an open issue. Ipsilesional biases have been described as being predictive of long-term deficits, altogether with unspecific slowing (Viken et al., 2014). The clinical value of these findings perfectly summarizes the possibility that, also within a context of lateralized deficits, performance can be heavily affected by unspecific impairments. Support for the interaction between specific and unspecific factors comes from the study of spatial perseverations in drawing and cancellation tests. Despite having a clear spatial gradient, perseverations are more commonly due to a complex interaction between spatial and non-spatial components (Nys et al., 2010). Ronchi et al. (2009) showed that the degree of perseverations could be explained neither by neglect severity nor by executive functions deficits alone (also see Pia et al., 2009). One could therefore wonder whether, also in a purely perceptual domain, the same explanation holds. This would be only in part at odds with the idea that ipsilesional processing is related to neglect severity because non-spatial impairments are also directly related to neglect severity. Finally, it seems difficult to disentangle whether this putatively more effective performance is due to a sort of lack of inhibition, as it seems the case when ipsilesional stimuli are not task-relevant (Ptak et al., 2007). The functionality of the left attentional network might provide a compensatory effect after critical right-hemisphere lesions and be relevant for contralesional spatial processing (Blini et al., 2016).

Overall, results suggest that the approach we used in the present study is promising for detecting asymmetries in spatial monitoring caused by lateralized brain damage, as previously observed in chronic RHD patients (Bonato et al., 2010). The presence of omissions under load is all-but a curiosity. A wealth of studies (Ball and Owsley, 1993; Owsley et al., 1998; Ball et al., 2002) demonstrated that the "shrinkage" of visual field under visual load reliably predicts functional impairment. The amplitude of this impairment correlates with important everyday life outcomes such as for instance the risk of car crashes (Owsley et al., 1998).

Given the ubiquity of multitasking in everyday activities, and the practical impossibility to test performance within the contralesional hemispace in a number of patients (e.g., those with severe neglect and/or hemianopia), this approach can provide information that is clinically relevant (see Bonato et al., 2012).

The present study suggests that awareness disorders might not be only present in a contralesional to ipsilesional gradient. Instead, they might be present even for the most lateralized ipsilesional space portions, at least in the most demanding task conditions. This finding is particularly interesting because it contrasts two widely held aspects of ipsilesional processing. First, it is at odds with the evidence (collected in the absence of dual-tasking) suggesting that the most ipsilesional spatial positions are processed flawlessly even by the most severe neglect patients (Smania et al., 1998). Second, it seems incompatible with the possibility that ipsilesional items trigger an automatic orienting of attention toward them. The fact that the most demanding condition resulted in omissions fits with the hypothesis that the individual spatial pattern of awareness is determined by an interaction between a generalized lack of (non-spatial) resources and a more specific spatial processing deficit (Robertson et al., 1998; Bonato et al., 2010; Corbetta and Shulman, 2011). Once more, dual-tasking exacerbated a spatial deficit (ipsilesional, in this specific context) which was not detectable under single-task conditions and was present only for the most demanding conditions.

Whether the origin of these space-based consciousness disorders are unspecific deficits or whether it is, rather directly, linked to the severity of the spatial impairments, remains undetermined. It would be interesting to couple a modified version of the present task with rehabilitation trials for contralesional visual (Casco et al., 2018) or attentional deficits (Antonucci et al., 1995), to quantify the extent of subtle neglect deficits, to monitor changes over time, and also to assess the effectiveness of rehabilitation (Azouvi, 2017; Chen et al., 2017).

The present study is a first attempt to explore the effects of multitasking in ipsilesional hemispace and has several limitations. First, our small sample size is more prone to a descriptive/qualitative approach. Second, we lack information as to whether homonymous hemianopia was present in patients (beyond the simple clinical testing with single and double simultaneous stimulation). There is no doubt that it would have been interesting to know whether the individual ipsilesional impairment was associated with a contralesional visual field deficit. For the sake of completeness, however, it should be mentioned that our patients were all functionally blind for the contralesional side of space and that a visual field assessment is often not sufficient to determine whether a patient suffers from hemianopia or "only" from severe neglect (Walker et al., 1991; Müller-Oehring et al., 2003). The third, and most important weakness is the absence of a control group of left-hemisphere damaged patients. Without such a reference it seems difficult to understand whether the deficits we preliminarily highlighted in the present study are specific or unspecific consequences of RHD. For future studies, it would be also interesting to more extensively map several eccentricities rather than only two.

In short, by using an adapted version of a multitasking approach we explored ipsilesional spatial awareness after right-hemisphere stroke in patients who could not detect the presence of briefly-presented, contralesional items. This promising approach allowed us to discard the possibility that stroke might preserve ipsilesional performance or make it hyper-efficient. Rather, systematic errors were found in the patients group in the case of two targets being simultaneously presented. When concurrent information had to be processed at fixation, several of the more lateralized items appearing within the putatively unaffected visual hemispace went unreported in patients but not in healthy controls.

ETHICS STATEMENT

The study and all procedures were approved by the Ethics Committee for Clinical Research (CESC) of the Venice region (Reference No. 2014.09) and were carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent to take part into the study.

AUTHOR CONTRIBUTIONS

MB, ZR, EB, MP, and MZ conceived the study. ZR, ED, and LP collected the data. FM and LP supervised patient recruitment. ZR and EB performed the analyses. MB drafted the manuscript, with contributions from ZR, EB, and MZ. All authors reviewed the manuscript.

FUNDING

This study was supported by grant RF-2013-02359306 from the Italian Ministry of Health (MZ). This work was also partially supported by Strategic Project Grant "NEURAT" from the University of Padova (MZ) and it was carried out within the scope of the research program "Dipartimenti di Eccellenza," which is supported by a grant from MIUR to the Department of General Psychology, University of Padova. EB received funding from the European Union's Horizon 2020 Research and Innovation Program (Marie Curie Actions) under Grant Agreement No. MSCA-IF-2016-746154.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.00697/full#supplementary-material

REFERENCES

Antonucci, G., Guariglia, C., Judica, A., Magnotti, L., Paolucci, S., Pizzamiglio, L., et al. (1995). Effectiveness of neglect rehabilitation in a randomized group study. *J. Clin. Exp. Neuropsychol.* 17, 383–389. doi: 10.1080/01688639508405131

Azouvi, P. (2017). The ecological assessment of unilateral neglect. *Ann. Phys. Rehabil. Med.* 60, 186–190. doi: 10.1016/j.rehab.2015.12.005

Baayen, R. H., Davidson, D. J., and Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *J. Mem. Lang.* 59, 390–412. doi: 10.1016/j.jml.2007.12.005

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 288, 2271–2281. doi: 10.1001/jama.288.18.2271

Ball, K., and Owsley, C. (1993). The useful field of view test: a new technique for evaluating age-related declines in visual function. *J. Am. Optom. Assoc.* 64, 71–79.

Bartolomeo, P., and Chokron, S. (1999). Left unilateral neglect or right hyperattention? *Neurology* 53, 2023–2027. doi: 10.1212/WNL.53.9.2023

Bartolomeo, P., and Chokron, S. (2000). "Levels of impairment in unilateral neglect," in *Handbook of Neuropsychology*, eds F. Boller and M. Behrmann (Amsterdam: Elsevier Inc), 67–98.

Bartolomeo, P., Chokron, S., and Siéroff, E. (1999). Facilitation instead of inhibition for repeated right-sided events in left neglect. *Neuroreport* 10, 3353–3357. doi: 10.1097/00001756-199911080-199911018

Bartolomeo, P., Thiebaut de Schotten, M., and Chica, A. B. (2012). Brain networks of visuospatial attention and their disruption in visual neglect. *Front. Hum. Neurosci.* 6:110. doi: 10.3389/fnhum.2012.00110

Bates, D., Kliegl, R., Vasishth, S., and Baayen, H. (2015a). Parsimonious Mixed Models. *ArXiv* 1506.04967.

Bates, D., Mächler, M., Bolker, B., and Walker, S. (2015b). Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* 67, 1–48. doi: 10.18637/jss.v067.i01

Bates, D., Maechler, M., Bolker, B., and Walker, S. (2014). *lme4: Linear Mixed-Effects Models Using Eigen and S4. R Package Version*. Available at: https://cran.r-project.org/web/packages/lme4/index.html.

Behrmann, M., Watt, S., Black, S. E., and Barton, J. J. S. (1997). Impaired visual search in patients with unilateral neglect: an oculographic analysis. *Neuropsychologia* 35, 1445–1458. doi: 10.1016/S0028-3932(97)00058-54

Blini, E., Romeo, Z., Spironelli, C., Pitteri, M., Meneghello, F., Bonato, M., et al. (2016). Multi-tasking uncovers right spatial neglect and extinction in chronic left-hemisphere stroke patients. *Neuropsychologia* 92, 147–157. doi: 10.1016/j.neuropsychologia.2016.02.028

Blini, E., Tilikete, C., Farnè, A., and Hadj-Bouziane, F. (2018). Probing the role of the vestibular system in motivation and reward-based attention. *Cortex* 103, 82–99. doi: 10.1016/j.cortex.2018.02.009

Bonato, M. (2012). Neglect and extinction depend greatly on task demands: a review. *Front. Hum. Neurosci.* 6:195. doi: 10.3389/fnhum.2012.00195

Bonato, M. (2015). Unveiling residual, spontaneous recovery from subtle hemispatial neglect three years after stroke. *Front. Hum. Neurosci.* 9:413. doi: 10.3389/fnhum.2015.00413

Bonato, M., Priftis, K., Marenzi, R., Umiltà, C., and Zorzi, M. (2010). Increased attentional demands impair contralesional space awareness following stroke. *Neuropsychologia* 48, 3934–3940. doi: 10.1016/j.neuropsychologia.2010.08.022

Bonato, M., Priftis, K., Marenzi, R., Umiltà, C., and Zorzi, M. (2012). Deficits of contralesional awareness: a case study on what paper-and-pencil tests neglect. *Neuropsychology* 26, 20–36. doi: 10.1037/a0025306

Butler, B. C., Eskes, G. A., and Vandorpe, R. A. (2004). Gradients of detection in neglect: comparison of peripersonal and extrapersonal space. *Neuropsychologia* 42, 346–358. doi: 10.1016/j.neuropsychologia.2003.08.008

Carlesimo, G. A., Caltagirone, C., Gainotti, G., Fadda, L., Gallassi, R., Lorusso, S., et al. (1996). The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *Eur. Neurol.* 36, 378–384. doi: 10.1159/000117297

Casco, C., Barollo, M., Contemori, G., and Battaglini, L. (2018). Neural restoration training improves visual functions and expands visual field of patients with homonymous visual field defects. *Restor. Neurol. Neurosci.* 36, 275–291. doi: 10.3233/RNN-170752

Chen, P., Pitteri, M., Gillen, G., and Ayyala, H. (2017). Ask the experts how to treat individuals with spatial neglect: a survey study. *Disabil. Rehabil.* 40, 2677–2691. doi: 10.1080/09638288.2017.1347720

Chokron, S., Peyrin, C., and Perez, C. (2018). Ipsilesional deficit of selective attention in left homonymous hemianopia and left unilateral spatial neglect. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2018.03.013 [Epub ahead of print].

Corbetta, M., and Shulman, G. L. (2011). Spatial neglect and attention networks. *Annu. Rev. Neurosci.* 34, 569–599. doi: 10.1146/annurev-neuro-061010-113731

Cubelli, R. (2017). Definition: spatial neglect. *Cortex* 92, 320–321. doi: 10.1016/j.cortex.2017.03.021

Driver, J., and Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition* 79, 39–88. doi: 10.1016/S0010-0277(00)00124-4

Ferber, S., and Karnath, H.-O. (2001). How to assess spatial neglect - line bisection or cancellation tasks? *J. Clin. Exp. Neuropsychol.* 23, 599–607. doi: 10.1076/jcen.23.5.599.1243

Friston, K. J., Ashburner, J., Kiebel, S. J., Nichols, T. E., and Penny, W. D. (2007). *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Cambridge: Academic Press. doi: 10.1016/B978-012372560-8/50002-4

Gainotti, G., D'Erme, P., and Bartolomeo, P. (1991). Early orientation of attention toward the half space ipsilateral to the lesion in patients with unilateral brain damage. *J. Neurol. Neurosurg. Psychiatry* 54, 1082–1089. doi: 10.1136/jnnp.54.12.1082

Halligan, P. W., and Marshall, J. C. (1991). Left neglect for near but not far space in man. *Nature* 350, 498–500. doi: 10.1038/350498a0

Halligan, P. W., Burn, J. P., Marshall, J. C., and Wade, D. T. (1992). Visuo-spatial neglect: qualitative differences and laterality of cerebral lesion. *J. Neurol. Neurosurg. Psychiatry* 55, 1060–1068. doi: 10.1136/jnnp.55.11.1060

Losier, B. J. W., and Klein, R. M. (2001). A review of the evidence for a disengage deficit following parietal lobe damage. *Neurosci. Biobehav. Rev.* 25, 1–13. doi: 10.1016/S0149-7634(00)00046-44

Machner, B., Könemund, I., von der Gablentz, J., Bays, P. M., and Sprenger, A. (2018). The ipsilesional attention bias in right-hemisphere stroke patients as revealed by a realistic visual search task: neuroanatomical correlates and functional relevance. *Neuropsychology* 32, 850–865. doi: 10.1037/neu0000493

Magni, E., Binetti, G., Bianchetti, A., Rozzini, R., and Trabucchi, M. (1996). Mini-mental state examination: a normative study in Italian elderly population. *Eur. J. Neurol.* 3, 198–202. doi: 10.1111/j.1468-1331.1996.tb00423.x

Mark, V. W., Kooistra, C. A., and Heilman, K. M. (1988). Hemispatial neglect affected by non-neglected stimuli. *Neurology* 38, 1207–1211. doi: 10.1212/WNL.38.8.1207

Marshall, J. C., and Halligan, P. W. (1989). When right goes left: an investigation of line bisection in a case of visual neglect. *Cortex* 25, 503–515. doi: 10.1016/S0010-9452(89)80065-80066

Morrow, L. A., and Ratcliff, G. (1988). The disengagement of covert attention and the neglect syndrome. *Psychobiology* 16, 261–269. doi: 10.3758/BF03327316

Müller-Oehring, E. M., Kasten, E., Poggel, D. A., Schulte, T., Strasburger, H., and Sabel, B. A. (2003). Neglect and hemianopia superimposed. *J. Clin. Exp. Neuropsychol.* 25, 1154–1168. doi: 10.1076/jcen.25.8.1154.16727

Nachev, P., Coulthard, E., Jäger, H. R., Kennard, C., and Husain, M. (2008). Enantiomorphic normalization of focally lesioned brains. *Neuroimage* 39, 1215–1226. doi: 10.1016/j.neuroimage.2007.10.002

Natale, E., Marzi, C., Bricolo, E., Johannsen, L., and Karnath, H.-O. (2007). Abnormally speeded saccades to ipsilesional targets in patients with spatial neglect. *Neuropsychologia* 45, 263–272. doi: 10.1016/j.neuropsychologia.2006.07.008

Nys, G. M. S., Stuart, M., and Dijkerman, H. C. (2010). Repetitive exploration towards locations that no longer carry a target in patients with neglect. *J. Neuropsychol.* 4, 33–45. doi: 10.1348/174866408X402424

Owsley, C., Ball, K., McGwin, G. Jr., Sloane, M. E., Roenker, D. L., White, M. F., et al. (1998). Visual processing impairment and risk of motor vehicle crash among older adults. *JAMA* 279, 1083–1088. doi: 10.1001/jama.279.14.1083

Pia, L., Folegatti, A., Guagliardo, M., Genero, R., and Gindri, P. (2009). Are drawing perseverations part of the neglect syndrome? *Cortex* 45, 293–299. doi: 10.1016/j.cortex.2007.11.015

Pitteri, M., Chen, P., Passarini, L., Albanese, S., Meneghello, F., and Barrett, A. M. (2018). Conventional and functional assessment of spatial neglect: clinical practice suggestions. *Neuropsychology* 32, 835–842. doi: 10.1037/neu0000469

Posner, M. I. (1980). Orienting of attention. *Q. J. Exp. Psychol.* 32, 3–25. doi: 10.1080/00335558008248231

Ptak, R., Schnider, A., Golay, L., and Müri, R. (2007). A non-spatial bias favouring fixated stimuli revealed in patients with spatial neglect. *Brain* 130, 3211–3222. doi: 10.1093/brain/awm234

Pustina, D., Coslett, H. B., Turkeltaub, P. E., Tustison, N., Schwartz, M. F., and Avants, B. (2016). Automated segmentation of chronic stroke lesions using LINDA: Lesion identification with neighborhood data analysis. *Hum. Brain Mapp.* 37, 1405–1421. doi: 10.1002/hbm.23110

R Core Team. (2018). *R: A Language and Environment for Statistical Computing*. Available at: https://www.R-project.org/

Robertson, I., and Frasca, R. (1992). Attentional load and visual neglect. *Int. J. Neurosci.* 62, 45–56. doi: 10.3109/00207459108999756

Robertson, I. H., Mattingley, J. B., Rorden, C., and Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature* 395, 169–172. doi: 10.1038/25993

Ronchi, R., Posteraro, L., Fortis, P., Bricolo, E., and Vallar, G. (2009). Perseveration in left spatial neglect: drawing and cancellation tasks. *Cortex* 45, 300–312. doi: 10.1016/j.cortex.2008.03.012

Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., and Karnath, H.-O. (2012). Age-specific CT and MRI templates for spatial normalization. *Neuroimage* 61, 957–965. doi: 10.1016/j.neuroimage.2012.03.020

Rorden, C., and Brett, M. (2000). Stereotaxic display of brain lesions. *Behav. Neurol.* 12, 191–200. doi: 10.1155/2000/421719

Russell, C., Malhotra, P., and Husain, M. (2004). Attention modulates the visual field in healthy observers and parietal patients. *Neuroreport* 15, 2189–2193. doi: 10.1097/00001756-200410050-200410059

Sarri, M., Greenwood, R., Kalra, L., and Driver, J. (2009). Task-related modulation of visual neglect in cancellation tasks. *Neuropsychologia* 47, 91–103. doi: 10.1016/j.neuropsychologia.2008.08.020

Singmann, H., Bolker, B., Westfall, J., and Aust, F. (2018). *Afex: Analysis of Factorial Experiments. R Package Version 0.21-2*. Available at: https://CRAN.R-project.org/package=afex

Smania, N., Martini, M. C., Gambina, G., Tomelleri, G., Palamara, A., Natale, E., et al. (1998). The spatial distribution of visual attention in hemineglect and extinction patients. *Brain* 121(Pt 9), 1759–1770. doi: 10.1093/brain/121.9.1759

Snow, J. C., and Mattingley, J. B. (2006). Goal-driven selective attention in patients with right hemisphere lesions: how intact is the ipsilesional field? *Brain* 129, 168–181. doi: 10.1093/brain/awh690

Viken, J. I., Jood, K., Jern, C., Blomstrand, C., and Samuelsson, H. (2014). Ipsilesional bias and processing speed are important predictors of functional dependency in the neglect phenomenon after a right hemisphere stroke. *Clin. Neuropsychol.* 28, 974–993. doi: 10.1080/13854046.2014.950335

Vossel, S., Eschenbeck, P., Weiss, P. H., Weidner, R., Saliger, J., Karbe, H., et al. (2011). Visual extinction in relation to visuospatial neglect after right-hemispheric stroke: quantitative assessment and statistical lesion-symptom mapping. *J. Neurol. Neurosurg. Psychiatry* 82, 862–868. doi: 10.1136/jnnp.2010.224261

Vuilleumier, P. (2013). Mapping the functional neuroanatomy of spatial neglect and human parietal lobe functions: progress and challenges. *Ann. N. Y. Acad. Sci.* 1296, 50–74. doi: 10.1111/nyas.12161

Walker, R., Findlay, J. M., Young, A. W., and Welch, J. (1991). Disentangling neglect and hemianopia. *Neuropsychologia* 29, 1019–1027. doi: 10.1016/0028-3932(91)90065-G

Wickham, H. (2016). *Ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag. doi: 10.1007/978-3-319-24277-4

Wickham, H., Francois, R., Henry, L., and Müller, K. (2015). *Dplyr: A grammar of Data Manipulation. R Package Version 0.7.6*. Available at: https://CRAN.R-project.org/package=dplyr

Wilson, B., Cockburn, J., and Halligan, P. (1987). Behavioural inattention test. *Arch. Phys. Med. Rehabil.* 68, 98–102. doi: 10.1130/G20654.1

Zorzi, M., Bonato, M., Treccani, B., Scalambrin, G., Marenzi, R., and Priftis, K. (2012). Neglect impairs explicit: processing of the mental number line. *Front. Hum. Neurosci.* 6:125. doi: 10.3389/fnhum.2012.00125

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a shared affiliation, though no other collaboration, with one of the authors MP at the time of review.

frontiers in Psychology

OPINION
published: 28 February 2019
doi: 10.3389/fpsyg.2019.00349

The Lack of Self-Consciousness in Right Brain-Damaged Patients Can Be due to a Disconnection From the Left Interpreter: The DiLeI Theory

*Roberta Daini**

Psychology, Università degli Studi di Milano Bicocca, Milan, Italy

Keywords: interpreter, anosognosia, corpus callosum, unilateral spatial neglect, self consciousness

INTRODUCTION

Consciousness is a very complex topic and nonetheless one of the most attractive for philosophers, psychologists, and cognitive neuroscientists.

In general terms, the consciousness of the self can be described as the ability to reflect on oneself, one's own mental abilities, defined as the set of one's own sensations, perceptions, and thoughts.

Hereby this function and its deficits from a neuropsychological perspective will be dealt with. Many different theories and models on consciousness exist (e.g., Crick and Koch, 1998; Tononi and Edelman, 1998; Dehaene and Naccache, 2001) and what is lacking is the effort to put together different phenomena and apparently conflicting interpretations to provide a plausible account. Self-awareness is unitary, despite the multiple processes that underlie it, and this unity is fundamental to the formulation of goals, to plan and perform actions. An alteration of self-consciousness can, therefore, be seen as a loss of unity in self-perception and attaining a loss of effectiveness in formulating and achieving goals. A well-known and most well-studied example of self-consciousness deficit is anosognosia, the lack of consciousness about one's own sensory, motor or cognitive disabilities after a brain injury (e.g., Prigatano, 1996; Pia et al., 2004).

THE PARADOX

Anosognosia is a symptom more associated with a right hemispheric lesion than a left one (e.g., Bisiach et al., 1986; Vossel et al., 2013; Pia et al., 2014). Moreover, right hemisphere damages consistently produce neuropathologies of the self, which are those related to the identity, the ego boundaries, and the relationship between the self and the external environment (e.g., Feinberg, 2011). Examples are the Capgras syndrome, delusional anosognosia, and somatoparaphrenia. This evidence could suggest a main role of the right hemisphere in the consciousness of the self-functioning. Nonetheless, studies on healthy participants tell a different story. When healthy participants are involved in tasks that require self-consciousness, as self-related judgments (Denny et al., 2012), functional neuroimaging studies showed a left hemisphere dominance.

Morin (2017) defined the inconsistency of results between healthy participants and right brain-damaged patients with anosognosia as the "self-awareness-anosognosia" paradox. He accounted for it by suggesting that the two types of studies measure aspects related to different processes, most likely associated with activity in distinct anatomical networks.

Edited by:
Silvia Savazzi,
University of Verona, Italy

Reviewed by:
Raffaella Ricci,
University of Turin, Italy

****Correspondence:***
Roberta Daini
roberta.daini@unimib.it

Specialty section:
This article was submitted to
Consciousness Research,
a section of the journal
Frontiers in Psychology

Received: *15 October 2018*
Accepted: *04 February 2019*
Published: *28 February 2019*

Citation:
Daini R (2019) The Lack of Self-Consciousness in Right Brain-Damaged Patients Can Be due to a Disconnection From the Left Interpreter: The DiLeI Theory.
Front. Psychol. 10:349.
doi: 10.3389/fpsyg.2019.00349

Moreover, not all brain-damaged patients' symptoms suggest a dominance of the right hemisphere for consciousness: for instance, the case of split-brain patients.

THE INTERPRETER

Fifty years of studies on split-brain patients (i.e., patients who underwent the resection of the corpus callosum) allowed Gazzaniga and his collaborators to frame the role of the left hemisphere in the consciousness of the self and to suggest the idea of an "Interpreter" (Volz and Gazzaniga, 2017). The typical observation is as follows: Visual stimuli tachistoscopically presented to the left hemifield are processed by the right hemisphere. Surprisingly, in this condition, split-brain patients verbally report that they do not see any stimulus. Even more surprisingly, when requested to point to a semantically related stimulus these patients point at the correct item with the left hand but do not verbally formulate the correct relationship. In healthy participants, information is transferred from the right hemisphere to the left one, interpreted and labeled. Results suggested that the "Interpreter" is located in the left hemisphere and it is strictly dependent not only on language but also on inferential reasoning (Volz and Gazzaniga, 2017).

The Interpreter represents a crucial aspect of consciousness and its localization, including left ventro-prefrontal cortex, left anterior and mid-insula, and dorsal caudate, is congruent with many studies about self-consciousness in healthy participants (e.g., Denny et al., 2012).

THE UNDERESTIMATION OF THE CORPUS CALLOSUM ROLE

The studies on split-brain patients suggest an essential role not only of the left hemisphere but also of the corpus callosum in the conscious experience.

The corpus callosum is the largest fiber bundle of the human brain and connects the two cerebral hemispheres. It allows transfer of inputs from one hemisphere to the other and is involved in several sensory, motor, and cognitive functions.

Two main mechanisms have been described in consciousness: synchronization (Engel and Singer, 2001) and integration (e.g., Tononi, 2004). The corpus callosum is strictly involved in both processes.

Steinmann et al. (2018) found that inter-hemispheric functional connectivity was significantly enhanced during left ear/right hemisphere conscious processing of auditory stimuli as compared to right ear/left hemisphere conscious processing of auditory stimuli. They found that conscious reports require causal interhemispheric inputs from the right to the left auditory cortices and that this interaction is mediated by synchronized gamma-band oscillations.

Studies on split-brain patients (Volz and Gazzaniga, 2017) and healthy participants (e.g., Banich and Belger, 1990) suggest that the corpus callosum cannot be thought of as a simple and passive information transfer channel. It is true, instead, that it is a complex set of fibers with different components acting separately and that the degree to which the cerebral hemispheres elaborate information independently or jointly is a relative phenomenon rather than absolute (Bloom and Hynd, 2005).

Moreover, the corpus callosum is thought to be a "symmetrical" connection between the left and right hemisphere. DTI studies on healthy participants found numerous asymmetries in the callosal connections; at the splenial level the direction of the connection, for the most part, is from the right to the left hemisphere rather than the opposite direction (Putnam et al., 2010; Iwabuchi et al., 2011).

A NEW PROPOSAL

If the interpreter is fundamental for the consciousness of the self-functioning and it is lateralized in the left hemisphere, why is anosognosia more often associated with lesions of the right hemisphere?

A possible interpretation is that the left hemisphere is relevant for self-consciousness and that a damage to the right hemisphere does not affect the areas strictly involved in self-consciousness but instead induces a "disconnection" between what is processed in the right hemisphere and the self-consciousness-related system in the left hemisphere. This hypothesis allows to put together many "distinct" phenomena and theories; first of all, the Gazzaniga's "interpreter," and calls for the double role of the corpus callosum.

On the one hand, the corpus callosum is one of most crucial structures for the synchronization and integration of sensory, motor and cognitive processes (e.g., Paul et al., 2007); mechanisms that are considered the neural basis of conscious perception.

On the other hand, callosal fibers have the task not only of transferring information from one hemisphere to the other one but also of inhibiting contralateral representations in "competitive" contexts (e.g., Bloom and Hynd, 2005). The more the function is lateralized, the more the connection is inhibitory to ensure that the dominant hemisphere is activated (Cook, 1984). Moreover, the fibers of the corpus callosum are not symmetrical. A lesion of the right hemisphere involving the white matter could result in a desynchronization/inhibition by the interhemispheric fibers of the left hemisphere, especially for strongly lateralized functions.

In this frame, a lesion of the left hemisphere can disrupt only intrahemispheric connections relevant for conscious content, while right hemispheric lesions affect both intrahemispheric and interhemispheric connectivity.

Although a damage to the corpus callosum fibers can be the reason for a disconnection deficit of anosognosia, a lesion within the right hemisphere (not necessarily involving the corpus callosum) determines an effect over the equilibrium of connectivity between the two hemispheres and this, in turn, alters the synchronization and integration between the processes that started within each hemisphere.

An essential role in anosognosia is attributed to the impairment of anatomo-functionally discrete monitoring systems (Berti et al., 2005; Vallar and Ronchi, 2006; Moro et al., 2011). The current proposal suggests that the self-monitoring is the consequence of the same processing responsible for conscious experience, going from the right hemisphere to the left Interpreter, which is impaired in those patients.

THE CASE OF UNILATERAL SPATIAL NEGLECT (NSU): A BRIDGE BETWEEN KINSBOURNE AND HEILMAN'S THEORIES

Brain-damaged patients affected by unilateral spatial neglect (USN) fail to report, respond to, and orient to stimuli presented on the side of space contralateral to the lesion. USN can also be described as a deficit of consciousness of the contralesional space, either of the own body or the external environment. It is also characterized by anosognosia, i.e., patients are not aware of having USN, and it is more severe after right hemisphere damage (Weintraub and Mesulam, 1987).

Two of the leading theories proposed to account for unilateral spatial neglect (USN) are those of Kinsbourne (1970) and Heilman and Valenstein (1979), which start from opposite assumptions. The former states that the left hemisphere is dominant for visuo-spatial attention and a right damage induces a rightward bias because it emphasizes the imbalance; the latter suggests that the right hemisphere is dominant for visuo-spatial attention and is entailed with the entire space, whereas the left hemisphere is involved only in orienting attention to the contralateral hemispace. Some data support Kinsbourne's model (e.g., Corbetta et al., 2005; Salatino et al., 2014), while others support the Heilman's one (e.g., Ricci et al., 2012; Bagattini et al., 2015).

According to the Disconnection from the Left Interpreter (DiLeI) theory, the dominance of the right hemisphere for visuo-spatial attention is compatible with the Kinsbourne's explanation of USN in terms of an attentional vector of the left hemisphere toward the ipsilesional side of space.

The right lesion, indeed, could affect the right-toward-left-hemisphere directional asymmetry of callosal fibers by reducing the inhibitory effect over the left–toward-right activity. The first consequence could be a reduction in interhemispheric functional connectivity of dorsal attention and sensory-motor networks shown by Baldassarre et al. (2014) for right brain-damaged patients with resting state fMRI. The authors measured spontaneous brain activity in a resting state functional connectivity mapping study and found a reduced interhemispheric functional connectivity for the dorsal attention and sensory-motor networks. This pattern was stronger in patients with right- hemisphere as compared to left-hemisphere damage, with neglect more than without neglect and, finally, correlated with the NSU tests performance.

Accordingly, disruption of callosal connections causes more severe neglect (Bozzali et al., 2012), and severely reduces interhemispheric functional connectivity (Johnston et al., 2008).

The DiLeI theory proposes that the "isolation" of the right hemisphere: (1) impedes the perceptual processing from reaching the Interpreter in the left hemisphere and then induces the lack of consciousness for the stimuli presented in the left hemispace; (2) enhances the activity of the left hemisphere and then the saliency of the stimuli in the right side of space and their power of orienting attention.

I am not supporting the idea that USN is due to the disconnection of the right hemisphere with the Interpreter. There are other specific mechanisms underlying USN that are linked with the right hemisphere functioning. Nevertheless, this disconnection can explain some phenomena linked with USN (i.e., the anosognosia for neglect, the conscious perception of only the stimuli processed by the left hemisphere and the perceptual saliency of the ipsilesional stimuli).

CONCLUSIONS

The DiLeI theory states that the lack of access to the Interpreter's system, and therefore, the lack of integration with the other contents of the conscience would explain the greater incidence of deficits for right brain damages for functions not necessarily lateralized on the right. In other words, the consciousness would not depend (only) on modules located in the right hemisphere, nor in the left, but on the integration of the two hemispheres through the corpus callosum.

This theory has the advantage of being applicable to many areas, from psychiatry to personality and cognitive psychology in general. Schizophrenia, for example, is considered to be the consequence of multiple dysfunctional mechanisms, including the one that underlies information binding (Tononi and Edelman, 2000) and self-monitoring (Frith, 1992). In this context, the mechanisms of information binding and self-monitoring would depend on the interpreter circuit and form the connection between the two hemispheres. Neuroimaging techniques, indeed, have shown both the functional alteration of the cortico-subcortical circuits of the left hemisphere (fronto-temporal areas, insula, cerebellum, thalamus), neural correlate of the Interpreter, and a hypoactivation of the left hemisphere, and hyperactivation of the right (e.g., Trimble and George, 2010). Nonetheless, this interpretation is suited to the disconnection syndrome theory by Friston and Frith (1995).

The DiLeI theory needs, of course, to be validated, and I predict that it will have heuristic meaning to "interpret" multiple phenomena with discrete mechanisms and processes.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

FUNDING

My Department of Psychology provides funds for Open Access Publication Fees.

REFERENCES

Bagattini, C., Mele, S., Brignani, D., and Savazzi, S. (2015). No causal effect of left hemisphere hyperactivity in the genesis of neglect-like behavior. *Neuropsychologia*, 72, 12–21. doi: 10.1016/j.neuropsychologia.2015.04.010

Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., et al. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain*, 137, 3267–3283. doi: 10.1093/brain/awu297

Banich, M. T., and Belger, A. (1990). Interhemispheric interaction: How do the hemispheres divide and conquer a task? *Cortex* 26, 77–94 doi: 10.1016/S0010-9452(13)80076-7

Berti, A., Bottini, G., Gandola, M., Pia, L., Smania, N., Stracciari, A., et al. (2005). Shared cortical anatomy for motor awareness and motor control. *Science* 309, 488–491. doi: 10.1126/science.1110625

Bisiach, E., Vallar, G., Perani, D., Papagno, C., and Berti, A. (1986). Unawareness of disease following lesions of the right hemisphere: Anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 24, 471–482. doi: 10.1016/0028-3932(86)90092-8

Bloom, J. S., and Hynd, G. W. (2005). The role of the corpus callosum in interemispheric transfer of information: excitation or inhibition. *Neuropsychol. Rev.* 15, 59–71. doi: 10.1007/s11065-005-6252-y

Bozzali, M., Mastropasqua, C., Cercignani, M., Giulietti, G., Bonnì, S., Caltagirone, C., et al. (2012). Microstructural damage of the posterior corpus callosum contributes to the clinical severity of neglect. *PLoS ONE* 7:e48079. doi: 10.1371/journal.pone.0048079

Cook, N. D. (1984). Homotopic callosal inhibition. *Brain Lang.* 23, 116–125. doi: 10.1016/0093-934X(84)90010-5

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., and Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat. Neurosci.* 8:1603. doi: 10.1038/nn1574

Crick, F., and Koch, C. (1998). Consciousness and neuroscience. *Cereb. Cortex* 8, 97–107 doi: 10.1093/cercor/8.2.97

Dehaene, S., and Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition* 79, 1–37. doi: 10.1016/S0010-0277(00)00123-2

Denny, B. T., Kober, H., Wager, T. D., and Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *J. Cognit. Neurosci.* 24, 1742–1752. doi: 10.1162/jocn_a_00233

Engel, A. K., and Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends Cogn. Sci.* 5, 16–25. doi: 10.1016/S1364-6613(00)01568-0

Feinberg, T. E. (2011). Neuropathologies of the self: Clinical and anatomical features. *Conscious. Cogn.* 20, 75–81. doi: 10.1016/j.concog.2010.09.017

Friston, K. J., and Frith, C. D. (1995). Schizophrenia: a disconnection syndrome. *Clin. Neurosci.* 3, 89–97.

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. Hove: Lawrence Erlbaum Associates.

Heilman, K. M., and Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Ann. Neurol.* 5, 166–170. doi: 10.1002/ana.410050210

Iwabuchi, S. J., Häberling, I. S., Badzakova-Trajkov, G., Patston, L. L., Waldie, K. E., Tippett, L. J., et al. (2011). Regional differences in cerebral asymmetries of human cortical white matter. *Neuropsychologia* 49, 3599–3604. doi: 10.1016/j.neuropsychologia.2011.09.011

Johnston, J. M., Vaishnavi, S. N., Smyth, M. D., Zhang, D., He, B. J., Zempel, J. M., et al. (2008). Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. *J. Neurosci.* 28, 6453–6458. doi: 10.1523/JNEUROSCI.0573-08.2008

Kinsbourne, M. (1970). The cerebral basis of lateral asymmetries in attention. *Acta Psychol.* 33, 193–201. doi: 10.1016/0001-6918(70)90132-0

Morin, A. (2017). The "self-awareness–anosognosia" paradox explained: How can one process be associated with activation of, and damage to, opposite sides of the brain? *Laterality* 22, 105–119. doi: 10.1080/1357650X.2016.1173049

Moro, V., Pernigo, S., Zapparoli, P., Cordioli, Z., and Aglioti, S. M. (2011). Phenomenology and neural correlates of implicit and emergent motor awareness in patients with anosognosia for hemiplegia. *Behav. Brain Res.* 225, 259–269. doi: 10.1016/j.bbr.2011.07.010

Paul, L. K., Brown, W. S., Adolphs, R., Tyszka, J. M., Richards, L. J., Mukherjee, P., et al. (2007). Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat. Rev. Neurosci.* 8:287. doi: 10.1038/nrn2107

Pia, L., Neppi-Modona, M., Ricci, R., and Berti, A. (2004). The anatomy of anosognosia for hemiplegia: a meta-analysis. *Cortex* 40, 367–377. doi: 10.1016/S0010-9452(08)70131-X

Pia, L., Spinazzola, L., Garbarini, F., Bellan, G., Piedimonte, A., Fossataro, C., et al. (2014). Anosognosia for hemianaesthesia: a voxel-based lesion-symptommapping study. *Cortex* 61, 158–166. doi: 10.1016/j.cortex.2014.08.006

Prigatano, G. P. (1996). *Anosognosia*. *Blackwell Dictionary of Neuropsychology*. Massachusetts: Blackwell, Cambridge. 80–84.

Putnam, M. C., Steven, M. S., Doron, K. W., Riggall, A. C., and Gazzaniga, M. S. (2010). Cortical projection topography of the human splenium: hemispheric asymmetry and individual differences. *J. Cogn. Neurosci.* 22, 1662–1669. doi: 10.1162/jocn.2009.21290

Ricci, R., Salatino, A., Li, X., Funk, A. P., Logan, S. L., Mu, Q., et al. (2012). Imaging the neural mechanisms of TMS neglect-like bias in healthy volunteers with the interleaved TMS/fMRI technique: preliminary evidence. *Front. Hum. Neurosci.* 6:326. doi: 10.3389/fnhum.2012.00326

Salatino, A., Berra, E., Troni, W., Sacco, K., Cauda, F., D'Agata, F., et al. (2014). Behavioral and neuroplastic effects of low-frequency rTMS of the unaffected hemisphere in a chronic stroke patient: a concomitant TMS and fMRI study. *Neurocase* 20, 615–626. doi: 10.1080/13554794.2013.826691

Steinmann, S., Meier, J., Nolte, G., Engel, A. K., Leicht, G., and Mulert, C. (2018). The callosal relay model of interhemispheric communication: new evidence from effective connectivity analysis. *Brain Topogr.* 31, 218–226. doi: 10.1007/s10548-017-0583-x

Tononi, G. (2004). An information integration theory of consciousness. *BMC Neurosci.* 5:42. doi: 10.1186/1471-2202-5-42

Tononi, G., and Edelman, G. (1998). Consciousness and complexity. *Science* 282, 1846–1851. doi: 10.1126/science.282.5395.1846

Tononi, G., and Edelman, G. M. (2000). Schizophrenia and the mechanisms of conscious integration. *Brain Res. Rev.* 31, 391–400. doi: 10.1016/S0165-0173(99)00056-9

Trimble, M. R., and George, M. (2010). *Biological Psychiatry*. Chichester: John Wiley and Sons. doi: 10.1002/9780470689394

Vallar, G., and Ronchi, R. (2006). Anosognosia for motor and sensory deficits after unilateral brain damage: a review. *Restor. Neurol. Neurosci.* 24, 247–257.

Volz, L. J., and Gazzaniga, M. S. (2017). Interaction in isolation: 50 years of insights from split-brain research. *Brain* 140, 2051–2060. doi: 10.1093/brain/awx139

Vossel, S., Weiss, P. H., Eschenbeck, P., and Fink, G. R. (2013). Anosognosia, neglect, extinction and lesion site predict impairment of daily living after right-hemispheric stroke. *Cortex* 49, 1782–1789. doi: 10.1016/j.cortex.2012.12.011

Weintraub, S., and Mesulam, M. M. (1987). Right cerebral dominance in spatial attention: further evidence based on ipsilateral neglect. *Arch. Neurol.* 44, 621–625. doi: 10.1001/archneur.1987.00520180043014

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 06 February 2019
doi: 10.3389/fpsyg.2019.00198

Neural Correlates of Visuospatial Attention to Unseen Stimuli in Hemianopic Patients. A Steady-State Visual Evoked Potential Study

Javier Sanchez-Lopez[1]*, Silvia Savazzi[1,2,3]*, Caterina Annalaura Pedersini[1], Nicolò Cardobi[1] and Carlo Alberto Marzi[1,3]

[1] Psychology and Physiology Section, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, [2] Perception and Awareness (PandA) Laboratory, Department of Neuroscience, Biomedicine, and Movement Sciences, University of Verona, Verona, Italy, [3] National Institute of Neuroscience, Verona, Italy

OPEN ACCESS

Edited by:
Zhicheng Lin,
The Ohio State University,
United States

Reviewed by:
Peng Zhang,
Chinese Academy of Sciences, China
Natalia Zaretskaya,
University of Graz, Austria

Correspondence:
Javier Sanchez-Lopez
javier.sanchezlopez@univr.it
Silvia Savazzi
silvia.savazzi@univr.it

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: *27 September 2018*
Accepted: *21 January 2019*
Published: *06 February 2019*

Citation:
Sanchez-Lopez J, Savazzi S, Pedersini CA, Cardobi N and Marzi CA (2019) Neural Correlates of Visuospatial Attention to Unseen Stimuli in Hemianopic Patients. A Steady-State Visual Evoked Potential Study. Front. Psychol. 10:198. doi: 10.3389/fpsyg.2019.00198

The relationship between attention and awareness is a topic of great interest in cognitive neuroscience. Some studies in healthy participants and hemianopic patients have shown dissociation between these two processes. In contrast, others confirmed the classic notion that the two processes are mutually exclusive. To try and cast further light on this fascinating dilemma, in the present study we have investigated the neural mechanisms of visual spatial attention when perceptual awareness is totally lacking. To do that, we monitored with steady-state visual evoked potentials (SSVEPs) the neurophysiological correlates of endogenous spatial attention to unseen stimuli presented to the blind field of hemianopic patients. Behaviourally, stimulus detection (a brief change in the orientation of a gabor grating) was absent in the blind hemifield while in the sighted field there was a lower, but non-significant, performance in hit rate with respect to a healthy control group. Importantly, however, in both blind and sighted hemifield of hemianopics (as well as in healthy participants) SSVEP recordings showed an attentional effect with higher frequency power in the attended than unattended condition. The scalp distribution of this effect was broadly in keeping with the location of the dorsal system of endogenous spatial attention. In conclusion, the present results provide evidence that the neural correlates of spatial attention are present regardless of visual awareness and this is in accord with the general hypothesis of a possible dissociation between attention and awareness.

