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Effective connectivity abnormalities in Lewy body disease with visual hallucinations

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HIGHLIGHTS

- Patients with Lewy Body Diseases and visual hallucinations have reduced effective connectivity of the right intraparietal sulcus.
- Visual hallucinations likely reflect defective top-down attentional control over bottom-up visual processing.
- Transcranial magnetic stimulation coupled with electroencephalography detects network changes underlying visual hallucinations.

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ABSTRACT

Objective: To assess the changes in effective connectivity of important regions of the visual network (VIS) and dorsal attention network (DAN) underlying visual hallucinations (VHs) in Dementia with Lewy Bodies (DLB), Parkinson's Disease (PD) and Parkinson's Disease Dementia (PDD), as measured by a transcranial magnetic stimulation-electroencephalographic technique (TMS-EEG).
Methods: We stimulated the right visual cortex (V1/V2), the right intraparietal sulcus and the right frontal eye fields, two key regions of the DAN, and measured TMS-evoked cortical activation within the VIS and the DAN. We compared 11 patients with VHs and 15 patients without VHs.
Results: Patients with VHs showed lower TMS-evoked cortical activation within the DAN following intraparietal sulcus and frontal eye fields stimulation than patients without VHs. No difference was found between patients with and without cognitive impairment. Also, when considering only patients with cognitive impairment, VHs were associated with lower TMS-evoked cortical activation following intraparietal sulcus stimulation.
Conclusions: DLB, PD, and PDD patients with VHs had less effective connectivity of the right intraparietal sulcus within the DAN than patients without VHs.
Significance: We provided the first evidence that VHs are associated with specific intraparietal sulcus dysfunction within the DAN in patients with PDD, PD, and DLB.

Abbreviations: DLB, Dementia with Lewy Bodies; DAN, Dorsal Attention Network; DMN, Default Mode Network; EEG, Electroencephalography; EMG, Electromyography; FEF, Frontal Eye Fields; FDI, First Dorsal Interosseus; FDR, False Discovery Rate; IPS, Intra Parietal Sulcus; MEP, Motor-Evoked Potential; MNI, Montreal Neurological Institute; PD, Parkinson's Disease; PDD, Parkinson's Disease Dementia; RMT, rest motor threshold; ROI, region of interest; SPL, superior parietal lobule; TOI, Time of interest; TMS, Transcranial Magnetic Stimulation; VHs, Visual Hallucinations; VIS, Visual Network; V1/V2, Primary and Secondary Visual Cortex.

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1. Introduction

Visual hallucinations (VHs) are one of the core clinical features of Dementia with Lewy Bodies (DLB) and can also be found in Parkinson's disease (PD) with dementia (PDD) and occasionally in patients with PD without dementia (Emre et al. 2007; McKeith et al. 2017; Shine et al. 2015). Patients who experience VHs may have increased nursing home requirements, mortality rates and cause distress to their caregivers (Barnes and David 2001; Ravina et al. 2007). Therefore, it is crucial to understand the pathophysiological mechanisms underlying VHs.

Experimental data suggest that changes in the activity of the primary and secondary visual cortex (V1/V2), which are both areas involved in the so-called bottom-up visual processing, may play a role in VHs (Khundakar et al. 2016; Taylor et al. 2011). Despite the conventional belief that VHs arise from visuo-perceptual dysfunction, clinical observations have found a correlation between VHs and visuo-attentional and executive impairment, implying defective top-down attentional control over visuo-perceptual information processing may be the underlying cause (Cagnin et al., 2013). This observation was supported by neuroimaging studies suggesting that VHs in Lewy Body pathologies (PD, PDD, DLB) may result from a defective top-down control of the dorsal attention network (DAN) during periods of conflicting visual processing, leading to a subsequent takeover of the default mode network (DMN) during stimulus interpretation (Diez-Cirarda et al. 2023; Iaccarino et al. 2018; McKeith et al. 2017; Muller et al. 2014; Onofrj et al. 2019). However, the role played by two critical DAN nodes, the frontal eye fields, and the intraparietal sulcus, remains unclear.

Transcranial magnetic stimulation (TMS) has been used in healthy subjects to probe V1/V2 excitability and to investigate the role of frontal eye fields and intraparietal sulcus in top-down control of visual processing (Szczepanski and Kastner 2009). The concurrent use of TMS during electroencephalographic recordings (TMS-EEG) had been previously used in healthy subjects to directly assess the effect of V1/V2, intraparietal sulcus, and frontal eye fields perturbation on distributed brain activity by measuring TMS-evoked potentials (TEPs) (Taylor and Thut 2012; Torriero et al. 2018). Recent experimental data support the principle according to which TMS-evoked neuronal activation of a specific cortical area propagates to functionally connected local and distant regions of the same network and can be considered an expression of effective connectivity within the stimulated network (Ozdemir et al., 2020; Momi et al. 2021).