Keywords: hemianopia, attention, visual awareness, blindsight, steady-state VEP

INTRODUCTION

Homonymous hemianopia is a visual defect characterized by complete or partial blindness in the hemifield of both eyes contralateral to a lesion of the central visual system (see Bouwmeester et al., 2007). In case of a partial lesion of the optic radiation the visual field defect is usually limited to the contralateral upper or lower quadrant. Importantly, some hemianopic patients have been found to present "blindsight" i.e., unconscious visually triggered behavior (Poppel et al., 1973; Weiskrantz et al., 1974). Following the discovery of this intriguing phenomenon hemianopic patients have become a fundamental source of information on the neural mechanisms of awareness by studying the effects of damage of specific brain areas (Weiskrantz, 2004). This endeavor is clearly impossible in healthy humans.

Many studies have found a dissociation between attention and perceptual awareness in healthy participants (McCormick, 1997; Ivanoff and Klein, 2003; Lu et al., 2012; Block, 2014; Herreros et al., 2017) and a few in hemianopic patients with blindsight (Kentridge et al., 1999, 2004). An important question is what kind of attention might operate without awareness: It has been suggested that this occurs with endogenous rather than exogenous attention (but see Chica et al., 2012 for a different opinion). In hemianopia it has been found that endogenous orientation of spatial attention facilitates performance (mainly reaction time-RT) even in absence of visual awareness and this has led to the conclusion that there exists a dissociation between this kind of spatial attention and perceptual awareness (Kentridge, 2011). How could endogenous spatial attention operate without awareness? In principle, if its mechanisms are similar to those operating consciously they should involve cortical areas such as the frontal eye fields (FEF) and the intraparietal sulcus/superior parietal lobe (IPS/SPL) that constitute the normal dorsal attention system network (Corbetta and Shulman, 2002; Corbetta et al., 2008) and exert top-down influences on visual areas during spatial orienting of attention (Hopfinger et al., 2000; Bressler et al., 2008). However, although the effects of visual spatial attention on behavioral performance to unseen stimuli have been clearly demonstrated, to our knowledge, no studies have been conducted to investigate their neurophysiological correlates. Thus, we still do not know whether attention operating independently from awareness has similar neural bases as those subserving conscious attention. Shedding light on this problem represents the aim of the present study.

Recently, we demonstrated the reliability and effectiveness of steady-state visual evoked potentials (SSVEP) in the study of unconscious passive visual processing in hemianopic patients (Sanchez-Lopez et al., 2017). SSVEPs are repetitive visual stimuli presented at a high rate, usually between 10 and 20 Hz that elicit an entrainment of the brain electrical activity at the same frequency of the driving stimulus and its harmonics. SSVEPs reflect high propagation properties, are less influenced by artifacts, require less time for data acquisition, have a higher signal-to-noise ratio (Di Russo et al., 2003; Vialatte et al., 2010), and can be measured in time and preferably in the frequency domain (Vialatte et al., 2010; Schomer and Lopes da Silva, 2011).

Morgan et al. (1996) have recorded SSVEPs from participants who were cued to attend to visual stimuli presented to one hemifield and to ignore the concurrent stimulation on the opposite hemifield. They found that the amplitude of the frequency SSVEP was significantly enlarged when attention was focused on the attended location and was larger over occipital and temporal scalp areas. This finding provided the basis for the study of the neural mechanisms of selective attention to multi-element visual displays (for a review see Vialatte et al., 2010; Andersen et al., 2011) in healthy participants. However, as mentioned above, it is still to be understood whether the neural mechanisms of attention operating in the absence of awareness are similar to those during awareness. This is an important query that we purported to tackle in the present study whose rationale is straightforward: If the mechanisms of attention are similar independently from stimulus awareness then we would expect a qualitatively similar enhancement of the SSVEP response to stimuli in the attended intact or the blind field of hemianopic patients. On the contrary, if attention operating without awareness relies on different neural bases this should show up as a differential response in the blind versus intact field of hemianopic patients or healthy participants.

MATERIALS AND METHODS

Participants

Patients

Five hemianopic patients (3 females and 2 males; mean age = 54.4 years, SD = 7.3) with post-chiasmatic lesions participated in the study. Two of them had quadrantanopia (one upper and the other lower). Three patients had right and the other two left hemisphere damage, see **Table 1**. Inclusion criteria were: Diagnosis of hemianopia made at least three months before testing, availability of visual campimetry and structural MRI documenting the site and extension of the brain damage. Exclusion criteria included pre-existing neurologic or psychiatric disorders, drugs or alcohol addiction, cognitive impairments evidenced by a score equal or less than 24 in the Mini Mental State Examination (Folstein et al., 1975), and presence of hemineglect as assessed with a neuropsychological battery including: Line Bisection (Schenkenberg et al., 1980), Diller letter H cancelation (Diller et al., 1974), and Bell Cancelation (Gauthier et al., 1989). Additionally, patients were evaluated with the Visual Function Questionnaire (VFQ25), in order to assess subjective impressions on their visual abilities in everyday life (Mangione et al., 2001). All patients were right handed and had normal or corrected to normal visual acuity. A brief description of patients' lesion location and campimetry can be found in **Table 1**; for a detailed description of the patients see also Sanchez-Lopez et al., 2017.

Healthy Participants

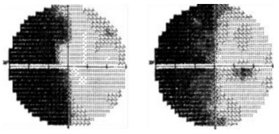
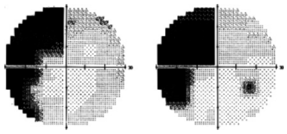
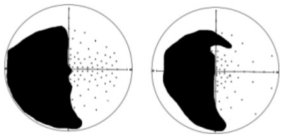
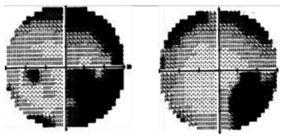
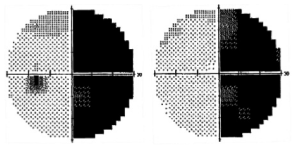
In addition to hemianopic patients we tested a group of 18 young healthy participants (13 females; mean age = 25.2 years old, SD = 4.0). All of them were right handed and had normal or corrected to normal visual acuity.

Informed consent to take part in the study was obtained from all healthy and hemianopic participants after they had been informed about the procedures and their rights. The study was approved by the Ethics Committee of the European Research Council and of the Verona Azienda Ospedaliera Universitaria Integrata (AOUI). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Stimuli

The visual stimuli consisted of circular black and white horizontal (standard stimulus) and 45° oriented (target stimulus) Gabor

TABLE 1 | Patients' clinical description.

Patient (age/gender)	Lesion/Visual Deficit	Campimetry (left eye/right eye)
FB (49/F) Right hemisphere lesion	*Neuroradiological description:* Lesion involving the temporal, parietal and occipital lobe. In the latter, the lesion includes the superior and part of the middle occipital gyri with interruption of the optic radiation. *Specific structures affected:* Anterior intraparietal sulcus, visual area V5, inferior parietal lobule, somatosensory cortex, primary auditory cortex, parietal operculum and insula in the right hemisphere. *Visual defect:* Left lateral homonymous hemianopia.	
LF (50/F) Right hemisphere lesion	*Neuroradiological description:* Ischemic lesion that involves the cortex of the anterior half of calcarine fissure to the origin of parieto-occipital fissure. *Specific structures affected:* Small internal portion of V1 and V2. *Visual defect:* Upper left homonymous quadrantanopia.	
LC (66/M) Right hemisphere lesion	*Neuroradiological description:* Temporal and parietal lesion, with posterior extension to the white matter of occipital lobe, involving the lateral part of optic radiation. *Specific structures affected:* Middle, inferior and a small portion of the superior temporal gyrus. Visual area V5 and inferior parietal lobe. *Visual defect:* Left lateral homonymous hemianopia.	
GA (60/M) Left hemisphere lesion	*Neuroradiological description:* Ischemic lesion involving parietal and occipital lobe. In the latter the lesion involves the superior, middle, inferior and descending occipital gyri, cuneus, pole and the posterior part of optic radiation, with relative sparing of the lingual and fusiform gyri. *Specific structures affected:* Small portion of anterior intraparietal sulcus and all visual areas (V1,V2,V3,V4 and V5). *Visual defect:* Lower right homonymous quadrantanopia.	
SL (47/F) Left hemisphere lesion	*Neuroradiological description:* Lesion involving the median para-sagittal portion of the occipital lobe. The lesion includes the lingual gyrus, with peri-calcarine fissure distribution. *Specific structures affected:* V1, V2, V3, and V4 visual areas. *Visual defect:* Right lateral homonymous hemianopia.	

gratings. The diameter of the stimuli was 2° of visual angle with a spatial frequency of 4 c/° (see **Figure 1**). The contrast of the Gabor grating was 0.8 and the background luminance was the same as the mean luminance of the Gabor (17.7 cd/m^2). Flickering stimulation was obtained by contrast reversal each 90.9 ms (i.e., 11 Hz) and 79.9 ms (i.e., 13 Hz) for left and right hemifields, respectively. Two different frequencies for left and right hemifield were used in order to evaluate simultaneously two-element visual displays i.e., attended and unattended stimuli as done in previous studies recording SSVEP during attention tasks (Morgan et al., 1996; Vialatte et al., 2010). The stimulation was performed by presenting simultaneously two flickering Gabor gratings on a LED video monitor (resolution = 1920 pixels width × 1080 pixels height, and refresh rate = 144 Hz), one to the left and one to the right, in the upper or lower visual field for the patients. The stimulation in the group of healthy participants was performed in both the upper and the lower visual field in a counterbalanced order across subjects. The eccentricity of stimulus presentation for patients depended upon the position of the visual field loss (see below). For healthy participants was $x = 5°$ and $y = 5°$.

SSVEP Stimulation

Participants were comfortably seated at a viewing distance of 57 cm from the screen. The stimuli were binocularly presented and participants were asked to maintain a stable fixation on a central cross during stimulus presentation. Ocular movements were externally controlled through a closed-circuit camera. Constant feedback about their ability to maintain fixation was given to the participants. SSVEP stimulations consisted of 40 blocks each of 18.3 s of simultaneous left and right hemifield stimulation. Brief breaks were intermingled between blocks. At the beginning of each block participants were asked to pay attention, for the entire block, to the left or right hemifield. Attention was alternated left and right hemifield across blocks (20 toward the left and 20 toward the right hemifield). Patients were instructed to press the space bar of the keyboard when the target stimulus, i.e., a brief modification of grating orientation (same duration as the standard stimuli 90.9 and 79.9 ms for left and right hemifield, respectively), appeared in the attended (5 times per block) and to ignore it when appeared in the unattended hemifield (5 times per block). Four hundred target stimuli were pseudo-randomly presented during the session:

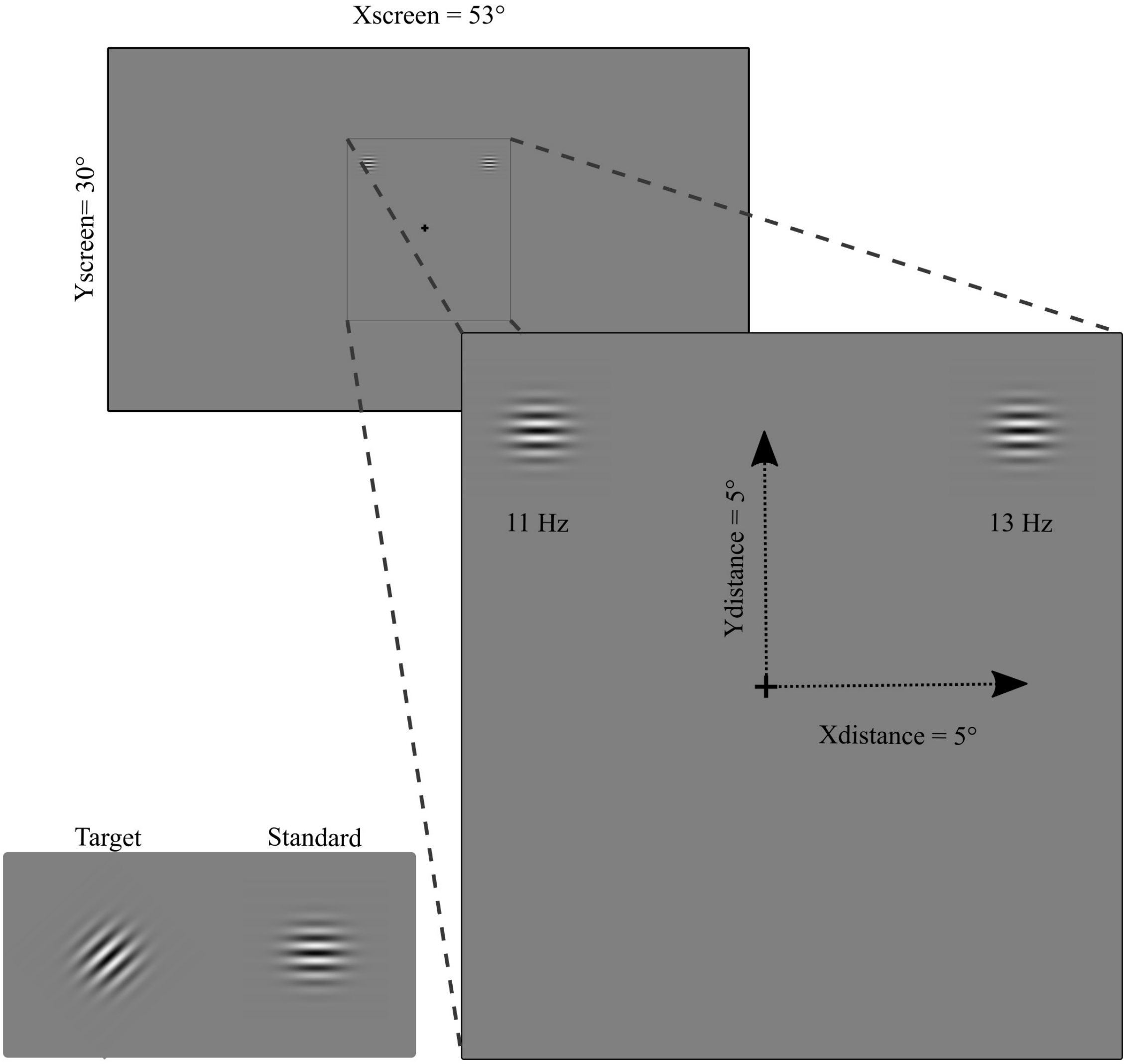


FIGURE 1 | Stimuli (target and standard), flickering frequency (11 Hz and 13 Hz on left and right hemifield, respectively), and eccentricity (for healthy participants).

200 in the attended side (100 in each left or right hemifield) and 200 in the unattended side (100 in each left or right hemifield). On the right hemifield 4,760 pattern-reversal stimuli were presented for each attended and unattended condition, while in the left hemifield 4,020 stimuli were presented per condition (see **Figure 1**).

For each participant in the patients' group the stimulus was positioned in the blind area and in a corresponding area in the intact hemifield on the basis of the results of clinical campimetry, as shown in **Table 1** and of a visual mapping test carried out in the lab (for more details see Sanchez-Lopez et al., 2017). In order to check for possible undetected residual vision, at the beginning of the experimental session we evaluated the subjective level of perceptual awareness by moving the stimulus in the blind portion of the visual field and asking the patient whether he/she had some visual sensation. Moreover, at the end of each block, patients were asked if they had ever detected the appearance of the stimulus in the blind field. In both tests all patients reported no visual sensation whatsoever. Patients' eccentricities of stimulus presentation are shown in **Table 2**.

EEG Recording

EEG was recorded during the performance of the task. An elastic cap with 59 active electrodes (ActiCap, Brain Products GmbH, Munich Germany) placed according to the 10-10 International System was used. An acquisition system with two BrainAmp amplifiers and the software Recorder 1.2 (Brain Products GmbH, Munich, Germany) was employed. On-line reference was placed on the left mastoid while the right mastoid electrode was used to re-reference the EEG recording offline to the average of the right and left mastoid electrodes. The ground electrode was placed in the AFz electrode position. Horizontal and vertical eye movements were recorded with four electrodes placed at the left and right canthi and above and below the right eye, respectively. The impedance of all electrodes was kept below 5 KΩ. The EEG was recorded at 1000 Hz sampling rate with a time constant of 10 Hz as low cut-off and a high cut-off of 1000 Hz with a 50 Hz notch filter.

Data Analysis

Behavior

The scoring analysis included hit rate (response to target in the attended field), false alarm rate (response to target in the unattended field), reaction times (RT), and d prime (d'). Since patients never responded to blind visual field stimuli, only performance in the sighted visual field was compared with that of a subset of healthy participants randomly sorted to obtain a similar distribution as the patients' group: 40% performed the task in the upper visual field (half scores obtained from the left hemifield and the other half from the right visual field); 60% of healthy participants performed the task in the lower visual field (2/3 of the scores from the right visual field and 1/3 from the left visual field). Group comparisons were carried out by means of one way ANCOVA using age as covariate independently for each comparison.

EEG Pre-processing

The EEG signal was pre-processed offline using EEGLAB toolbox (Delorme and Makeig, 2004), and MATLAB (version R2018a, The MathWorks, Inc., Natick, MA, United States, 2010) scripts. Data pre-processing was carried out for all channels by re-referencing to the average of the right and left mastoid electrodes. Vertical eye movements were corrected by means of Independent Component Analysis (ICA) ocular correction (Makeig et al., 1996). EEG analysis aimed at investigating the rhythmic entrainment produced by the standard stimuli, therefore 2 s overlapped epochs locked to the standard stimuli were obtained from the continuous EEG recording separately for each condition: attended left/blind, unattended left/blind, attended right/sighted, and unattended right/sighted; all segments were band pass filtered from 0.1 to 40 Hz. Baseline correction was performed for each segment by removing the mean value of the signal per channel per trial. Finally, semiautomatic rejection of segments with artifacts was carried out. Clean segments were separately averaged for each condition. Finally, the frequency power, by means of the fast Fourier transformation (FFT), was extracted for each channel of the averaged SSVEP as 2 s segments.

TABLE 2 | Stimulus position (in degrees), and stimulated visual field for the group of patients. Stimuli were symmetrically positioned in left and right quadrants.

Patient	Stimulus Position (°)		Visual field
	x	y	
FB	13.8°	6.3°	Lower visual field
LF	12.2°	6.4°	Upper visual field
LC	14°	3.3°	Lower visual field
GA	7.3°	2.7°	Lower visual field
SL	4.8°	4.8°	Upper visual field

SSVEP

For the statistical analysis of the SSVEP responses to the entrainment produced by the standard stimuli, the peak of power at the frequency of stimulation of 11 Hz for left visual field and 13 Hz for right visual field was extracted after the FFT for each condition, electrode and participant. In order to create a single group of patients, the EEG montage of those with left lesion (right hemianopia; *n* = 2) was flipped left to right. For the healthy participants group the EEG montage of the 40% of the participants was flipped left to right as in the patients group. A non-parametric permutation test using 10,000 permutations as implemented in EEGLAB function "statcond" (Delorme and Makeig, 2004) was used.

Within-subjects comparisons were performed for each group (healthy participants and patients) separately, by comparing attended versus unattended conditions for each hemifield (left/blind and right/sighted). In order to evaluate hemispheric differences in the effect of attention between contralateral and ipsilateral hemisphere with respect to the visual hemifield, the same statistical analysis was performed for each hemifield in both healthy and patients group.

Between-subjects comparisons **(patients versus healthy participants)** concerned the net effect of attention (attended minus unattended condition) for each hemifield.

In consideration of the more localized topographical distribution of the SSVEP over posterior electrodes in the group of patients in comparison with healthy participants (see **Figure 2**), the statistical analyses, where patients were included, were carried out in nine topographical sites separately: frontal left (Fp1, F7, F5, F3, and F1), frontal right (Fp2, F2, F4, F6, and F8), central left (FC5, FC3, FC1, C5, C3, C1, CP5, CP3, and CP1), central right (FC2, FC4, FC6, C2, C4, C6, CP2, CP4, and CP6), temporal left (FT9, FT7, T7, and TP7), temporal right (FT10, FT8, T8, and TP8), posterior left (P7, P5, P3, P1, PO9, PO7, PO3, and O1), posterior right (P2, P4, P6, P8, PO4, PO8, PO10, and O2), and midline (Fz, FCz, Cz, CPz, Pz, POz, and Oz). For the comparison of the effect of attention between contralateral and ipsilateral hemisphere in each hemifield, in the healthy group all electrodes from the contralateral were compared with their counterpart on the ipsilateral hemisphere, and in patients, separately, for each group of lateral electrodes (frontal, central, temporal, and posterior). No midline electrodes were included in this analysis. False discovery rate (FDR) correction was used to adjust *p*-values for multiple comparisons.

RESULTS

Behavior

As described in the Methods section, since patients did not respond to the target stimuli in the blind hemifield, only the sighted hemifield was analyzed and compared with its counterpart in the healthy participants group. No differences between groups were observed in any variable tested: percentage

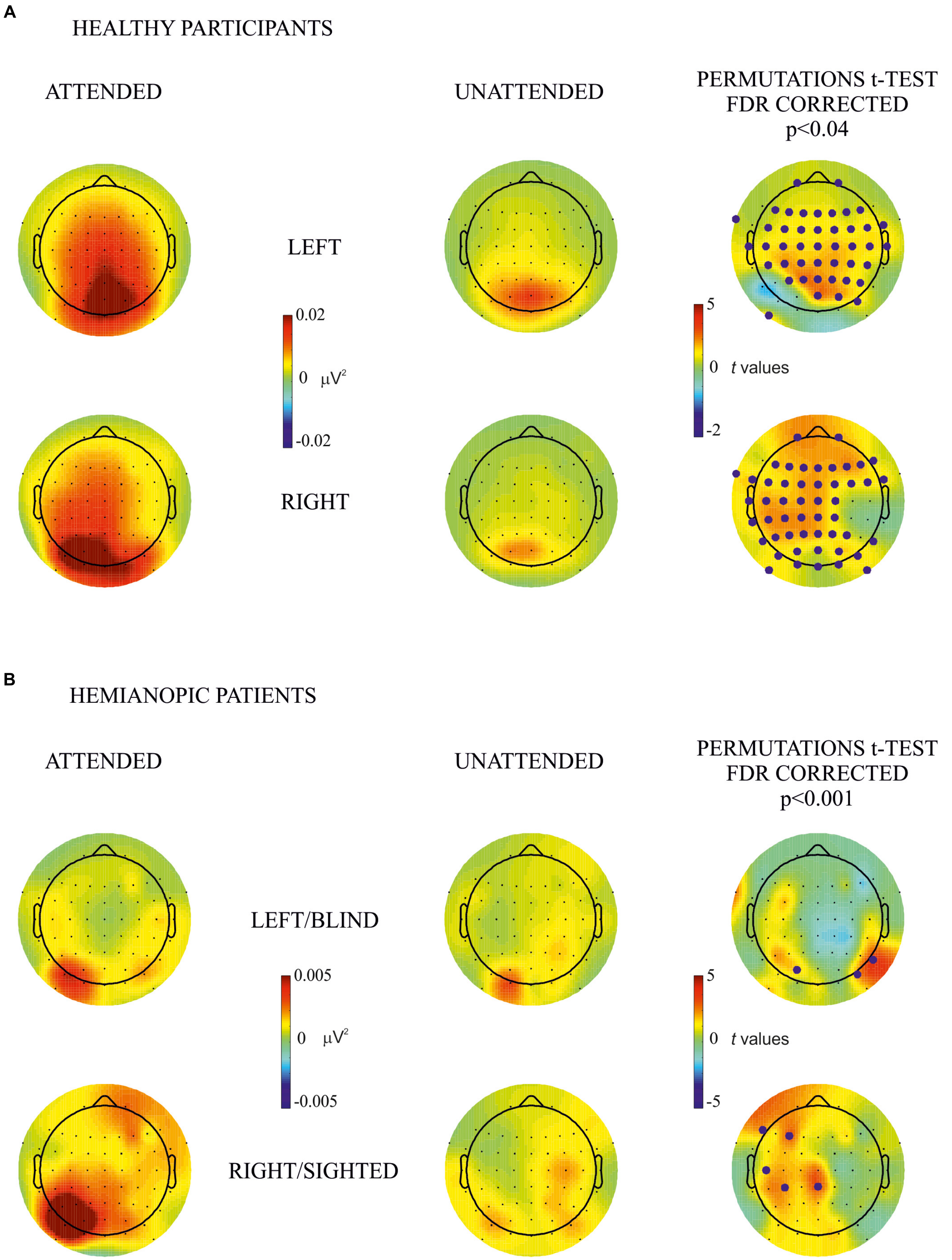


FIGURE 2 | Within-subjects attention effect. Permutation *t*-test comparisons between attended (first column) and unattended (second column) for **(A)** healthy participants and **(B)** hemianopic patients. Topographical maps in columns 1 and 2 represent the power of frequency (μV^2) for each condition attended and unattended, respectively. Maps in the 3rd column represent *t* values of the comparison between attended and unattended conditions; blue points indicate the electrode sites where the power of frequency in the attended condition was significantly higher than in the unattended condition after the FDR correction calculated separately for each comparison. The maximum *p* value accepted after FDR correction is indicated in the tittle of the 3rd column.

of hit rate ($F < 1$; Mean-healthy = 79.2 ± 16.4; Mean-patients = 45.8 ± 30.94), percentage of false alarms ($F < 1$; Mean-healthy = 1.6 ± 2.1; Mean-patients = 15.8 ± 20.6), RT ($F < 1$; Mean-healthy = 494.1 ± 54.6 ms; Mean-patients = 534.6 ± 132.1 ms), and d' ($F_{(1,20)} = 1.4$; p = 0.2; Mean-healthy = 2.6 ± 1; Mean-patients = 1.4 ± 1.6). The other hemifield of the healthy participants group was analyzed only in terms of descriptive statistics: Mean percentage of hits rate = 80.1 ± 4.5; Mean RT = 479.6 ± 52.5 ms; Mean percentage of false alarms = 2.1 ± 2.5; and Mean d' = 2.61 ± 0.9.

SSVEP

By visual inspection of the topographic maps it appears that the effect of attention was present for the blind as well as the sighted hemifield of hemianopic patients and was similar, although less pronounced, to that of healthy participants in whom the effect was bilateral while in patients it was more pronounced over the intact hemisphere regardless of hemifield (see **Figures 2**, **3**).

Within-Subjects Attentional Effect

The main objective of this analysis was to investigate the difference in frequency power between attended and unattended conditions for stimulus presentation to the same hemifield. Comparisons were carried out for each hemifield separately for both groups. In the **healthy participants group** permutation *t*-test showed a significantly higher power in the attended than the unattended condition in most of bilateral occipital, parietal, temporal and frontal electrode sites (p values < 0.04; see **Figure 2A**). In the **hemianopic patients group** the permutation tests yielded the following statistically reliable differences: For the left/blind hemifield the SSVEP response was higher in the attended than the unattended condition in the posterior groups of electrodes of the intact and lesioned hemispheres (p values < 0.001): PO3 (intact hemisphere), PO8, and P8 (lesioned hemisphere). For the right/sighted hemifield there were differences with higher frequency power in the attended than in the unattended condition in the central and frontal group of electrodes over the intact hemisphere ($p < 0.001$) on CPz, CP3, C5, F3, and F7 (see **Figure 2B**).

In the analysis of hemispheric differences (contralateral versus ipsilateral) of the effect of attention on hemifield of stimulus presentation, no significant differences were observed in both hemifields (left/blind or right/sighted) of either healthy participants or patients (see **Figure 4**).

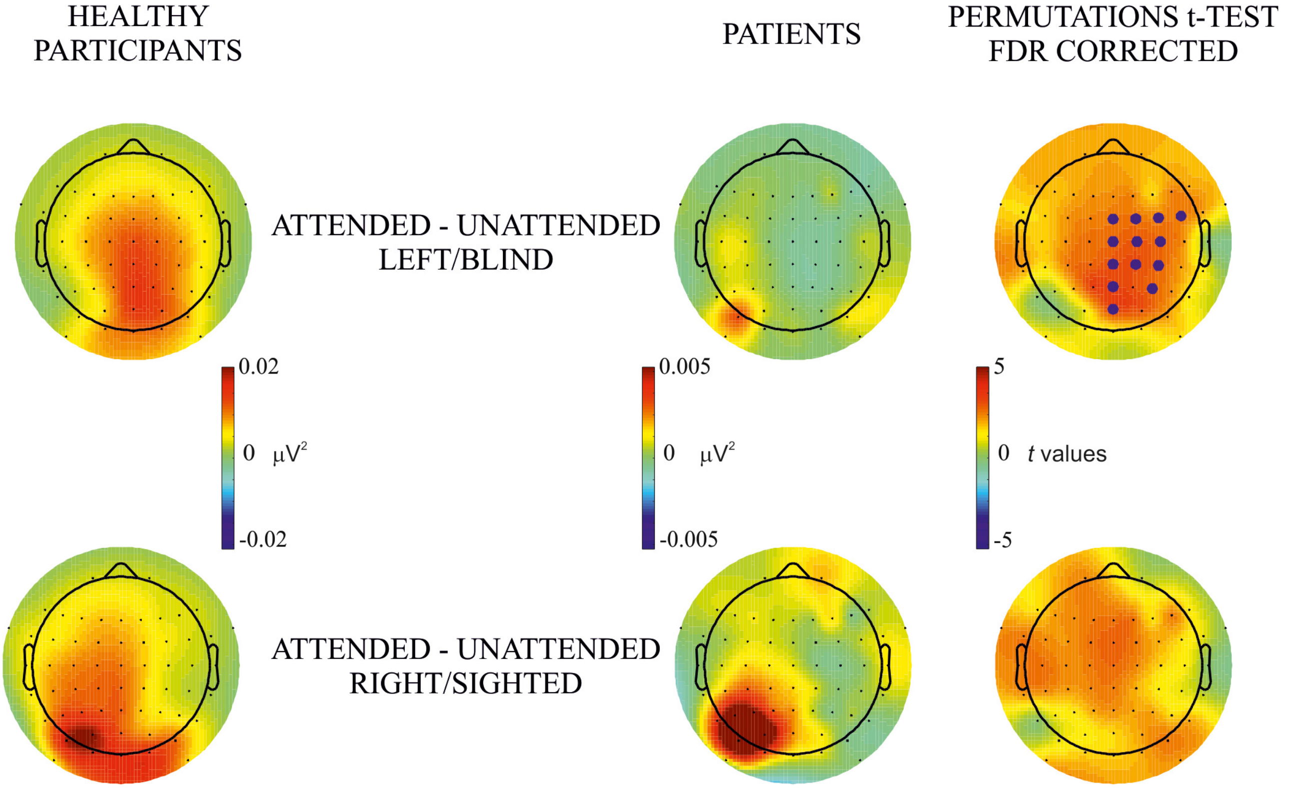


FIGURE 3 | Between-subjects attentional effect. Permutation *t*-test comparisons of the effect of attention (i.e., attended – unattended) between healthy participants and hemianopic patients in blind (upper row) and sighted (lower row) hemifields. Topographical maps in columns 1 and 2 represent the power of frequency (μV^2) for each condition attended and unattended, respectively. Maps in the 3rd column represent *t* values of the comparison between attended and unattended conditions; blue points indicate the electrode sites where the power of frequency in the attended condition was significantly higher than in the unattended condition after the FDR correction calculated separately for each comparison. The maximum *p* value accepted after FDR correction is indicated in the tittle of the 3rd column.

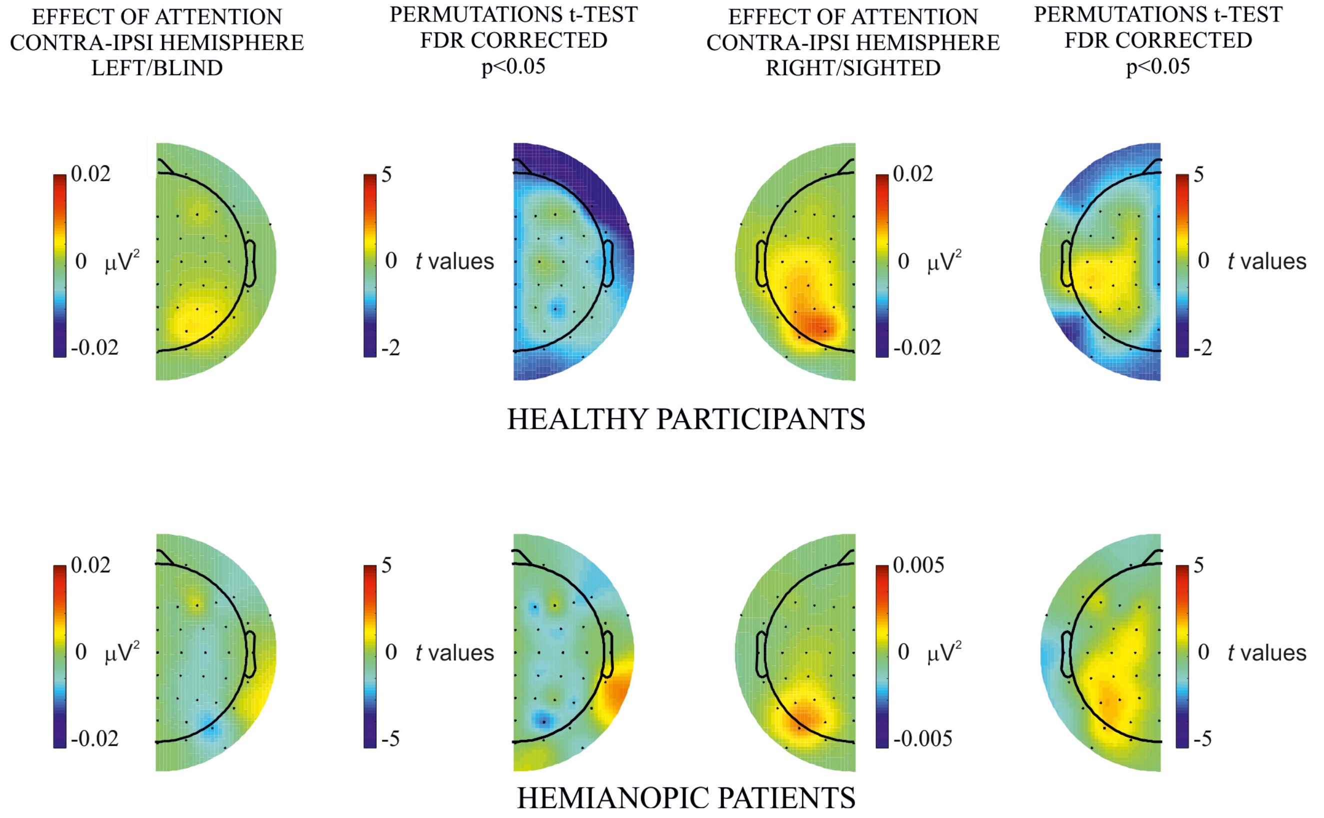


FIGURE 4 | Hemispheric differences of the attentional effect. Permutation *t*-test comparisons of the effect of attention (i.e., attended – unattended) between contralateral and ipsilateral hemisphere for each hemifield, left/blind (left column), and right/sighted (right column), in both healthy (upper row) and patients (lower row) group. No significant differences were observed.

Between-Subjects Attention Effect

The purpose of this analysis was to investigate group differences in the effect of attention (attended minus unattended in the same hemifield). Topographical maps of frequency power showed a widespread bilateral effect in **healthy participants** which, in **hemianopic patients** was present mainly over posterior electrodes of the intact hemisphere for both blind and sighted hemifield stimulus presentation, see **Figure 3**. Permutations tests showed significant differences in posterior, central and frontal groups of electrodes along the midline and in the lesioned hemisphere of patients, while no significant differences were found for the sighted hemifield.

DISCUSSION AND CONCLUSION

The aim of this study was to investigate the neurophysiological correlates of endogenous spatial attention to unseen stimuli. In the group of **healthy participants** we found significantly larger SSVEP responses in the attended versus unattended condition mainly in occipital but also in frontal, temporal, and parietal sites. These results are in line with previous findings on SSVEP and endogenous sustained attention (Morgan et al., 1996; Andersen and Muller, 2010; Vialatte et al., 2010; Andersen et al., 2011). Importantly, a reliable, albeit less pronounced similar effect, was found in the group of **hemianopic patients**: Following stimulus presentation in the blind hemifield a higher frequency power in the attended than unattended condition was found bilaterally over occipital electrodes. This suggests the influence of top-down attentional mechanisms over spared portions of the striate cortex (Hopfinger et al., 2000; Bressler et al., 2008) and of extrastriate areas. This is a reasonable possibility given that striate (V1) and extrastriate visual areas are considered as responsible for the SSVEP response (see Di Russo et al., 2002; Vialatte et al., 2010; Sanchez-Lopez et al., 2017; Mitka and Riecansky, 2018). In particular, following stimulus presentation to the blind hemifield the contralateral activity observed over PO8 and P8 is likely to originate from extrastriate areas (Di Russo et al., 2002) of the lesioned hemisphere while the activity over PO3 might origin from striate as well as extrastriate areas (Di Russo et al., 2002) of the ipsilateral intact hemisphere. In the sighted hemifield of hemianopics a significant SSVEP difference between attended and unattended stimuli was found over central and frontal electrodes in the intact hemisphere likely originating from extrastriate visual areas (hMT/V5), precuneus, superior, and inferior parietal lobe and middle frontal lobe (Mitka and Riecansky, 2018) of the intact hemisphere, i.e., areas of the dorsal system for endogenous spatial attention (Vossel et al., 2014). One might wonder why we found a significant occipital effect of attention in the blind hemifield and a central and frontal effect in the sighted hemifield. One possibility is that even though in the blind field there was a trend toward an attentional effect in the latter areas it was not larger enough to reach statistical reliability. This might be due to inter subject variability of the lesion in some parietal and temporal areas in different patients which provide a forward input to central and frontal areas. As to the lack of occipital attentional effect in the sighted hemifield, one possibility is that given the presence of a blind hemifield, the attentional focus might be inevitably attracted to the sighted hemifield in both valid and invalid condition and therefore the visual input is overwhelming in the occipital areas. As a consequence, a differential attentional effect is less pronounced in early visual areas and more evident in the dorsal attentional system. As to hemispheric differences (contralateral versus ipsilateral) as a function of the visual hemifield stimulated, we did not find significant results in keeping with those of Gray et al. (2015) who found a bilateral occipital activity as a correlate of visual spatial attention and suggest that this depends on recruitment of neuronal populations from both hemispheres when attending only one hemifield. Thus, the contribution of the intact hemisphere of hemianopics is likely to have an important role as compensatory mechanism that maintains the ability to allocate spatial attention, even in absence of perceptual awareness.

The group analysis of the differential effect of attention (attended minus unattended) showed differences for the blind/left but not for the sighted/right hemifield. This difference did not involve the electrodes where the significant effect of attention was found in the blind field of patients. This might reflect, firstly, a similar effect of attention over extrastriate generators in the lesioned hemisphere and its counterpart in healthy participants, while the difference over the most anterior electrodes is likely due to the anatomical damage that reduces the capacity of the system to spread the activity forward. Secondly, the absence of difference over the ipsilateral hemisphere (i.e., intact hemisphere in patients) could be explained by a compensatory plastic mechanism following brain injury, e.g., enhanced interhemispheric interactions between the damaged and intact hemisphere (see Celeghin et al., 2017). These results provide important evidence that the neural mechanism of endogenous spatial attention can be at work independently from the presence of awareness as previously demonstrated by behavioral experiments (Kentridge et al., 1999, 2008). Thus, the main thrust of our study is to provide evidence that sustained attention to a blind hemifield triggers compensatory neural mechanisms that enhance the neurophysiological response but are not sufficient for perceptual awareness and this represents a kind of interesting dissociation between the two processes.

Putting together the results of our previous study (Sanchez-Lopez et al., 2017) in which we found reliable neural responses to visual stimuli presented to the blind hemifield and the present study, one obvious crucial question is what is missing for the emergence of perceptual awareness despite the presence of neural correlates of attention. One should consider that most of our hemianopic patients have large lesions including not only the primary visual cortex but also extrastriate areas and in some cases parietal and temporal areas. Moreover, three of them have clear evidence of optic radiation lesion. This complex picture of brain damage is obviously common to many hemianopic patients. A reasonable possibility is that a disruption of the interplay between striate/extrastriate visual cortex and parietal/frontal areas does not enable perceptual awareness to emerge because of a lack of top-down feedback. A broadly similar account has been proposed by Silvanto (2015). Interestingly, however, our present results show that the lack of the above mentioned interplay does not abolish the influence of attention on visual areas of the lesioned hemisphere even though this is not sufficient for perceptual awareness. At variance with the results of Kentridge and colleagues (Kentridge et al., 1999, 2004, 2008) our patients did not show unconscious behavioral evidence of an attention effect probably because their lesion was more extensive than the circumscribed visual cortex lesion of blindsight patient GY who was tested in the above mentioned studies. Of course, it would be important to test with SSVEP hemianopic patients with and without blindsight and with lesion strictly limited to V1.

A further related question is at what stage of central visual processing attention and awareness are dissociable. Important evidence comes from a magnetoencephalography (MEG) study by Wyart et al. (2012) who, with a metacontrast paradigm, found that at 100 ms from stimulus onset endogenous spatial attention enhanced early occipital MEG responses for both detected and undetected stimuli, and, therefore, was unrelated to conscious access and had no effect on stimulus detection. Thus, at an early stage, attention and awareness are dissociated and full perceptual awareness emerges later on when the two parallel independent processes cumulate their effects (see Tallon-Baudry, 2012). We believe that this picture is in accord with our present results.

In conclusion, we showed for the first time that the neural mechanisms of attention at early stages of visual processing are present independently from perceptual awareness. We believe that this result has relevance for constraining theories of the neural basis of awareness.

AUTHOR CONTRIBUTIONS

JS-L, SS, and CM contributed to the conception and design the study. JS-L and CP contributed to the data acquisition and organization of database. JS-L and SS performed the statistical analysis. JS-L and CM wrote the first draft of the manuscript. CP and NC wrote sections of the manuscript. All authors contributed to manuscript discussion, revision, reading, and finally approved the submitted version.

FUNDING

The study was supported by the European Research Council (ERC) Grant number 339939 “Perceptual Awareness” (P.I.: CM).

REFERENCES

Andersen, S. K., and Muller, M. M. (2010). Behavioral performance follows the time course of neural facilitation and suppression during cued shifts of feature-selective attention. *Proc. Natl. Acad. Sci.U.S.A.* 107, 13878–13882. doi: 10.1073/pnas.1002436107

Andersen, S. K., Müller, M. M., and Hillyard, S. A. (2011). "Tracking the allocation of attention in visual scenes with steady-state evoked potentials," in *Cognitive Neuroscience of Attention*, ed. M. I. Posner (New York, NY: The Guilford Press), 197–216.

Block, N. (2014). Rich conscious perception outside focal attention. *Trends Cogn. Sci.* 8, 445–447. doi: 10.1016/j.tics.2014.05.007

Bouwmeester, L., Heutink, J., and Lucas, C. (2007). The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 78, 555–564. doi: 10.1136/jnnp.2006.103853

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., and Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *J. Neurosci.* 28, 10056–10061. doi: 10.1523/JNEUROSCI.1776-08.2008

Celeghin, A., Diano, M., de Gelder, B., Weiskrantz, L., Marzi, C. A., and Tamietto, M. (2017). Intact hemisphere and corpus callosum compensate for visuomotor functions after early visual cortex damage. *Proc. Natl. Acad. Sci.U.S.A.* 114, E10475–E10483. doi: 10.1073/pnas.1714801114

Chica, A. B., Botta, F., Lupiáñez, J., and Bartolomeo, P. (2012). Spatial attention and conscious perception: interactions and dissociations between and within endogenous and exogenous processes. *Neuropsychologia* 50, 621–629. doi: 10.1016/j.neuropsychologia.2011.12.020

Corbetta, M., Patel, G., and Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron* 58, 306–324. doi: 10.1016/j.neuron.2008.04.017

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3, 201–215. doi: 10.1038/nrn755

Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Di Russo, F., Martínez, A., Sereno, M. I., Pitzalis, S., and Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Hum. Brain Mapp.* 15, 95–111. doi: 10.1002/hbm.10010

Di Russo, F., Teder-Sälejärvi, W. A., and Hillyard, S. A. (2003). "Steady-State VEP and Attentional Visual Processing," in *The Cognitive Electrophysiology of Mind and Brain*, eds A. Zani, A. M. Proverbio, and M. I. Posner (Cambridge: Academic Press), 259–274. doi: 10.1016/B978-012775421-5/50013-3

Diller, L., Ben-Yishay, Y., and Gerstman, L. (1974). *Studies in Cognition And Rehabilitation in Hemiplegia*. New York, NY: New York University Medical Center Institute of Rehabilitation Medicine.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gauthier, L., Dehaut, F., and Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *Int. J. Clin. Neuropsychol.* 11, 49–54.

Gray, M. J., Frey, H.-P., Wilson, T. J., and Foxe, J. J. (2015). Oscillatory recruitment of bilateral visual cortex during spatial attention to competing rhythmic inputs. *J. Neurosci.* 35, 5489–5503. doi: 10.1523/JNEUROSCI.2891-14.2015

Herreros, L., Lambert, A. J., and Chica, A. B. (2017). Orienting of attention with and without cue awareness. *Neuropsychologia* 99, 165–171. doi: 10.1016/j.neuropsychologia.2017.03.011

Hopfinger, J. B., Buonocore, M. H., and Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nat. Neurosci.* 3, 284–291. doi: 10.1038/72999

Ivanoff, J., and Klein, R. M. (2003). Orienting of attention without awareness is affected by measurement-induced attentional control settings. *J. Vis.* 3, 32–40. doi: 10.1167/3.1.4

Kentridge, R. (2011). "Attention without awareness: a brief review," in *Philosophical and Psychological Essays*, eds M. Christopher, D. Smithies, and W. Wayne (Oxford: Oxford University Press), 228–246.

Kentridge, R. W., Heywood, C. A., and Weiskrantz, L. (1999). Attention without awareness in blindsight. *Proc. R. Soc. B Biol. Sci.* 266, 1805–1811. doi: 10.1098/rspb.1999.0850

Kentridge, R. W., Heywood, C. A., and Weiskrantz, L. (2004). Spatial attention speeds discrimination without awareness in blindsight. *Neuropsychologia* 42, 831–835. doi: 10.1016/j.neuropsychologia.2003.11.001

Kentridge, R. W., Nijboer, T. C. W., and Heywood, C. A. (2008). Attended but unseen: visual attention is not sufficient for visual awareness. *Neuropsychologia* 46, 864–869. doi: 10.1016/j.neuropsychologia.2007.11.036

Lu, S., Cai, Y., Shen, M., Zhou, Y., and Han, S. (2012). Alerting and orienting of attention without visual awareness. *Conscious. Cogn.* 21, 928–938. doi: 10.1016/j.concog.2012.03.012

Makeig, S., Bell, A. J., Jung, T.-P., and Sejnowski, T. J. (1996). Independent component analysis of electroencephalographic data. *Adv. Neural. Inf. Process. Syst.* 8, 145–151. doi: 10.1109/ICOSP.2002.1180091

Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., Hays, R. D., et al. (2001). Development of the 25-item national eye institute visual function questionnaire. *Arch. Ophthalmol.* 119, 1050–1058. doi: 10.1097/00132578-200201000-00028

McCormick, P. A. (1997). Orienting attention without awareness. *J. Exp. Psychol. Hum. Percept. Perform.* 23, 168–180. doi: 10.1037/0096-1523.23.1.168

Mitka, M., and Riecansky, I. (2018). Links between brain cortical regions and EEG recording sites derived from forward modelling. *Gen. Physiol. Biophys.* 37, 359–361. doi: 10.4149/gpb_2017060

Morgan, S. T., Hansen, J. C., and Hillyard, S. A. (1996). Selective attention to stimulus location modulates the steady-state visual evoked potential. *Proc. Natl. Acad. Sci.U.S.A.* 93, 4770–4774. doi: 10.1073/pnas.93.10.4770

Poppel, E., Held, R., and Frost, D. (1973). Residual visual function after brain wounds involving the central visual pathways in man. *Nature* 243, 295–296. doi: 10.1038/243295a0

Sanchez-Lopez, J., Pedersini, C. A., Di Russo, F., Cardobi, N., Fonte, C., Varalta, V., et al. (2017). Visually evoked responses from the blind field of hemianopic patients. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.10.008 [Epub ahead of print].

Schenkenberg, T., Bradford, D. C., and Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 30, 509–509. doi: 10.1212/WNL.30.5.509

Schomer, D. L., and Lopes da Silva, F. H. (2011). *Niedermeyer's Electroencephalography. sixth.* Philadelphia, PA: Wolters Kluwer Health.

Silvanto, J. (2015). Why is "blindsight" blind? A new perspective on primary visual cortex, recurrent activity and visual awareness. *Conscious. Cogn.* 32, 15–32. doi: 10.1016/j.concog.2014.08.001

Tallon-Baudry, C. (2012). On the neural mechanisms subserving consciousness and attention. *Front. Psychol.* 2:397. doi: 10.3389/fpsyg.2011.00397

Vialatte, F. B., Maurice, M., Dauwels, J., and Cichocki, A. (2010). Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Prog. Neurobiol.* 90, 418–438. doi: 10.1016/j.pneurobio.2009.11.005

Vossel, S., Geng, J. J., and Fink, G. R. (2014). Dorsal and ventral attention systems. *Neuroscience* 20, 150–159. doi: 10.1177/1073858413494269

Weiskrantz, L. (2004). Roots of blindsight. *Prog. Brain Res.* 144, 229–241. doi: 10.1006/ccog.1998.0358

Weiskrantz, L., Warrington, E. K., Sanders, M. D., and Marshall, J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain* 97, 709–728. doi: 10.1093/brain/97.1.709

Wyart, V., Dehaene, S., and Tallon-Baudry, C. (2012). Early dissociation between neural signatures of endogenous spatial attention and perceptual awareness during visual masking. *Front. Hum. Neurosci.* 6:16. doi: 10.3389/fnhum.2012.00016

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Psychology

BRIEF RESEARCH REPORT
published: 31 January 2019
doi: 10.3389/fpsyg.2019.00082

Later Positivity Reflects Post-perceptual Processes: Evidence From Immediate Detection and Delayed Detection Tasks

*Muwang Ye and Yong Lyu**

Academy of Psychology and Behavior, Tianjin Normal University, Tianjin, China

Electrophysiological recordings are usually used to study neural correlates of consciousness (NCCs). The aim of our present study was to use two detection tasks to dissociate the electrophysiological correlates of visual awareness from the post-perceptual processes. In immediate detection task, participants had to quickly report whether the stimulus was presented after stimulus, whereas in delayed detection task, participants had to put off reporting whether the stimulus was presented after stimulus. The results showed that two previously frequently observed electrophysiological NCCs were observed: visual awareness negativity (VAN) and later positivity (LP). Importantly, the amplitude of VAN over posterior temporal and occipital areas was not influenced by the task manipulation. However, the amplitude of LP over parietal, posterior temporal and occipital areas was influenced by the task manipulation during 650–850 ms. These data suggest that VAN is an early electrophysiological correlates of visual awareness, and LP reflects post-perceptual processes required in reporting perceptual awareness.

Keywords: neural correlates of consciousness, immediate detection, delayed detection, visual awareness negativity, later positivity, event-related potential

Edited by:
Anna Maria Berti,
University of Turin, Italy

Reviewed by:
Chiara Mazzi,
University of Verona, Italy
Caterina Bertini,
University of Bologna, Italy

****Correspondence:***
Yong Lyu
ly6312@163.com

Specialty section:
This article was submitted to
Consciousness Research,
a section of the journal
Frontiers in Psychology

Received: *31 October 2018*
Accepted: *11 January 2019*
Published: *31 January 2019*

Citation:
Ye M and Lyu Y (2019) Later Positivity Reflects Post-perceptual Processes: Evidence From Immediate Detection and Delayed Detection Tasks. Front. Psychol. 10:82.
doi: 10.3389/fpsyg.2019.00082

INTRODUCTION

What is the biological basis of consciousness? An important way to answer this question is to identify neural correlates of consciousness (NCCs). In NCC studies, researchers commonly use contrastive experimental design comparing event-related potential (ERP) elicited by physically identical stimuli of which participants are aware *vs.* unaware (Koch et al., 2016; Rutiku and Bachmann, 2017). Using this design, many researchers often found two potential electrophysiological NCCs: visual awareness negativity (VAN) and late positivity (LP; Koivisto and Revonsuo, 2010). VAN is a negative amplitude difference. It typically appears around 200 ms after visual stimulus onset at posterior temporal and occipital electrodes (Koivisto and Revonsuo, 2007; Railo et al., 2011; Koivisto and Grassini, 2016). In addition, LP is a positive amplitude difference. It typically appears after about 300 ms at parietal electrodes (Lamy et al., 2009; Salti et al., 2012; Naccache et al., 2016).

However, more and more researchers realized that the result of NCC studies using contrastive experimental designs is not only NCC but also reflects pre-conscious and post-perceptual processing (Bachmann, 2009; Aru et al., 2012; De Graaf et al., 2012). Therefore, NCC would be confounded by pre-conscious and post-perceptual processing in previous studies.

Especially, participants are commonly instructed to report awareness or unawareness of the liminal stimulus in NCC studies. Therefore, the NCC would be easily confounded with post-perceptual processes required in reporting perceptual awareness (Tsuchiya et al., 2015; Koivisto et al., 2016). The aim of our present study was to dissociate the electrophysiological correlates of visual awareness from the post-perceptual processes. So, we used two task conditions that differed in their requirements on reporting. In immediate detection task, participants had to quickly report whether the stimulus was presented after stimulus, whereas in delayed detection task, participants had to put off reporting whether the stimulus was presented after stimulus. If a potential electrophysiological NCC is modulated by the task manipulation, it must occur after awareness has emerged and reflect post-perceptual processes required in reporting perceptual awareness.

MATERIALS AND METHODS

Participants

Nineteen right-handed undergraduates participated in the study. The data sets of two participants had to be excluded, because they reported awareness in less than 25% of the critical trials or more than 75% of the critical trials. In addition, the data from one participant had to be also excluded, because his data did not contain enough trials for computing the ERPs for each condition (at least 35 per stimulus type) after artifact rejection. The remaining sixteen participants (eight males) had a mean age of 21.25 years (*SD* = 2.46). With normal or corrected to normal vision, none of them reported any history of neurological diseases or brain injuries.

Stimuli and Apparatus

The stimuli were controlled with E-prime software on a monitor with 1024 × 768 pixels resolution and 60 Hz screen refresh rate, and presented on the center of the gray background (22 cd/m^2). The critical stimulus was a low contrast sinusoidal Gabor patch (4.24 degree in diameter), tilted 45 degree to left. The Michelson contrast of the critical stimulus was 0.05, 0.06, or 0.07, depending participants performance in pre-experimental calibration phase. In addition, the duration of the critical stimulus was 16.67, 33.34, 50.01, or 66.68 ms, depending participants performance in pre-experimental calibration phase.

Procedure

Two tasks (immediate detection task and delayed detection task) were performed by each participant in counterbalanced order. **Figure 1** shows a flowchart of the trial procedure. The participants were instructed to make their decision whether they had seen the stimulus or not by means of button presses with their left or right index finger. The assignment of seen or unseen to the left or right index finger were counterbalanced across participants.

Both tasks were conducted in two blocks of stimuli, separated by brief resting periods. Half of the participants performed the immediate detection task first (calibration + two experimental blocks), followed by the delayed detection task (calibration + two experimental blocks). Half of the participants performed the tasks in the reversed order. Each stimulus block consisted of eighty critical trials, twenty catch trials, and twenty control trials. The catch trials were no stimuli. In control trials, a higher stimulus contrast (Michelson contrast: 0.08) and a longer stimulus duration (five refresh frames) was used than in the critical trials. During the calibration phase, we used a threshold estimation procedure. For more information regarding the calibration phase (see Koivisto et al., 2016).

Electroencephalogram (EEG) Recording and Data Analysis

Electroencephalogram was recorded from 64-channel Ag/AgCl electrode cap (Neuroscan, Melbourne, VIC, Australia) with the 10–20 system. The reference electrode was placed on the nose. The ground electrode was placed in front of Fz. EEG was sampled at a digitization rate of 1000 Hz and filtered with a band pass of 0.05–400 Hz. Vertical electrooculogram (VEOG) recording electrodes were positioned above and below the left eye, and horizontal electrooculogram (HEOG) recording electrodes were positioned 1.5 cm from the outer canthus of each eye. The impedance was kept below 5 kΩ.

Electroencephalogram data were analyzed offline with the software of Curry 7. Offline correction of eye movement artifact was performed. To exclude trials contaminated by artifacts, trials with voltages exceeding ±100 μV at any electrode were discarded. The EEG signals were segmented in segmented in series of epochs of 1100 ms. Each epoch started 100 ms before the stimulus onset. Baseline correction was performed over the 100 ms window before the stimulus presentation. The data were filtered with 0.1 Hz high pass and 30 Hz low pass filters. Based on the previous studies (Koivisto and Revonsuo, 2010; Koivisto et al., 2016, 2017) and visual inspection, the mean amplitudes of the ERPs for VAN (250–350 ms) were analyzed (SPSS 22) with repeated-measures analysis of variance (ANOVA) with Awareness (2: aware and unaware), Task (2: immediate detection and delayed detection), Area [2: posterior temporal (P7 and P8), occipital (O1 and O2)], and Hemisphere (2: left vs. right) as factors. In addition, the mean amplitudes of the ERPs for LP (450–650 ms) were statistically analyzed with repeated-measures analysis of variance with Awareness (2: aware and unaware), Task (2: immediate detection and delayed detection), Area [3: parietal (P3 and P4), posterior temporal (P7 and P8), occipital (O1 and O2)], and Hemisphere (2: left vs. right) as factors. The Greenhouse-Geisser correction was applied when the sphericity assumption was violated.

RESULTS

Behavioral Results

In critical trials, the participants (*n* = 16) reported awareness in 40.04% (*SD* = 9.35) of the critical trials during the immediate detection task, and in 43.2% (*SD* = 11.49) of the critical trials during the delayed detection task. Moreover, the number of the critical trials with awareness did not differ between the two tasks

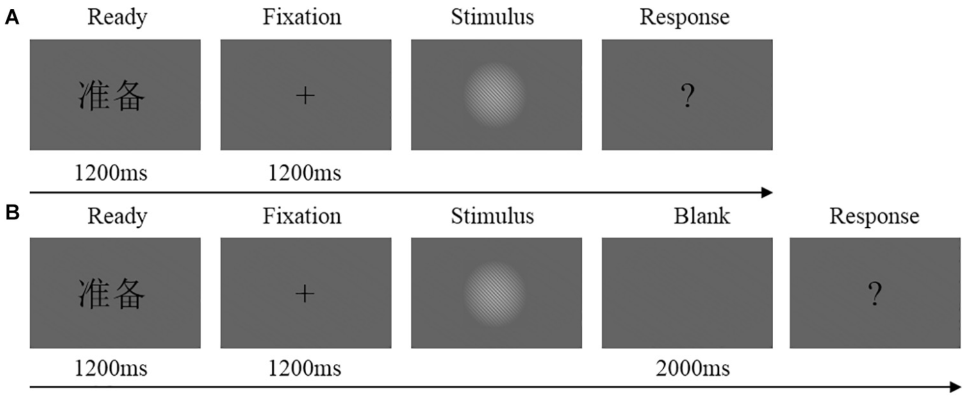


FIGURE 1 | (A) Flowchart of experimental trial procedure in the immediate detection task. Each trial started with the presentation of a Chinese word "准备"(i.e., "READY") at the center of the screen for 1200 ms, flowed by the fixation cross for 1200 ms and the stimulus for an individually calibrated duration (or blank screen in catch trials). After the stimulus (or blank), a question mark was presented until the participants make their decision whether they had seen the stimulus or not. **(B)** Flowchart of experimental trial procedure in the delayed detection task. Each trial started with the presentation of a Chinese word "准备" at the center of the screen for 1200 ms, flowed by the fixation cross for 1200 ms and the stimulus for an individually calibrated duration (or blank screen in catch trials). Then, the screen was blank for 2000 ms. After the blank, a question mark was presented until the participants make their decision whether they had seen the stimulus or not.

($t_{15} = 0.89$, $P > 0.05$). The contrast level of the critical stimulus that participants were tested with was 0.05 Michelson contrast. The duration of the critical stimuli did not differ between the two tasks ($t_{15} < 0.001$, $P > 0.05$).

The participants performed well on the control trials and the catch the trials. They reported awareness in 97.03% (*SD* = 5.18) of the control trials during the immediate detection task, and in 97.03% (*SD* = 6.21) of the control trials during the delayed detection task. In addition, they reported awareness in 4.84% (*SD* = 5.59) of the catch the trials during the immediate detection task, and in 3.91% (*SD* = 6.39) of the catch the trials during the delayed detection task. So, the participants followed the instructions.

ERPs Results

Figure 2 shows the ERP data for each condition. For VAN (250–350 ms), the repeated measures ANOVA showed a significant main effect for Awareness [F (1, 15) = 15, $P < 0.01$, $\eta_p^2 = 0.5$], showing larger negativity in aware trials than in unaware trials (–1.32 ± 0.56 μV vs. 0.53 ± 0.29 μV). However, any other interaction involving Awareness as factor was not statistically significant (*P*s > 0.05).

For LP (450–650 ms), the repeated measures ANOVA showed a significant main effect for Awareness [F (1, 15) = 11.25, $P < 0.01$, $\eta_p^2 = 0.43$], showing larger positivity in aware trials than in unaware trials (6.17 ± 0.9 μV vs. 4.03 ± 0.89 μV). In addition, the Awareness × Area interaction [F (2, 30) = 16.41, $P < 0.01$, $\eta_p^2 = 0.52$] showed that LP was largest over the parietal areas (2.99 μV). However, any other interaction involving Awareness as factor was not statistically significant (*P*s > 0.05). Our results did not show any effects for the task manipulation in the time window of 450–650 ms. However, **Figure 2B** clearly illustrates that the amplitude of LP decreased to zero during 650–850 ms in the immediate response condition, while the amplitude of LP in the delayed condition did not decrease at all but stayed at the peak level. So, the 650–850 ms time window was also statistically analyzed. The repeated measures ANOVA on mean amplitudes in the time window of 650–850 ms showed a significant main effect for Awareness [F (1, 15) = 15.77, $P < 0.01$, $\eta_p^2 = 0.51$], showing larger positivity in aware trials than in unaware trials (5.34 ± 0.81 μV *vs.* 4 ± 0.81 μV). In addition, the Awareness × Area interaction [F (2, 30) = 7.14, $P < 0.01$, $\eta_p^2 = 0.32$] showed that LP was largest over the parietal areas (1.8 μV). Most importantly, the Awareness × Task × Area interaction was statistically significant [F (2, 30) = 3.83, $P < 0.05$, $\eta_p^2 = 0.2$]. Further, simple simple-effect analysis showed larger positivity in aware trials than in unaware trials during the delayed detection condition over parietal (7.45 ± 1.02 μV vs. 4.55 ± 0.9 μV, $P < 0.01$), posterior temporal (5.29 ± 1.14 μV vs. 3.56 ± 0.98 μV, $P < 0.05$) and occipital (4.51 ± 1.05 μV vs. 2.44 ± 0.88 μV, $P < 0.05$) areas. However, the amplitude changes of the immediate detection condition did not reach statistical significance over parietal ($P > 0.05$), posterior temporal ($P > 0.05$), and occipital ($P > 0.05$) areas. Any other interaction involving Awareness as factor was not statistically significant (*P*s > 0.05).

DISCUSSION

The results showed that VAN and LP were observed in the immediate detection task and the delayed detection task, respectively. Importantly, our study showed that the amplitude of VAN was not influenced by the task manipulation. VAN was equally strong in the immediate detection task than in the delayed detection task. Thus, our results suggest that VAN correlates with visual awareness. Our finding was consistent with previous studies (Wilenius-emet et al., 2004; Rutiku et al., 2015; Koivisto and Grassini, 2016; Eklund and Wiens, 2018), which suggested

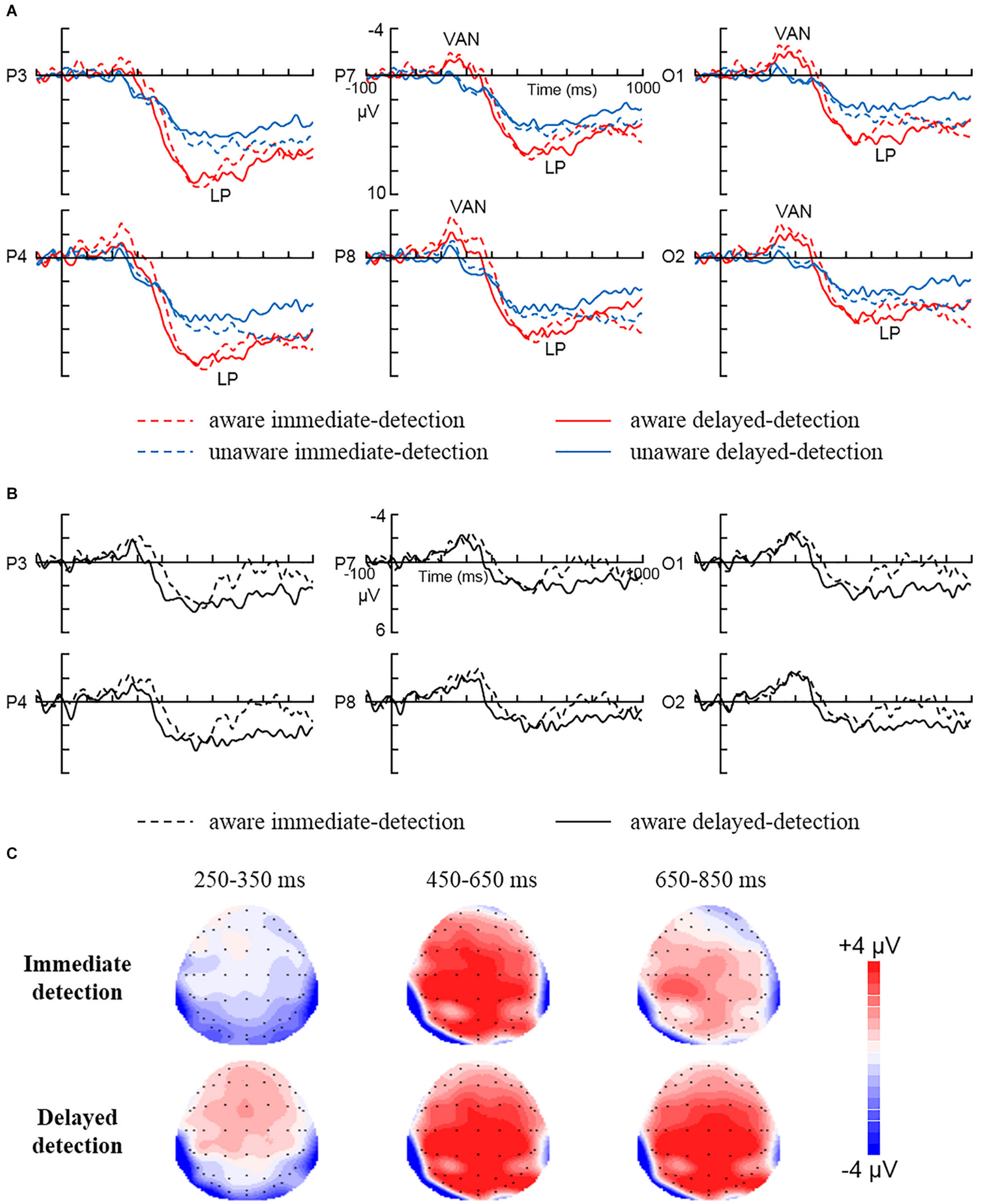


FIGURE 2 | The grand average ERPs for each condition. **(A)** The grand average ERPs to aware immediate-detection, aware delayed-detection, unaware immediate-detection, and unaware delayed-detection in parietal electrodes (P3 and P4), posterior temporal electrodes (P7 and P8), and occipital electrodes (O1 and O2). **(B)** The difference waves (aware minus unaware trials) related to immediate detection and delayed detection over parietal electrodes (P3 and P4), posterior temporal electrodes (P7 and P8), and occipital electrodes (O1 and O2). **(C)** The scalp topography of the mean amplitude difference between aware and unaware during 250–350, 450–650, and 650–850 ms in the immediate detection and delayed detection tasks.

that VAN was an early electrophysiological correlate of visual awareness.

In addition, our study showed that the amplitude of LP was influenced by the task manipulation. Our results did not show any effects for the task manipulation during 450–650 ms, but LP was influenced by the task manipulation during 650–850 ms. Both immediate and delayed detection tasks required a similar perceptual decision about the presence or absence of the stimulus. Specifically, working memory need to be updated to map the experience to a response (motor preparation). This may explain why the amplitude of LP during 450–650 ms was similar in both tasks. However, what was different in the tasks was that in the delayed condition overt responding had to be inhibited and the decision kept in memory for the 2 s delay period. LP may correlate with post-perceptual processes such as working memory or perceptual decision (Koivisto et al., 2016; Rutiku and Bachmann, 2017). The delay lengthens the requirement to remember the percept and response; thus, this seems to add or extend a post-perceptual process. This may explain why the amplitude of LP during 650–850 ms was different in both tasks. Thus, our results suggest that LP reflects post-perceptual processing.

Overall, our study adds new data showing that VAN is an early electrophysiological correlates of visual awareness, and LP reflects post-perceptual processes required in reporting perceptual awareness. The further studies are needed to examine the possibility that VAN, which has been assumed to be an early NCC, might reflect pre-conscious processing.

ETHICS STATEMENT

This experiment was approved by the ethical committee in Academy of Psychology and Behavior, Tianjin Normal University. All participants gave written informed consent in accordance with the 2013 Declaration of Helsinki and were paid for their attendance.

AUTHOR CONTRIBUTIONS

Both authors designed and performed the experiment, prepared the materials, wrote the manuscript, and approved the final version of the manuscript for submission. MY analyzed the data.

REFERENCES

Aru, J., Bachmann, T., Singer, W., and Melloni, L. (2012). Distilling the neural correlates of consciousness. *Neurosci. Biobehav. Rev.* 36, 737–746. doi: 10.1016/j.neubiorev.2011.12.003

Bachmann, T. (2009). Finding ERP-signatures of target awareness: puzzle persists because of experimental co-variation of the objective and subjective variables q. *Conscious. Cogn.* 18, 804–808. doi: 10.1016/j.concog.2009.02.011

De Graaf, T. A., Hsieh, P. J., and Sack, A. T. (2012). The "correlates" in neural correlates of consciousness. *Neurosci. Biobehav. Rev.* 36, 191–197. doi: 10.1016/j.neubiorev.2011.05.012

Eklund, R., and Wiens, S. (2018). Visual awareness negativity is an early neural correlate of awareness: a preregistered study with two gabor sizes. *Cogn. Affect. Behav. Neurosci.* 18, 176–188. doi: 10.3758/s13415-018-0562-z

Koch, C., Massimini, M., Boly, M., and Tononi, G. (2016). Neural correlates of consciousness: progress and problems. *Nat. Rev. Neurosci.* 17, 307–321. doi: 10.1038/nrn.2016.22

Koivisto, M., and Grassini, S. (2016). Neural processing around 200 ms after stimulus-onset correlates with subjective visual awareness. *Neuropsychologia* 84, 235–243. doi: 10.1016/j.neuropsychologia.2016.02.024

Koivisto, M., Grassini, S., Salminenvaparanta, N., and Revonsuo, A. (2017). Different electrophysiological correlates of visual awareness for detection and identification. *J. Cogn. Neurosci.* 29, 1621–1631. doi: 10.1162/jocn_a_01149

Koivisto, M., and Revonsuo, A. (2007). Electrophysiological correlates of visual consciousness and selective attention. *Neuroreport* 18, 753–756. doi: 10.1097/WNR.0b013e3280c143c8

Koivisto, M., and Revonsuo, A. (2010). Event-related brain potential correlates of visual awareness. *Neurosci. Biobehav. Rev.* 34, 922–934. doi: 10.1016/j.neubiorev.2009.12.002

Koivisto, M., Salminen-Vaparanta, N., Grassini, S., and Revonsuo, A. (2016). Subjective visual awareness emerges prior to P3. *Eur. J. Neurosci.* 43, 1601–1611. doi: 10.1111/ejn.13264

Lamy, D., Salti, M., and Bar-Haim, Y. (2009). Neural correlates of subjective awareness and unconscious processing: an ERP study. *J. Cogn. Neurosci.* 21, 1435–1446. doi: 10.1162/jocn.2009.21064

Naccache, L., Marti, S., Sitt, J. D., Trübutschek, D., and Berkovitch, L. (2016). Why the P3b is still a plausible correlate of conscious access? *Cortex* 85, 126–128. doi: 10.1016/j.cortex.2016.04.003

Railo, H., Koivisto, M., and Revonsuo, A. (2011). Tracking the processes behind conscious perception: a review of event-related potential correlates of visual consciousness. *Conscious. Cogn.* 20, 972–983. doi: 10.1016/j.concog.2011.03.019

Rutiku, R., and Bachmann, T. (2017). Juxtaposing the real-time unfolding of subjective experience and ERP neuromarker dynamics. *Conscious. Cogn.* 54, 3–19. doi: 10.1016/j.concog.2017.05.003

Rutiku, R., Martin, M., Bachmann, T., and Aru, J. (2015). Does the P300 reflect conscious perception or its consequences? *Neuroscience* 298, 180–189. doi: 10.1016/j.neuroscience.2015.04.029

Salti, M., Bar-Haim, Y., and Lamy, D. (2012). The P3 component of the ERP reflects conscious perception, not confidence. *Conscious. Cogn.* 21, 961–968. doi: 10.1016/j.concog.2012.01.012

Tsuchiya, N., Wilke, M., Frässle, S., and Lamme, V. A. F. (2015). No-report Paradigms: extracting the True neural correlates of consciousness. *Trends Cogn. Sci.* 19, 757–770. doi: 10.1016/j.tics.2015.10.002

Wilenius-emet, M., Revonsuo, A., and Ojanen, V. (2004). An electrophysiological correlate of human visual awareness. *Neurosci. Lett.* 354, 38–41. doi: 10.1016/j.neulet.2003.09.060

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Psychology

REVIEW
published: 30 January 2019
doi: 10.3389/fpsyg.2019.00050

Neuropsychology of Consciousness: Some History and a Few New Trends

Giovanni Berlucchi* and Carlo Alberto Marzi

Department of Neurosciences, Biomedicine and Movement, University of Verona, Verona, Italy

Consciousness is a global activity of the nervous system. Its physiological and pathological mechanisms have been studied in relation to the natural sleep-wake cycle and various forms of normal or morbid unconsciousness, mainly in neurophysiology and clinical neurology. Neuropsychology has been more interested in specific higher brain functions, such as perception and memory and their disorders, rather than in consciousness *per se*. However, neuropsychology has been at the forefront in the identification of conscious and unconscious components in the processing of sensory and mnestic information. The present review describes some historical steps in the formulation of consciousness as a global brain function with arousal and content as principal ingredients, respectively, instantiated in the subcortex and the neocortex. It then reports a few fresh developments in neuropsychology and cognitive neuroscience which emphasize the importance of the hippocampus for thinking and dreaming. Non-neocortical structures may contribute to the contents of consciousness more than previously believed.

Keywords: neuropsychology, consciousness and unconsciousness, arousal and content, hippocampus, thinking – dreaming

OPEN ACCESS

Edited by:
Anna Maria Berti,
Università degli Studi di Torino, Italy

Reviewed by:
Lorenzo Pia,
Università degli Studi di Torino, Italy
Elisabetta Ladavas,
University of Bologna, Italy

****Correspondence:***
Giovanni Berlucchi
giovanni.berlucchi@univr.it

Specialty section:
This article was submitted to
Consciousness Research,
a section of the journal
Frontiers in Psychology

Received: *27 October 2018*
Accepted: *09 January 2019*
Published: *30 January 2019*

Citation:
Berlucchi G and Marzi CA (2019)
Neuropsychology of Consciousness:
Some History and a Few New Trends.
Front. Psychol. 10:50.
doi: 10.3389/fpsyg.2019.00050

INTRODUCTION

In neuropsychology, localization of psychological functions in the brain has been classically based on the observation that patients carrying a lesion in a particular cerebral region exhibit a loss or disorders of a particular psychological ability, while other abilities are preserved. Speech has been localized in the frontal lobe of the left hemisphere because lesions in that region cause expressive aphasia, whereas similar destructions in the right hemisphere have no such effect. Similarly, certain visual perceptual abilities can be localized in the occipito-temporal cortex because they are disturbed by lesions in that part of the cortex but not by lesions in other cortical regions. Of course, such localizations do not imply that any given psychological function can unfold only in a given part of the brain: they only mean that a specific part of the brain houses a "hub," a crucial focus of activity, in the overall cerebral organization of that function. Attempts at localizing a hub for consciousness in the brain on the basis of the effects of brain lesions or dysfunctions that lead to unconsciousness are probably misconceived, insofar as consciousness is best seen as a global function of the brain in action which can be interfered with by nervous tissue damage or malfunctioning from a variety of factors. Large portions of the brain which are certainly known to be involved in consciousness can be removed without causing loss of consciousness, as in the case of the ablation of a whole cerebral hemisphere. If there are in the brain "master switches" which can turn consciousness on and off (Blumenfeld, 2014), these must be able to change the entire cerebral organization at once.

FORMULATION OF CONSCIOUSNESS

The philosopher Searle (1993) defines consciousness as "those subjective states of sentience or awareness that begin when one awakes in the morning from a dreamless sleep and continue throughout the day until one goes to sleep at night or falls into a coma, or dies, or otherwise becomes, as one would say, 'unconscious.'" While this terse definition captures many essential aspects of the natural dichotomy between consciousness and unconsciousness, as well as their relations with the physiological sleep-wake cycle and with the pathology of consciousness, it requires several qualifications based on current neuroscientific knowledge. It is true that there is a strong association between wakefulness and consciousness, but to be awake does not necessarily mean to be conscious, and to be asleep does not necessarily mean to be unconscious. Brain damaged patients in the vegetative state are persistently unaware of themselves and their environment, despite exhibiting irregular sleep-wake cycles whereby waking occurs with eye opening, but without any meaningful contact with the environment. Brief dissociations between consciousness and a wakeful appearance characterize the absence seizures or the complex partial seizures of epileptic patients and can be interpreted as momentary vegetative states (Plum and Schiff, 2003), although the presence of a minimal form of consciousness in at least some cases cannot be excluded (Bayne, 2011).

In everyday life, wakeful healthy individuals appear continuously conscious to themselves and to others (although of course many of their purposeful actions are carried out without the intervention of consciousness), but there is evidence for the occurrence of occasional "mind-blanking" moments of behavioral inaction and inability to report subjective inner experiences (Ward and Wegner, 2013). In turn, sleep can hardly be equated with unconsciousness, given that reportable dreams occupy parts of all stages of sleep, and not only of the REM (rapid eye movement) stage which in the past had been specifically linked to dreaming. By current estimates, dreaming takes up 80% of total REM sleep time and 50% of total non-REM sleep time, which means that on average one can be considered unconscious during only 44% of the time of a night's sleep (Cipolli et al., 2017; Siclari et al., 2017). Paradoxically, dreaming consciousness is probably absent in somnambulism, such that perpetrators of crimes during sleepwalking have been absolved on account of their presumed temporary unconsciousness (Kannape et al., 2017).

In normal everyday life, consciousness and unconsciousness are two distinct states of the whole organism, depending on different active modes of brain functioning, which alternate in some relation with the sleep-wake cycle but are partially independent of it. The normal brain is always active, and the natural unconsciousness of dreamless sleep is a physiological mode of brain functioning, as contrasted with the pathological modes of brain dysfunction underlying the unconsciousness of coma. The main behavioral difference between the physiological unconsciousness of dreamless sleep and the pathological unconsciousness of coma is that a healthy sleeping individual can always be aroused and brought back to conscious wakefulness by sensory stimuli of appropriate intensity, whereas a comatose patient cannot. Pharmacological unconsciousness induced by general anesthesia mimics coma, except for the quick return of arousability with the wearing off of the effects of the anesthetic agent (Brown et al., 2010).

SOME HISTORICAL LANDMARKS IN THE NEUROLOGY OF AROUSAL, WAKEFULNESS AND CONSCIOUSNESS

The neurophysiological mechanisms of arousal were discovered by Moruzzi and Magoun (1949) by inducing behavioral and electroencephalographic arousal reactions in lightly anesthetized cats upon electrical stimulation of the bulbo-ponto-mesencephalic reticular formation. They attributed the natural arousal reaction from sensory stimuli to the activation of the reticular formation and its prolongation in the hypothalamus and thalamus, resulting in the activation of the whole cerebral cortex. They also suggested that a continuous reticular activity, whether of endogenous or exogenous origin, could be a major factor in the maintenance of the waking state. By damaging the ascending projections of the reticular formation, Magoun and collaborators rendered cats and macaques comatose, confirming that a waking brain is the result of a continuous reticular activating action on the cerebral cortex (Magoun, 1952). The neurosurgeon French, a collaborator of Magoun, extended the results to human wakefulness and consciousness by studying a few patients with prolonged loss of consciousness after lesions of either the cephalic end of the brainstem reticular formation, or of its subcortical radiation, or of the entire cerebral cortex by meningoencephalitis (French, 1952). He was the first to call attention to "a possible conflict in terminology denoting the physiological and pathological conscious conditions of sleep and coma," because he had observed in his patients occasional brief periods of wakefulness with open eyes which were devoid of any evidence of conscious awareness. He thus implied that wakefulness is not necessarily a proof of consciousness, and advised against considering the reticular activating system as a center of wakefulness or consciousness, insofar as the manifestations of its activity are expressed only through its influences on other subcortical structures, such as the posterior hypothalamus, which had long been implicated in disorders of consciousness, or on the entire cortex (French, 1952).

In the 1960s and 1970s century some neurophysiological mechanisms of sleep and waking were identified in experimental animals (Moruzzi, 1963, 1972) and their results were used in the interpretation of major disturbances of consciousness in humans. Two syndromes characterized by clear dissociations between behavior and consciousness were described and named in brain damaged patients. Jennett and Plum (1972) gave the name "persistent vegetative state" (now also called unresponsive wakefulness) to a syndrome whose essential component "is the absence of any adaptive response to the external environment, the absence of any evidence of a functioning mind which is either receiving or projecting information, in a patient who has long periods of wakefulness." These waking periods, attested by the opening of the eyes, whether spontaneous or elicited by sensory stimulation, differentiate the vegetative state from coma, in which the eyes remain permanently closed even under strong stimulations. In vegetative state patients, diencephalic and brainstem arousal mechanisms appear sufficiently functional for supporting a behavioral expression of wakefulness, but conscious contents are lacking because of widespread cortical damage or due to a disconnection between the subcortical arousal mechanisms and the cerebral cortex. In Jennett and Plum's (1972) words, "common to all patients in this vegetative, mindless state is that, as best can be judged behaviorally, the cerebral cortex is not functioning, whether the lesion be in the cerebral cortex itself, in subcortical structures, the brain-stem, or in all these sites." In a localizing attempt, Plum and Posner (1980) famously argued that consciousness has two components, content and arousal, the first mediated by unique combinations of local cortical circuits specialized for different stimuli, the second depending on brainstem and diencephalic pathways that regulate the overall level of cortical function and hence the level of consciousness.