This study investigated whether changes in effective connectivity of key brain regions of the right visual network (VIS) and DAN play a role in VHs pathophysiology in patients with DLB and PD with and without dementia. We recorded TEPs from stimulation of V1/V2, frontal eye fields, and intraparietal sulcus and compared TMS-evoked source cortical activity within the VIS and DAN in patients with and without VHs.

2. Materials and methods

2.1. Subjects' selection

Twenty-six right-handed patients (Mean Age 70, S.E. 3.0, 15 males) were recruited after screening for eligibility to undergo TMS investigations. Twelve patients had PD according to international clinical diagnostic criteria, eight had PD with dementia (PDD) (Emre et al. 2007), and six had DLB (McKeith et al. 2017). Eleven patients had VHs (3 PD, 2 PDD, 6 DLB, Mean Age 74.3, S.E. 2.95, 8 males), whereas fifteen did not (9 PD, 6 PDD, Mean Age 67.6, S.E. 2.8, 7 males). Acetylcholinesterase inhibitors and memantine were discontinued 24 hours before the study. No patient was taking benzodiazepine, neuroleptics, or dopamine agonists. The study protocol was approved by the institutional review board and conducted in compliance with the Declaration of Helsinki. All patients gave their written informed consent.

2.2. Experimental session

Each patient participated in a single experimental session, carried out in the morning between 9:00 and 12:00 a.m. Patients were seated on a chair designed for TMS (EMS, Italy) with their right forearms pronated and resting on armrests and were instructed to keep their eyes open and look at a fixed point (a black cross) displayed on a PC screen at 70 cm.

EEG was recorded from 32 electrodes mounted on s 10–20 system (BrainCap, EASYCAP, Germany), bandpass filtered at DC-2.5 kHz, and digitized at 10 kHz using a TMS-compatible amplifier (NeurOne, Bittium Corporation, Finland). All electrodes were grounded to FPz and online referenced to POz. Impedance for each channel was kept below 5 kΩ. Surface electromyography (EMG) was recorded from the right first dorsal interosseous (D360, Digitimer, UK), bandpass filtered (10 Hz-1 kHz), sampled at 5 kHz (CED 1401; CED, UK), and stored for offline analysis (Signal v6.4, CED, UK).

TMS was delivered using a 70-mm figure-of-eight coil connected to a Magstim2002 stimulator (Magstim, Whitland, UK), whereas sham stimulation was performed by tilting the coil. Neuronavigation (SofTaxic, EMS, Italy) with an optical tracking system (Polaris Vicra, Northern Digital Inc., Canada) was used to monitor coil positioning and identify stimulation areas based on a reconstructed brain template available at the Montreal Neurological Institute (MNI), using non-linear fitting. The motor hotspot was identified as eliciting the largest motor-evoked potentials (MEPs) in the right FDI with the posterior-anterior current direction. Resting motor threshold (RMT) was defined as the minimum intensity required to elicit MEPs of $\geq$ 50 μV peak-to-peak amplitude in at least 5 of 10 consecutive trials.

One hundred TMS pulses (inter-pulse interval 5 seconds with 10 % jitter) were delivered in separate blocks over the right V1/V2, frontal eye fields and intraparietal sulcus in both real and sham condition over each node, for a total of 600 pulses per subject (Fig. 1A). For right frontal eye fields stimulation, the coil was placed with the handle parallel to the precentral sulcus (Chanes et al. 2012) and centered over the Talairach coordinates x = 32, y = -9, z = 48 (Capotosto et al. 2009). For right intraparietal sulcus stimulation, Talairach coordinates were x = 23, y = -65, z = 48 and the coil was placed perpendicular to the posterior parietal sulcus (Capotosto et al. 2009). The right side was studied for all patients since previous studies suggested that changes in the right networks' activity are associated with VHs (Iaccarino et al., 2018; Shine et al., 2015). For right V1/V2 stimulation, the coil was placed over the occipital pole, slightly above O2 electrode, with the handle pointing upward (Taylor et al. 2011).