The locked-in syndrome, first described by Plum and Posner (1966), is usually caused by pontine lesions that produce an almost complete motor de-efferentation by interrupting the cortico-spinal and cortico-bulbar components of the pyramidal tract, resulting in tetraplegia and inability to speak (Herculano-Houzel et al., 2016). Voluntary palpebral and vertical eye movements may be preserved and may be used for a coded communication based on blinking or up and down ocular movements, revealing the existence of a fully preserved conscious awareness and near-normal sensory and cognitive functions. An animal model of the human locked-in syndrome (Ikegami et al., 1977; Zernicki et al., 1978; Berlucchi, 2017) is the midpontine pretrigeminal cat (Moruzzi, 1963, 1972), in which a disconnection from lower brain stem hypnogenic neurons (Berlucchi et al., 1964; Anaclet and Fuller, 2017) disinhibits the arousal systems.

The differential diagnosis between the vegetative state, the minimally conscious state (as defined by Giacino et al., 2002) and the locked-in syndrome is subject to a high error rate (Gill-Thwaites, 2006; Schnakers et al., 2009; Wade, 2018). For example, some locked-in patients are considered unconscious because their eyes and eyelids are also paralyzed, thus making communication impossible. In the last two decades, the possible presence of consciousness in totally paralyzed, non-communicating patients has been investigated by exploiting the capacity of a few of these patients to modulate their brain activities, as assessed with neuroimaging or electrophysiological techniques, in response to commands or to engaging cognitive stimulation (Owen, 2013; Bayne et al., 2017; Graham et al., 2018). When present, such cerebral, non-behavioral evidence for consciousness can help reclassify patients previously supposed to be in a vegetative state as minimally conscious or even as functionally locked-in. To borrow one of Jennett and Plum (1972) expressions, these patients demonstrate the possession of a functioning conscious mind by projecting information as patterns of brain activity. Very recent findings suggest that different states of consciousness can be discriminated in clinical practice on the basis of machine-analyzed signals extracted from the electroencephalogram (Engemann et al., 2018).

CORTEX VERSUS SUBCORTEX

The famous neurosurgeon Penfield (1978) has written that "to suppose that consciousness or the mind has localization is a failure to understand neurophysiology" (page 109). Nevertheless, he has also postulated that a centrencephalic system, more or less coincident with the higher brain stem and hypothalamus, contains the nervous mechanisms "which are prerequisite to intellectual activity ... and the initiation of the planned action of the conscious man" (Penfield, 1954). Most of his contemporary neurologists and neurosurgeons disagreed with him by conceding to the brainstem reticular system at most a menial role, metaphorically equated to that of janitors who warm up class-rooms and laboratories in a University (Levin, 1960). Granting that in an intact brain the cortex plays a major role in consciousness, to regard the ascending reticular system merely as an agent of arousal, an "energizer" concerned solely with maintaining the general excitability of the cortex, is a fallacy (Moruzzi, 1972). Indeed, after Moruzzi (1958) had criticized the concept of a single unitary arousal system on theoretical grounds (Berlucchi, 1997), the concept was made untenable by the discovery that in addition to the "classic" reticular ascending projections, which most probably use glutamate as their synaptic transmitter, other multiple ascending projections from the brainstem, the hypothalamus and the basal forebrain use other transmitters to modulate the activities of the thalamus and the cortex (Jones, 2011; Brown et al., 2012; Saper and Fuller, 2017). These multiple systems include monoaminergic projections from the pontine locus ceruleus, cholinergic projections from the ponto-mesencephalic latero-dorsal and pedunculo-pontine nuclei and from the basal forebrain, serotoninergic projections from the mesencephalic and pontine raphe nuclei, histaminergic projections from the tuberomammillary nucleus of the posterior hypothalamus and glutamatergic projections from the supramammillary nucleus of the lateral hypothalamus. Further, there are peptidergic projections to the forebrain and to all other ascending systems from lateral and posterior hypothalamic neurons which use the orexin peptide as a neurotransmitter. In experimental animals all these systems are active during waking and silent during sleep, except for the ponto-mesencephalic cholinergic projections which become active also during REM sleep. Each of these systems alone is sufficient for sustaining wakefulness, and none of them alone is necessary for that purpose except orexin, the absence of which is a cause of narcolepsy (Jones, 2011). So many arousing system working in parallel may seem redundant, but their collective activity is orchestrated, at least partly, by orexin, so that each of them can function in a different manner in different emotional and motivational conditions, thus possibly influencing some dimension of consciousness. Lesions of the rostral brainstem and posterior diencephalon which result in coma in experimental animals and humans alike probably destroy the ascending projections of all arousal systems and interfere with homeostatic regulation (Parvizi and Damasio, 2001). However, coma has also been attributed to small lesions of the rostral laterodorsal pontine tegmentum, projecting to cortical areas and neurons thought to be critical for consciousness (Fischer et al., 2016), and sudden disruption of consciousness has been produced with electrical stimulation of the left claustrum and anterior insula (Koubeissi et al., 2014). Giacino et al. (2014) have proposed that a common mechanism in disorder of consciousness may be the downregulation of an anterior forebrain mesocircuit, including thalamocortical and thalamostriatal connections focused on the central thalamus, with a possible contribution from the pedunculopontine nucleus.

The old question of whether processes implementing conscious contents occur only in the cortex or to some extent also subcortically is at the center of the current debate between affective and cognitive neuroscience. As detailed in a recent discussion (Panksepp et al., 2017; see also Adolph and Anderson, 2018), affective neuroscience places the ancestral indicators of affective consciousness in evolutionary ancient non-cortical survival networks, and maintains that subcortical activation is both necessary and sufficient for primitive affective experience. In contrast, cognitive neuroscience views all types of consciousness as involving the same global cortical broadcasting mechanism and holds that subcortical processes are necessary but not sufficient for affective experience. Cognitive neuroscience concedes that the cerebral cortex alone, without interaction with subcortical processes, cannot sustain consciousness, but insists that absence of a cortex implies absence of consciousness. In a survey entitled "consciousness without a cerebral cortex: a challenge for neuroscience and medicine," Merker (2007) has forcefully argued that an upper brainstem system, extending from the roof of the midbrain to the basal diencephalon, serves by itself as a medium for the elaboration of conscious contents. In his view this system accounts for the elaborate goal-directed behaviors of decorticated rodents, as well as for the presence of conscious experiences in some hydranencephalic children, born without most of the cerebral cortex because of massive loss of hemispheric tissue during gestation. Both ordinary neurological examination and the reports of primary caregivers attest that these children, though affected by severe sensory deficits such as blindness, are capable of experiencing pain, discomfort and suffering, but also other hedonic states including comfort, pleasure and joy (Aleman and Merker, 2014). The possibility that the emergence of consciousness can precede the development and maturation of the cortex has long been advocated by Trevarthen and Reddy (2017) on the basis of the presence in fetuses and premature newborns of an exploratory search for, and an appropriate reaction to, sensory stimuli, along with motor expressions of distress, curiosity, or pleasure, clearly aimed at the social communication of interests and feelings.

On the other hand, current authoritative theories of consciousness, such as the global neuronal workspace theory (Dehaene and Changeux, 2011) and the integrated information theory (Tononi et al., 2016), keep alive the concept that the terms arousal and waking refer to a global regulation of cerebral organization by brainstem and diencephalic activities, whereas conscious contents depend on local and specific cortical or thalamo-cortical organizations. Hill and Tononi (2005) have provided a large-scale computer model that accounts for sleep-wake transitions in brain activity in terms of specific changes at the neuronal level in the thalamocortical, corticothalamic, and corticocortical connections. According to the model, both waking and physiological sleep require a specific balance of excitation and inhibition in these connections, a balance which may be disrupted in severe disorders of consciousness. By measuring the electroencephalographic response to transcranial magnetic stimulation, Rosanova et al. (2018) have recently documented in awake vegetative state patients a pathological tendency of intact cortical circuits to fall into silence upon receiving an input, at variance with the complex pattern of propagation and interactions set up in the cortex of healthy awake individuals by the initial activation, but similar to the non-propagated cortical reaction observed in unconscious healthy individuals during natural sleep. As one possible cause for the presence of cortical responses typical of the normal sleeping brain in awake but unconscious brain damaged patients, the authors mention the possibility that a diffuse axonal injury deprives the cortical circuits of a critical amount of fibers of the ascending activating systems.

In this connection, Koch et al. (2016) distinguish two neuronal correlates of consciousness, a full correlate, i.e., the neural substrate supporting experience in general, irrespective of its specific content, and a content-specific correlate, i.e., the neural substrate supporting a particular content of experience – for example, faces, whether seen, dreamed or imagined. According to them the arousal systems are background factors that enable consciousness by ensuring an adequate excitability of the neuronal correlates of consciousness, but do not contribute directly to the content of experience. As for the possible nature of the neuronal cortical correlates of conscious contents, recordings in epileptic patients have demonstrated the existence in the human medial temporal cortex of single neurons representing specific objects or events or persons (Quian Quiroga et al., 2013; Quian Quiroga, 2016), corresponding to the gnostic units of Konorski (1967) or to the cardinal cells of Barlow (1972). However, many believe that aggregations of neurons like the cell assemblies proposed by Hebb (1949) are more likely to constitute the correlates of conscious contents (e.g., Huyck and Passmore, 2013; Eichenbaum, 2018), although the possible contribution of highly specialized single neurons, like the so-called grandmother neurons (Gross, 2002), is not ruled out completely (Bowers, 2009).

Traditionally, neuropsychology has been more interested in the brain lesions that cause fractional losses of consciousness, such as various forms of agnosias, rather than in the brain dysfunction which entail a total loss of consciousness. Interest for the study of consciousness in neuropsychology is typically attested by the many dissociations discovered by neuropsychologists whereby residual cognitive abilities following brain damage occur in the absence of acknowledged awareness by the patients, as exemplified by blindsight, implicit memories in amnesia, hidden information processing in unilateral neglect, covert recognition of faces in prosopagnosia, and so forth. In blindsight, for example, some patients who are blind in one half of the visual field as a result of a cortical lesion can detect or discriminate visual stimuli of which they are utterly unaware (Weiskrantz, 1998; Marzi, 1999), and the "Gestalt" configurations of visual stimuli can be implicitly detected even when such stimuli are presented to a completely decorticated cerebral hemisphere (Georgy et al., 2016). Other dissociations allowing an at least partial identification of the neural bases of conscious and unconscious aspects of vision have been examined in neuropsychological experiments on healthy participants, using for example binocular rivalry or "masking" paradigms allowing a comparison between supraliminal and subliminal stimuli in vision or other perceptual modalities (Seth, 2018). In the following we will deal with a new neuropsychological approach to the study of the neural bases of consciousness, focusing on the hippocampus, thinking and dreaming.

HIPPOCAMPUS IN THINKING AND DREAMING

Intuitively most contents of consciousness correspond to the perceived objects and events of the present environment, but there also exist internally generated contents that are not directly driven by immediate perceptual input. These contents of consciousness, or thoughts, can reflect the present situation as well as dissociate themselves from the "here and now" by referring to the remembered past, or to the foreseen future, or to entirely fictitious scenarios. Thoughts are produced during mental activities, variously named task-dependent and task-independent thinking, daydreaming, mind wandering, and mental time travel, which have been calculated to occupy as much as 30–50% of our waking mental activities, ranging from future planning, problem-solving and creativity to rumination and metacognition. Mental time travel involves a metaphorical navigation of the past as well of the future, and considerable evidence points to the hippocampus as a crucial brain structure not only for the actual navigation of the current environment, but also for the mental navigation of time past and future (Corballis, 2015; Smallwood and Schooler, 2015; Christoff et al., 2016; Fox and Christoff, 2018). The manners in which the hippocampus contributes to memory, visual imagery, navigation and cognition have been spelled out recently by Lisman et al. (2017). The Nobel prize winning discovery of place cells in the hippocampus and grid cells in the entorhinal cortex of rats (Moser et al., 2015; Hartley et al., 2017) has revealed the existence of a neural system that allows the navigation not only of the present environment, but also of the record of an animal's life (Cohen, 2015). Activities of neurons and neuronal assemblies in the hippocampal regions can tell the story of where the animal has been, where it will or might go, and which stimuli have been encountered in various locations. As elaborated by Nadel and Ranganath (in Lisman et al., 2017), the hippocampus has presumably evolved as a brain mechanism that organizes experiences according to their spatial and temporal relationships, not only by specifying the locations of foraging sites and potential predators, but also by enabling enduring and meaningful representations of these locations in a spatio-temporal context. In their words, "the hippocampal map can support memory for the location of a tree that only has fruits in the summertime, or the site of a water source that is frequented by predators at night but safe during the daytime."

In humans, brain imaging shows that thinking about the past and future episodes activates a common network in the brain of which the hippocampus is a major component (Addis et al., 2007; Beaty et al., 2018). Medial temporal lobe lesions including the hippocampus cause a most severe anterograde amnesia combined with a variable retrograde amnesia, as well as an inability to plan future actions. Many years ago, in their first description of a human Klüver-Bucy syndrome due to a two-stage extensive bilateral removal of the temporal lobes of an epileptic patient, Terzian and Dalle Ore (1955) prophetically wrote that the operation, though successful in improving the epileptic condition, had left the patient without a past to remember and consequently with no future to look forward to. The purest case of amnesia caused by a bilateral medial temporal surgical ablation is the late Henry Molaison, originally studied by neuropsychologist Brenda Milner (Milner and Klein, 2016). Milner's former student Suzanne Corkin has published a best-selling biography of this patient, the title of which, "Permanent present tense," refers to the fact that after his brain operation the patient's consciousness was totally stuck to the "here and now" (Corkin, 2013). The incapacity for mental time travel of amnesic patients with hippocampal lesions cannot be attributed to dementia because of their spared sense of the self, as manifest in the appropriate use of personal pronouns and adjectives in verbal communication. Nor do hippocampal lesions destroy the objective cognition of physical time as measured by clocks and calendars, since patients with these lesions can conceive about either past and future, although for them both past and future are empty of actual and foreseeable personal episodes. In brief, amnesic patients with hippocampal lesions appear to possess a factual, semantic knowledge of a physical time, whereby present is preceded by past and followed by future, but are unable to travel in it with their mind because they cannot retrieve personal episodes from their past or imagine themselves in future episodes. In a recent experiment (McCormick et al., 2018), spontaneous thinking was studied in patients affected by small hippocampal lesions from limbic encephalitis and deficits of episodic memory, though less severe than those of Henry Molaison. Spontaneous thoughts of these patients were compared with those of healthy controls by systematic sampling in both groups and by asking participants about the thought content and whether the thought concerned the present moment or past or future time points at different distances from the present. Though perfectly able to entertain spontaneous thoughts detached from the current external environment, patients with hippocampal damage reported conscious contents markedly different from those of healthy controls. While the controls' thoughts could concern past, present, and future, and were couched primarily in terms of detailed visual episodes, the patients' thoughts were anchored in the present, verbally mediated and devoid of visual images. In the authors' words, these findings "expose the hippocampus as a key pillar in the neural architecture of mind-wandering and reveal its impact beyond episodic memory, placing it at the heart of our mental life" (McCormick et al., 2018).

There are various phenomenological and conceptual parallels between spontaneous thoughts, particularly during mind wandering, on one hand, and the contents of dreams during sleep on the other (Fox et al., 2013). Is the hippocampus important for dreaming as well as for mental time travel? A few years ago Llewellyn (2013) answered this question in the affirmative, mainly based on theoretical arguments linking REM sleep dreams with episodic memory. Many years previously an authoritative book of Solms (1997) had amassed considerable evidence in support of the notion that cessation or reduction of dreaming can occur after either a left posterior cortical lesion or a deep bilateral frontal lesion, but not after hippocampal lesions. In a commentary to Llewellyn's article, Solms (2013) reiterated that it is a clinical fact that bilateral hippocampal lesions have no demonstrable effect on the occurrence of REM-like dreams. He wrote that he was looking forward to reading the vivid dream reports of the celebrated amnesic patient HM of Corkin, whose book had not yet appeared at the time. The book has now been out for some time and anyone can read in it that Henry Molaison's dreams, if any, were by no means as vivid as expected by Solms. According to Corkin (2013), Henry's dream reports were quite dull, merely describing images of houses and fields probably belonging to his old preoperatory memories, and such as to make Corkin suspect that they were merely anecdotes that he created on the spot in order to oblige his interlocutors. Corkin also makes the important point that Henry's dream reports might have been warped by their 30 s span of immediate memory, after which the dream content was bound to evaporate. To our knowledge a thorough investigation of dreaming in amnesic patients with hippocampal lesions is still lacking, but a recent review presents several pieces of neuroimaging and electrophysiological evidence for an important participation of the hippocampus to dreaming process and to the contents of dreams (Cipolli et al., 2017). The hippocampus has probably a major role in providing the episodic memories, both recent and remote, that make up specific dream contents, while activation of the amygdala complex, anterior cingulate cortex and orbitofrontal cortex could instead be related to the emotional features of dreams.

EPILOG AND POSSIBLE DEVELOPMENTS

Consciousness is the expression of a global organization of the central nervous system which is subject to physiological modifications, as in dreamless sleep, to pharmacological alterations, as in general anesthesia, and to pathological disruptions, as in epilepsy, coma or vegetative state. These global states of neural organization or disorganization have been traditional objects of study of neurophysiology, neuropharmacology and clinical neurology. Neuropsychology has been more interested in specific aspects of higher brain function (perception, attention, memory, language, emotion, and so forth), and their disorders, rather than in consciousness *per se*. The evidence that the hippocampus may influence the temporal scope of thinking as well as the types of thought suggests that the neocortex may not be alone in the elaboration of conscious contents, and prompts further inquiries into the participation of subcortical structures to the multiple dimensions of consciousness, above and beyond a simple arousal function. For example, the cerebellum is generally considered to have little or no role in the neural organization underlying consciousness (e.g., Koch et al., 2016), in spite of the cognitive and affective deficits exhibited by patients with cerebellar lesions (Schmahmann, 2010). To our knowledge, studies similar to those of McCormick et al. (2018) on the influence of hippocampal lesions on conscious thinking have not been carried out on patients with cerebellar lesions. To be sure, the evidence for a role for the cerebellum in cognitive functions is rather weak compared to its major role in several forms of motor learning (Glickstein, 2007), and even large cerebellar lesions do not result in unconsciousness. However, also the ablation of an entire cerebral hemisphere appears to leave the patient with a conscious mind and a conscious sense of a personal self, regardless of which side is removed (Sperry, 1984). Though Sperry's split-brain experiments are famous for suggesting a dimidiation of consciousness after section of the corpus callosum, Sperry himself has stated that attitudinal, orientational, emotional, contextual, semantic, and related cognitive components of conscious awareness stay unified in split-brain patients because they are mediated through undivided deep brain structures. The superior colliculus is almost certainly one of these structures (Corballis et al., 2018), but the contribution of other brainstem components remains to be investigated.

AUTHOR CONTRIBUTIONS

GB drafted the manuscript. CM discussed it and added changes and information.

FUNDING

The writing of this manuscript was supported by ERC grant 339939 "Perceptual Awareness" (PI. CM).

REFERENCES

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377. doi: 10.1016/j.neuropsychologia.2006.10.016

Adolph, R., and Anderson, D. J. (2018). *The Neuroscience of Emotion. A New Synthesis*. Princeton, NJ: Princeton University Press. doi: 10.23943/9781400889914

Aleman, B., and Merker, B. (2014). Consciousness without cortex: a hydranencephaly family survey. *Acta Paediatr.* 103, 1057–1065. doi: 10.1111/apa.12718

Anaclet, C., and Fuller, P. M. (2017). Brainstem regulation of slow-wave-sleep. *Curr. Opin. Neurobiol.* 44, 139–143. doi: 10.1016/j.conb.2017.04.004

Barlow, H. B. (1972). Single units and sensation: a neuron doctrine for perceptual psychology. *Perception* 1, 371–394. doi: 10.1068/p010371

Bayne, T. (2011). The presence of consciousness in absence seizures. *Behav. Neurol.* 24, 47–53. doi: 10.3233/BEN-2011-0318

Bayne, T., Hohwy, J., and Owen, A. M. (2017). Reforming the taxonomy in disorders of consciousness. *Ann. Neurol.* 82, 866–872. doi: 10.1002/ana.25088

Beaty, R. E., Thakral, P. P., Madore, K. P., Benedek, M., and Schacter, D. L. (2018). Core network contributions to remembering the past, imagining the future, and thinking creatively. *J. Cogn. Neurosci.* 20, 1–13. doi: 10.1162/jocn_a_01327

Berlucchi, G. (1997). One or many arousal systems? Reflections on some of giuseppe moruzzi's foresights and insights about the intrinsic regulation of brain activity. *Arch. Ital. Biol.* 135, 5–14.

Berlucchi, G. (2017). Wandering thoughts about consciousness, the brain, and the commentary system of larry weiskrantz. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.10.011 [Epub ahead of print].

Berlucchi, G., Maffei, L., Moruzzi, G., and Strata, P. (1964). EEG and behavioral effects elicited by cooling of medulla and pons. *Arch. Ital. Biol.* 102, 372–392.

Blumenfeld, H. (2014). A master switch for consciousness? *Epilepsy Behav.* 37, 234–235. doi: 10.1016/j.yebeh.2014.07.008

Bowers, J. S. (2009). On the biological plausibility of grandmother cells: implications for neural network theories in psychology and neuroscience. *Psychol. Rev.* 116, 220–251. doi: 10.1037/a0014462

Brown, E. N., Lydic, R., and Schiff, D. (2010). General anesthesia, sleep, and coma. *N. Engl. J. Med.* 363, 2638–2650. doi: 10.1056/NEJMra0808281

Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., and McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiol. Rev.* 92, 1087–1187. doi: 10.1152/physrev.00032.2011

Christoff, K., Irving, Z. C., Fox, K. C., Spreng, R. N., and Andrews-Hanna, J. R. (2016). Mind-wandering as spontaneous thought: a dynamic framework. *Nat. Rev. Neurosci.* 17, 718–731. doi: 10.1038/nrn.2016.113

Cipolli, C., Ferrara, M., De Gennaro, L., and Plazzi, G. (2017). Beyond the neuropsychology of dreaming: insights into the neural basis of dreaming with new techniques of sleep recording and analysis. *Sleep Med. Rev.* 35, 8–20. doi: 10.1016/j.smrv.2016.07.005

Cohen, N. J. (2015). Navigating life. *Hippocampus* 25, 704–708. doi: 10.1002/hipo.22443

Corballis, M. C. (2015). *The Wandering Mind: What the Brain does When You're not Looking*. Chicago, IL: University of Chicago Press. doi: 10.7208/chicago/9780226238753.001.0001

Corballis, M. C., Corballis, P. M., Berlucchi, G., and Marzi, C. A. (2018). Perceptual unity in the split brain: the role of subcortical connections. *Brain* 141:e46. doi: 10.1093/brain/awy085

Corkin, S. (2013). *Permanent Present Tense: The Unforgettable Life of the Amnesic Patient, H. M*. New York, NY: Basic Books.

Dehaene, S., and Changeux, J. P. (2011). Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227. doi: 10.1016/j.neuron.2011.03.018

Eichenbaum, H. (2018). Barlow versus Hebb: when is it time to abandon the notion of feature detectors and adopt the cell assembly as the unit of cognition? *Neurosci. Lett.* 680, 88–93. doi: 10.1016/j.neulet.2017.04.006

Engemann, D. A., Raimondo, F., King, J. R., Rohaut, B., Louppe, G., Faugeras, F., et al. (2018). Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain* 141, 3179–3192. doi: 10.1093/brain/awy251

Fischer, D. B., Boes, A. D., Demertzi, A., Evrard, H. C., Laureys, S., Edlow, B. L., et al. (2016). A human brain network derived from coma-causing brainstem lesions. *Neurology* 87, 2427–2434. doi: 10.1212/WNL.0000000000003404

Fox, C. R., and Christoff, K. (eds) (2018). *The Oxford Handbook of Spontaneous Thought: Mind-Wandering, Creativity, and Dreaming*. Oxford: Oxford Library of Psychology.

Fox, K. C., Nijeboer, S., Solomonova, E., Domhoff, G. W., and Christoff, K. (2013). Dreaming as mind wandering: evidence from functional neuroimaging and first-person content reports. *Front. Hum. Neurosci.* 30:412. doi: 10.3389/fnhum.2013.00412

French, J. D. (1952). Brain lesions associated with prolonged unconsciousness. *Arch. Neurol. Psychiatry* 68, 727–740. doi: 10.1001/archneurpsyc.1952.02320240002001

Georgy, L., Celeghin, A., Marzi, C. A., Tamietto, M., and Ptito, A. (2016). The superior colliculus is sensitive to gestalt-like stimulus configuration in hemispherectomy patients. *Cortex* 81, 151–161. doi: 10.1016/j.cortex.2016.04.018

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: definition and diagnostic criteria. *Neurology* 58, 349–353. doi: 10.1212/WNL.58.3.349

Giacino, J. T., Fins, J. J., Laureys, S., and Schiff, N. D. (2014). Disorders of consciousness after acquired brain injury: the state of the science. *Nat. Rev. Neurol.* 10, 99–114. doi: 10.1038/nrneurol.2013.279

Gill-Thwaites, H. (2006). Lotteries, loopholes and luck: misdiagnosis in the vegetative state patient. *Brain Inj.* 20, 1321–1328. doi: 10.1080/02699050601081802

Glickstein, M. (2007). What does the cerebellum really do? *Curr. Biol.* 17, R824–R827. doi: 10.1016/j.cub.2007.08.009

Graham, M., Owen, A. M., Weijer, C., and Naci, L. (2018). Using neuroimaging to uncover awareness in brain-injured and anesthetized patients. *Front. Biosci.* 10:337–349.

Gross, C. G. (2002). Genealogy of the "grandmother cell". *Neuroscientist* 8, 512–518. doi: 10.1177/107385802237175

Hartley, T., Lever, C., Burgess, N., and O'Keefe, J. (2017). Space in the brain: how the hippocampal formation supports spatial cognition. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20120510. doi: 10.1098/rstb.2012.0510

Hebb, D. O. (1949). *The Organization of Behavior. A Neuropsychological Theory*. New York, NY: Wiley.

Herculano-Houzel, S., Kaas, J. H., and de Oliveira-Souza, R. (2016). Corticalization of motor control in humans is a consequence of brain scaling in primate evolution. *J. Comp. Neurol.* 524, 448–455. doi: 10.1002/cne.23792

Hill, S., and Tononi, G. (2005). Modeling sleep and wakefulness in the thalamocortical system. *J. Neurophysiol.* 93, 1671–1698. doi: 10.1152/jn.00915.2004

Huyck, C. R., and Passmore, P. J. (2013). A review of cell assemblies. *Biol. Cybern.* 107, 263–288. doi: 10.1007/s00422-013-0555-5

Ikegami, S., Nishioka, S., and Kawamura, H. (1977). Operant discriminative conditioning of vertical eye movements in the midpontine pretrigeminal cat. *Brain Res.* 124, 99–108. doi: 10.1016/0006-8993(77)90866-6

Jennett, B., and Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1, 734–737. doi: 10.1016/S0140-6736(72)90242-5

Jones, B. E. (2011). Neurobiology of waking and sleeping. *Handb. Clin. Neurol.* 98, 131–149. doi: 10.1016/B978-0-444-52006-7.00009-5

Kannape, O. A., Perrig, S., Rossetti, A. O., and Blanke, O. (2017). Distinct locomotor control and awareness in awake sleepwalkers. *Curr. Biol.* 27, R1102–R1104. doi: 10.1016/j.cub.2017.08.060

Koch, C., Massimini, M., Boly, M., and Tononi, G. (2016). Neural correlates of consciousness: progress and problems. *Nat. Rev. Neurosci.* 17, 307–321. doi: 10.1038/nrn.2016.22

Konorski, J. (1967). *Integrative Activity of the Brain. An Interdisciplinary Approach*. Chicago, IL: The University of Chicago Press.

Koubeissi, M. Z., Bartolomei, F., Beltagy, A., and Picard, F. (2014). Electrical stimulation of a small brain area reversibly disrupts consciousness. *Epilepsy Behav.* 37, 32–35. doi: 10.1016/j.yebeh.2014.05.027

Levin, M. (1960). Consciousness and the highest cerebral centres, with remarks on the Penfield-Walshe controversy. *J. Ment. Sci.* 106, 1398–1404. doi: 10.1192/bjp.106.445.1398

Lisman, J., Buzsáki, G., Eichenbaum, H., Nadel, L., Ranganath, C., and Redish, A. D. (2017). Viewpoints: how the hippocampus contributes to memory, navigation and cognition. *Nat. Neurosci.* 20, 1434–1447. doi: 10.1038/nn.4661

Llewellyn, S. (2013). Such stuff as dreams are made on? Elaborative encoding, the ancient art of memory, and the hippocampus. *Behav. Brain Sci.* 36, 589–607. doi: 10.1017/S0140525X12003135

Magoun, H. W. (1952). The ascending reticular activating system. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* 30, 480–492.

Marzi, C. A. (1999). Why is blindsight blind? *J. Conscious. Stud.* 6, 12–18.

McCormick, C., Rosenthal, C. R., Miller, T. D., and Maguire, E. A. (2018). Mind-wandering in people with hippocampal damage. *J. Neurosci.* 38, 2745–2754. doi: 10.1523/JNEUROSCI.1812-17.2018

Merker, B. (2007). Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. *Behav. Brain Sci.* 30, 63–81. doi: 10.1017/S0140525X07000891

Milner, B., and Klein, D. (2016). Loss of recent memory after bilateral hippocampal lesions: memory and memories-looking back and looking forward. *J. Neurol. Neurosurg. Psychiatry* 87:230. doi: 10.1136/jnnp-2015-311092

Moruzzi, G. (1958). The functional significance of the reticular formation. *Arch. Ital. Biol.* 96, 17–28.

Moruzzi, G. (1963). Active processes in the brain stem during sleep. *Harvey Lect.* 58, 233–297.

Moruzzi, G. (1972). The sleep-waking cycle. *Ergeb. Physiol.* 64, 1–165.

Moruzzi, G., and Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.* 1, 455–473. doi: 10.1016/0013-4694(49)90219-9

Moser, M. B., Rowland, D. C., and Moser, E. I. (2015). Place cells, grid cells, and memory. *Cold Spring Harb. Perspect. Biol.* 7:a021808. doi: 10.1101/cshperspect.a021808

Owen, A. M. (2013). Detecting consciousness: a unique role for neuroimaging. *Ann. Rev. Psychol.* 64, 109–133. doi: 10.1146/annurev-psych-113011-143729

Panksepp, J., Lane, R. D., Solms, M., and Smith, R. (2017). Reconciling cognitive and affective neuroscience perspectives on the brain basis of emotional experience. *Neurosci. Biobehav. Rev.* 76(Pt B), 187–215. doi: 10.1016/j.neubiorev.2016.09.010

Parvizi, J., and Damasio, A. (2001). Consciousness and the brainstem. *Cognition* 79, 135–160. doi: 10.1016/S0010-0277(00)00127-X

Penfield, W. (1954). "Studies on the cerebral cortex of man. A review and an interpretation," in *Brain Mechanisms and Consciousness*, eds E. D. Adrian, F. Bremer, and H. H. Jasper (Oxford: Blackwell), 284–304.

Penfield, W. (1978). *Mystery of the Mind. A Critical Study of Consciousness and the Human Brain*. Princeton, NJ: Princeton University Press.

Plum, F., and Posner, J. B. (1966). *The Diagnosis of Stupor and Coma*. Philadelphia, PA: Davis.

Plum, F., and Posner, J. B. (1980). *The Diagnosis of Stupor and Coma*, 2nd Edn. Philadelphia, PA: Davis.

Plum, F., and Schiff, N. D. (2003). "Disorders of consciousness," in *Encyclopedia of Cognitive Science*, ed. L. Nadel (London: Nature Publishing Group), 744–750.

Quian Quiroga, R. (2016). Neuronal codes for visual perception and memory. *Neuropsychologia* 83, 227–241. doi: 10.1016/j.neuropsychologia.2015.12.016

Quian Quiroga, R., Fried, I., and Koch, C. (2013). Brain cells for grandmother. *Sci. Am.* 308, 30–35. doi: 10.1038/scientificamerican0213-30

Rosanova, M., Fecchio, M., Casarotto, S., Sarasso, S., Casali, A. G., Pigorini, A., et al. (2018). Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients. *Nat. Commun.* 9:442. doi: 10.1038/s41467-018-06871-1

Saper, C. B., and Fuller, P. M. (2017). Wake–sleep circuitry: an overview. *Curr. Opin. Neurobiol.* 44, 186–192. doi: 10.1016/j.conb.2017.03.021

Schmahmann, J. D. (2010). The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. *Neuropsychol. Rev.* 20, 236–260. doi: 10.1007/s11065-010-9142-x

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol.* 9:35. doi: 10.1186/1471-2377-9-35

Searle, J. R. (1993). "The problem of consciousness," in *Novartis Foundation Symposium*, eds G. R. Bock and J. Mash (London: The Ciba Foundation). doi: 10.1006/ccog.1993.1026

Seth, A. (2018). Consciousness: the last 50 years (and the next). *Brain Neurosci. Adv.* 2, 1–6. doi: 10.1177/2398212818816019

Siclari, F., Baird, B., Perogamvros, L., Bernardi, G., LaRocque, J. J., Riedner, B., et al. (2017). The neural correlates of dreaming. *Nat. Neurosci.* 20, 872–878. doi: 10.1038/nn.4545

Smallwood, J., and Schooler, J. W. (2015). The science of mind wandering: empirically navigating the stream of consciousness. *Annu. Rev. Psychol.* 66, 487–518. doi: 10.1146/annurev-psych-010814-015331

Solms, M. (1997). The neuropsychology of dreams: a clinico-anatomical study.

Solms, M. (2013). Dreaming is not controlled by hippocampal mechanisms. *Behav. Brain Sci.* 36, 629. doi: 10.1017/S0140525X13001441

Sperry, R. W. (1984). Consciousness, personal identity and the divided brain. *Neuropsychologia* 22, 661–673. doi: 10.1016/0028-3932(84)90093-9

Terzian, H., and Dalle Ore, G. D. (1955). Syndrome of klüver and bucy; reproduced in man by bilateral removal of the temporal lobes. *Neurology* 5, 373–380. doi: 10.1212/WNL.5.6.373

Tononi, G., Boly, M., Massimini, M., and Koch, C. (2016). Integrated information theory: from consciousness to its physical substrate. *Nat. Rev. Neurosci.* 17, 450–461. doi: 10.1038/nrn.2016.44

Trevarthen, C., and Reddy, V. (2017). "Consciousness in Infants," in *The Blackwell Companion to Consciousness*, eds S. Schneider and M. Velmans (New York, NY: Wiley).

Wade, D. T. (2018). How often is the diagnosis of the permanent vegetative state incorrect? A review of the evidence. *Eur. J. Neurol.* 25, 619–625. doi: 10.1111/ene.13572

Ward, A. F., and Wegner, D. M. (2013). Mind-blanking: when the mind goes away. *Front. Psychol.* 4:650. doi: 10.3389/fpsyg.2013.00650

Weiskrantz, L. (1998). *Blindsight: A Case Study and Implications*. Oxford: Oxford University Press.

Zernicki, B., Michalski, A., Radil-Weiss, T., and Kaczkowska, E. (1978). Instrumental ocular conditioning in acute pretrigeminal cat. *Acta Neurobiol. Exp.* 38, 71–77.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Psychology

OPINION
published: 23 January 2019
doi: 10.3389/fpsyg.2019.00039

A Mind Free to Wander: Neural and Computational Constraints on Spontaneous Thought

Elisa Ciaramelli[1]* *and Alessandro Treves*[2]*

[1] Dipartimento di Psicologia, Università di Bologna, Bologna, Italy, [2] SISSA - Cognitive Neuroscience, Trieste, Italy

Keywords: mind-wandering, attention, episodic memory retrieval, ventromedial prefrontal cortex, hippocampus, neuropsychology, computational modeling

One prominent feature of human conscious experience is mind-wandering, the automatic drift of attention away from an ongoing task toward thoughts often completely unrelated to the task at hand (e.g., thinking about running while reading a manuscript; Antrobus et al., 1966; Christoff et al., 2016). Humans spend about 25–50% of their daily lives mind-wandering (Killingsworth and Gilbert, 2010), with obvious disadvantages for performance on ongoing tasks (Smallwood and Schooler, 2015). We do not mind-wander so frequently because it is fun. In fact, mind-wandering most often causes bad mood, regardless of whether the content of off-task thoughts was negative or positive (Killingsworth and Gilbert, 2010). Rather, mind-wandering may be adaptive. For example, after an incubation period filled with a trivial task promoting mind-wandering, individuals were better at conceiving unusual uses of common objects, as if mind-wandering favored the unconscious, unconstrained interaction of multiple, distant concepts typical of creative thinking (Baird et al., 2012). This advantage was not observed if during the incubation period participants rested, possibly because rest increases the tendency to think (consciously) about the terms of the problem, constraining excessively the content of thought.

Mind-wandering may have an internal origin (be self-initiated), but it can also be triggered by external cues (e.g., reading the word "experiment" leads to think to try and become a runner; e.g., McVay and Kane, 2013; Maillet et al., 2017; Vannucci et al., 2017). Once initiated, either because internally or externally cued, mind-wandering tends to unfold in a rather unconstrained fashion, with a peculiar phenomenology consisting—to say it with James (1890)—of birds' perchings and flights, with perchings being the discrete contents of thought on which memory retrieval converges (and attention focuses), and flights being the transitions of attention from one content to the next. How do we mind-wander? Which brain regions and dynamics govern the triggering of mind-wandering and its trajectories in the space of thoughts?

In the last decade, there has been an increasing interest in the cognitive and neural mechanisms of mind-wandering and other forms of spontaneous cognition, after the field had been dominated by the study of goal-directed cognition. Functional neuroimaging (fMRI) evidence indicates that mind-wandering is associated with activity in the "default network," a set of interconnected brain regions, including the medial temporal lobes (MTLs), ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex, and the angular gyrus, whose activity is enhanced during relatively passive states and internally focused thought (Buckner et al., 2008; Christoff et al., 2009; Smallwood et al., 2012; Fox et al., 2015). According to one prominent view, activity in the default network is related to the production of the mental contents populating mind-wandering, with separate subsystems mediating the memory-based construction of mental events and their self-relevant connotation (Andrews-Hanna et al., 2010). An alternative view, sprung from the observation that the default network is active during the unfocused monitoring of external events (Gilbert et al., 2006a), is that activity in this network does not necessarily reflect mind-wandering, but, more in general, the capture of attention by salient task-unrelated stimuli, which also includes external distractions (e.g., noises). This latter view

OPEN ACCESS

Edited by:
Silvia Savazzi,
University of Verona, Italy

Reviewed by:
Emiliano Macaluso,
Claude Bernard University Lyon 1,
France

Correspondence:
Elisa Ciaramelli
elisa.ciaramelli@unibo.it
Alessandro Treves
ale@sissa.it

Specialty section:
This article was submitted to
Consciousness Research,
a section of the journal
Frontiers in Psychology

Received: *29 November 2018*
Accepted: *08 January 2019*
Published: *23 January 2019*

Citation:
Ciaramelli E and Treves A (2019) A
Mind Free to Wander: Neural and
Computational Constraints on
Spontaneous Thought.
Front. Psychol. 10:39.
doi: 10.3389/fpsyg.2019.00039

relates to the "gateway hypothesis" of medial prefrontal cortex as implicated in orchestrating the allocation of attention between internal and external events, and its monitoring/awareness (Gilbert et al., 2006b). There is initial fMRI evidence, however, that medial prefrontal cortex is generally more engaged by mind-wandering than by external distractions, though different subregions of medial prefrontal cortex respond preferentially to different forms of distraction (Stawarczyk et al., 2011).

One important question is whether activity in key nodes of the brain default network is necessary for mind-wandering. Lesion studies can relate brain activity causally with behavior, and constrain the interpretation of the function of targeted brain regions in a way that is not possible with neuroimaging data alone. The results from two neuropsychological studies of mind-wandering in patients with bilateral damage in vmPFC vs. the hippocampus are initial evidence that these two regions play necessary but distinct roles in mind-wandering. Bertossi and Ciaramelli (2016) had vmPFC patients and brain-damaged and healthy controls perform various tasks varying in difficulty, hence conduciveness to mind-wandering. Across tasks, participants were occasionally probed to report whether their thoughts had been fully on-task or, to some extent, off-task, and about the contents of off-task thoughts. They found that vmPFC patients showed a reduced frequency of mind-wandering, and, when they did mind-wander, their thoughts were mostly about the present, never about the future. Interestingly, vmPFC damage did not change the frequency with which participants claimed they were unaware of the content of their off-task thoughts, suggesting it caused impaired construction, not meta-awareness, of mind-wandering contents (see also Bertossi et al., 2017). We are currently collecting indirect (physiological) indices of mind-wandering in vmPFC patients to clarify whether lack of meta-awareness contributed to reduced mind-wandering. McCormick et al. (2018b), on the other hand, examined mind-wandering in patients with hippocampal damage probing the contents of their thoughts over a 2-day period. They found that hippocampal patients reported mind-wandering as frequently as controls. However, off-task thoughts were context-rich (episodic) in healthy controls, but semanticized and mainly present-oriented in hippocampal patients. Although the designs of the two studies differs, the results suggest that vmPFC patients are impaired at decoupling from the external environment and initiating mind-wandering, whereas hippocampal patients do engage in mind-wandering, but have it devoid of episodic content. We tentatively proposed, therefore, that during mind-wandering (as well as voluntary event construction), vmPFC initiates the construction of events alternative to direct (perceptual) experience, by coordinating the activation of relevant schemata (e.g., the park where I run; Gilboa and Marlatte, 2017), which the hippocampus uses to build a rudimentary sketch of the event. vmPFC would then help fill the mental event by engaging in iterative retrieval and integration of schema-congruent elements via feedback loops with the hippocampus and neocortex (e.g., what typically happens when I run; see also Benoit et al., 2014; Moscovitch et al., 2016; McCormick et al., 2018a).

Yet, vmPFC patients may not be pervasively unable to mind-wander. Ciaramelli and Ghetti (2007) observed that in recognition memory tasks vmPFC patients tend to falsely recognize test (distractor) items because they make vivid but task-irrelevant associations during retrieval (e.g., I remember the word CUP because I bought a red cup in London). These vivid associations may in fact be instances of externally-triggered mind-wandering, and evidence that this form of mind-wandering is still possible following vmPFC damage, consistent with fMRI evidence (Stawarczyk et al., 2011). Similarly, in explicit memory tasks, vmPFC patients may fail to retrieve any memory, and then start confabulating floridly if probed (Moscovitch and Melo, 1997). Thus, vmPFC patients' mind-wandering and event construction seem to depend critically on the presence of external cues, whose availability determines striking qualitative changes in patients' behavior.

Another dissociation between vmPFC and hippocampal patients is worth mentioning here. Kurczek et al. (2015) investigated episodic remembering and future thinking in vmPFC vs. hippocampal patients by having them first produce past/future events and then select one moment from the event and describe it in detail. Individuals with MTLs damage were unable to describe such moments in detail, but vmPFC patients could. In another study, however, Bertossi et al. (2016) required vmPFC patients to construct entire past and future events, and found a striking impairment. These findings suggest that hippocampal patients are impaired in conjuring up even single scenes/moments from an event, while vmPFC patients may be impaired in constructing extended events (McCormick et al., 2018a). This dissociation, too, points to differences in the role of vmPFC and the hippocampus in the dynamic construction of the flow of thoughts, with the hippocampus contributing the discrete contents of events (the perchings) and vmPFC prescribing the appropriate transition between moments of the events (the flights). What is unclear is what allows vmPFC and the hippocampus to contribute to mind-wander differentially, whether their specialized internal organization or merely their sitting at the appropriate confluence of the relevant information streams. Characterizing the cortical dynamics of mind-wandering may be helped by combining behavioral studies in brain-lesioned patients with mathematically defined network models incorporating core principles of cortical organization. Comparing the functional contribution of vmPFC and the hippocampus acquires extra significance, given the contrast between the neocortical architecture of the former vs. the peculiar internal organization of the latter, centered on the unique characteristics of the dentate gyrus (Treves et al., 2008) and on the CA3-CA1 differentiation (Treves, 2004).

At a very general level, streams of thought may be conceived as trajectories among declarative memories. Mathematical models of memory storage and retrieval in the hippocampus, pioneered by Marr (1971) and later empowered by the analysis of the Hopfield model (Amit et al., 1987), conceive episodic memories as attractor states in the CA1 and CA3 regions of the hippocampus. While the intrinsic CA3 connectivity would enable the cued retrieval of temporally-defined scenes of arbitrary content, CA1 may allow for their limited temporal association, e.g., the concatenation of scenes within an episode (Kesner et al., 2002; Treves, 2004). Local recurrent connectivity within cortical

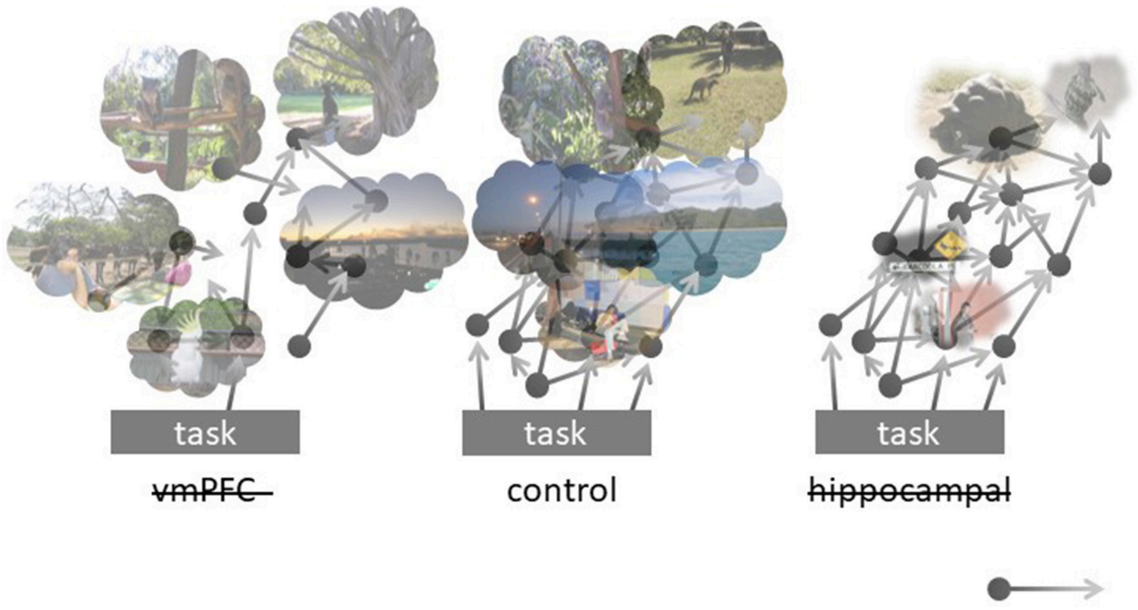


FIGURE 1 | Schematic representation of the model implemented in the Potts network, in its control **(center)**, vmPFC-lesioned **(left)**, and hippocampally-lesioned **(right)** versions. The black circles represent schemata, some of which are stored as continuous attractors in vmPFC, that often lead (arrows) to the activation of other schemata, in multiple interacting sequences. Ongoing activity in the cortex sometimes elicits the activation of memories in the hippocampus (clouds), boosting its contents with episodic details. Mind-wandering can be initiated by schemata activated by aspects of the current task or endogenously, or by the direct activation of episodic memories, particularly in vmPFC patients, in which the chain of continuous attractors is weakened. Hippocampal patients, on the other hand, experience rarer and weaker episodic boosting of their mind-wandering chains.

regions is thought to endow them, too, with attractor states, with contents specific to each region. The collection of local attractor networks can engage in "latching" dynamics, when in response to a cue the whole neocortex does not just settle into a single attractor (whether instantaneous like a snapshot or somewhat extended in time), but instead continues to hop from one attractor to the next (Treves, 2005). Mathematically defined "Potts" networks have been shown to undergo, depending on their parameters (e.g., number of units, number of states they are endowed with; Kang et al., 2017), phase transitions—abrupt changes in their dynamics—passing from a "no latching" region to a "finite latching" region, to an "infinite latching" region, in which latching dynamics go on spontaneously and indefinitely (Russo and Treves, 2012; Naim et al., 2018). Importantly, current work is analyzing how such spontaneous hopping may be supplemented by schemata stored in parts of the extended network, e.g., vmPFC.

Mind-wandering (as well as the conflation of memories in confabulation) is reminiscent of a latching process in which some of the transitions appear random, others rather more guided by local schemata. We propose that vmPFC participates in the mechanics of neocortical latching, facilitating congruent consecutive retrieval of stored memories, while their content is boosted by the hippocampus. vmPFC-mediated transitions between contents of thought would occur through the instantiation of specific local schemata (see Gilboa and Marlatte, 2017, for a review). Mathematizing the psychological concept, a "schema" may be conceived as the association of attractor state *k* in local network *i* with the subsequent attractor state *l* in local network *j*, an association extracted over multiple similar occurrences (Gilboa and Marlatte, 2017). If σ_i^k denotes the activation of attractor *k* in network *i*, the schema could be instantiated in a Potts network by adding to its "free-energy" function a term proportional to $\sigma_i^k \cdot \sigma_j^l$, which would cause substantial interference among memories. The latching Potts network, however, naturally envisages additional ramping variables θ_i^k, which parametrize how long a temporally extended attractor σ_i^k has been activated. A free-energy term proportional to $\theta_i^k \cdot \sigma_j^l$ facilitates schema-guided transitions, in relation to the contents represented by local networks *i* and *j* (for example, in vmPFC, or in Broca's area), while the remaining content may be stationary, or undergo spontaneous transitions, or be guided by other schemata. On the other hand, a Potts model connected with a hippocampal model may utilize it as an "episodic content booster," reinvigorating streams of thoughts in the cortex, and is expected to show saltatory characteristics, in that hippocampal output representations would be activated not too frequently relative to the sequence of neocortical states.

Despite many open issues requiring detailed model analysis, we expect it to support our view that the hippocampus fuels voluntary as well as spontaneous cognition with detail-rich scenes/snapshots, whereas vmPFC (among areas storing specific schemata) governs appropriate latching across memory attractors to form extended events. Our model and related predictions are portrayed in **Figure 1**. In healthy controls, attention shifts from an ongoing task inward, toward mentally constructed experiences. These flow, guided by relevant schemata and boosted by context-rich hippocampal memories. A lesion to the hippocampal component is expected to result in reduced episodic content boosts, with preserved schema-driven transitions: the flow of thoughts now "browses" on context-poor items/moments. Conversely, a lesion to vmPFC is expected to disarticulate mind-wandering, leaving it over-dependent on the hippocampal content booster: ephemeral, inconsequential mind-wandering is now triggered by the infrequent hippocampal output and poorly assisted by schema-guided construction processes.

Future neuropsychological studies and computational analyses will help test and refine the model and clarify the role of vmPFC vs. the hippocampus in the dynamics of mind-wandering. For example, if vmPFC is necessary to initiate and maintain mind-wandering endogenously, vmPFC lesions should lead to reduced mind-wandering when no cue is provided or no strong memory attractor is probed (due to weak schema-assisted latching), but preserve mind-wandering if externally cued, especially in response to highly imaginable words or strong words probing schemas (e.g., the self, one's own goals), which both act as strong retrieval cues (McVay and Kane, 2013; Vannucci et al., 2017). With hippocampal lesions, external cues are expected to be less beneficial. Another prediction pertains to the temporal trajectory and content of mind-wandering following an external trigger. In patients/networks with vmPFC lesions, mind-wandering is expected to be largely limited to short delays after the external cue (weak latching), and to often depart from the schema probed by the cue, to reflect diverse hippocampal output. Conversely, in patients/networks with hippocampal lesions, mind-wandering should be more long-lasting but more constrained in content to schema-instructed latching dynamics.

Observing a phase-dependent behavior as in a Potts network (endowed with a hippocampal content booster) would substantially improve our understanding of the role of vmPFC in the schema-driven temporal development of mind-wandering and constructed experience. An abnormal balance between spontaneous and schema-guided latching dynamics may account for the somewhat paradoxical behaviors of vmPFC patients, who range, depending on the experimental condition, from being unable to retrieve any memory or engage in mind-wandering to floridly confabulate and make off-task associations (Moscovitch and Melo, 1997; Ciaramelli and Ghetti, 2007; Bertossi and Ciaramelli, 2016). Understanding the model may also facilitate clinical applications. Previous attempts to reduce confabulation have reinforced retrieval goals (Ciaramelli, 2008) or muffled the cognitive resources available for task-irrelevant associations (Ciaramelli et al., 2009). In hindsight, we were acting on parameters of a Potts network—what we can now do explicitly, to study, and hopefully manage thought-flow impairments.

AUTHOR CONTRIBUTIONS

EC and AT conceived, wrote, and provided approval for publication of this work.

ACKNOWLEDGMENTS

Partial support from Human Frontier Research Grant RGP0057/2016 and discussions with the partners in that collaboration and in the M-GATE network are gratefully acknowledged.

REFERENCES

Amit, D. J., Gutfreund, H., and Sompolinsky, H. (1987). Statistical mechanics of neural networks near saturation. *Ann. Phys.* 173, 30–67. doi: 10.1016/0003-4916(87)90092-3

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., and Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron* 65, 550–562. doi: 10.1016/j.neuron.2010.02.005

Antrobus, J. S., Singer, J. L., and Greenberg, S. (1966). Studies in the stream of consciousness: experimental enhancement and suppression of spontaneous cognitive processes. *Percept. Mot. Skills* 23, 399–417. doi: 10.2466/pms.1966.23.2.399

Baird, B., Smallwood, J., Mrazek, M. D., Kam, J. W., Franklin, M. S., and Schooler, J. W. (2012). Inspired by distraction: mind wandering facilitates creative incubation. *Psych. Sci.* 23, 1117–1122. doi: 10.1177/0956797612446024

Benoit, R. G., Szpunar, K. K., and Schacter, D. L. (2014). Ventromedial prefrontal cortex supports affective future simulation by integrating distributed knowledge. *Proc Natl. Acad. Sci. U.S.A.* 111, 16550–16555. doi: 10.1073/pnas.1419274111

Bertossi, E., and Ciaramelli, E. (2016). Ventromedial prefrontal damage reduces mind-wandering and biases its temporal focus. *Soc. Cogn. Affect. Neurosci.* 11, 1783–1791. doi: 10.1093/scan/nsw099

Bertossi, E., Peccenini, L., Solmi, A., Avenanti, A., and Ciaramelli, E. (2017). Transcranial direct current stimulation of the medial prefrontal cortex dampens mind-wandering in men. *Sci. Rep.* 7:16962. doi: 10.1038/s41598-017-17267-4

Bertossi, E., Tesini, C., Cappelli, A., and Ciaramelli, E. (2016).Ventromedial prefrontal damage causes a pervasive impairment of episodic memory and future thinking. *Neuropsychologia* 81, 107–116. doi: 10.1016/j.neuropsychologia.2015.12.015

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi: 10.1196/annals.1440.011

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., and Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc. Natl. Acad. Sci. U.S.A.* 106, 8719–8724. doi: 10.1073/pnas.0900234106

Christoff, K., Irving, Z. C., Fox, K. C., Spreng, R. N., and Andrews-Hanna, J. R. (2016). Mind-wandering as spontaneous thought: a dynamic framework. *Nat. Rev. Neurosci.* 17, 718–731. doi: 10.1038/nrn.2016.113

Ciaramelli, E. (2008). The role of ventromedial prefrontal cortex in navigation: a case of impaired wayfinding and rehabilitation. *Neuropsychologia* 46, 2099–2105. doi: 10.1016/j.neuropsychologia.2007.11.029

Ciaramelli, E., and Ghetti, S. (2007). What are confabulators' memories made of? A study of subjective and objective measures of recollection in confabulation. *Neuropsychologia* 45, 1489–1500. doi: 10.1016/j.neuropsychologia.2006.11.007

Ciaramelli, E., Ghetti, S., and Borsotti, M. (2009). Divided attention during retrieval suppresses false recognition in confabulation. *Cortex* 45, 141–153. doi: 10.1016/j.cortex.2007.10.006

Fox, K. C., Spreng, R. N., Ellamil, M., Andrews-Hanna, J. R., and Christoff, K. (2015). The wandering brain: meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. *Neuroimage* 111, 611–621. doi: 10.1016/j.neuroimage.2015.02.039

Gilbert, S. J., Simons, J. S., Frith, C. D., and Burgess, P. W. (2006a). Performance-related activity in medial rostral prefrontal cortex (area 10) during low-demand tasks. *J. Exp. Psychol. Hum. Percept. Perform*. 32, 45–58. doi: 10.1037/0096-1523.32.1.45

Gilbert, S. J., Spengler, S., Simons, J. S., Steele, J. D., Lawrie, S. M., Frith, C. D., et al. (2006b). Functional specialization within rostral prefrontal cortex (area 10): a metaanalysis. *J. Cogn. Neurosci.* 18, 932–948. doi: 10.1162/jocn.2006.18.6.932

Gilboa, A., and Marlatte, H. (2017). Neurobiology of Schemas and Schema-mediated memory. *Trends Cogn. Sci*. 21, 618–631. doi: 10.1016/j.tics.2017.04.013

James, W. (1890). *The Principles of Psychology*. New York, NY: Henry Holt and Company.

Kang, C. J., Naim, M., Boboeva, V., and Treves, A. (2017). Life on the edge: latching dynamics in a potts neural network. *Entropy* 19:468. doi: 10.3390/e19090468

Kesner, R. P., Gilbert, P. E., and Lee, I. (2002). "Subregional analysis of hippocampal function in the rat," in *Neuropsychologyof Memory. 3rd Edn*, eds L. R. Squire and D. L. Schacter (New York, NY: Guilford Press), 395–411.

Killingsworth, M. A., and Gilbert, D. T. (2010). A wandering mind is an unhappy mind. *Science* 330:932. doi: 10.1126/science.1192439

Kurczek, J., Wechsler, E., Ahuja, S., Jensen, U., Cohen, N. J., Tranel, D., et al. (2015). Differential contributions of hippocampus and medial prefrontal cortex to self-projection and self-referential processing. *Neuropsychologia* 73, 116–126. doi: 10.1016/j.neuropsychologia.2015.05.002

Maillet, D., Seli, P., and Schacter, D. L. (2017). Mind-wandering and task stimuli: stimulus-dependent thoughts influence performance on memory tasks and are more often past- versus future-oriented. *Conscious Cogn*. 52, 55–67. doi: 10.1016/j.concog.2017.04.014

Marr, D. (1971). Simple memory: a theory of archicortex'. *Phil. Trans. B* 370:1666.

McCormick, C., Ciaramelli, E., De Luca, F., and Maguire, E. A. (2018a). Comparing and contrasting the cognitive effects of hippocampal and ventromedial prefrontal cortex damage: a review of human lesion studies. *Neuroscience* 374, 295–318. doi: 10.1016/j.neuroscience.2017.07.066

McCormick, C., Rosenthal, C. R., Miller, T. D., and Maguire, E. A. (2018b). Mindwandering in people with hippocampal damage. *J. Neurosci*. 38, 2745–2754. doi: 10.1523/JNEUROSCI.1812-17.2018

McVay, M. Jc., and Kane, M. J. (2013). Dispatching the wandering mind? Toward a laboratory method for cuing "spontaneous" off-task thought. *Front. Psychol.* 4:570. doi: 10.3389/fpsyg.2013.00570

Moscovitch, M., Cabeza, R., Winocur, G., and Nadel, L. (2016). Episodic memory and beyond: the hippocampus and neocortex in transformation. *Annu. Rev. Psychol*. 67, 105–134. doi: 10.1146/annurev-psych-113011-143733

Moscovitch, M., and Melo, B. (1997). Strategic retrieval and the frontal lobes: evidence from confabulation and amnesia. *Neuropsychologia* 35, 1017–1034. doi: 10.1016/S0028-3932(97)00028-6

Naim, M., Boboeva, V., Kang, C. J., and Treves, A. (2018). Reducing a cortical network to a Potts model yields storage capacity estimates. *J. Stat. Mech*. 2018:043304. doi: 10.1088/1742-5468/aab683

Russo, E., and Treves, A. (2012). Cortical free-association dynamics: distinct phases of a latching network. *Phys. Rev. E* 85:051920. doi: 10.1103/PhysRevE.85.051920

Smallwood, J., Brown, K., Baird, B., and Schooler, J. W. (2012). Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. *Brain Res.* 1428, 60–70. doi: 10.1016/j.brainres.2011.03.072

Smallwood, J., and Schooler, J. W. (2015). The science of mind wandering: empirically navigating the stream of consciousness. *Annu. Rev.Psychol*. 66, 487–518. doi: 10.1146/annurev-psych-010814-015331

Stawarczyk, D., Majerus, S., Maquet, P., and D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PLoS ONE* 6:e16997. doi: 10.1371/journal.pone.0016997

Treves, A. (2004). Computational constraints between retrieving the past and predicting the future, and the CA3-CA1 differentiation. *Hippocampus* 14, 539–556. doi: 10.1002/hipo.10187

Treves, A. (2005). Frontal latching networks: a possible neural basis for infinite recursion. *Cogn. Neuropsychol.* 22, 276–291. doi: 10.1080/02643290442000329

Treves, A., Tashiro, A., Witter, M. P., and Moser, E. I. (2008). What is the mammalian dentate gyrus good for? *Neuroscience* 154, 1155–1172. doi: 10.1016/j.neuroscience.2008.04.073

Vannucci, M., Pelagatti, C., and Marchetti, I. (2017). Manipulating cues in mind wandering: verbal cues affect the frequency and the temporal focus of mind wandering. *Conscious Cogn*. 53, 61–69. doi: 10.1016/j.concog.2017.06.004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

OPINION
published: 21 December 2018
doi: 10.3389/fpsyg.2018.02606

The Neuropsychology of Feature Binding and Conscious Perception

*Barbara Treccani**

Department of Psychology and Cognitive Science, University of Trento, Trento, Italy

Keywords: consciousness, spatial coding, feature integration, binding, neuropsychology, unilateral neglect, Balint's syndrome, blindsight

No possible discussion about consciousness and neuropsychology can be made without acknowledging the contribution of the recently deceased, worldwide known cognitive psychologist Anne Treisman. Her renowned feature integration theory (FIT; Treisman and Gelade, 1980) has inspired a huge number of studies about the relationship between attentional processes, perception, and consciousness, both in conditions where such processes were intact and in conditions where they were impaired following brain damage. Actually, this theory has also shown some critical limitations (Humphreys, 2016). My aim in this paper is to highlight that, despite such limitations, FIT may still be a powerful interpretative framework for major phenomena related to loss of conscious perception in brain-damaged patients. In particular, I will argue that the core mechanisms of this theory (i.e., spatial attention, object spatial coding and feature binding) are critically involved in visual conscious experience. Neuropsychological evidence challenging such an involvement may just actually contribute to understand better the role of these mechanisms in conscious perception.

According to the original version of FIT, individual (basic) features of an object can be processed pre-attentively and independent of their location, but they are bound together by means of spatial attention, thanks to the fact that they occupy the same location. For example, the blue color and the orientation of the contours defining the shape of a triangular geometric figure presented in a given spatial position are first processed separately but, once this spatial position is selected by attention, these individual features are integrated to form an unitary object (i.e., a blue triangle is perceived). Individual object features can be processed implicitly, but only bound object features can access consciousness.

This is consistent with the commonly held idea that a special relation exists between space and consciousness (Campbell, 2002). Undeniably, while we can imagine, e.g., colorless objects, it is hard to represent to ourselves spaceless objects. Contents of consciousness would be inherently and necessarily "situated" (Searle, 1992): it would not be logically possible to know consciously an object without perceiving it as occupying a place in which it exists.

Such an idea implies that space is a prerequisite and predecessor of conscious awareness: the encoding of stimulus location would be a necessary condition for it to enter consciousness (cf., Driver and Vuilleumier, 2001). Aside from being intuitively compelling, this notion is also plausible from an evolutionary point of view. Indeed, spatial features are among the first characteristics of objects to be discriminated both from an ontogenetic and phylogenetic perspective (cf., e.g., Xu, 1999). Moreover, this idea appears to be fully consistent with a number of neuropsychological reports concerning the effect of human brain lesions on conscious processing.

Lesions of the human brain can produce relatively isolated visual deficits, which may or may not be accompanied by an impairment of stimulus awareness. Data show some clear consistencies that, since the original formulation of FIT, have been seen as fitting nicely the idea of a special role of spatial coding and feature binding in stimulus conscious perception (cf., Robertson, 2003). Several neuropsychological conditions have been indeed interpreted based on such an idea and in the context of this theory (see **Table 1** for a schematic overview).

Edited by:
Silvia Savazzi,
Università degli Studi di Verona, Italy

Reviewed by:
Chiara Mazzi,
Università degli Studi di Verona, Italy
Mario Bonato,
Università degli Studi di Padova, Italy

***Correspondence:**
Barbara Treccani
barbara.treccani@unitn.it

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: *29 September 2018*
Accepted: *04 December 2018*
Published: *21 December 2018*

Citation:
Treccani B (2018) The Neuropsychology of Feature Binding and Conscious Perception. Front. Psychol. 9:2606. doi: 10.3389/fpsyg.2018.02606

TABLE 1 | Schematic overview of how, according to the original version of FIT (Treisman and Gelade, 1980), dissociations between the processing of spatial and content (non-spatial) features of visual stimuli observed in some (emblematic) neuropsychological conditions may account for the loss of conscious perception of these stimuli.

Neuropsychological syndrome/symptom	Content features processing	Spatial features processing	Feature binding	Conscious perception
Disorders of visual gnosis limited to one specific content feature	All except one (e.g., color)			
e.g., Achromatopsia	+	+	+	+
Cortical blindness				
Blindsight	−	+	−	−
Balint's syndrome				
Simultanagnosia	+	−	−	−
Illusory conjunctions	+	−	×	+
Unilateral neglect				
Contralesional omissions	+	−	−	−
Allochiria	+	×	+	+

Following FIT, stimulus awareness, or the lack of it, observed in these conditions may be traced back to whether these features can be bound together to form integrated percepts (cf., e.g., Làdavas et al., 2000; Deouell, 2002; Robertson, 2003, 2004). See text for a description of recent findings (e.g., evidence of implicit content feature processing in blindsight patients) that question such a view. +, unimpaired (proper); −, impaired (absent); ×, impaired (improper).

The visual deficit caused by a brain lesion can involve a specific class of stimulus attributes or be even limited to one attribute, which can be a spatial (e.g., stimulus location) or content feature of the stimulus, and concern the shape of the stimulus or its surface properties (e.g., stimulus color). Cerebral achromatopsia (i.e., acquired color blindness caused by localized brain damage) is one of the most cited examples of the category of disorders in which the deficit involves only the processing of one surface feature. Following FIT, binding of features other than color can occur, given that all the other (spatial and content) features of the object are correctly analyzed, and spatial attention can be directed toward the object location. Accordingly, not only are the patients aware of the presence of the object, but they are also aware of all its proprieties (shape, fine details, depth, etc.), with the exception of color.

Different is the case when the impairment involves the processing of stimulus spatial features. According to FIT, indeed, losing the ability to represent the location of an object would also involve the loss of consciousness of other properties of this object, and possibly of the object itself, being the spatial representation of objects the medium for binding their features. Friedman-Hill et al. (1995) described data from a patient (R.M.) with bilateral parietal-occipital lesions and a diagnosis of Balint's syndrome, who has been often presented as one of the most severe examples of loss of space perception observed in neuropsychology (Robertson, 2012). R.M., as other Balint patients, showed simultanagnosia, that is, lack of awareness of visual objects, except for one object at a time. Furthermore, he frequently combined features of different objects into the reported one (e.g., when presented with a yellow square and a blue triangle, he might report to see a yellow triangle). He was not able to report where objects were located, even when he stared at them, whereas he showed relatively intact content feature processing. Search for a target defined by one single visual feature was somewhat spared, whereas he found it very difficult to search for the conjunction of two visual features (Robertson et al., 1997). These findings are all consistent with FIT and can be accounted for by R.M.'s inadequate spatial representation of visual stimuli. Without a correct spatial representation of an object's position, allocation of attention to this position would not be possible, and accurate binding would also be hampered. Unbound features cannot be consciously perceived. Yet, in these conditions, object features might be bound incorrectly, resulting in misconjunctions that, albeit not being veridical but illusory, can access consciousness.

A similar reasoning has been used to account for another neuropsychological syndrome, which frequently follows right hemisphere parietal damage, that is, unilateral neglect (UN). In this case too, there would be spatial loss, which, however, would be limited to one side of space (Robertson, 2004).

UN is characterized by the patient's failure to orient attention toward the side of space contralateral to the lesion (Cubelli, 2017). According to one of the most known accounts of UN, this attentional deficit would precisely result from a defective spatial representation of the contralesional hemispace (Bisiach, 1993): attention would not be orientated toward locations that patients are not able to represent. Although UN patients are often unware of contralesional stimuli, several patients have now been documented who show to be able to process implicitly the color, shape, identity, and even meaning of symbols, words, and pictures presented in the affected hemispace (e.g., Làdavas et al., 1993). To account for this surprising dissociation, it has been proposed that the impaired spatial representation of contralesional stimuli is what prevent the other stimulus features, which would be fully and adequately processed, from entering consciousness (Berti and Rizzolatti, 1992; Berti et al., 2015). Consistent with FIT, the lack of spatial coding of contralesional objects would prevent attention from being oriented toward them, thus also preventing the binding of their features and their access to consciousness (Deouell, 2002).

Some UN patients show a phenomenon known as allochiria[1] (i.e., the tendency to perceive stimuli presented on the

---

[1] Allochiria is usually observed in association e with unilateral neglect (UN), and it is indeed prominent in some UN patients (Robertson, 2004). However, it has also been described in patients who do not show any signs of UN (Venneri et al., 2012).

contralesional side of the body or space as on the ipsilesional side), which would also be in line with this view: allochiria would suggest that when a spatial code, albeit inaccurate, is attributed to contralesional stimuli (i.e., they are coded as presented on the ipsilesional side), their features can be bound together and they can enter consciousness. Provided that the representation of constituent features is intact, spatial coding would enable conscious perception (cf., Làdavas et al., 2000; Deouell, 2002).

Yet, mere stimulus spatial coding, without constituent feature processing, would not result in stimulus awareness according to FIT. Indeed, just as it is difficult to represent objects without space, it is hard to imagine conscious experiences of "locations without content" (Paillard et al., 1983). It is precisely from this perspective that some authors have interpreted the lack of stimulus awareness shown by patients with damage to the primary visual cortex (V1) who prove to be able to localize visual stimuli that they deny seeing (i.e., the so-called phenomenon of blindsight; Cowey, 2010). Blindsight in cortically blind patients and implicit processing in UN patients have been often compared with each other, and described as diametrically opposed phenomena (e.g., Làdavas et al., 2000). The former would result from the relatively intact functioning of the spatial coding system, in the face of a severe impairment of the system that analyzes object constituent features, whereas the latter would result from the opposite dissociation. In both cases, no conscious awareness of the stimulus would emerge because only bound objects can be consciously perceived: in UN, the spatial deficit would prevent feature binding, whereas, in the case of blindsight, there would be nothing to bind.

FIT has provided a useful framework within which to interpret the dissociations between impaired and preserved cognitive processing of different stimulus features observed in many neuropsychological syndromes and their relation with conscious perception. In the 39 years since the original formulation of this theory, however, data from both neurologically intact participants and brain-damaged patients have been produced that show important limitations of FIT (cf., Humphreys, 2016). In particular, several neuropsychological patients have been described who proved to be able to process implicitly much more, and more complex, stimulus properties than previously thought, making it clear that lack of stimulus visual awareness cannot be traced back to lack of processing of one specific aspect of visual stimuli.

For example, some cortically blind patients have been shown to be able, not only to localize implicitly visual stimuli presented in the blind part of the visual field, but also to *discriminate* such stimuli according to either form or surface features (Cowey, 2010). For these patients too, therefore, locations might have a content. Nevertheless, patients might remain unaware of the stimuli they are able to discriminate.

Likewise (and conversely), both Balint and UN patients have been shown to process implicitly many different spatial properties of stimuli. Indeed, spared implicit spatial processing in these patients, in spite of the severe explicit spatial deficit, can be simply inferred from the previously mentioned effects on performance of complex stimuli, such as words and pictures, of which patients are not aware. In order for the identity or meaning of such stimuli to affect performance, the spatial relations between lines, angles and other elements defining their shapes must be necessarily analyzed. Some evidence of spatial coding in the neglected hemispace of UN patients also comes from allochiria. Misallocations of contralesional stimuli in allochiria usually occur to homologous locations on the ipsilesional side (Bisiach, 1993), which suggests that the stimulus position within the contralesional hemispace is accurately represented. These findings, however, can still be accounted for by both FIT and the spatial-deficit accounts of UN and Balint syndromes: there is growing evidence that the brain utilizes multiple spatial maps (Bisiach and Vallar, 2000) and it has been proposed that parietal damage (whether it is bilateral, as in Balint syndrome, or unilateral, as in UN) does not result in the impairment of spatial maps sub-serving the analysis and representation of the structure of objects, or the position of the stimulus with reference to other objects laying in the same hemispace (cf., Robertson, 2004). Such maps may depend on the activity of spared areas of the brain and work outside awareness. In contrast, the spatial deficit in these syndromes may specifically involve spatial coordinates that relies on the viewer position (e.g, the attribution of a "left" or "right" code to stimuli with reference to ego-centric spatial axes, such as the body midline), which would be the master reference frames for the guidance of attention, and, consequently, underlie feature binding processes that can bring objects to awareness (see Robertson, 2004, for the idea that both space-based and object-based attention can be trace back to a single system of hierarchical spatial frames centered on the viewer's body and its parts).

Yet, Balint and UN patients have also been shown to process implicitly the location of stimuli according to these very ego-centered spatial reference frames (Robertson, 2004). For example, Treccani et al. (2012) tested a UN patient with a unilateral flanker task and found that, even though the patient was unaware of the stimulus flanking the central target, reaction times to the target color were influenced by both the color of the flanker and its left vs. right position with respect to the patient's body midline. Similar results have been obtained with Balint patients (cf., Robertson, 2004, 2012). Such findings clearly show that spatial coding of visual stimuli is not sufficient to let them enter consciousness even when content features of these stimuli are properly processed: the spatial, as well as non-spatial, features of stimuli can be processed and, still, these stimuli may remain at an unconscious level (e.g., Treccani et al., 2012). Therefore, the lack of awareness of a stimulus whose spatial structure and content features are adequately encoded cannot be simply traced back to the lack of the representation of its position (cf., Berti and Rizzolatti, 1992; Deouell, 2002).

These findings, albeit being inconsistent with spatial-deficit accounts of UN and Balint syndromes, are reconcilable with FIT. Indeed, in the light of this evidence, it has been proposed that the lack of stimulus awareness after brain damage may depend not so much on inadequate feature binding resulting from the impairment of either spatial or nonspatial feature processing, but on a deficit of the binding process itself (Treccani et al., 2012; see also, e.g., Van Vleet and DeGutis, 2013).

However, what is also clear from the available evidence of implicit processing in brain-damage patients is that some types of feature binding can occur without awareness and without the results of the binding process entering consciousness at all. In particular, implicit binding in the form domain (i.e., binding processes underlying the representation of visual shapes) has been shown to occur after either bilateral or unilateral parietal damage (i.e., in Balint or UN patients; Humphreys, 2016) and in cortically blind patients (e.g., Trevethan et al., 2007; Celeghin et al., 2015): even though patients may remain unware of the presented stimuli (e.g., stimuli presented in the neglected or blind field) they may show intact ability of integrating objects' parts into wholes and binding visual primitives (i.e., lines and angles) defining object shapes, as well as completing figures which partially fall within the affected part of the visual field and grouping elements belonging to the same perceptual unit according to Gestalt principles of perceptual organization (e.g., proximity, similarity).

The occurrence of implicit feature binding in brain-damaged patients may be seen as the final blow to the idea of feature binding as the underlying mechanism of object conscious experience, and may lead to the conclusion that binding does not play a major role (or, even, any role at all) in conscious perception. Yet, accumulating evidence strongly suggests that there is not a single feature binding mechanism, as originally proposed by FIT, but several mechanisms, which may vary in their dependence on both attention and conscious processing (Humphreys, 2016).

Indeed, in the most current versions of FIT (Treisman, 2006), attention is not anymore supposed to be the mechanism of binding *per se*, and it is not thought to be necessary for binding to occur either (see also Robertson, 2012; Humphreys, 2016). Pre-attentive (bottom-up) binding of features can occur thanks to processes (i.e., coding of features conjunctions in single neurons and synchronized firing of separate neurons coding different features) that take place in cortical regions involved in early steps of visual analysis (as early as V1; e.g., Seymour et al., 2010). Such types of bindings might therefore not be consciously processed. Attention-related (top-down) activation, from posterior parietal cortex, may instead have a crucial role in selecting (Treisman, 2006; Robertson, 2012) or confirming (Humphreys, 2016) certain bottom-up bindings, which would then be enabled to enter consciousness.

In particular, attention and conscious processing might not be critically involved in binding content features that have learned, rather than arbitrary, relationships (i.e., they have usually experienced together) or that share local Gestalt properties (cf., Humphreys, 2016). In these cases, correct bottom-up bindings may take place without the intervention of attention (learned feature conjunctions and Gestalt cues can guide the binding process; Humphreys, 2016) and without them entering consciousness. This would indeed account for the intact implicit binding processes underlying shape representation (e.g., binding of objects' parts) observed in UN, Balint and cortically blind patients. In contrast, attention might be crucial in integrating content features from different domains (e.g., shapes with surface features such as colors), especially when feature pairings are arbitrary and correct feature binding cannot be based on stored knowledge (Humphreys, 2016). In this case, critical confirmation of bottom-up bindings from attentive processes is needed. Most researchers in this field agree that this also provides for (i.e., requires or results in) an explicit representation of space: there is no evidence of this kind of (different-domain) bindings when there is no awareness of the position from which the to-be-bound features come from (Robertson, 2004, 2012; Humphreys, 2016).

Indeed, space might play a major role in the confirmation process: the features of an object have to be bound to its location in order to verify which features or combinations of features are presented in that location. Accordingly, I propose that it is specifically this kind of content-feature-to-location binding that requires the direct intervention of attention and that enables stimulus awareness. Spatial representations of objects (i.e., the generation of spatial codes pointing to the positions where objects have been presented) and the representation of their content features may not be sufficient to bring them into awareness, however space provides the medium for the action of attention, which, binding content features to their location, would allow conjunctions of these features to be confirmed and to be consciously experienced. Such an account would reconcile the findings of intact *implicit* spatial and binding processes in brain-damaged patients with the similarly compelling evidence of a major involvement of spatial and binding processing in conscious perception (cf., Robertson, 2004, 2012).

Consistent with the idea of a critical role of attention in binding spatial and content features, in the (previously mentioned) unilateral flanker task administered by Treccani et al. (2012), additive, rather than interactive, effects of flanker color and position were observed when the flanker was presented in the contralesional, neglected hemispace, contrary to what observed both in the patient's attended hemispace and with normal perceivers (Treccani et al., 2009). As shown by previous studies, the interaction between the effects of two flanker features critically depends on the fact that such features are perceived as belonging to the same object. These findings thus suggest that, without attention, spatial and non-spatial attributes of an object can be both coded, but as separate features (i.e., as they were conveyed by two different objects): an object's spatial code might be generated, but it would not be bound to the content features of the object to which it refers.

This idea is also consistent with other (above-mentioned) phenomena related to attentional deficits that may follow parietal damage: when content features are not tightly bound to the representation of their locations, because of a damage to the attentional mechanisms subtending this binding process, false conjunctions of features of different objects (e.g., in Balint patients) or allochiric misallocation of objects toward the focus of attention (e.g., in UN patients) can occur. Accordingly, an increased number of allochiric misallocations in UN patients has been observed when the availability of patients' attentional resources were further reduced by increasing the attentional load, that is, under dual-task (vs. single-task) conditions (Bonato and Cutini, 2016).

In conclusion, the lesson so far from neuropsychology is that, even though stimulus awareness, spatial coding and feature binding might not be connected by the close causal link originally posited by FIT, binding plays an important role in conscious experience. Consciousness does not seem to result necessarily from either stimulus spatial coding, even when it occurs along with a proper processing of stimulus content features (Treccani et al., 2012), or integration of stimulus features in the form domain (Humphreys, 2016). However, there is more than one cue that some types of feature bindings, in particular the binding of content features of objects to their location in order to form integrated and "situated" percepts, might be necessary conditions for conscious perception to occur. Neuropsychological research has still plenty to say in this regard and may help to clarify whether or not content-feature-to-location binding is sufficient to bring objects to awareness, that is, whether it really is the key mechanism that triggers conscious perception.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

Berti, A., Garbarini, F., and Neppi-Modona, M. (2015). "Disorders of higher cortical function," in *Neurobiology of Brain Disorders,* eds M. J. Zigmond, L. P. Rowland, and J. T. Coyle (Amsterdam: Elsevier Academic Press), 526–540.

Berti, A., and Rizzolatti, G. (1992). Visual processing without awareness: evidence from unilateral neglect. *J. Cogn. Neurosci.* 4, 345–351. doi: 10.1162/jocn.1992.4.4.345

Bisiach, E. (1993). Mental representation in unilateral neglect and related disorders: the twentieth Bartlett memorial lecture. *Q. J. Exp. Psychol.* 46, 435–461. doi: 10.1080/14640749308401056

Bisiach, E., and Vallar, G. (2000). "Unilateral neglect in humans," in *Handbook of Neuropsychology,* Vol. 1, eds F Boller, J. Grafman, and G. Rizzolatti (Amsterdam: Elsevier), 459–502.

Bonato, M., and Cutini, S. (2016). Increased attentional load moves the left to the right. *J. Clin. Exp. Neuropsychol.* 38,158–170. doi: 10.1080/13803395.2015.1091065

Campbell, J. (2002). *Reference and Consciousness.* Oxford, UK: Clarendon Press.

Celeghin, A., Savazzi, S., Barabas, M., Bendini, M., and Marzi, C. A. (2015). Blindsight is sensitive to stimulus numerosity and configuration: evidence from the redundant signal effect. *Exp Brain Res.* 233, 1617–1623. doi: 10.1007/s00221-015-4236-6

Cowey, A. (2010). The blindsight saga. *Exp. Brain Res.* 200, 3–24. doi: 10.1007/s00221-009-1914-2

Cubelli, R. (2017). Definition: spatial neglect. *Cortex* 92, 320–321. doi: 10.1016/j.cortex.2017.03.021

Deouell, L. Y. (2002). Pre-requisites for conscious awareness: clues from electrophysiological and behavioural studies of unilateral neglect patients. *Conscious. Cogn.* 11, 546–567. doi: 10.1016/S1053-8100(02)00024-7

Driver, J., and Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition* 79, 39–88.

Friedman-Hill, S., Robertson, L. C., and Treisman, A. (1995). Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions. *Science* 269, 853–855. doi: 10.1126/science.7638604

Humphreys, G. W. (2016). Feature confirmation in object perception: feature integration theory 26 years on from the Treisman Bartlett lecture. *Q. J. Exp. Psychol.* 69, 1910–1940. doi: 10.1080/17470218.2014.988736

Làdavas, E., Berti, A., and Farnè, A. (2000). "Dissociation between conscious and non-conscious processing in neglect," in *Beyond Dissociation: Interaction Between Dissociated Implicit and Explicit Processing*, eds Y. Rossetti and A. Revounsuo (Philadelphia, PA: John Benjamins), 175–193.