For each stimulated node, a real stimulation intensity was 160 % RMT. Sham stimulation intensity was defined by asking each participant to report the maximal stimulation output value that better matched the perception of the loudness of the TMS click produced by real stimulation on the same site. Sham stimulation intensities had a maximal stimulation output on average 5–10 % higher than real ones. The order of stimulated sites and real and sham TMS blocks was randomized for each participant. To limit residual TMS-associated auditory stimulation during EEG recordings, participants wore ear defenders (SNR = 30) (Massimini et al. 2005; Rocchi et al. 2020) on top of earphones continuously playing a noise designed to mask the TMS click (ter Braack et al. 2015). Additionally, a 0.5 cm foam layer was placed under the coil to minimize

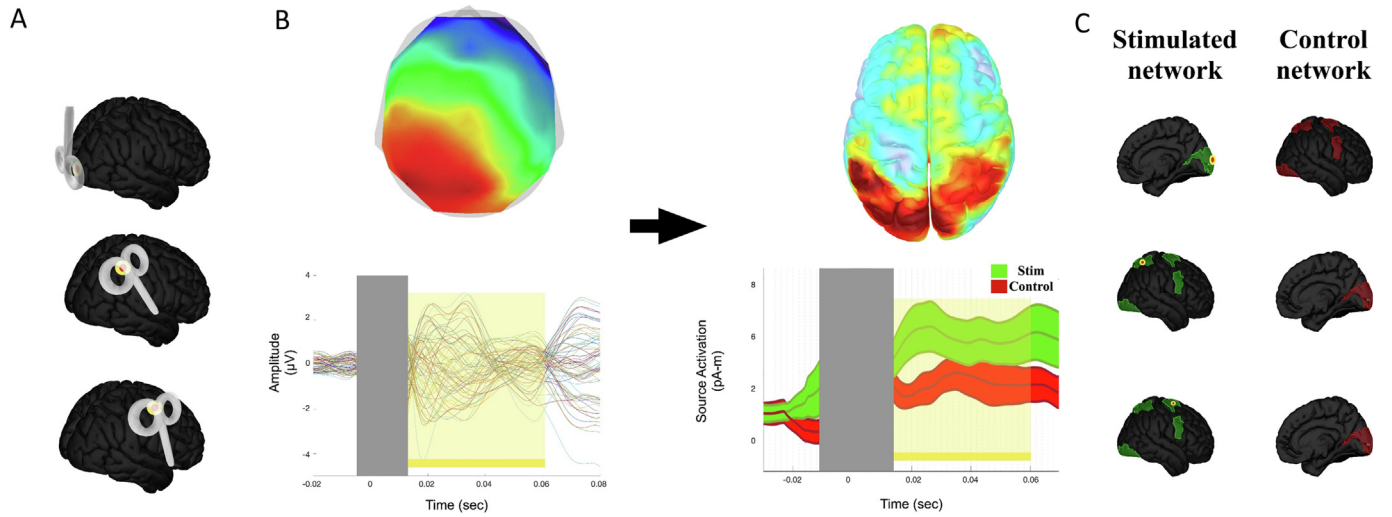

Fig. 1. Experimental set-up. A. The three stimulated areas with respective coil positioning: primary/secondary visual cortex (V1/2) (top), intraparietal sulcus (IPS) (middle), and frontal eye fields (FEF) (bottom). B. TMS-EEG responses from V1/V2 stimulation from one exemplificative subject. Left: the EEG signal was first preprocessed in the sensor space (scalp topography (top), butterfly plot (bottom)). Right: the EEG signal was then projected in the source space through Minimum Norm imaging using dynamic statistical parametric mapping (dSPM). Group comparisons were performed on a time window of interest (TOI) of 15–60 ms post-stimulus (yellow rectangle). C. For each stimulated area, group comparisons were performed on a region of interest (ROIs) consisting of the stimulated network (red, DAN mask when IPS and FEF were stimulated, VIS mask when V1/V2 was stimulated), and non-stimulated network (VIS mask when IPS and FEF were stimulated, DAN mask when V1/V2 was stimulated). DAN: dorsal attention network; VIS: visual network; TMS-EEG: transcranial magnetic stimulation-electroencephalography. *To be reproduced in color on the Web (free of charge) and in black-and-white in print.*

bone conduction of the TMS click and the scalp sensation caused by coil vibration (Rocchi et al. 2020).