Làdavas, E., Paladini, R., and Cubelli, R. (1993). Implicit associative priming in a patient with left visual neglect. *Neuropsychologia* 31, 1307–1320. doi: 10.1016/0028-3932(93)90100-E

Paillard, J., Michel, F., and Stelmach, G. (1983). Localization without content. A tactile analogue of "blind sight." *Arch. Neurol.* 40, 548–551.

Robertson, L.C. (2004). *Space, Objects, Minds and Brains*. New York, NY: Psychology Press; Essays in Cognitive Science.

Robertson, L. C. (2003). Binding, spatial attention and perceptual awareness. *Nat. Rev. Neurosci.* 4, 93–102. doi: 10.1038/nrn1030

Robertson, L. C. (2012). "Spatial deficits and feature integration theory," in *Oxford Series in Visual Cognition. From Perception to Consciousness: Searching With Anne Treisman,* eds J. Wolfe and L. Robertson (New York, NY: Oxford University Press), 318–323.

Robertson, L. C., Treisman, A., Friedman-Hill, S., and Grabowecky, M. (1997). The interaction of spatial and object pathways: evidence from Balint's syndrome. *J. Cogn. Neurosci.* 9, 295–317.

Searle, J. R. (1992). *The Rediscovery of the Mind*. Cambridge, MA: MIT Press.

Seymour, K., Clifford, C. W., Logothetis, N. K., and Bartels, A. (2010). Coding and binding of color and form in visual cortex. *Cereb. Cortex* 20, 1946–1954. doi: 10.1093/cercor/bhp265

Treccani, B., Cubelli, R., Della Sala, S., and Umiltà, C. (2009). Flanker and Simon effects interact at the response selection stage. *Q. J. Exp. Psychol.* 62, 1784–1804. doi: 10.1080/17470210802557751

Treccani, B., Cubelli, R., Sellaro, R., Umiltà, C., and Della Sala, S. (2012). Dissociation between awareness and spatial coding: evidence from unilateral neglect. *J. Cogn. Neurosci.* 24, 854–867. doi: 10.1162/jocn_a_00185

Treisman, A., and Gelade, G. (1980). A feature-integration theory of attention. *Cogn. Psychol.* 12, 97–136. doi: 10.1016/0010-0285(80)90005-5

Treisman, A. M. (2006). How the deployment of attention determines what we see. *Vis. Cogn.* 14, 411–443. doi: 10.1080/13506280500195250

Trevethan, C. T., Sahraie, A., and Weiskrantz, L. (2007). Form discrimination in a case of blindsight. *Neuropsychologia* 45, 2092–2103.

Van Vleet, T., and DeGutis, J. (2013). The non-spatial side of spatial neglect and related approaches to treatment. *Prog. Brain Res.* 207, 327–349. doi: 10.1016/B978-0-444-63327-9.00012-6

Venneri, A., Pentore, R., Cobelli, M., Nichelli, P., and Shanks, M. F. (2012). Translocation of the embodied self without visuospatial neglect. *Neuropsychologia* 50, 973–978. doi: 10.1016/j.neuropsychologia.2012.02.004

Xu, F. (1999). Object individuation and object identity in infancy: the role of spatiotemporal information, object property information, and language. *Acta Psychol.* 102, 113–136. doi: 10.1016/S0001-6918(99)00029-3

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 17 December 2018
doi: 10.3389/fpsyg.2018.02507

Action Shapes the Sense of Body Ownership Across Human Development

Elena Nava[1]*, *Chiara Gamberini*[1], *Agnese Berardis*[1] and *Nadia Bolognini*[1,2]

[1] *Department of Psychology and NeuroMi – Milan Center for Neuroscience, University of Milano–Bicocca, Milan, Italy,*
[2] *Laboratory of Neuropsychology, IRCSS Istituto Auxologico Italiano, Milan, Italy*

In this study we investigated, both in childhood and adulthood, the role of action in promoting and shaping the sense of body ownership, which is traditionally viewed as dependent on multisensory integration. By means of a novel action-based version of the rubber hand illusion (RHI), in which participants could actively self-stroke the rubber hand, with (Version 1) or without visual feedback (Version 2) of their own actions, we showed that self-generated actions promote the emergence of a sense of ownership over the rubber hand in children, while it interferes with the embodiment of the rubber hand in adults. When the movement is missing (Version 3, i.e., mere view of the rubber hand being stroked concurrently with one's own hand), the pattern of results is reversed, with adults showing embodiment of the rubber hand, but children lacking to do so. Our novel findings reveal a dynamic and plastic contribution of the motor system to the emergence of a coherent bodily self, suggesting that the development of the sense of body ownership is shaped by motor experience, rather than being purely sensory.

Keywords: body ownership, development, motor system, sensorimotor integration, rubber hand illusion

Edited by:
Silvia Savazzi,
Università degli Studi di Verona, Italy

Reviewed by:
Alessandro Farne,
Institut National de la Santé et de la Recherche Médicale (INSERM), France
Lorenzo Pia,
Università degli Studi di Torino, Italy

****Correspondence:***
Elena Nava
elena.nava@unimib.it

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: *23 October 2018*
Accepted: *26 November 2018*
Published: *17 December 2018*

Citation:
Nava E, Gamberini C, Berardis A and Bolognini N (2018) Action Shapes the Sense of Body Ownership Across Human Development. Front. Psychol. 9:2507. doi: 10.3389/fpsyg.2018.02507

INTRODUCTION

The sense of body ownership is the product of complex mechanisms, primarily relying on the binding of multisensory body-related signals. Studies investigating the neural principles of the bodily-self have shown that multisensory inputs converge into a fronto-parietal network, in which they likely contribute to the building of a unique, sensory-based percept of the sense of body ownership (see Blanke et al., 2015 for a recent review). Interestingly, studies in adult animals and humans have shown that a crucial role in this network is played by the premotor cortex (Graziano, 1999; Ehrsson et al., 2004), which mediates sophisticated sensorimotor interactions relevant for action and the representation of the whole body and its single parts in space.

Some aspects of body representation may be innate, as suggested by studies conducted in patients with congenital limb aplasia, a condition in which individuals were born with one or more missing limbs (Melzack et al., 1997; Brugger et al., 2000). Despite complete absence of the physical limb, and thus the experience of seeing, touching, and moving it, a number of patients report phantom limb sensations, suggesting that the neural representation of the body may be partially genetically programmed.

In support to the claim that there may be a predisposition to some aspects of body representation, studies conducted in human newborns have revealed that within the first hours of life, newborns look longer to an image of a baby face being stroked concurrently with one owns face than an image of a baby face being stroked asynchronously. Interestingly, this preference is abolished in both synchronous and asynchronous stroking mode when the face is inverted by 180°, suggesting that newborns have a rudimentary sense of self (Filippetti et al., 2013, 2015).

An adult-like sense of body ownership seems to gradually develop in humans, and mostly depend upon multisensory integration skills. These skills have a protracted development in childhood, in that they are suboptimal until at least 8 years of age (Gori et al., 2008; Gori, 2015). Before this age, children are mostly dominated by one sensory modality at a time, which likely calibrates the others. Evidence that the sense of body ownership depends upon multisensory integration skills come from recent studies investigating the sense of body ownership in preschool children, showing that children are insensitive to classical multisensory bodily illusion, such as the RHI. Absence of recalibration of own hand's position toward the rubber hand has typically been interpreted as children's inability to fuse the multisensory information necessary to embody the rubber hand (Cowie et al., 2013, 2016; Nava et al., 2017).

So far, studies using the RHI to assess body ownership in adults and children have focused on the underlying multisensory mechanisms (Serino et al., 2013; Blanke et al., 2015), largely neglecting the potential existence of a motor side of this component of the bodily self. However, neuroimaging and non-invasive brain stimulation studies have revealed that activity in the premotor cortex (Ehrsson et al., 2004, 2005; Convento et al., 2018) is associated with feelings of owning the rubber hand, and that neurons in the ventral premotor cortex react to multisensory stimuli that guide action (Graziano et al., 1994; Fogassi et al., 1996). That is, motor functions are strictly interconnected to sensory feedback and are at the roots of the body schema.

Furthermore, there is a growing body of evidence in healthy and brain-damaged adult patients, indicating that the motor system may shape and guide the emergence of a multisensory bodily self, in general, and of the sense of body ownership, in particular (Vallar and Ronchi, 2009; Garbarini et al., 2013; Bolognini et al., 2014; Hara et al., 2015; della Gatta et al., 2016). For instance, in adults, della Gatta et al. (2016) showed that the illusory ownership of a rubber hand, brought about by the RHI, is accompanied by a decrease of motor cortical excitability in the participants' real disembodied hand, as measured through motor evoked potentials induced by transcranial magnetic stimulation (TMS) of the primary motor cortex (M1). Accordingly, down-regulating the excitability of M1 by means of repetitive TMS attenuates the sense of body ownership, in turn rendering individuals more prone to incorporate an alien body through the RHI (Fossataro et al., 2018). Even on a more extreme hand, individuals whose limb was immobilized for 1 week show stronger RHI effects on the immobilized hand (Burin et al., 2017) after this period, suggesting that being able to performed self-generated movements has a crucial role in shaping the experience of one's own body.

The strong link between movements and body ownership is also well proved by neuropsychological evidence: patients with upper-limb hemiplegia following an acquired stroke are more susceptible to the RHI (Burin et al., 2015; see also Nava et al., 2017), further suggesting that impairment of the motor system directly affects the multisensory sense of body ownership. Furthermore, in Critchley's (1953) taxonomy, seminal in the neuropsychological literature, somatoparaphrenia, namely a delusion of disownership of contralesional body parts seldom observed after a stroke (Vallar and Ronchi, 2009), is closely associated with unawareness and active denial of motor deficits.

While the relationship between the motor and sensory systems has received attention in healthy adult and neuropsychological studies, to date no study has investigated the role of the motor system in the construction of a coherent sense of body ownership during development.

In this framework, the present study explores whether and how self-produced actions may shape body ownership across human development, by testing both children and adults on a novel, action-based version of the RHI, in which participants could actively stroke the rubber hand (Version 1 and Version 2), as compared to the standard, purely sensory, version of the RHI (Version 3) (see Botvinick and Cohen, 1998).

Our manipulation may sound very similar to the somatic RHI introduced by Ehrsson et al. (2005), in which blindfolded participants touch the rubber hand while the experimenter touches the participant's hand concurrently, leading to the sensation of owning the rubber hand. However, our action-based version of the RHI differs from the somatic RHI in that here participants have to actively stroke the rubber hand with a brush, always watching the rubber hand (both Versions 1 and 2). On the contrary, in Ehrsson et al. (2005) the participants' hand was passively moved from the experimenter over the rubber hand. This is an important difference, because the aim of the study was precisely to assess the role of self-generated movements on the sense of embodiment.

MATERIALS AND METHODS

Participants

One hundred and eight children and 108 adults took part in the experiment, and were assigned to one of the three versions of the experiment as follows: 36 children (mean age = 5.0, *SD* = 0.7, 18 females) and 36 adults (mean age = 25.1, *SD* = 4.5, 22 females) took part in Version 1; 36 children (mean age = 4.6, *SD* = 0.5, 15 females) and 36 adults (mean age = 24.5, *SD* = 4.4, 23 females) took part in Version 2; 36 children (mean age = 5.0, *SD* = 0.7, 18 females) and 36 adults (mean age = 26.6, *SD* = 7.2, 22 females) took part in Version 3. In every version of the experiment, the sample slightly exceeded the computed required sample size ($N = 64$), as calculated with G Power, with an expected Effect size = 0.25, $\alpha = 0.05$, Power = 0.90.

Ten additional children (across versions) were tested but excluded from the final sample because they either did not want to continue the experiment ($N = 5$) or did not understand the task ($N = 5$).

All children were recruited from local kindergartens. All were cognitively and neurologically healthy and took part in the experiment after at least one parent gave written informed consent to participating in the study.

Adults were recruited from the University of Milan-Bicocca, received course credits for their participation, and signed and informed consent prior to the beginning of the experiment. All adult participants were right-handed by self-report. For children, we asked them to write their name on a sheet of paper, and to tell which hand they use to, e.g., brush teeth, hold a spoon.

In every version of the experiment, children and adults were split into two groups, with 50% assigned to one of the two testing conditions, corresponding to type of stroking - synchronous or asynchronous; that is, in each version the overall groups were 4 (2 for each age and type of stroking). This between-subjects design was aimed at minimizing testing time, particularly to make it more likely to children to stay focused throughout the testing.

More importantly, while the use of a between-subjects design may appear less robust than using a within-subjects design, it should be noted that re-testing the same individual on different conditions (e.g., synchronous and asynchronous) causes carry-over effects on the proprioceptive drift. For example, data from 30 adults (see Convento et al., 2018) have shown that carry-over effect persisted in these individuals even after 1 week (in which we they were not administered any test). For this reason, we opted for a between-subjects design, as previously done in other studies too (see Nava et al., 2014, 2018).

The study was approved by the Ethics Committee of the University of Milan-Bicocca, in line with the ethical principles of the Declaration of Helsinki.

Material

A wooden horizontal surface (60 length × 40 width cm), with a vertical wooden surface (40 width × 60 height cm) attached in the middle of it served as main testing space. The participant was seated in front of the horizontal surface, with the left hand positioned behind the vertical surface, so to impede visibility of own hand. A life-sized rubber left hand was placed in front of the participant, keeping a distance of approximately 20 cm between the index finger of the hand of the participant and the index finger of the rubber hand.

At approximately 20 cm of the vertical surface was placed a wooden rod, which was of the same length of the horizontal surface. In the rod itself, three holes were made to insert two paintbrushes at a time: in the synchronous condition, one was placed above the rubber hand, and the other above the participants' left hand; in the asynchronous condition, one paintbrush was placed above the rubber hand, and the other 2 cm away from the participant's left hand (see **Figure 1**, left panel, for a graphic description of the set-up).

In Version 2 of the experiment, the material was the same as the one used in Version 1, with the only exception of the presence of a black bloth, which was placed over the participants' hand to prevent sight of own movements (see **Figure 1**, central panel).

The material used in Version 3 of the experiment resembled Version 1 and 2, with the following important difference: because the participants did not have to actively stroke the rubber hand, but passively watched the experimenter stroking the rubber hand either synchronously or asynchronously with the real hand of the participant (see **Figure 1**, right panel), the wooden rod was removed from the vertical surface.

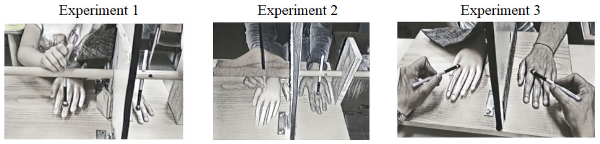


FIGURE 1 | Illustrations of the three versions of the experiment, in which participants (children and adults) watch the rubber hand while actively stroking the rubber hand (Version 1), actively stroke the rubber hand with no visual feedback of the own movements (Version 2), or observe the rubber hand being stroked by another person (Version 3).

Assessment of the RHI

Questionnaire: Subjective Report of Body Ownership

To assess whether participants explicitly felt embodiment of the rubber hand, we administered a questionnaire composed of two simple items, similar to the ones previously used in children (Cowie et al., 2013; Nava et al., 2017). One question was designed to reflect the strength of the embodiment of the rubber hand: "I felt as if the rubber hand was my own hand," and the other question served to control for suggestibility: "I felt as if I had three hands." The questions corresponded to 7 possible ratings, ranging from −3 ("I strongly disagree") to +3 ("I strongly agree"). Zero indicated "I neither agree or disagree." For children, each rating corresponded to: +3 ("Definitely yes"), +2 ("Yes"), +1 ("A little bit), 0 ("Not sure"), −1 ("Not really), −2 ("No"), −3 ("Absolutely not"). The questions and the rating scale were read out loud, and they were repeated more times if necessary to make sure children understood the questions and the options for responding. Note that this procedure was previously used in other experiments (Cowie et al., 2013, 2016; Nava et al., 2017) in similar set-ups and the children did not manifest any problem understanding the questions and how to respond to them. Furthermore, as in Nava et al. (2017), we made use of a control question specifically to prevent from obtaining responses that could only reflect compliance with the experimenter or susceptibility to any illusion.

Proprioceptive Drift: Implicit Index of Self-Location in the RHI

To assess whether participants' sense of self-location changed following induction of the illusion, we measured the pointing error, namely the so-called 'proprioceptive drift'. This was achieved by putting the participants' hand under a small transparent plastic table (ca 60 cm length × 40 cm height), on which a measuring tape was placed. The left middle finger was placed under the "zero" signaled by the measuring tape. Participants were required to point three times toward their left middle finger before (P1) and after the illusion induction (P2), and the difference between P2 and P1 represented the pointing error. This measure has been widely used as a behavioral, implicit index of the integration of vision, proprioception and touch, which are a necessary component of the body schema and of the sense of body ownership (Tsakiris, 2010; Convento et al., 2018).

General Procedure

In all 3 versions, half of the participant in each group (adults and children) were assigned to the synchronous condition, that is, the movements performed on the rubber hand were perfectly matched to the strokes provided on the participant's hand. The other half of the participants were assigned to the asynchronous condition, in which the strokes given on the rubber hand and the real hand were not matched, thus the participant always perceived one stroke at a time, one on her own hand, followed by a stroke on the rubber hand.

In Version 1 and 2, the participants were asked to hold the paintbrush and move it along the rubber hand.

The participants were free to change the velocity during stroking.

In Version 3, the participants watched the rubber hand being stroked by the experimenter, while concurrently being stroked on owns hand.

The whole induction session for the three versions lasted ca. 3 min, with short breaks allowed every minute.

Each version of the experiment started by asking participants to make the pointing task. Immediately after, the induction of the illusion started. At the end of this phase, each participant was asked to perform the pointing task again. At last, the questionnaire was administered.

RESULTS

Parametric statistics was applied to both questionnaire and proprioceptive drift analyses because data were normally distributed across groups (as assessed through Shapiro-Wilks tests) and because the data were continuous.

Subjective Report of Body Ownership

Raw scores of the two items were compared using a repeated-measures analysis of variance (rmANOVA), with Question (illusion vs. control question) as within-subjects factor, and the between-subjects factors: Group (children vs. adults), Synchrony (synchronous vs. asynchronous stroking), and Version (the 3 versions of the experiment). Newman-Keuls *post hoc* comparisons were used to explore significant interactions.

The Group X Question X Synchrony X Version rmANOVA revealed main effects of Question [$F(1,204) = 118.74$, $p < 0.001$, $\eta^2 = 0.37$], Group [$F(1,204) = 9.81$, $p = 0.002$, $\eta^2 = 0.05$] and Synchrony [$F(1,204) = 36.74$, $p < 0.001$, $\eta^2 = 0.15$], and the following interactions: Version X Synchrony $F(2,204) = 8.31$, $p < 0.001$, $\eta^2 = 0.07$], Question X Synchrony $F(1,204) = 64.62$, $p < 0.001$, $\eta^2 = 0.24$], Group X Question X Version [$F(2,204) = 3.86$, $p = 0.02$, $\eta^2 = 0.04$], Group X Question X Synchrony [$F(1,204) = 8.51$, $p = 0.04$, $\eta^2 = 0.04$]. Crucially, even the Group X Question X Synchrony X Version [$F(2,204) = 7.72$, $p = 0.001$, $\eta^2 = 0.07$] reached significance; this interaction was explored by conducting further analyses separately for the two questionnaire's items: the illusion and the control questions.

With respect to the illusion question, we found a main effect of Synchrony [$F(1,204) = 75.31$, $p < 0.001$, $\eta^2 = 0.27$], and the following interactions: Group X Synchrony [$F(1,204) = 6.87$, $p = 0.009$, $\eta^2 = 0.03$], Version X Synchrony [$F(2,204) = 5.42$, $p = 0.005$, $\eta^2 = 0.05$], and Group X Version X Synchrony [$F(2,204) = 4.59$, $p = 0.01$, $\eta^2 = 0.04$]. However, while for the asynchronous condition no main effect or interaction emerged (all $p > 0.46$), for the synchronous condition we found significant effects of Group [$F(1,102) = 8.45$, $p = 0.004$, $\eta^2 = 0.08$], Version [$F(2,102) = 6.60$, $p = 0.002$, $\eta^2 = 0.12$], as well as of the Group X Version interaction [$F(2,102) = 6.68$, $p = 0.002$, $\eta^2 = 0.12$], the last revealing that children reported higher sense of body ownership in comparison to the adults in the two motor versions of the RHI, hence both in Version 1 (children: Mean, $M = 1.50$, Standard Error, $SE = 0.48$; adults: $M = -0.78$, $SE = 0.48$, $p = 0.007$) and Version 2 (children: $M = 0.94$, $SE = 0.48$; adults: $M = -1.11$, $SE = 0.48$, $p = 0.009$). On the contrary, children and adult reported comparable sense of body ownership in Version 3, when the movement was absent (children: $M = 1.17$, $SE = 0.48$; adults: $M = 2.06$, $SE = 0.48$, $p = 0.40$, see **Figure 2**). Morevore, within the children group, there was no difference between the three RHI versions (all $p > 0.7$), while adults did report a feeling of ownership over the rubber hand only when the action was precluded (positive score, Version 3), as compared to scores obtained in either Version 1 and 2 (all $p < 0.001$).

With respect to the control question, there was a main effect of Group [$F(1,204) = 12.24$, $p = 0.001$, $\eta^2 = 0.06$], caused by adults rejecting the control question more than children regardless of the RHI version (p = and synchrony (adults: $M = -2.60$, $SE = 0.14$; children: $M = -1.89$, $SE = 0.14$), and a Synchrony X Version interaction [$F(2,204) = 5.02$, $p = 0.007$, $\eta^2 = 0.05$], since both children and adults rejected the control question in Version 1 more than Version 3.

Proprioceptive Drift

Recalibration toward the rubber hand was calculated as the difference between the mean of the 3 pointings performed after and before the induction of the illusion; this index represents the so-called 'proprioceptive drift'. The proprioceptive drift was then analyzed via an univariate ANOVA, with Group (children vs. adults), Synchrony (synchronous vs. synchronous stroking), and Version (the 3 versions of the experiment) as between-subjects factors. Newman-Keuls *post hoc* comparisons were used to explore significant interactions.

This analysis revealed a main effect of Synchrony [$F(1,204) = 53.35$, $p < 0.001$, $\eta^2 = 0.21$] and significant Group X Version [$F(1,204) = 9.09$, $p < 0.001$, $\eta^2 = 0.08$], and Group X Version X Synchrony interactions [$F(2,204) = 7.96$, $p < 0.001$, $\eta^2 = 0.07$].

As for the questionnaire, we conducted separate analyses for the synchronous and asynchronous conditions. While the asynchronous condition did not show any significant effect of the main factors and of their interactions (all $p > 0.63$), the analysis of the synchronous condition revealed only a significant Group X Version interaction [$F(2,102) = 23.38$, $p < 0.001$,

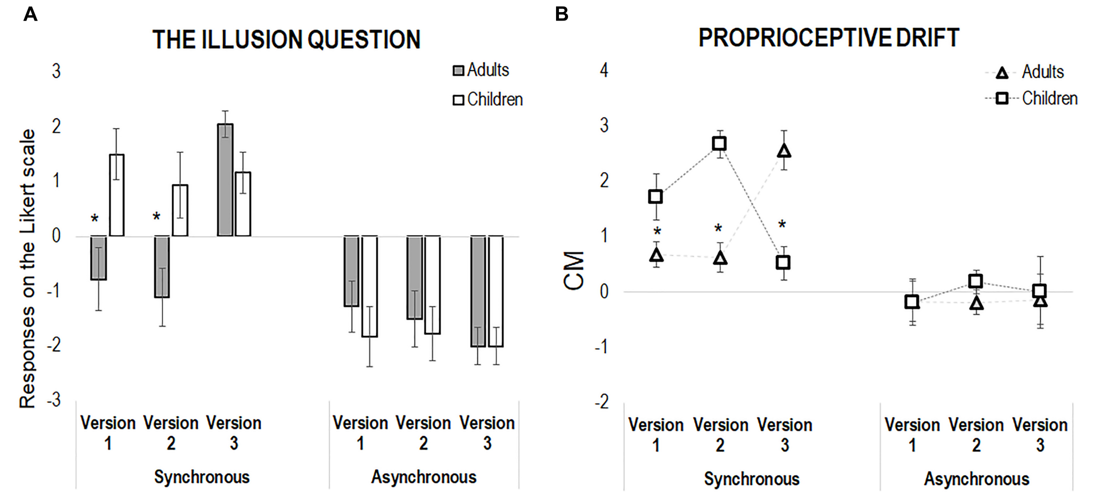


FIGURE 2 | (A) Shows the results from the illusion question only ("Did you feel as if the rubber hand was your hand?") in both adults and children across the three versions of the experiment, in the synchronous and asynchronous condition. **(B)** Shows the results from the proprioceptive drift, calculated as the difference between post-illusion and pre-illusion pointing, in both children and adults in the three versions of the experiment, in the synchronous and asynchronous condition. In both panels, error bars indicate standard error of the mean. The asterisks highlight differences between adults and children.

$\eta^2 = 0.31$]. Indeed, in both Version 1 (children: $M = 1.72$, $SE = 0.31$; adults: $M = 0.68$, $SE = 0.31$, $p = 0.02$) and Version 2 (children: $M = 2.68$, $SE = 0.31$; adults: $M = 0.63$, $SE = 0.31$, $p < 0.001$) children showed a larger proprioceptive drift in comparison to adults. Interestingly, the pattern reversed in Version 3: when no movement occurred, adults presented with a larger proprioceptive drifts than children (children: $M = 1.72$, $SE = 0.31$; adults: $M = 2.57$, $SE = 0.31$, $p < 0.001$, see **Figure 2**).

Moreover, within-groups comparisons show that the visuo-tactile version of RHI, in the absence of movement (Version 3), induced a larger proprioceptive drift in adults, which was nearly to zero in the other two action-based versions ($p < 0.001$). In children, the larger effect emerged in the two action-based versions of the RHI, namely when children actively stroked the rubber hand with (Version 1, $p < 0.04$) or without visual feedback ($p = 0.001$), as compared to the purely sensory version (Version 3); on the contrary, no difference emerged between Version 1 and 2 ($p = 0.08$).

DISCUSSION

In this study, we explored the contribution of the motor system, in particular of self-generated actions, in shaping and maintaining a coherent sense of self across development by using a novel, motor-based version of the RHI. We showed that action may either promote or disrupt the sense of body ownership depending on age, differently affecting the explicit and implicit self-location component.

In children, the subjective feeling of ownership over the rubber hand is overall similar in the three RHI versions, hence actively stroking one's own hand does not significantly affect the illusory, subjective, experience of embodiment of the rubber hand. Instead, when children act on the rubber hand (i.e., being the agent of the delivered touch), the active movement promotes an efficient binding of the visual information (i.e., the seen rubber hand) and the tactile and proprioceptive inputs (i.e., the participant's hand), necessary to recalibrate self-location following the embodiment of the rubber hand. Such effect is not dependent upon visual capture of attention by the participants' own hand moving. Indeed, in the absence of active movements (Version 2), children lack to integrate multisensory signals, and thus the illusion does not shift their self-location. Therefore, at least until the preschool years, active movements selectively modulate the proprioceptive drift, but not the explicit feelings of owning the rubber hand, as assessed through the questionnaire.

The stability of self-reports in children is in line with previous studies in children of similar age (Cowie et al., 2013; Nava et al., 2017), corroborating the notion that the abstract representation of the body (also termed "Body Image"), which distinguishes between objects that may or may not be part of one's body (Tsakiris, 2010), is likely innate, and shapes the conscious perception of feeling the rubber hand as one owns hand.

In adults, we found an opposite pattern, with action dramatically disrupting both the subjective sense of body ownership, and its implicit self-location component. Our findings complement previous evidence from the adult literature documenting the link between the sense of body ownership and the motor system activity. In clinical populations, it is the frequent association between movement disorders and a more malleable sense of body ownership: brain—damaged patients with hemiplegia (Burin et al., 2015), multiple sclerosis (Nava et al., 2017) or spinal cord injury (Scandola et al., 2014) all are more prone to the illusory effects the RHI. It is also noteworthy that somatoparaphrenia, a delusion of disownership of controlesional body parts, has been reported with a few exceptions, in right-brain-damaged patients, with motor deficits (Vallar and Ronchi, 2009; Bolognini et al., 2014). In the same vein, in healthy adults, reducing temporarily the level of activation of the motor cortex (with TMS or limb immobilization) attenuates the sense of body ownership, in turn making subjects more prone to incorporate an alien body part (Fossataro et al., 2018). Overall, this evidence is specular to the present one: here we showed that the activation of the motor system (through action) disrupts the RHI in adults, while in the above mentioned studies the opposite occurs, with a reduced (or even abolished in the case of permanent injuries) motor system activation increasing RHI effects. One possible explanation is that in adulthood, the presence of movement-related signals are able to lessens the impact of conflicting multisensory signals shaping the sense of body ownership.

Our results could also be interpreted in terms of attention to either visuo-motor or proprioceptive cues. Indeed, the participants were asked to stroke the visible fake hand (i.e., visuo-motor feedback), while passively feeling the stroke on the real hand (i.e., proprioceptive feedback), which may have automatically shifted their attention to the visuo-motor component. If this were the case, it suggests that visuo-motor integration may be particularly strong in children; strong enough to abolish proprioceptive cues, so that the task would be made solely following the former cues. In other words, instead of promoting the binding of visuo-proprioceptive signals, attention to the rubber hand may have added salience to the visuo-motor cues.

In adults, the same attentional mechanism may have favored proprioceptive cues because the active stroking of the fake hand may have heighten the awareness of ‘fakeness’ of the rubber hand. This, in turn, may have strengthens awareness over the real hand and thus abolished any recalibration of owns hand felt position.

An alternative interpretation of our results regards the possibility that sensory attenuation of self-produced tactile stimulations may strongly change throughout development. Studies in animal models have reported weaker neuronal responses to self-produced in comparison to externally generated stimuli across sensory modalities (Curio et al., 2000; Cullen and Roy, 2004), which is particularly striking in the case of self-tickling in human adults. Indeed, most adult individuals are insensitive to self-tickling, while many are when the tickling is done by someone else. From a neuronal point of view, this has been shown to correspond to weaker activity in the somatosensory cortices when the tickling or simply the touch is self-generated vs. externally produced (Blakemore et al., 1998, 2000; Hesse et al., 2010). Computational models suggest that this attenuation may be due to sensory predictions made by an internal forward model of the motor system. In other words, when the brain programs a movement, it also immediately predicts the sensory consequences of it. If the predicted and actual sensory feedbacks perfectly match, then the brain will alter the sensory signals online, and code the actions as self-produced. On the contrary, if there is a mismatch between predicted and actual sensory feedback, the brain will code the actions as non-intended, thus likely coming from an external source (from here the sensation of being tickled, for example).

Applied to our data, such evidence suggests that adults do not perceive the illusion because the self-produced strokes on the rubber hand increase self-awareness. In other words, adults expect that their own movements would cause a tactile sensation in correspondence to their own hand. Because their real hand is spatially misaligned with respect to the seen rubber hand, this causes a mismatch between predicted and actual sensory feedback, thus disrupting embodiment of the rubber hand.

In this view, the opposite pattern observed in children suggests a lower sensory attenuation in children, at least until 5 years of age, which may impair the capacity of dissociating sensory signals resulting from own vs. externally generated actions. Children’s inability to predict the consequences of their actions strengthen the RHI, as measured through the proprioceptive drift. While it is difficult to conclusively state whether larger drifts are really caused by predictive (or postdictive) mechanisms, and how these models causally interacts with self-location and body ownership, future studies should investigate how voluntary motor control generates sensory expectations in early development, how these expectations are compared with actual sensory feedback and whether they allow children to learn and distinguish between internal and external (bodily) events.

CONCLUSION

In conclusion, the activation of a motor representation of one’s own body through action may recalibrate coherence among afferent sensory signals, in turn shaping the sense of body ownership in childhood and adults. At least until the preschool years, the immature sense of body ownership is strongly action-based, hence actions facilitate crossmodal interactions based on which a coherent sense of body ownership can emerge. Once the sensorimotor system has reached its maturity, the motor representation dominates bodily self-consciousness, lowering the susceptibility to conflicting sensory information that may cause body disembodiment. The sensory-based body representation dynamically interfaces with the motor system across the life span, supporting the view that self- representation and body awareness are not purely sensory or motor, but rather sensory and motor (Rizzolatti et al., 2002; Serino et al., 2013).

AUTHOR CONTRIBUTIONS

EN and NB conceived and designed the experiments. CG and AB carried out the experiments. EN analyzed the data and drafted the manuscript, revised by NB. All authors read and approved the final version of the manuscript.

FUNDING

This work was supported by ATE grant from the University of Milano–Bicocca to NB (2017-ATE-0173) and EN (2017-ATE-0176).

REFERENCES

Blakemore, S. J., Wolpert, D. M., and Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nat. Neurosci.* 1, 635–640. doi: 10.1038/2870

Blakemore, S. J., Wolpert, D. M., and Frith, C. D. (2000). Why can't you tickle yourself? *Neuroreport* 11, R11–R16. doi: 10.1097/00001756-200008030-00002

Blanke, O., Slater, M., and Serino, A. (2015). Behavioral, neural, and computational principles of bodily self-consciousness. *Neuron* 88, 145–166. doi: 10.1016/j.neuron.2015.09.029

Bolognini, N., Ronchi, R., Casati, C., Fortis, P., and Vallar, G. (2014). Multisensory remission of somatoparaphrenic delusion. My hand is back! *Neurology* 4, 216–225. doi: 10.1212/CPJ.0000000000000033

Botvinick, M., and Cohen, J. (1998). Rubber hands 'feel'touch that eyes see. *Nature* 391:756. doi: 10.1038/35784

Brugger, P., Kollias, S. S., Müri, R. M., Crelier, G., Hepp-Reymond, M. C., and Regard, M. (2000). Beyond re-membering: phantom sensations of congenitally absent limbs. *Proc. Natl. Acad. Sci. U.S.A.* 97, 6167–6172. doi: 10.1073/pnas.100510697

Burin, D., Garbarini, F., Bruno, V., Fossataro, C., Destefanis, C., Berti, A., et al. (2017). Movements and body ownership: evidence from the rubber hand illusion after mechanical limb immobilization. *Neuropsychologia* 107, 41–47. doi: 10.1016/j.neuropsychologia.2017.11.004

Burin, D., Livelli, A., Garbarini, F., Fossataro, C., Folegatti, A., Gindri, P., et al. (2015). Are movements necessary for the sense of body ownership? Evidence from the rubber hand illusion in pure hemiplegic patients. *PLoS One* 10:e0117155. doi: 10.1371/journal.pone.0117155

Convento, S., Romano, D., Maravita, A., and Bolognini, N. (2018). Roles of the right temporo-parietal and premotor cortices in self-location and body ownership. *Eur. J. Neurosci.* 47, 1289–1302. doi: 10.1111/ejn.13937

Cowie, D., Makin, T. R., and Bremner, A. J. (2013). Children's responses to the rubber-hand illusion reveal dissociable pathways in body representation. *Psychol. Sci.* 24, 762–769. doi: 10.1177/0956797612462902

Cowie, D., Sterling, S., and Bremner, A. J. (2016). The development of multisensory body representation and awareness continues to 10 years of age: evidence from the rubber hand illusion. *J. Exp. Child Psychol.* 142, 230–238. doi: 10.1016/j.jecp.2015.10.003

Critchley, M. (1953). *The Parietal Lobes*. New York, NY: Hafner.

Cullen, K. E., and Roy, J. E. (2004). Signal processing in the vestibular system during active versus passive head movements. *J. Neurophysiol.* 91, 1919–1933. doi: 10.1152/jn.00988.2003

Curio, G., Neuloh, G., Numminen, J., Jousmäki, V., and Hari, R. (2000). Speaking modifies voice-evoked activity in the human auditory cortex. *Hum. Brain Mapp.* 9, 183–191. doi: 10.1002/(SICI)1097-0193(200004)9:4<183::AID-HBM1>3.0.CO;2-Z

della Gatta, F., Garbarini, F., Puglisi, G., Leonetti, A., Berti, A., and Borroni, P. (2016). Decreased motor cortex excitability mirrors own hand disembodiment during the rubber hand illusion. *eLife* 5:e14972. doi: 10.7554/eLife.14972

Ehrsson, H. H., Holmes, N. P., and Passingham, R. E. (2005). Touching a rubber hand: feeling of body ownership is associated with activity in multisensory brain areas. *J. Neurosci.* 25, 10564–10573. doi: 10.1523/JNEUROSCI.0800-05.2005

Ehrsson, H. H., Spence, C., and Passingham, R. E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science* 305, 875–877. doi: 10.1126/science.1097011

Filippetti, M. L., Johnson, M. H., Lloyd-Fox, S., Dragovic, D., and Farroni, T. (2013). Body perception in newborns. *Curr. Biol.* 23, 2413–2416. doi: 10.1016/j.cub.2013.10.017

Filippetti, M. L., Orioli, G., Johnson, M. H., and Farroni, T. (2015). Newborn body perception: sensitivity to spatial congruency. *Infancy* 20, 455–465. doi: 10.1111/infa.12083

Fogassi, L., Gallese, V., Fadiga, L., Luppino, G., Matelli, M., and Rizzolatti, G. (1996). Coding of peripersonal space in inferior premotor cortex (area F4). *J. Neurophysiol.* 76, 141–157. doi: 10.1152/jn.1996.76.1.141

Fossataro, C., Bruno, V., Giurgola, S., Bolognini, N., and Garbarini, F. (2018). Losing my hand. Body ownership attenuation after virtual lesion of the primary motor cortex. *Eur. J. Neurosci.* 48, 2272–2287. doi: 10.1111/ejn.14116

Garbarini, F., Pia, L., Piedimonte, A., Rabuffetti, M., Gindri, P., and Berti, A. (2013). Embodiment of an alien hand interferes with intact-hand movements. *Curr. Biol.* 23, R57–R58. doi: 10.1016/j.cub.2012.12.003

Gori, M. (2015). Multisensory integration and calibration in children and adults with and without sensory and motor disabilities. *Multisens. Res.* 28, 71–99. doi: 10.1163/22134808-00002478

Gori, M., Del Viva, M., Sandini, G., and Burr, D. C. (2008). Young children do not integrate visual and haptic form information. *Curr. Biol.* 18, 694–698. doi: 10.1016/j.cub.2008.04.036

Graziano, M. S. (1999). Where is my arm? The relative role of vision and proprioception in the neuronal representation of limb position. *Proc. Natl. Acad. Sci. U.S.A.* 96, 10418–10421. doi: 10.1073/pnas.96.18.10418

Graziano, M. S., Yap, G. S., and Gross, C. G. (1994). Coding of visual space by premotor neurons. *Science* 266, 1054–1057. doi: 10.1126/science.7973661

Hara, M., Pozeg, P., Rognini, G., Higuchi, T., Fukuhara, K., Yamamoto, A., et al. (2015). Voluntary self-touch increases body ownership. *Front. Psychol.* 6:15. doi: 10.3389/fpsyg.2015.01509

Hesse, M. D., Nishitani, N., Fink, G. R., Jousmäki, V., and Hari, R. (2010). Attenuation of somatosensory responses to self-produced tactile stimulation. *Cereb. Cortex* 20, 425–432. doi: 10.1093/cercor/bhp110

Melzack, R., Israel, R., Lacroix, R., and Schultz, G. (1997). Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain* 120, 1603–1620. doi: 10.1093/brain/120.9.1603

Nava, E., Bolognini, N., and Turati, C. (2017). The development of a cross-modal sense of body ownership. *Psychol. Sci.* 28, 330–337. doi: 10.1177/0956797616682464

Nava, E., Mattioli, F., Gamberini, C., Stampatori, C., Bellomi, F., Turati, C., et al. (2018). Altered bodily self-consciousness in multiple sclerosis. *J. Neuropsychol.* 12, 463–470. doi: 10.1111/jnp.12134

Nava, E., Steiger, T., and Röder, B. (2014). Both developmental and adult vision shape body representations. *Sci. Rep.* 4:6622. doi: 10.1038/srep06622

Rizzolatti, G., Fogassi, L., and Gallese, V. (2002). Motor and cognitive functions of the ventral premotor cortex. *Curr. Opin. Neurobiol.* 12, 149–154. doi: 10.1016/S0959-4388(02)00308-2

Scandola, M., Tidoni, E., Avesani, R., Brunelli, G., Aglioti, S. M., and Moro, V. (2014). Rubber hand illusion induced by touching the face ipsilaterally to a deprived hand: evidence for plastic "somatotopic" remapping in tetraplegics. *Front. Hum. Neurosci.* 8:404. doi: 10.3389/fnhum.2014.00404

Serino, A., Alsmith, A., Costantini, M., Mandrigin, A., Tajadura-Jimenez, A., and Lopez, C. (2013). Bodily ownership and self-location: components of bodily self-consciousness. *Conscious. Cogn.* 22, 1239–1252. doi: 10.1016/j.concog.2013.08.013

Tsakiris, M. (2010). My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia* 48, 703–712. doi: 10.1016/j.neuropsychologia.2009.09.034

Vallar, G., and Ronchi, R. (2009). Somatoparaphrenia: a body delusion. A review of the neuropsychological literature. *Exp. Brain Res.* 192, 533–551. doi: 10.1007/s00221-008-1562-y

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Psychology

ORIGINAL RESEARCH
published: 22 November 2018
doi: 10.3389/fpsyg.2018.02329

Pulvinar Lesions Disrupt Fear-Related Implicit Visual Processing in Hemianopic Patients

*Caterina Bertini[1,2], Mattia Pietrelli[1,2], Davide Braghittoni[1,2] and Elisabetta Làdavas[1,2]**

[1] Department of Psychology, University of Bologna, Bologna, Italy, [2] Centre for Studies and Research in Cognitive Neuroscience, University of Bologna, Cesena, Italy

The processing of emotional stimuli in the absence of awareness has been widely investigated in patients with lesions to the primary visual pathway since the classical studies on affective blindsight. In addition, recent evidence has shown that in hemianopic patients without blindsight only unseen fearful faces can be implicitly processed, inducing enhanced visual encoding (Cecere et al., 2014) and response facilitation (Bertini et al., 2013, 2017) to stimuli presented in their intact field. This fear-specific facilitation has been suggested to be mediated by activity in the spared visual subcortical pathway, comprising the superior colliculus (SC), the pulvinar and the amygdala. This suggests that the pulvinar might represent a critical relay structure, conveying threat-related visual information through the subcortical visual circuit. To test this hypothesis, hemianopic patients, with or without pulvinar lesions, performed a go/no-go task in which they had to discriminate simple visual stimuli, consisting in Gabor patches, displayed in their intact visual field, during the simultaneous presentation of faces with fearful, happy, and neutral expressions in their blind visual field. In line with previous evidence, hemianopic patients without pulvinar lesions showed response facilitation to stimuli displayed in the intact field, only while concurrent fearful faces were shown in their blind field. In contrast, no facilitatory effect was found in hemianopic patients with lesions of the pulvinar. These findings reveal that pulvinar lesions disrupt the implicit visual processing of fearful stimuli in hemianopic patients, therefore suggesting a pivotal role of this structure in relaying fear-related visual information from the SC to the amygdala.

Keywords: hemianopia, affective blindsight, pulvinar, fear, implicit visual processing

Edited by:
Anna Maria Berti,
Università degli Studi di Torino, Italy

Reviewed by:
Hisao Nishijo,
University of Toyama, Japan
Marco Tamietto,
Tilburg University, Netherlands

***Correspondence:**
Elisabetta Làdavas
elisabetta.ladavas@unibo.it

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: 03 July 2018
Accepted: 06 November 2018
Published: 22 November 2018

Citation:
Bertini C, Pietrelli M, Braghittoni D and Làdavas E (2018) Pulvinar Lesions Disrupt Fear-Related Implicit Visual Processing in Hemianopic Patients. Front. Psychol. 9:2329. doi: 10.3389/fpsyg.2018.02329

INTRODUCTION

The ability to extract emotional information from facial expressions is crucial for successful adaptation in social environment. Due to its importance for survival, this ability seems to be preserved also in the absence of awareness (for a review, Tamietto and de Gelder, 2010; Celeghin et al., 2015; Diano et al., 2017). In line, the studies investigating the peculiar phenomenon of affective blindsight have shown that patients with lesions of the primary visual cortex (V1) can unconsciously perceive emotional signals, demonstrating performance above chance when guessing the emotional content of faces shown in their blind field, in forced choice tasks (de Gelder et al., 1999, 2001). In addition, recent studies have revealed the presence of implicit emotional processing also in hemianopic patients without any form of blindsight or affective blindsight (Bertini et al., 2013, 2017; Cecere et al., 2014). In these studies, patients with visual field defects, who perform at the chance level in discriminating the emotional content of stimuli in their blind field in forced choice tasks, have shown behavioral and electrophysiological evidence of implicit processing of unseen fearful stimuli. Specifically, when hemianopic patients were required to respond to faces displayed in their intact field, while emotional faces were simultaneously presented in their blind field, they showed a reduction of response time (i.e., a response facilitation) only when fearful faces were concurrently displayed in their blind visual field (Bertini et al., 2013). In contrast, no facilitation was found during the concurrent presentation of unseen happy or neutral faces (Bertini et al., 2013). In addition, the presentation of fearful faces in the blind field has been shown to increase the amplitude of the electrophysiological component N170, evoked by faces presented in the intact field, therefore suggesting an enhancement of the visual structural encoding of seen faces, occurring at the early stages of visual processing (Cecere et al., 2014). Similarly, a recent study has also demonstrated that the facilitatory effects of unseen fearful faces can generalize outside the facial domain, showing a reduction of response time to simple visual stimuli (Gabor patches) displayed in the intact field (Bertini et al., 2017). Overall, these findings suggest that when a lesion occurs to the cortical visual pathway, fear-related visual information in the blind visual field can be extracted in the absence of awareness, improving visual processing in the intact visual field.

This implicit visual processing for unseen threat-related information has been suggested to be mediated by a subcortical pathway from the superior colliculus (SC) to the amygdala, via the pulvinar nuclei of the thalamus (LeDoux, 1996). In line, the structures encompassing this circuit have demonstrated enhanced positive covariation of activity to unconsciously perceived emotional expressions (Morris et al., 1999; Liddell et al., 2005).

The specificity of this pathway for rapid visual processing of socially relevant stimuli, such as faces, has been reported in studies on primates, demonstrating that the neurons in the superficial layers of the SC show early responses (firing ∼25–50 ms after stimulus onset) to facial information (Rizzolatti et al., 1980; Nguyen et al., 2014, 2016). In addition, neurons in the dorsal lateral pulvinar and the ventral part of the medial pulvinar have shown responses to face and face-like stimuli with latencies <60 ms (Nguyen et al., 2013). Notably, pulvinar neurons also showed differential responses to facial expressions (Maior et al., 2010). Finally, both human intracranial (Méndez-Bértolo et al., 2016) and MEG data (Luo et al., 2007) have revealed early responses to faces expressing fear in the amygdala occurring with latencies lower than 75 ms after stimulus-onset. Importantly, the existence of direct connections between these anatomical structures has been supported by neurophysiological evidence on rats (Day-Brown et al., 2010) and research using diffusion tractography in both monkeys and humans (Tamietto et al., 2012; Rafal et al., 2015; Koller et al., 2018).

These converging findings propose the pulvinar as a crucial connectional hub of the subcortical pathway mediating fear-related visual processing in the absence of awareness. In line with this reasoning, previous evidence on hemianopic patients have demonstrated the relevance of the pulvinar also in mediating implicit visual processing of motion stimuli: indeed, while hemianopics without pulvinar lesions showed enhanced BOLD responses, in hemianopics with lesions involving the pulvinar no activity was observed after the presentation of motion stimuli in their blind field (Barleben et al., 2015), thus corroborating the relevance of this subcortical structure in mediating visual processing for relevant stimuli in the absence of awareness. Therefore, it might be hypothesized that in the presence of lesions to the pulvinar, also the facilitatory effects due to implicit visual processing of fearful faces should not be evident. In order to test this hypothesis, hemianopic patients without blindsight, with or without pulvinar lesions, were required to discriminate the orientation of Gabor patches displayed in their intact visual field, while fearful, happy or neutral faces were simultaneously shown in their blind field. In line with previous evidence (Bertini et al., 2017), hemianopic patients without pulvinar lesions are expected to show reduced response times to stimuli in the intact field, only when fearful faces are displayed in the blind visual field. In contrast, no response facilitation is expected in hemianopic patients with pulvinar lesions, therefore suggesting a prominent role of this subcortical structure in relaying fear-related visual information from the SC to the amygdala.

MATERIALS AND METHODS

Participants

Twelve patients with right visual field defects, as documented by an automated perimetry test, participated in Experiments 1 and 2. All patients were right-handed and had corrected-to-normal or normal visual acuity. In addition, no concurrent psychiatric or neurological disorders or cognitive deficits were present. After being informed about the procedure, all patients provided written informed consent to participate. The study was approved by the Ethics Committee of the Department of Psychology of the University of Bologna, according to the ethical principles of the World Medical Association Declaration of Helsinki.

All patients had post-geniculate lesions in the left hemisphere, resulting in deafferentation or damage of the striate cortex, documented by magnetic resonance imaging (MRI) or computed tomography (CT). Six patients had additional pulvinar lesions (1 female; *M* age = 54.8 years; *M* education = 11.7 years; *M* time since lesion onset = 27 months), while in the other six patients the pulvinar was spared (1 female; *M* age = 49.5 years; *M* education = 12.2 years; *M* time since lesion onset = 9.6 months; **Table 1** and **Figures 1**, **2**). Brain lesions were mapped using MRIcro (Rorden and Brett, 2000; Rorden et al., 2007), based on the most recent clinical CT or MRI. Although manual lesion tracing procedures have the limit to rely greatly on anatomical expertise, and to be subjective in nature, they circumvent problems frequently encountered by automated normalization procedures. Indeed, while automated procedures have greatly

TABLE 1 | Summary of clinical, demographic, and lesional data.

Case	Sex	Age	Years of education	Time since lesion onset (months)	Visual field defect	Etiology	Cortical lesion site
P1	M	71	13	6	Right superior quadrantanopia	Vascular	Left temporal-occipital
P2	M	39	13	3	Right hemianopia	Vascular	Left occipital
P3	F	38	18	33	Right inferior quadrantanopia	Vascular	Left frontal-temporal-parietal
P4	M	45	13	42	Right hemianopia	Vascular	Left temporal-parietal
P5	M	81	5	18	Right hemianopia	Vascular	Left temporal-occipital
P6	M	55	8	60	Right superior quadrantanopia	Vascular	Left temporal-occipital
P7	M	57	13	5	Right hemianopia	Vascular	Left occipital
P8	F	32	18	4	Right hemianopia	Vascular	Left temporal-parietal-occipital
P9	M	50	13	15	Right superior quadrantanopia	Vascular	Left temporal-parietal-occipital
P10	M	65	8	5	Right inferior quadrantanopia	Vascular	Left occipital
P11	M	52	8	25	Right hemianopia	Traumatic	Left temporal
P12	M	41	13	4	Right inferior quadrantanopia	Vascular	Left occipital

M, male; F, female.

improved (Clas et al., 2012; Rorden et al., 2012; Zhang et al., 2014; de Haan et al., 2015; Pustina et al., 2016), variation in clinical image quality, which might be due to the nature of the imaging protocol, the quality of the imaging hardware and differences in head movement, might prevent automatic normalization into a standard template (Kimberg et al., 2007). Therefore, lesions were manually traced onto the T1-weighted MRI template provided with MRIcro software (with the exception of P12, whose MRI scans were not available; Rorden and Brett, 2000; Rorden et al., 2007). The number of damaged voxels was calculated for each patient and the lesion volumes were compared between the two groups. No significant differences were found in lesion volumes between hemianopic patients with additional pulvinar lesions (70188 mm^3; **Figure 3A**) and hemianopic patients without pulvinar lesions [47915 mm^3; $t(9) = 1.24$; $p = 0.25$; **Figure 3E**]. As shown by overlaps of brain lesions in **Figure 3**, in patients with pulvinar lesions, the superior colliculus and the amygdala were spared (**Figures 3B–D**). Patients without pulvinar lesions reported damage to brain areas not including the amygdala, pulvinar, and superior colliculus (**Figures 3F–H**). No differences between the two groups were found relative to time since lesion onset [$t(10) = 1.79$; $p = 0.1$], age [$t(10) = -0.61$; $p = 0.55$] or education [$t(10) = -0.21$; $p = 0.84$]. Clinical details are reported in **Table 1**.

Procedure

Experiments 1 and 2 were performed in a sound attenuated room with dimmed light. Patients sat at a distance of 57 cm, in front of a 17″ LCD monitor (refresh rate: 60 Hz). A Pan/Tilt optic eye-tracker (Eye-Track ASL-6000; sampling rate 60 Hz) monitored eye movements. Presentation software[1] (version 0.60) controlled stimulus presentation and recorded responses. Patients were required to fixate a central white cross (2°), avoiding eye movements. For patients P1, P6, and P9 (right superior quadrantanopia) and P3, P10, and P12 (right inferior quadrantanopia), the fixation cross was horizontally centered, on either the upper or the lower edge of the monitor (2° from the edge), to ensure stimuli were presented in the blind quadrant.

Experiment 1: Two-Alternative Forced Choice Tasks

To make sure that hemianopic patients with or without pulvinar lesions showed no sign of blindsight, they performed a two-alternative forced choice (2AFC) task, testing different stimuli in four separate sessions. We used the same experimental paradigm used in previously published studies (for details, see Bertini et al., 2013, 2017). Stimuli were only shown in their blind visual field, while no stimuli were presented in their intact visual field. Each stimulus was presented at 10° of eccentricity on the horizontal plane (either to the left or to the right of the central fixation cross, based on the side of hemianopia). For patients with upper quadrantanopia, the fixation cross was placed at the lower edge of the monitor, while for patients with lower quadrantanopia it was placed at the upper edge of the monitor, to ensure that stimuli were presented in the blind quadrant. The stimuli and the central fixation cross were presented on a gray background. In the visual detection task, a white dot (2° diameter) was used as stimulus. In the emotional task, emotional faces consisting of grayscale photographs (7° × 5°) of six different actors (three males), with happy or fearful expressions, were used as stimuli (Ekman and Friesen, 1976). In the gender task, the stimulus consisted of grayscale photographs (7° × 5°) of different faces (three males) showing a neutral expression (Ekman and Friesen, 1976). In each photograph of both the emotional and the gender task the hairline was removed using Adobe Photoshop. In the geometrical shapes task, stimuli consisted of white circles and squares (5° × 5°). At the beginning of each trial, a central fixation cross (500 ms) was presented. Subsequently, the target stimulus, if present, was displayed for a duration of 1500 ms. After the presentation of each stimulus, a fixation cross appeared again (250 ms; total trial duration: 2250 ms) and a sound prompted patients to verbally respond. The experimenter manually recorded patients' verbal responses.

---

[1] www.neurobs.com

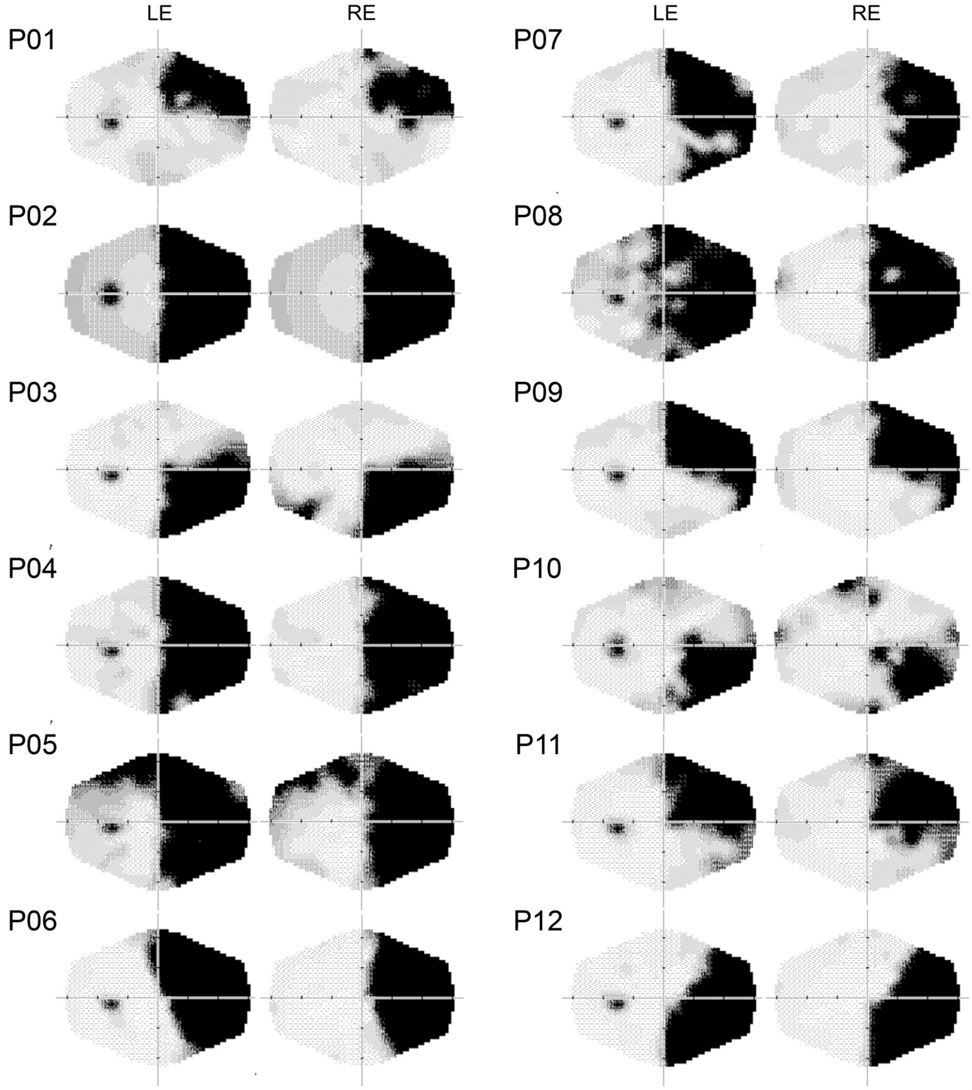


FIGURE 1 | Computerized automated visual perimetry (Medmont M700 automated perimetry apparatus, Melbourne, VIC, Australia). Axial hash marks denote 10 visual degree increments. LE, left eye; RE, right eye.

After the response, the experimenter, monitoring patients' eye position, manually started a new trial, only when their gaze was on the fixation cross. Trials contaminated with eye movements were removed (0.5%). Stimuli were presented in a random order. When performing the visual detection task, hemianopics were instructed to decide whether or not the stimulus was shown in the blind visual field. In the emotional, gender and shape tasks, they were asked to guess, choosing between two alternatives, which sort of stimuli was shown in their blind field. More precisely, in the emotional task, they had to discriminate happy or fearful faces, in the gender task they were asked to discriminate female or male faces, while in the geometrical shapes task they had to discriminate square or circle. The order of the 2AFC tasks was counterbalanced between participants. One hundred and eighty trials were presented in each 2AFC task (90 trials of each of the two possible alternatives). The percentage of correct choices was calculated in each task, for each patient. A Binomial test was used to compare the accuracy to the chance level (50% correct choices).

Experiment 2: Go/No-Go Task With Redundant Stimuli

Patients were tested with a go/no-go task, in which stimuli were presented concurrently in the blind and the intact visual field, exploiting the same experimental paradigm used in previously published studies (for details, see Bertini et al., 2017). Target stimuli were shown in the intact field and were paired with concurrently presented stimuli in the blind field. Concurrent stimuli were presented in a random order 10° to the left and to the right of the center of the monitor on the horizontal plane. For patients with upper quadrantanopia, the fixation cross was placed at the lower edge of the monitor, while for patients with lower quadrantanopia it was placed at the upper edge of the monitor,

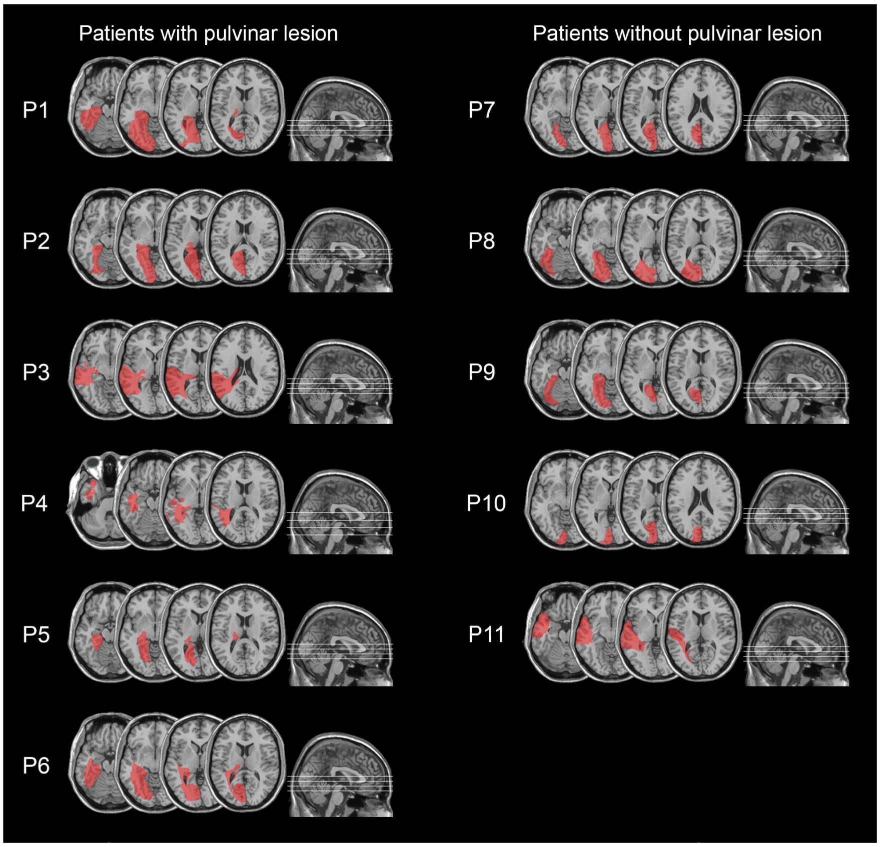


FIGURE 2 | Lesion reconstruction images from CT or MRI scans, projected onto the normalized MNI template for hemianopic patients with pulvinar lesions (P1–P6; left column) and hemianopic patients without pulvinar lesions (P7–P11; right column).

to ensure that stimuli contralateral to the lesion were presented in the blind quadrant. The stimuli and the central fixation cross were presented on a gray background. Gabor patches (diameter: 2°; spatial frequency: 8 Hz) were used as target stimuli and were created with Matlab (The MathWorks Inc., Natick, MA, United States). The Gabor patches were displayed in patients' intact visual field, while emotional faces were simultaneously presented in their blind field. Emotional faces consisted of 18 grayscale photographs (7° × 5°) of six different actors (three males) displaying fearful, happy, or neutral expressions (Ekman and Friesen, 1976). In each photograph, the hairline was removed using Adobe Photoshop. At the beginning of each trial, a fixation cross (500 ms) appeared. Then, the pairs of stimuli were displayed for a duration of 200 ms, followed by a blank screen (1000 ms). After a random inter-trial interval (500–800 ms), a new trial automatically started. Trials contaminated with eye movements were removed (2%). Patients performed a total of six blocks of the go/no-go task with redundant stimuli. In three blocks, they were required to provide rapid responses (by pressing the spacebar on a keyboard) to Gabor patches with a horizontal orientation and to avoid response to Gabor patches with a vertical orientation; in the remaining three blocks, the response requirements were reversed. They performed a total of 216 trials (in half of the trials the horizontal Gabor patch was the target: 54 trials for the target/distractor stimuli – 18 for each of the three unseen emotional faces-; in the remaining half of the trials the vertical Gabor patch was the target: 54 trials for the target/distractor stimuli – 18 for each of the three unseen emotional faces-). Response times more than two standard deviations below or above the mean were discarded (4.5%), to control for outliers. The responses to vertical and horizontal Gabor patches were collapsed. We analyzed response times and the percentage of correct responses with two analyses of variance (ANOVAs) with Group (hemianopic patients WITH pulvinar lesions, hemianopic patients WITHOUT pulvinar lesions), as between-group factor, and Condition (unseen fearful faces, unseen happy faces, and unseen neutral faces), as within-group factor. Newman–Keuls test was used for *post hoc* comparisons.

RESULTS

Experiment 1: Two-Alternative Forced Choice Tasks

Individual performance of patients with or without pulvinar lesions did not significantly differ from chance in any of 2AFC tasks (percentages of correct answers are reported in **Table 2**). Specifically, in the visual detection task, no significant difference

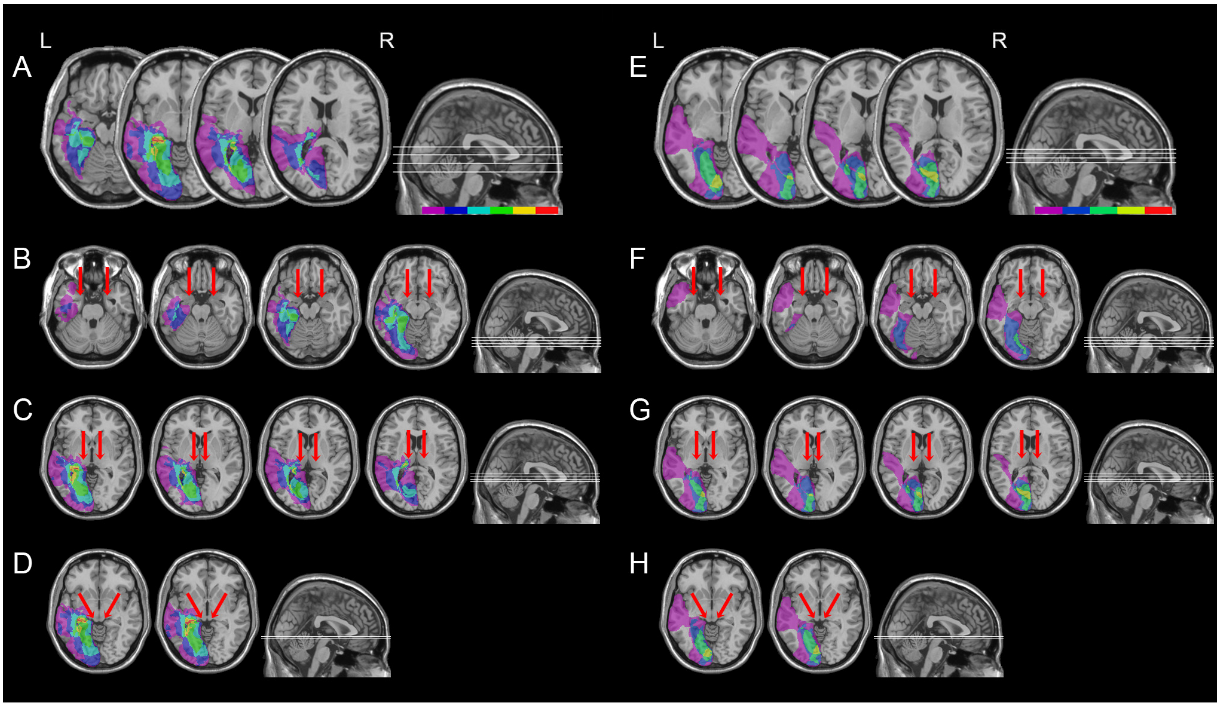


FIGURE 3 | Location and overlap of brain lesions of hemianopic patients with or without pulvinar lesions. The image shows the lesions of the hemianopic patients with pulvinar lesions **(A)** and hemianopic patients without pulvinar lesions **(E)** projected onto four axial slices of the standard MNI brain. In each slice, the left hemisphere is on the left side. The levels of the axial slices are marked by white lines on the sagittal view of the brain. The color bar indicates the number of overlapping lesions. Panels **B–D** show overlap of the lesions of hemianopic patients with pulvinar lesions projected onto the axial slices where the amygdala **(B)**, the pulvinar **(C)**, and the superior colliculus **(D)** are visible. Panels **F–H** show overlap of the lesions of hemianopic patients without pulvinar lesions projected onto the axial slices where the amygdala **(F)**, the pulvinar **(G)**, and the superior colliculus **(H)** are visible. The arrows indicate the amygdala **(B,F)**, the pulvinar **(C,G)**, and the superior colliculus **(D,H)**.

from the chance level was found (all *ps* > 0.18). No significant difference form the chance level was also found in performance in the remaining 2AFC tasks: emotional task (all *ps* > 0.18), gender task (all *ps* > 0.18), geometrical shapes task (all *ps* > 0.1). This provide evidence that hemianopics with or without pulvinar lesions had no form of blindsight, showing no awareness for the presence or the nature of unseen stimuli, displayed in their blind visual field.

Experiment 2: Go/No-Go Task With Redundant Stimuli

The ANOVA on the response times to Gabor patches displayed in the intact visual field showed no significant effect of Group ($F_{1,10} = 0.58$, $p = 0.47$; $\eta_p^2 = 0.05$) or Condition ($F_{2,20} = 1.50$, $p = 0.25$; $\eta_p^2 = 0.13$). On the contrary, the ANOVA reveled a significant Group × Condition interaction ($F_{2,20} = 4.18$, $p = 0.03$; $\eta_p^2 = 0.29$). The results of the *post hoc* test showed, in hemianopic patients without pulvinar lesions, a significant reduction of response times to seen Gabor patches paired with unseen fearful faces (589 ms), compared to the conditions in which they were paired with unseen happy (624 ms; $p = 0.02$) or neutral faces (621 ms; $p = 0.02$; **Figure 4**). Response times in the happy and neutral conditions revealed no significant difference ($p = 0.78$). In contrast, in hemianopics with pulvinar lesions, response times to targets were not modulated by unseen stimuli. Indeed, the response times to Gabor patches in the intact field, paired with simultaneous unseen fearful faces (672 ms) did not show significant differences compared to response times to seen targets, paired with simultaneous happy (665 ms; $p = 0.58$) and neutral faces (661 ms; $p = 0.63$). Again, these two latter conditions revealed no significant difference ($p = 0.73$; see **Figure 4**).

Results of the ANOVA on the percentage of correct responses showed no significant main effect or interaction (all *ps* > 0.1; mean percentage of correct responses = 89% ± 7%).

DISCUSSION

Hemianopic patients without blindsight with pulvinar lesions do not show implicit visual processing for fearful faces, in contrast with hemianopics with lesions not involving the pulvinar. Indeed, in keeping with previous studies (Bertini et al., 2017), hemianopic patients without blindsight and whose lesions do not encompass the pulvinar show response facilitation to Gabor patches displayed in their intact visual field, during the simultaneous presentation of faces expressing fear in their blind visual field, but not happy or neutral faces. In contrast, in hemianopic patients with pulvinar lesions, no response facilitation for stimuli presented in the intact field was found.

TABLE 2 | Percentages of correct answers in the two-alternative forced choice tasks.

Case	Visual detection task	Emotional task	Gender task	Shape task
P1	49%	52%	52%	54%
P2	52%	47%	46%	53%
P3	48%	49%	53%	51%
P4	51%	54%	51%	48%
P5	54%	52%	48%	52%
P6	47%	53%	45%	54%
P7	55%	45%	51%	44%
P8	46%	49%	52%	53%
P9	52%	53%	53%	49%
P10	47%	55%	49%	52%
P11	48%	48%	46%	50%
P12	52%	50%	48%	54%

The fear-specific facilitation in hemianopic patients without blindsight, in which the pulvinar is spared, suggests that, after damage to the cortical visual route, only threat-related visual information can be processed in the absence of awareness. This is in line with previous findings on hemianopic patients without blindsight, showing enhanced visual encoding (Cecere et al., 2014) and response facilitation (Bertini et al., 2013, 2017) to stimuli presented in their intact field, only when fearful faces were displayed at the same time in their blind field. Similarly, a specific implicit visual processing for fearful stimuli has been shown also using fear conditioned neutral faces in patients with visual field defects, corroborating the hypothesis that salient and ecologically relevant stimuli might receive a preferential processing in the absence of awareness (Anders et al., 2004, 2009). This effect has been attributed to the subcortical colliculus-pulvinar-amygdala circuit, spared after the lesion (Bertini et al., 2016). Indeed, this subcortical circuit seems pivotal for the rapid, coarse, and unconscious processing of salient and emotional visual stimuli (for a review: Tamietto and de Gelder, 2010; Garrido et al., 2012; Garvert et al., 2014; McFadyen et al., 2017). In this perspective, the processing of fearful stimuli in the absence of awareness seems to represent an adaptive mechanism, in which the fear-related signals processed by the subcortical circuit might indicate a potential threat, facilitating visual processing in the intact visual field and thus ensuring rapid visual analysis of the surroundings. Alternatively, the observed facilitation in the presence of unseen fearful stimuli might depend also on influences of the subcortical circuit on interconnected motor cortices, which might facilitate the motor response to stimuli toward the intact field. In keeping, a large body of evidence has shown that fearful stimuli alter the state of the motor cortex (de Gelder et al., 2004; Schutter et al., 2008; Borgomaneri et al., 2015, 2017), albeit findings of effects of unconsciously perceived fear on the motor system are rather sparse (Engelen et al., 2018). However, previous EEG investigations on hemianopics without blindsight (Cecere et al., 2014) have shown that the implicit visual processing of fearful

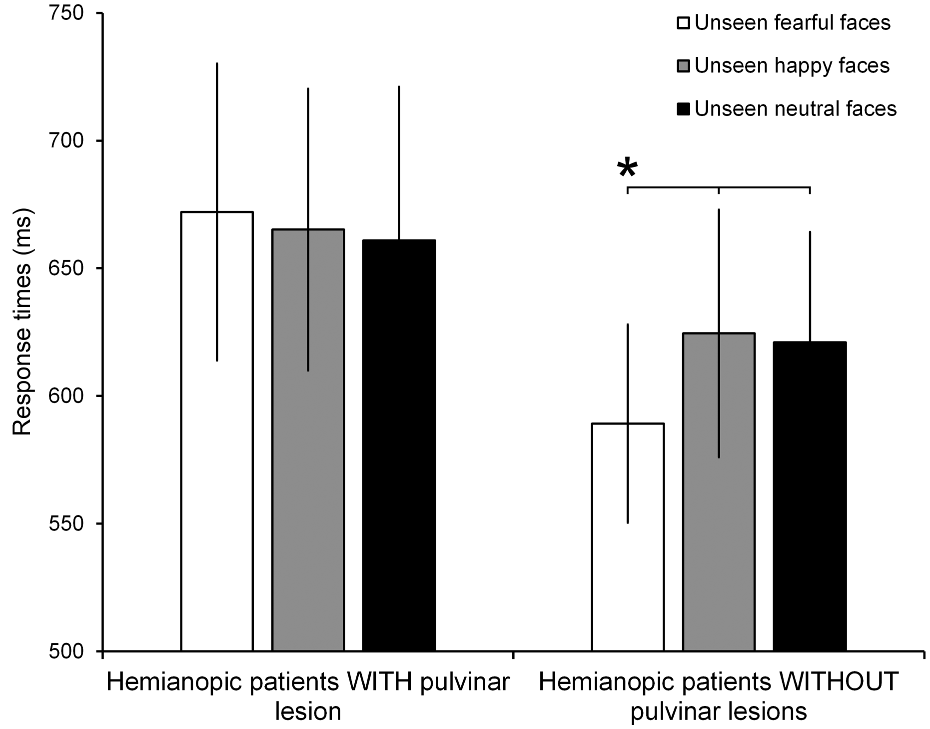


FIGURE 4 | Mean RTs for each condition (unseen fearful faces, unseen happy faces, and unseen neutral faces) in patients with and without pulvinar lesions. Error bars represent the standard error of the mean (SEM). Asterisks indicate a $p < 0.05$.

stimuli affect the stage of structural encoding of the visual stimuli in the intact field (i.e., the N170 component), therefore suggesting that unconscious fear has influences on the early visual process.

The present results add to previous data by demonstrating that the pulvinar represents a critical relay structure of this subcortical pathway, conveying threat-related visual information from the SC to the amygdala, in the absence of awareness. The pulvinar has been extensively reported to assist in shifting to relevant visual stimuli (Benevento and Miller, 1981; Benevento and Port, 1995; Arend et al., 2008), therefore supporting its pivotal role in the processing of salient visual information. Most knowledge of the importance of the pulvinar in the rapid processing of visual threat has been obtained from primates and humans with selective pulvinar lesions. In monkeys, medial and dorsolateral pulvinar neurons revealed selective responses to snakes, showing larger mean response magnitude and shorter latencies, than responses to other stimuli, therefore suggesting a mechanism facilitating rapid visual detection of fear-relevant stimuli (Van Le et al., 2013, 2014). Evidence on patients has shown that unilateral pulvinar lesions impair discrimination of fearful faces in the visual field contralateral to the lesion (Ward et al., 2007) and undermine the fast processing of threatening stimuli (Ward et al., 2005). In addition, patients with lesions to the pulvinar also demonstrated reduced attentional effects of salient distracter (Snow et al., 2009). In line, increasingly converging evidence from neuroimaging studies show pulvinar activation in the presence of threatening stimuli (Almeida et al., 2015) and fearful facial expressions (Vuilleumier et al., 2003).

The prominent role of the pulvinar as a convergence point for transmitting ascending visual information to the amygdala seems to account for its relevance in fear-related processing (Bridge et al., 2016). Studies on animals have reported that the superficial layers of the SC send visual information to the intermediate and deep layers of the SC (May, 2006; Stein et al., 2009), which, in turn, project to the medial subdivision of the pulvinar (Benevento and Fallon, 1975; Linke et al., 1999; Grieve et al., 2000). Importantly, the medial pulvinar has reciprocal connections with the amygdala (Grieve et al., 2000; Shipp, 2003). Although most of the evidence on the connectivity patterns of the pulvinar arises from anatomical studies on non-human primates, recent tractography studies have demonstrated direct connectivity between the SC, the pulvinar and the amygdala also in humans (Tamietto et al., 2012; Rafal et al., 2015; Koller et al., 2018). Specifically, the fibers connecting these structures ascend from the SC, pass through the medial pulvinar to the pole of the pulvinar, and then descend to the lateral pulvinar to finally connect to the amygdala (Rafal et al., 2015; Koller et al., 2018). Crucially, these fibers are spared and reportedly strengthened after lesions to the visual cortex in patients with affective blindsight (Tamietto et al., 2012), providing further evidence that these connections might represent the anatomical circuit subserving implicit emotional processing. However, it is worth noting that the performance of patients with affective blindsight is different from the performance of hemianopic patients without blindsight in this and in previous studies (Anders et al., 2004, 2009; Bertini et al., 2013, 2017; Cecere et al., 2014). Indeed, affective blindsight patients show above-chance discrimination of emotional faces in forced choice tasks and response facilitation to emotionally–congruent pairs of facial stimuli (de Gelder et al., 1999, 2001; Pegna et al., 2005), regardless the type of emotion. On the contrary, hemianopics without blindsight show fear-specific response facilitation (Anders et al., 2004, 2009, Bertini et al., 2013, 2017; Cecere et al., 2014). Although the subcortical colliculus-pulvinar-amygdala visual pathway seems to contribute to the implicit emotional processing in both patients with affective blindsight and hemianopics without blindsight, their distinct patterns of performance might be attributed to different neural substrates. More precisely, we can speculate that the performance of affective blindsight patients might depend on the contribution of spared and functionally reorganized visual cortices. Such a peculiar functional reorganization might have different accounts, depending both on the etiology or the site of patients' lesions.

For instance, in the case of the most extensively studied patient with affective blindsight, i.e., G.Y. such a functional reorganization might be the result of plastic changes occurring due to the early onset of his lesion (Celeghin et al., 2015), possibly involving also interhemispheric contributions (Celeghin et al., 2017, 2018). Another well documented case, i.e., patient D.B., with implicit visual processing for a variety of visual features (Weiskrantz, 1986), including the emotional content (de Gelder et al., 2002; Tamietto et al., 2009), underwent surgical removal of a benign tumor at the age of 30, but suffered from visual symptoms from his teens (Weiskrantz, 1986). The slow growth of low-grade benign tumors is known to promote profound plastic changes and, therefore, might account for his peculiar residual abilities (Duffau, 2017). Finally, affective blindsight has been mainly reported in a series of single case studies investigating patients with cortical blindness following bilateral occipital disruption (e.g., Pegna et al., 2005; Solcà et al., 2015; Burra et al., 2017; Striemer et al., 2017). In these patients, the disruption of both visual cortices might have induced a more radical reorganization of the visual pathways conveying visual information from the subcortical structures to the cortex, thus promoting the emergence of their striking visual residual abilities. Overall, although the functional neuroanatomy of the affective blindsight still remain elusive, post-lesional plastic changes occurring to the subcortical V1-independent pathways and their multiple connections with extrastriate areas, both within the dorsal and the ventral stream (Tamietto and Morrone, 2016), might represent a plausible account for this phenomenon. In this perspective, it has been recently proposed that in affective blindsight patients, facial emotional visual information is conveyed from the SC to the pulvinar, from which it is directly projected to extrastriate and temporal cortices, such as the superior temporal sulcus, to finally reach the amygdala (Gerbella et al., 2017). This suggests a significant contribution of extrastriate areas in mediating the above chance performance in discriminating emotional faces and the facilitatory effects for congruent pairs of emotional stimuli, typical of patients with affective blindsight.

In contrast, the fear-specific implicit visual processing observed in hemianopics without blindsight might be subserved only by activity in the subcortical colliculus-pulvinar-amygdala circuit. Behavioral evidence on healthy participants tested with backward-masked emotional faces have provided support to this hypothesis (Cecere et al., 2013). Indeed, participants exhibited fear-specific facilitatory effects (resembling the ones observed in hemianopics) when the activity of the occipital cortex was temporary inhibited by transcranial direct current stimulation (tDCS). In contrast, when tDCS was delivered to a control area and, thus, the activity in visual cortices was not suppressed, congruency-dependent response facilitation (resembling the one observed in blindsight patients) was found (Cecere et al., 2013). However, further studies investigating the fiber tracts spared in hemianopics without blindsight are needed to disentangle the additional possible contribution of subcortical-cortical connections (Tamietto and Morrone, 2016) in mediating fear-specific implicit visual processing. In the present study, only hemianopic patients with left hemispheric lesions were tested, since previous evidence have shown that hemianopic patients with lesions to right hemisphere do not demonstrate the facilitatory effects due to the implicit visual processing of emotional stimuli (Cecere et al., 2014; Bertini et al., 2017). This suggests a prevalence of the subcortical pathway in the right hemisphere for unconscious processing of emotional information (Ladavas et al., 1984; Cimatti et al., 1993; for a review, Gainotti, 2012). This view is also supported by neuroimaging evidence showing right amygdala activation to unseen fearful faces in a patient with cortical blindness (Burra et al., 2017) and to masked emotional stimuli in healthy participants (Costafreda et al., 2008).

CONCLUSION

To conclude, the present findings provide evidence that lesions to the pulvinar prevent implicit visual processing of fear in hemianopic patients, supporting the hypothesis that the pulvinar nuclei of the thalamus play a considerable role in connecting unconscious threat-related visual information, from the SC to the amygdala. This is in line with the notion that the primate pulvinar might have evolved in part to assist in rapid threat detection and avoidance (Isbell, 2006), favoring adaptive defensive mechanisms.

AUTHOR CONTRIBUTIONS

CB and DB collected the data. CB and MP analyzed the data. CB, MP, DB, and EL designed the experiments and wrote the manuscript.

FUNDING

This study was funded by grant from MIUR (PRIN2015 NA455) to EL.

ACKNOWLEDGMENTS

We are grateful to Prof. Giuseppe di Pellegrino and Dr. Vincenzo Antonelli for their support in lesions reconstruction.