2.3. TMS-EEG preprocessing

TMS-EEG data were pre-processed using the EEGLAB (13.6.5b) and TESA (1.0.1) toolboxes in MATLAB (Version R2017b) according to a previously described pipeline (Rogasch et al. 2017). The continuous EEG signal was epoched from −2.2 s before to 2.2 s after the TMS and demeaned with a reference window of −1000 to −5 ms with respect to the TMS pulse. Data from −10 to 12 ms around the stimulus were removed to eliminate the stimulation artifact and then interpolated using a cubic function fitting on data 20 ms before and 20 ms after the removed data. Data was then downsampled to 1000 Hz, including an anti-aliasing low-pass filter at 500 Hz. Subsequently, a first round of independent component analysis (ICA) was applied, using the FastICA algorithm, to remove the residual stimulation and decay artifact (1 or 2 components removed). Then, the signal was filtered using a zero-phase, band pass, 4th-order Butterworth filter between 1–90 Hz, and then a zero-phase, 4th-order band-stop Butterworth filter between 48–52 Hz. Epoching was repeated, with −2.0 to 2.0 peristimulus windows to remove edge artifact, and a second −500 to −5 ms window demeaning was applied. A second round of ICA was used to remove residual artifacts (eye movement artifact, blinking, movement, bad electrode contact, EMG) (mean (SD) components removed were 10 (4) for V1/V2 stimulation, 8 (3) for the intraparietal sulcus, and 12 (5) for the frontal eye fields).

To assess the network level evoked activity as a measure of effective connectivity, we analyzed TMS-induced source activation (Ozdemir et al. 2020). To do so, cleaned TMS-EEG epochs were imported into Brainstorm (Tadel et al. 2011) (https://neuroimage.usc.edu/brainstorm) to perform the source-level reconstruction. A common default anatomy was created using an MRI template (ICBM152). A 3D template of a 10–20 system 32-channel EEG cap was adjusted to the anatomical template according to the fixed points Inion, Nasion, preauricular points, and Vertex. Forward modeling of neuroelectric fields was performed using the open MEEG symmetric boundary element method, all with default parameter settings. Noise covariance was estimated from individual trials for each subject using the pre-TMS (-900 to −100) time window as a baseline. The inverse modeling of the cortical sources was performed using the Minimum Norm Imaging, with dSPM as the source activation measure and an unconstrained model. A median eigenvalue noise covariance regularization was used. The resulting output of the source reconstruction was the unscaled dSPM of the TMS-evoked EEG activity for each cortical vertex. All averages and differences were computed using source data unconstrained to the flat map i.e., norm data, and z-scored to −900 ms to −100 ms (Fig. 1B).

2.4. Statistical analysis

Statistical analysis at the source level was performed by extracting the average source signal from a DAN and VIS mask for each stimulation site. Each mask was computed by merging nodes from a previous study by Shine and colleagues (Shine et al. 2015) after computing a scout of 100 voxels around each node coordinates (“*increase scout size*” function in Brainstorm). The VIS was then obtained by merging scouts around V1 and a Calcarine fissure scout, whereas DAN was obtained by merging the superior parietal lobule (SPL), the lingular gyrus, frontal eye fields, and the dorsolateral prefrontal cortex. Then we measured the TMS-evoked source activity within a region of interest (ROI) consisting of the stimulated network (DAN mask when intraparietal sulcus and frontal eye fields were stimulated, VIS mask when V1/V2 were stimulated), and within a time-window of interest (TOI) from 15 msec to 60 msec post-stimulus to limit sensory contamination (Rocchi et al. 2020) (Fig. 1C). Finally, TMS-evoked source activity was compared between patients with (n = 11) and without VHs (n = 15) using a false discovery rate (FDR)-corrected permutation test on Brainstorm, setting p-value correction to 0.05. We repeated the group comparison using TMS-evoked source activity measured in the non-stimulated network (DAN mask when V1/V2 were stimulated, VIS mask when intraparietal sulcus and frontal eye fields were stimulated) to test the network specificity of our results. To

exclude the possibility of dementia as a possible confounder, TMS-evoked source activity that was found to be different between patients with and without VHs was also compared between cognitively intact (n = 12 PD patients) and patients with dementia (n = 14 patients, 8 with PDD and 6 with DLB), and, within cognitively impaired patients, between those with (n = 8 patients, 2 with PDD and 6 with DLB), and without VHs (n = 6 patients with PDD).

3. Results

Unless specified otherwise, all results presented are reported at a p-value < 0.05.

No patient reported VHs during the experimental procedures.