REFERENCES

Almeida, I., Soares, S. C., and Castelo-Branco, M. (2015). The distinct role of the amygdala, superior colliculus and pulvinar in processing of central and peripheral snakes. *PLoS One* 10:e0129949. doi: 10.1371/journal.pone.0129949

Anders, S., Birbaumer, N., Sadowski, B., Erb, M., Mader, I., Grodd, W., et al. (2004). Parietal somatosensory association cortex mediates affective blindsight. *Nat. Neurosci.* 7, 339–340. doi: 10.1038/nn1213

Anders, S., Eippert, F., Wiens, S., Birbaumer, N., Lotze, M., and Wildgruber, D. (2009). When seeing outweighs feeling: a role for prefrontal cortex in passive control of negative affect in blindsight. *Brain* 132, 3021–3031. doi: 10.1093/brain/awp212

Arend, I., Rafal, R., and Ward, R. (2008). Spatial and temporal deficits are regionally dissociable in patients with pulvinar lesions. *Brain* 131, 2140–2152. doi: 10.1093/brain/awn135

Barleben, M., Stoppel, C. M., Kaufmann, J., Merkel, C., Wecke, T., Goertler, M., et al. (2015). Neural correlates of visual motion processing without awareness in patients with striate cortex and pulvinar lesions. *Hum. Brain Mapp.* 36, 1585–1594. doi: 10.1002/hbm.22725

Benevento, L. A., and Fallon, J. H. (1975). The ascending projections of the superior colliculus in the rhesus monkey (*Macaca mulatta*). *J. Comp. Neurol.* 160, 339–361. doi: 10.1002/cne.901600306

Benevento, L. A., and Miller, J. (1981). Visual responses of single neurons in the caudal lateral pulvinar of the macaque monkey. *J. Neurosci.* 1, 1268–1278. doi: 10.1523/JNEUROSCI.01-11-01268.1981

Benevento, L. A., and Port, J. D. (1995). Single neurons with both form/color differential responses and saccade-related responses in the nonretinotopic pulvinar of the behaving macaque monkey. *Vis. Neurosci.* 12, 523–544. doi: 10.1017/S0952523800008439

Bertini, C., Cecere, R., and Làdavas, E. (2013). I am blind, but I "see" fear. *Cortex* 49, 985–993. doi: 10.1016/j.cortex.2012.02.006

Bertini, C., Cecere, R., and Làdavas, E. (2017). Unseen fearful faces facilitate visual discrimination in the intact field. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.07.029 [Epub ahead of print].

Bertini, C., Grasso, P. A., and Làdavas, E. (2016). The role of the retino-colliculo-extrastriate pathway in visual awareness and visual field recovery. *Neuropsychologia* 90, 72–79. doi: 10.1016/J.NEUROPSYCHOLOGIA.2016.05.011

Borgomaneri, S., Gazzola, V., and Avenanti, A. (2015). Transcranial magnetic stimulation reveals two functionally distinct stages of motor cortex involvement during perception of emotional body language. *Brain Struct. Funct.* 220, 2765–2781. doi: 10.1007/s00429-014-0825-6

Borgomaneri, S., Vitale, F., and Avenanti, A. (2017). Behavioral inhibition system sensitivity enhances motor cortex suppression when watching fearful body expressions. *Brain Struct. Funct.* 222, 3267–3282. doi: 10.1007/s00429-017-1403-5

Bridge, H., Leopold, D. A., and Bourne, J. A. (2016). Adaptive pulvinar circuitry supports visual cognition. *Trends Cogn. Sci.* 20, 146–157. doi: 10.1016/J.TICS.2015.10.003

Burra, N., Hervais-Adelman, A., Celeghin, A., de Gelder, B., and Pegna, A. J. (2017). Affective blindsight relies on low spatial frequencies. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.10.009 [Epub ahead of print].

Cecere, R., Bertini, C., and Làdavas, E. (2013). Differential contribution of cortical and subcortical visual pathways to the implicit processing of emotional faces: a tDCS study. *J. Neurosci.* 33, 6469–6475. doi: 10.1523/JNEUROSCI.3431-12.2013

Cecere, R., Bertini, C., Maier, M. E., and Làdavas, E. (2014). Unseen fearful faces influence face encoding: evidence from ERPs in hemianopic patients. *J. Cogn. Neurosci.* 26, 2564–2577. doi: 10.1162/jocn_a_00671

Celeghin, A., Bagnis, A., Diano, M., Méndez, C. A., Costa, T., and Tamietto, M. (2018). Functional neuroanatomy of blindsight revealed by activation likelihood estimation meta-analysis. *Neuropsychologia* doi: 10.1016/J.NEUROPSYCHOLOGIA.2018.06.007 [Epub ahead of print].

Celeghin, A., de Gelder, B., and Tamietto, M. (2015). From affective blindsight to emotional consciousness. *Conscious. Cogn.* 36, 414–425. doi: 10.1016/J.CONCOG.2015.05.007

Celeghin, A., Diano, M., de Gelder, B., Weiskrantz, L., Marzi, C. A., and Tamietto, M. (2017). Intact hemisphere and corpus callosum compensate for visuomotor functions after early visual cortex damage. *Proc. Natl. Acad. Sci. U.S.A.* 114, E10475–E10483. doi: 10.1073/pnas.1714801114

Cimatti, D., Pesce, M., Del Tuozzi, G., and Ladavas, E. (1993). Emotional evaluation with and without conscious stimulus identification: evidence from a split-brain patient. *Cognit. Emot.* 7, 95–114. doi: 10.1080/02699939308409179

Clas, P., Groeschel, S., and Wilke, M. (2012). A semi-automatic algorithm for determining the demyelination load in metachromatic leukodystrophy. *Acad. Radiol.* 19, 26–34. doi: 10.1016/J.ACRA.2011.09.008

Costafreda, S. G., Brammer, M. J., David, A. S., and Fu, C. H. Y. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res. Rev.* 58, 57–70. doi: 10.1016/J.BRAINRESREV.2007.10.012

Day-Brown, J. D., Wei, H., Chomsung, R. D., Petry, H. M., and Bickford, M. E. (2010). Pulvinar projections to the striatum and amygdala in the tree shrew. *Front. Neuroanat.* 4:143. doi: 10.3389/fnana.2010.00143

de Gelder, B., Pourtois, G., van Raamsdonk, M., Vroomen, J., and Weiskrantz, L. (2001). Unseen stimuli modulate conscious visual experience: evidence from inter-hemispheric summation. *Neuroreport* 12, 385–391. doi: 10.1097/00001756-200102120-00040

de Gelder, B., Pourtois, G., Weiskrantz, L., Perozzo, P., Geminiani, G., Weiskrantz, L., et al. (2002). Fear recognition in the voice is modulated by unconsciously recognized facial expressions but not by unconsciously recognized affective pictures. *Proc. Natl. Acad. Sci. U.S.A.* 99, 4121–4126. doi: 10.1073/pnas.062018499

de Gelder, B., Snyder, J., Greve, D., Gerard, G., and Hadjikhani, N. (2004). Fear fosters flight: a mechanism for fear contagion when perceiving emotion expressed by a whole body. *Proc. Natl. Acad. Sci. U.S.A.* 101, 16701–16706. doi: 10.1073/pnas.0407042101

de Gelder, B., Vroomen, J., Pourtois, G., and Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport* 10, 3759–3763. doi: 10.1097/00001756-199912160-00007

de Haan, B., Clas, P., Juenger, H., Wilke, M., and Karnath, H.-O. (2015). Fast semi-automated lesion demarcation in stroke. *Neuroimage* 9, 69–74. doi: 10.1016/J.NICL.2015.06.013

Diano, M., Celeghin, A., Bagnis, A., and Tamietto, M. (2017). Amygdala response to emotional stimuli without awareness: facts and interpretations. *Front. Psychol.* 7:2029. doi: 10.3389/fpsyg.2016.02029

Duffau, H. (2017). *Diffuse Low-Grade Gliomas in Adults*. London: Springer. doi: 10.1007/978-3-319-55466-2

Ekman, P., and Friesen, W. (1976). *Pictures of Facial Affect*. Palo Alto, CA: Consulting Psychologists Press.

Engelen, T., Zhan, M., Sack, A. T., and de Gelder, B. (2018). The influence of conscious and unconscious body threat expressions on motor evoked potentials studied with continuous flash suppression. *Front. Neurosci.* 12:480. doi: 10.3389/fnins.2018.00480

Gainotti, G. (2012). Unconscious processing of emotions and the right hemisphere. *Neuropsychologia* 50, 205–218. doi: 10.1016/J.NEUROPSYCHOLOGIA.2011.12.005

Garrido, M. I., Barnes, G. R., Sahani, M., and Dolan, R. J. (2012). Functional evidence for a dual route to amygdala. *Curr. Biol.* 22, 129–134. doi: 10.1016/J.CUB.2011.11.056

Garvert, M. M., Friston, K. J., Dolan, R. J., and Garrido, M. I. (2014). Subcortical amygdala pathways enable rapid face processing. *Neuroimage* 102, 309–316. doi: 10.1016/J.NEUROIMAGE.2014.07.047

Gerbella, M., Caruana, F., and Rizzolatti, G. (2017). Pathways for smiling, disgust and fear recognition in blindsight patients. *Neuropsychologia* doi: 10.1016/J.NEUROPSYCHOLOGIA.2017.08.028 [Epub ahead of print].

Grieve, K. L., Acuña, C., and Cudeiro, J. (2000). The primate pulvinar nuclei: vision and action. *Trends Neurosci.* 23, 35–39. doi: 10.1016/S0166-2236(99)01482-4

Isbell, L. A. (2006). Snakes as agents of evolutionary change in primate brains. *J. Hum. Evol.* 51, 1–35. doi: 10.1016/J.JHEVOL.2005.12.012

Kimberg, D. Y., Coslett, H. B., and Schwartz, M. F. (2007). Power in voxel-based lesion-symptom mapping. *J. Cogn. Neurosci.* 19, 1067–1080. doi: 10.1162/jocn.2007.19.7.1067

Koller, K., Rafal, R. D., Platt, A., and Mitchell, N. D. (2018). Orienting toward threat: contributions of a subcortical pathway transmitting retinal afferents to the amygdala via the superior colliculus and pulvinar. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2018.01.027 [Epub ahead of print].

Ladavas, E., Nicoletti, R., Umiltá, C., and Rizzolatti, G. (1984). Right hemisphere interference during negative affect: a reaction time study. *Neuropsychologia* 22, 479–485. doi: 10.1016/0028-3932(84)90042-3

LeDoux, J. E. (1996). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. New York, NY: Simon & Schuster.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem–amygdala–cortical 'alarm' system for subliminal signals of fear. *Neuroimage* 24, 235–243. doi: 10.1016/J.NEUROIMAGE.2004.08.016

Linke, R., De Lima, A. D., Schwegler, H., and Pape, H.-C. (1999). Direct synaptic connections of axons from superior colliculus with identified thalamo-amygdaloid projection neurons in the rat: possible substrates of a subcortical visual pathway to the amygdala. *J. Comp. Neurol.* 403, 158–170. doi: 10.1002/(SICI)1096-9861(19990111)403:2<158::AID-CNE2>3.0.CO;2-6

Luo, Q., Holroyd, T., Jones, M., Hendler, T., and Blair, J. (2007). Neural dynamics for facial threat processing as revealed by gamma band synchronization using MEG. *Neuroimage* 34, 839–847. doi: 10.1016/J.NEUROIMAGE.2006.09.023

Maior, R. S., Hori, E., Tomaz, C., Ono, T., and Nishijo, H. (2010). The monkey pulvinar neurons differentially respond to emotional expressions of human faces. *Behav. Brain Res.* 215, 129–135. doi: 10.1016/J.BBR.2010.07.009

May, P. J. (2006). The mammalian superior colliculus: laminar structure and connections. *Prog. Brain Res.* 151, 321–378. doi: 10.1016/S0079-6123(05)51011-2

McFadyen, J., Mermillod, M., Mattingley, J. B., Halász, V., and Garrido, M. I. (2017). A rapid subcortical amygdala route for faces irrespective of spatial frequency and emotion. *J. Neurosci.* 37, 3864–3874. doi: 10.1523/JNEUROSCI.3525-16.2017

Méndez-Bértolo, C., Moratti, S., Toledano, R., Lopez-Sosa, F., Martínez-Alvarez, R., Mah, Y. H., et al. (2016). A fast pathway for fear in human amygdala. *Nat. Neurosci.* 19, 1041–1049. doi: 10.1038/nn.4324

Morris, J. S., Öhman, A., and Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc. Natl. Acad. Sci. U.S.A.* 96, 1680–1685. doi: 10.1073/PNAS.96.4.1680

Nguyen, M. N., Hori, E., Matsumoto, J., Tran, A. H., Ono, T., and Nishijo, H. (2013). Neuronal responses to face-like stimuli in the monkey pulvinar. *Eur. J. Neurosci.* 37, 35–51. doi: 10.1111/ejn.12020

Nguyen, M. N., Matsumoto, J., Hori, E., Maior, R. S., Tomaz, C., Tran, A. H., et al. (2014). Neuronal responses to face-like and facial stimuli in the monkey superior colliculus. *Front. Behav. Neurosci.* 8:85. doi: 10.3389/fnbeh.2014.00085

Nguyen, M. N., Nishimaru, H., Matsumoto, J., Van Le, Q., Hori, E., Maior, R. S., et al. (2016). Population coding of facial information in the monkey superior colliculus and pulvinar. *Front. Neurosci.* 10:583. doi: 10.3389/fnins.2016.00583

Pegna, A. J., Khateb, A., Lazeyras, F., and Seghier, M. L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nat. Neurosci.* 8, 24–25. doi: 10.1038/nn1364

Pustina, D., Branch Coslett, H., Turkeltaub, P. E., Tustison, N., Schwartz, M. F., and Avants, B. (2016). Automated segmentation of chronic stroke lesions using LINDA: lesion identification with neighborhood data analysis. *Hum. Brain Mapp.* 37, 1405–1421. doi: 10.1002/hbm.23110

Rafal, R. D., Koller, K., Bultitude, J. H., Mullins, P., Ward, R., Mitchell, A. S., et al. (2015). Connectivity between the superior colliculus and the amygdala in humans and macaque monkeys: virtual dissection with probabilistic DTI tractography. *J. Neurophysiol.* 114, 1947–1962. doi: 10.1152/jn.01016.2014

Rizzolatti, G., Buchtel, H. A., Camarda, R., and Scandolara, C. (1980). Neurons with complex visual properties in the superior colliculus of the macaque monkey. *Exp. Brain Res.* 38, 37–42. doi: 10.1007/BF00237928

Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., and Karnath, H.-O. (2012). Age-specific CT and MRI templates for spatial normalization. *Neuroimage* 61, 957–965. doi: 10.1016/J.NEUROIMAGE.2012.03.020

Rorden, C., and Brett, M. (2000). Stereotaxic display of brain lesions. *Behav. Neurol.* 12, 191–200. doi: 10.1155/2000/421719

Rorden, C., Karnath, H.-O., and Bonilha, L. (2007). Improving lesion-symptom mapping. *J. Cogn. Neurosci.* 19, 1081–1088. doi: 10.1162/jocn.2007.19.7.1081

Schutter, D. J. L. G., Hofman, D., and Van Honk, J. (2008). Fearful faces selectively increase corticospinal motor tract excitability: a transcranial magnetic stimulation study. *Psychophysiology* 45, 345–348. doi: 10.1111/j.1469-8986.2007.00635.x

Shipp, S. (2003). The functional logic of cortico-pulvinar connections. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 1605–1624. doi: 10.1098/rstb.2002.1213

Snow, J. C., Allen, H. A., Rafal, R. D., and Humphreys, G. W. (2009). Impaired attentional selection following lesions to human pulvinar: evidence for homology between human and monkey. *Proc. Natl. Acad. Sci. U.S.A.* 106, 4054–4059. doi: 10.1073/pnas.0810086106

Solcà, M., Guggisberg, A. G., Schnider, A., and Leemann, B. (2015). Facial blindsight. *Front. Hum. Neurosci.* 9:522. doi: 10.3389/fnhum.2015.00522

Stein, B. E., Stanford, T. R., and Rowland, B. A. (2009). The neural basis of multisensory integration in the midbrain: its organization and maturation. *Hear. Res.* 258, 4–15. doi: 10.1016/J.HEARES.2009.03.012

Striemer, C. L., Whitwell, R. L., and Goodale, M. A. (2017). Affective blindsight in the absence of input from face processing regions in occipital-temporal cortex. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2017.11.014 [Epub ahead of print].

Tamietto, M., Castelli, L., Vighetti, S., Perozzo, P., Geminiani, G., Weiskrantz, L., et al. (2009). Unseen facial and bodily expressions trigger fast emotional reactions. *Proc. Natl. Acad. Sci. U.S.A.* 106, 17661–17666. doi: 10.1073/pnas.0908994106

Tamietto, M., and de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nat. Rev. Neurosci.* 11, 697–709. doi: 10.1038/nrn2889

Tamietto, M., and Morrone, M. C. (2016). Visual plasticity: blindsight bridges anatomy and function in the visual system. *Curr. Biol.* 26, R70–R73. doi: 10.1016/J.CUB.2015.11.026

Tamietto, M., Pullens, P., de Gelder, B., Weiskrantz, L., and Goebel, R. (2012). Subcortical connections to human amygdala and changes following destruction of the visual cortex. *Curr. Biol.* 22, 1449–1455. doi: 10.1016/J.CUB.2012.06.006

Van Le, Q., Isbell, L. A., Matsumoto, J., Le, V. Q., Hori, E., Tran, A. H., et al. (2014). Monkey pulvinar neurons fire differentially to snake postures. *PLoS One* 9:e114258. doi: 10.1371/journal.pone.0114258

Van Le, Q., Isbell, L. A., Matsumoto, J., Nguyen, M., Hori, E., Maior, R. S., et al. (2013). Pulvinar neurons reveal neurobiological evidence of past selection for rapid detection of snakes. *Proc. Natl. Acad. Sci. U.S.A.* 110, 19000–19005. doi: 10.1073/pnas.1312648110

Vuilleumier, P., Armony, J. L., Driver, J., and Dolan, R. J. (2003). Distinct spatial frequency sensitivities for processing faces and emotional expressions. *Nat. Neurosci.* 6, 624–631. doi: 10.1038/nn1057

Ward, R., Calder, A. J., Parker, M., and Arend, I. (2007). Emotion recognition following human pulvinar damage. *Neuropsychologia* 45, 1973–1978. doi: 10.1016/J.NEUROPSYCHOLOGIA.2006.09.017

Ward, R., Danziger, S., and Bamford, S. (2005). Response to visual threat following damage to the pulvinar. *Curr. Biol.* 15, 571–573. doi: 10.1016/J.CUB.2005.01.056

Weiskrantz, L. (1986). *Blindsight: a Case Study and Implications*. Available at: https://philpapers.org/rec/WEIBAC

Zhang, Y., Kimberg, D. Y., Coslett, H. B., Schwartz, M. F., and Wang, Z. (2014). Multivariate lesion-symptom mapping using support vector regression. *Hum. Brain Mapp.* 35, 5861–5876. doi: 10.1002/hbm.22590

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Psychology

OPINION
published: 26 October 2018
doi: 10.3389/fpsyg.2018.02068

Multiple Dissociations in Patients With Disorders of Body Awareness: Implications for the Study of Consciousness

Gabriella Bottini[1,2,3]*, *Francesca Giulia Magnani*[2,3], *Gerardo Salvato*[1,2,3] *and*
Martina Gandola[1,2]

[1] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [2] NeuroMI—Milan Center for Neuroscience, University of Milano Bicocca, Milan, Italy, [3] Cognitive Neuropsychology Centre, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Keywords: awareness, anosognosia for hemiplegia, somatoparaphrenia, caloric vestibular stimulation, consciousness

Edited by:
*Cecilia Guariglia,
Università degli Studi di Roma La Sapienza, Italy*

Reviewed by:
*Paul Mark Jenkinson,
University of Hertfordshire, United Kingdom*

***Correspondence:**
*Gabriella Bottini
g.bottini@unipv.it;
gabriella.bottini@gmail.com*

Specialty section:
This article was submitted to Consciousness Research, a section of the journal Frontiers in Psychology

Received: 27 July 2018
Accepted: 08 October 2018
Published: 26 October 2018

Citation:
Bottini G, Magnani FG, Salvato G and Gandola M (2018) Multiple Dissociations in Patients With Disorders of Body Awareness: Implications for the Study of Consciousness. Front. Psychol. 9:2068. doi: 10.3389/fpsyg.2018.02068

Elucidating the nature of consciousness has become one of the most relevant challenges in modern neuroscience. The study of patients with brain damage who exhibit selective impairments in awareness has contributed significantly to redefining the concept of consciousness, shedding light on at least two interesting aspects of its organization: the presence of behavioral and anatomical domain-specific dissociations and the possibility of modulating disturbances in awareness via both central and peripheral stimulations (e.g., caloric vestibular stimulation[1]—CVS—or transcranial Direct Current Stimulation[2]—tDCS). Evidence emerging from these lines of research has provided information regarding the nature of conscious processes, their neural substrates, and their associated physiological processes.

Anosognosia for hemiplegia (AHP), in which patients with brain damage deny the presence of their contralesional motor deficits (Babinski, 1914), represents how the conscious experience may be finely segmented. Indeed, motor anosognosia can manifest in a limb-specific and modality-specific fashion: For instance, it may affect the upper or lower limbs only (Von Hagen and Ives, 1937; Berti et al., 1996; Moro et al., 2011) and may concern either motor or sensory impairments (i.e., dissociations between AHP and anosognosia for hemianesthesia: AHA; see for example Marcel et al., 2004; Spinazzola et al., 2008; Pia et al., 2014). Moreover, previous studies have reported double dissociations between anosognosia and neglect (Bisiach et al., 1986; Berti et al., 1996; Marcel et al., 2004), revealing that AHP does not depend on the attentional deficits typical of Unilateral Spatial Neglect (Bisiach et al., 1986; Berti et al., 1996; Marcel et al., 2004). The existence of these dissociations suggests that brain lesions selectivity affect conscious processes, rather than inducing general and global impairments in awareness. Thus, patients may be aware of one deficit (e.g., hemianesthesia) yet unaware of another (e.g., hemiplegia).

---

[1] CVS involves irrigation of the left or right external auricular canal with warm or cold water. This produces effects on several cognitive processes by eliciting neural responses from vestibular neurons, which are strongly interconnected with higher-order brain regions (see review in Bottini and Gandola, 2015).

[2] By applying a low-intensity electric current to the scalp, tDCS allows for controlled interference with brain activity. Inhibitory (cathodal) or excitatory (anodal) modulation can be induced in the stimulated brain region (Fregni et al., 2015).

The use of structured interviews (see for example Bisiach et al., 1986; Berti et al., 1996) and systematic experimental paradigms (Jenkinson and Fotopoulou, 2010) has revealed that motor denial can manifest in various ways. For example, when required to perform a specific action (such as clapping), some patients became aware that they are unable to execute the movement (moderate AHP, score 2/2, in Bisiach et al., 1986; emergent awareness in Moro et al., 2011), while others claim to have performed the action despite their paralysis (severe AHP, score 3/3 in Bisiach et al., 1986). These differences in awareness have been classically conceptualized as different degrees of severity (Bisiach et al., 1986). Alternatively, these two behaviors may be related to different cognitive mechanisms. Among patients who claim they have performed the movement despite demonstrations that no movements have occurred (i.e., those with apparently more severe anosognosia), this obstinate motor delusion seems to be related to the loss of on-going monitoring mechanisms. In other words, this denial is embedded into the neural systems subserving the comparison between the intended and performed movements (Frith et al., 2000; Blakemore et al., 2002). Conversely, among patients who realize they have not moved after failure of the action, the initial denial of impairment may depend on the semantic knowledge that the body segments can move, and on the memory of being able to move prior to the occurrence of the brain lesion (Marcel et al., 2004). Thus, the false belief of preserved motor competence is supported by a left hemisphere *"narrator"* telling what he knows about bodily functions (Geschwind, 1965).

Previous research has also revealed interesting dissociations between *implicit* and *explicit* awareness: Indeed, patients with AHP may have implicit knowledge of their deficit, which is otherwise denied explicitly (see for example Marcel et al., 2004; Fotopoulou et al., 2010; Vocat and Vuilleumier, 2010; Moro et al., 2011). Explicit awareness can be explored directly by asking patients to verbally declare whether they can move, while implicit awareness is generally indirectly inferred based on behavioral observations (Fotopoulou et al., 2010; Moro et al., 2011). Several reports have indicated that different levels of awareness may coexist within the same patient: "Patients who verbally deny their hemiplegia usually do not object of being confined to bed" (Bisiach and Geminiani, 1991). More recently, this dissociation has been explored systematically using either verbal (Fotopoulou et al., 2010) or motor paradigms (Moro et al., 2011). These studies also provide partially convergent anatomical patterns of the dissociation between explicit and implicit awareness.

Anatomical evidence also supports the modular organization of consciousness. In 2005, Berti et al. (2005) demonstrated that AHP occurs due to lesions of the cerebral regions that monitor motor functions, such as the premotor cortex, rather than damage to a general supramodal neural system. Notably, the brain lesion of a single patient, who exhibited anosognosia without signs of neglect, overlapped with the damage associated with AHP in the between groups comparisons, supporting the hypothesis that motor-monitoring deficits can be disentangled from USN. However, Karnath et al. (2005) reported different results, instead emphasizing the role of the posterior insula in AHP. Further evidence supports the notion that different forms of anosognosia correspond to discrete anatomical substrates depending on the sensory-motor disorders observed. These studies have suggested that AHA is associated with lesions of brain areas such as the putamen, which is well known to subserve sensory processing, contrasting somewhat with the regions involved in AHP (Spinazzola et al., 2008; Pia et al., 2014).

However, more recent studies (Fotopoulou et al., 2010; Vocat et al., 2010; Moro et al., 2011, 2016) have provided a more complex picture of the brain regions involved in awareness, suggesting that AHP is a multi-component disorder caused by lesions of complex and distributed cortical-subcortical anatomical networks, rather than isolated regions (see discussion in Fotopoulou, 2014). Given the available evidence, combined use of the lesion-symptom method and modern neuroanatomical approaches such as fMRI/resting-state fMRI, diffusion tensor imaging, and fiber tractography may allow researchers to overcome limitations associated with defining large-scale networks involved in complex cognitive functions (e.g., body and motor awareness), based on classical clinical anatomical correlations alone (Catani et al., 2012; Thiebaut de Schotten and Foulon, 2018). Elucidating these networks may advance our understanding of the neural and physiological bases of consciousness (see for example Gandola et al., 2014a).

Disorders of consciousness may affect different levels of body representation. AHP is frequently associated with asomatognosia (see Jenkinson et al., 2018) and somatoparaphrenia (SP), which is characterized by the delusion that the paralyzed limb does to not belong to oneself (Gerstmann, 1942). In AHP and SP, impairments in consciousness are associated with bodily functions and body ownership, respectively. Rare cases of SP without AHP have been described (see for example Invernizzi et al., 2012; Moro et al., 2016). Invernizzi et al. (2012) demonstrated that SP is mainly associated with lesions to the right thalamus, basal ganglia, and posterior limb of the internal capsule, sparing the dorsal and premotor regions typically associated with AHP (Berti et al., 2005). The lesional pattern defines the neuropsychological manifestations observed, although the level of interdependence among the different components contributing to mental representation of the body remains unknown. The existence of patients who, surprisingly enough, deny ownership of their paralyzed limb although they recognize that they cannot move it may be explained by the influence of selective awareness modules on unshared senses of agency and body ownership as independent components, supporting an independent rather than additive model of body representation (Tsakiris et al., 2006; Invernizzi et al., 2012). More recently, Moro et al. (2016) revealed that disturbed sensation of limb ownership (DSO) is associated with more medial and subcortical lesions (mainly involving the basal ganglia and surrounding white matter) than those involved in AHP. This evidence supports the existence of a neural dissociation between DSO and AHP in contrast to previous evidence, which suggested a crucial role of the right posterior insula for both the sense of limb ownership and motor anosognosia (Baier and Karnath, 2008).

Extensive research has suggested that central and peripheral stimulation (e.g., CVS, tDCS) can induce transient and selective remission in patients with various disorders of awareness (e.g., USN, anosognosia, and somatoparaphrenia), supporting the notion that conscious experience can be selectively modified. For instance, CVS may restore motor awareness (see for example Vallar et al., 1990, 2003; Bisiach et al., 1991; Rode et al., 1992), the sense of body ownership (Bisiach and Geminiani, 1991; Rode et al., 1992; Salvato et al., 2016), and sensory perception (Vallar et al., 1990, 1993; Bottini et al., 1995, 2005). Moreover, the effects of CVS on these disorders suggest that physiological components play a role in the conscious bodily experience, interacting with cognitive processes. In our recent study, for example, we utilized CVS in a patient with SP, who regained the sense of body part ownership following stimulation. We also observed an increase in body temperature following CVS, which correlated with the temporarily restored sense of limb ownership (Salvato et al., 2018). We speculated that this effect may have been due to partial overlap between the neural correlates of body ownership, thermoregulatory control, and the area stimulated by left-CVS. Alternatively, CVS may modulate interoceptive signals (e.g., body temperature), which may in turn have increased the sense of body ownership. Interestingly, in healthy volunteers, CVS induces a temperature drop in both arms, which is accompanied by bilateral improvements in tactile acuity (Sedda et al., 2016). Other research has indicated that selective remission can be induced in patients with disorders of awareness using simple verbal (Case F. B. in Bottini et al., 2002) or spatial manipulations (Salvato et al., 2016) or using mirror techniques (Jenkinson et al., 2013), highlighting the malleability of conscious processes.

Moreover, tDCS is effective in modulating disorders of motor awareness. For instance, tDCS over the right premotor cortex has been shown to induce selective remission of AHP (Gandola et al., 2014b). Such improvements manifested only when the patient was requested to perform the action (online judgment) with his eyes open, while motor anosognosia remained when the patient judged non-attempted actions (offline condition) and during the eyes-closed online condition. Selective modulation of motor awareness has also been observed in healthy volunteers, revealing that posterior parietal modulation interferes with non-intentional movement awareness, while premotor cortex modulation interferes with intentional movement awareness (Bolognini et al., 2016; Bruno et al., 2017).

In conclusion, although the neurophysiological organization of awareness into discrete neural systems may explain the multiple dissociations of symptoms observed in patients with brain damage, alternative hypotheses have also been proposed. Recently, the influential theoretical framework, which is based on the free-energy principle and Bayesian inference (Friston, 2005), has been applied to the study of AHP (Fotopoulou, 2014, 2015) and self-recognition (Apps and Tsakiris, 2014). This framework may provide an alternative to highly modular models of motor and self-awareness and may represent a unified explanation of the clinical variability/dissociations of such deficits (Fotopoulou, 2014, 2015).

AUTHOR CONTRIBUTIONS

GB, FGM, GS, and MG equally contributed in drafting and revising the final version of the manuscript.

REFERENCES

Apps, M. A., and Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neurosci. Biobehav. Rev.* 41, 85–97. doi: 10.1016/j.neubiorev.2013.01.029

Babinski, J. (1914). Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie). *Rev. Neurol.* 27, 845–848.

Baier, B., and Karnath, H. O. (2008). Tight link between our sense of limb ownership and self-awareness of actions. *Stroke* 39, 486–488. doi: 10.1161/STROKEAHA.107.495606

Berti, A., Bottini, G., Gandola, M., Pia, L., Smania, N., Stracciari, A., et al. (2005). Shared cortical anatomy for motor awareness and motor control. *Science* 309, 488–491. doi: 10.1126/science.1110625

Berti, A., Làdavas, E., and Della Corte, M. (1996). Anosognosia for hemiplegia, neglect dyslexia, and drawing neglect: clinical findings and theoretical considerations. *J. Int. Neuropsychol. Soc.* 2, 426–440. doi: 10.1017/S135561770000151X

Bisiach, E., and Geminiani, G. (1991). "Anosognosia related to hemiplegia and hemianopia," in *Awareness of Deficits After Brain Injury,* eds G. P. Prigatano and D. L. Schacter (New York, NY: Oxford University Press), 17–39.

Bisiach, E., Rusconi, M. L., and Vallar, G. (1991). Remission of somatoparaphrenic delusion through vestibular stimulation. *Neuropsychologia* 29, 1029–1031. doi: 10.1016/0028-3932(91)90066-H

Bisiach, E., Vallar, G., Perani, D., Papagno, C., and Berti, A. (1986). Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 24, 471–482. doi: 10.1016/0028-3932(86)90092-8

Blakemore, S. J., Wolpert, D. M., and Frith, C. D. (2002). Abnormalities in the awareness of action. *Trends Cogn. Sci.* 6, 237–242. doi: 10.1016/S1364-6613(02)01907-1

Bolognini, N., Zigiotto, L., Carneiro, M. I., and Vallar, G. (2016). "How Did I Make It?": uncertainty about own motor performance after inhibition of the premotor cortex. *J. Cogn. Neurosci.* 28, 1052–1061. doi: 10.1162/jocn_a_00950

Bottini, G., Bisiach, E., Sterzi, R., and Vallar, G. (2002). Feeling touches in someone else's hand. *Neuroreport* 13, 249–252. doi: 10.1097/00001756-200202110-00015

Bottini, G., and Gandola, M. (2015). Beyond the non-specific attentional effect of caloric vestibular stimulation: evidence from healthy subjects and patients. *Multisens. Res.* 28, 591–612. doi: 10.1163/22134808-00002504

Bottini, G., Paulesu, E., Gandola, M., Loffredo, S., Scarpa, P., Sterzi, R., et al. (2005). Left caloric vestibular stimulation ameliorates right hemianesthesia. *Neurology* 65, 1278–1283. doi: 10.1212/01.wnl.0000182398.14088.e8

Bottini, G., Paulesu, E., Sterzi, R., Warburton, E., Wise, R. J., Vallar, G., et al. (1995). Modulation of conscious experience by peripheral sensory stimuli. *Nature* 376, 778–781. doi: 10.1038/376778a0

Bruno, V., Fossataro, C., Bolognini, N., Zigiotto, L., Vallar, G., Berti, A., et al. (2017). The role of premotor and parietal cortex during monitoring of involuntary movement: a combined TMS and tDCS study. *Cortex* 96, 83–94. doi: 10.1016/j.cortex.2017.09.001

Catani, M., Dell'acqua, F., Bizzi, A., Forkel, S. J., Williams, S. C., Simmons, A., et al. (2012). Beyond cortical localization in clinico-anatomical correlation. *Cortex* 48, 1262–1287. doi: 10.1016/j.cortex.2012.07.001

Fotopoulou, A. (2014). Time to get rid of the 'Modular' in neuropsychology: a unified theory of anosognosia as aberrant predictive coding. *J. Neuropsychol.* 8, 1–19. doi: 10.1111/jnp.12010

Fotopoulou, A. (2015). The virtual bodily self: mentalisation of the body as revealed in anosognosia for hemiplegia. *Conscious. Cogn.* 33, 500–510. doi: 10.1016/j.concog.2014.09.018

Fotopoulou, A., Pernigo, S., Maeda, R., Rudd, A., and Kopelman, M. A. (2010). Implicit awareness in anosognosia for hemiplegia: unconscious interference without conscious re-representation. *Brain* 133 (Pt 12), 3564–3577. doi: 10.1093/brain/awq233

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., et al. (2015). Regulatory considerations for the clinical and research use of transcranial Direct Current Stimulation (tDCS): review and recommendations from an expert panel. *Clin Res Regul Aff.* 32, 22–35. doi: 10.3109/10601333.2015.980944

Friston, K. (2005). A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci.* 360, 815–836. doi: 10.1098/rstb.2005.1622

Frith, C. D., Blakemore, S. J., and Wolpert, D. M. (2000). Abnormalities in the awareness and control of action. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 355, 1771–1788. doi: 10.1098/rstb.2000.0734

Gandola, M., Bottini, G., Zapparoli, L., Invernizzi, P., Verardi, M., Sterzi, R., et al. (2014a). The physiology of motor delusions in anosognosia for hemiplegia: Implications for current models of motor awareness. *Conscious. Cogn.* 24C, 98–112. doi: 10.1016/j.concog.2014.01.001

Gandola, M., Sedda, A., Manera, M., Pingue, V., Salvato, G., Spitoni, G. F., et al. (2014b). Selective improvement of anosognosia for hemiplegia during transcranial direct current stimulation: a case report. *Cortex* 61, 107–119. doi: 10.1016/j.cortex.2014.08.007

Gerstmann, J. (1942). Problem of imperception of disease and of impaired body territories with organic lesions. Relation to body scheme and its disorders. *Arch. Neurol. Psychiatry* 48, 890–913.

Geschwind, N. (1965). Disconnexion syndromes in animals and man II. *Brain* 88, 585–644. doi: 10.1093/brain/88.3.585

Invernizzi, P., Gandola, M., Romano, D., Zapparoli, L., Bottini, G., and Paulesu, E. (2012). What is mine? Behavioral and anatomical dissociations between somatoparaphrenia and anosognosia for hemiplegia. *Behav. Neurol.* 26, 139–150. doi: 10.3233/BEN-2012-110226

Jenkinson, P. M., and Fotopoulou, A. (2010). Motor awareness in anosognosia for hemiplegia: experiments at last! *Exp. Brain Res.* 204, 295–304. doi: 10.1007/s00221-009-1929-8

Jenkinson, P. M., Haggard, P., Ferreira, N. C., and Fotopoulou, A. (2013). Body ownership and attention in the mirror: insights from somatoparaphrenia and the rubber hand illusion. *Neuropsychologia* 51, 1453–1462. doi: 10.1016/j.neuropsychologia.2013.03.029

Jenkinson, P. M., Moro, V., and Fotopoulou, A. (2018). Definition: asomatognosia. *Cortex* 101, 300–301. doi: 10.1016/j.cortex.2018.02.001

Karnath, H. O., Baier, B., and Nägele, T. (2005). Awareness of the functioning of one's own limbs mediated by the insular cortex? *J. Neurosci.* 25, 7134–7138. doi: 10.1523/JNEUROSCI.1590-05.2005

Marcel, A. J., Tegnér, R., and Nimmo-Smith, I. (2004). Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. *Cortex* 40, 19–40. doi: 10.1016/S0010-9452(08)70919-5

Moro, V., Pernigo, S., Tsakiris, M., Avesani, R., Edelstyn, N. M., Jenkinson, P. M., et al. (2016). Motor versus body awareness: voxel-based lesion analysis in anosognosia for hemiplegia and somatoparaphrenia following right hemisphere stroke. *Cortex* 83, 62–77. doi: 10.1016/j.cortex.2016.07.001

Moro, V., Pernigo, S., Zapparoli, P., Cordioli, Z., and Aglioti, S. M. (2011). Phenomenology and neural correlates of implicit and emergent motor awareness in patients with anosognosia for hemiplegia. *Behav. Brain Res.* 225, 259–269. doi: 10.1016/j.bbr.2011.07.010

Pia, L., Spinazzola, L., Garbarini, F., Bellan, G., Piedimonte, A., Fossataro, C., et al. (2014). Anosognosia for hemianaesthesia: a voxel-based lesion-symptom mapping study. *Cortex* 61, 158–166. doi: 10.1016/j.cortex.2014.08.006

Rode, G., Charles, N., Perenin, M. T., Vighetto, A., Trillet, M., and Aimard, G. (1992). Partial remission of hemiplegia and somatoparaphrenia through vestibular stimulation in a case of unilateral neglect. *Cortex* 28, 203–208. doi: 10.1016/S0010-9452(13)80048-2

Salvato, G., Gandola, M., Veronelli, L., Agostoni, E. C., Sberna, M., Corbo, M., et al. (2016). The spatial side of somatoparaphrenia: a case study. *Neurocase* 22, 154–160. doi: 10.1080/13554794.2015.1077257

Salvato, G., Gandola, M., Veronelli, L., Berlingeri, M., Corbo, M., and Bottini, G. (2018). "The vestibular system, body temperature and sense of body ownership: a potential link? Insights from a single case study". *Physiol Behav.* 194, 522–526. doi: 10.1016/j.physbeh.2018.07.008

Sedda, A., Tonin, D., Salvato, G., Gandola, M., and Bottini, G. (2016). Left caloric vestibular stimulation as a tool to reveal implicit and explicit parameters of body representation. *Conscious. Cogn.* 41, 1–9. doi: 10.1016/j.concog.2016.01.012

Spinazzola, L., Pia, L., Folegatti, A., Marchetti, C., and Berti, A. (2008). Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. *Neuropsychologia* 46, 915–926. doi: 10.1016/j.neuropsychologia.2007.12.015

Thiebaut de Schotten, M., and Foulon, C. (2018). The rise of a new associationist school for lesion-symptom mapping. *Brain* 141, 2–4. doi: 10.1093/brain/awx332

Tsakiris, M., Prabhu, G., and Haggard, P. (2006). Having a body versus moving your body: how agency structures body-ownership. *Conscious. Cogn.* 15, 423–432. doi: 10.1016/j.concog.2005.09.004

Vallar, G., Bottini, G., Rusconi, M., and Sterzi, R. (1993). Exploring somatosensory hemineglect by vestibular stimulation. *Brain* 116, 71–86. doi: 10.1093/brain/116.1.71

Vallar, G., Bottini, G., and Sterzi, R. (2003). Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemiinattention: is there a relationship? *Prog. Brain Res.* 142, 289–301. doi: 10.1016/S0079-6123(03)42020-7

Vallar, G., Sterzi, R., Bottini, G., Cappa, S., and Rusconi, M. L. (1990). Temporary remission of left hemianesthesia after vestibular stimulation. A sensory neglect phenomenon. *Cortex* 26, 123–131. doi: 10.1016/S0010-9452(13)80078-0

Vocat, R., Staub, F., Stroppini, T., and Vuilleumier, P. (2010). Anosognosia for hemiplegia: a clinical-anatomical prospective study. *Brain* 133 (Pt 12), 3578–3597. doi: 10.1093/brain/awq297

Vocat, R., and Vuilleumier, P. (2010). "Neuroanatomy of impaired body awareness in anosognosia and hysteria: a multi-component account," in *The Study of Anosognosia*, ed G. Prigatano (Oxford: Oxford University Press), 359–403.

Von Hagen, K., and Ives, E. (1937). Anosognosia (Babinski), imperception of hemiplegia: report of six cases, one with autopsy. *Bull. Los Angeles Neurol. Soc.* 2, 95–103.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read
for greatest visibility
and readership

FAST PUBLICATION
Around 90 days
from submission
to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative,
and constructive
peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers
acknowledged by name
on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data
and methods to enhance
research reproducibility

DIGITAL PUBLISHING
Articles designed
for optimal readership
across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics
track visibility across
digital media

EXTENSIVE PROMOTION
Marketing
and promotion
of impactful research

LOOP RESEARCH NETWORK
Our network
increases your
article's readership