In patients without VHs we observed distinct TEPs patterns within our TOI depending on the stimulated node (Fig. 2). Following V1/V2 stimulation, we recorded a positive component in the ipsilateral occipital cortex at 23 ms, followed by a dipolar response at 34 ms characterized by posterior negativity and centro-frontal positivity, and a centro-medial positive component at 52 ms (Fig. 2A). Stimulation of the intraparietal sulcus evoked a dipole component at 21 ms with local positivity and contralateral frontal negativity, followed by a dipole at 29 ms exhibiting ipsilateral frontal positivity and contralateral posterior negativity, and a 42 ms dipole with ipsilateral parietal negativity (Fig. 2B). Finally, when stimulating the frontal eye fields, we observed an initial dipole at 18 ms displaying ipsilateral parieto-occipital negativity and contralateral frontal positivity, followed by a dipole at 31 ms with ipsilateral frontal positivity, and a dipole at 51 ms with ipsilateral fronto-parietal positivity and contralateral fronto-parietal negativity (Fig. 2C). Patients with VHs displayed TEP topographies that were largely similar to those without VHs except for a more anteriorly shifted component at 23 ms following V1/V2 stimulation, and a less pronounced 52 ms component following frontal eye fields stimulation.

When stimulating V1, TMS-evoked source activation within the VIS was not statistically different between patients with and without VHs (Fig. 3A). After intraparietal sulcus stimulation, TMS-evoked source activation within the DAN was lower in patients with VHs than in patients without VHs, between 16–22 ms and 49–60 ms post-stimulus (Fig. 3B). After frontal eye fields stimulation, TMS-evoked source activation between 15–19 ms and 21–58 ms post-stimulus within the DAN was lower in patients with VHs compared to patients without VHs (Fig. 3C).

After frontal eye fields, intraparietal sulcus, and V1/V2 stimulation, no difference was found in TMS-evoked source activity measured in the non-stimulated network between patients with and without VHs (Fig. 4). No difference emerged from any area in TMS-evoked source activity measured in the stimulated network between patients with and without dementia, although we observed a tendency for greater source signal in frontal eye fields stimulation between 18 and 50 ms in patients without dementia (p = 0.15) (Fig. 5A). When considering only patients with dementia, TMS-evoked source activation between 17–22 ms and 51–59 ms post-stimulus within the DAN was lower in patients with VHs in comparison to patients without VHs after intraparietal sulcus stimulation; no difference was found when stimulating frontal eye fields between patients with and without VHs (Fig. 5B), and in any area in sham-evoked source activity in stimulated and non-stimulated networks between groups.

4. Discussion

In the present study, we found that TMS stimulation of the right frontal eye fields and intraparietal sulcus evoked less cortical activity within the DAN in patients with VHs compared to those without. On the other hand, TMS targeting the right primary and secondary visual cortex (V1/V2) evoked similar activity within the VIS in patients with and without VHs. TMS-evoked activation after frontal eye fields and intraparietal sulcus stimulation was not statistically different between patients with and without dementia. When only patients with dementia were considered, TMS stimulation of the right intraparietal sulcus evoked again less activity within the DAN in patients with VHs compared to those without, whereas no difference was found following frontal eye field stimulation. In summary, VHs are specifically associated with reduced TMS-evoked activity following intraparietal sulcus stimulation in the DAN, regardless of cognitive status.

Since we found no between-group difference either following sham stimulation or stimulation of nodes outside the network of interest (i.e., DAN activation following V1/V2 stimulation and vice versa), our findings cannot be explained by a possible sensory co-stimulation and reflect genuine and node-specific TMS-evoked network dynamics. No patient was taking medication knowing to cause VHs or medication that could confound TMS-evoked activity at the time of the study. Since similar pathophysiological mechanisms are thought to be underlying hallucinations in PD, PDD and DLB (D'Antonio et al. 2022; Shine et al. 2014), differences in Lewy Bodies pathologies in the patients with VHs we studied do not likely influence the findings we found on VH mechanisms.

We found that TEPs showed features specific to the stimulation site, thus confirming their validity as an index of the functional state of the stimulated area. The TEPs we elicited by V1/V2 stimulation showed a first positive peak around 20 ms local to the stimulated areas followed by a negative component around 40 ms, consistent with scalp topographies reported in previous research (Herring et al. 2015). TEPs from intraparietal sulcus stimulation showed an initial dipolar response at 21 ms showing positivity at the stimulation site, followed by frontal ipsilateral positivity at 29 ms and ipsilateral parieto-occipital negativity at 42 ms. This TEP topography partially aligns with those from a study by Casula et al. (2023), who stimulated the left posterior parietal cortex (PPC) in Alzheimer disease patients. Studies involving healthy controls have reported variable TEP patterns from different left, posterior parietal sites (Freedberg 2020; Grasso et al. 2021; Rogasch et al. 2020). These findings highlight TMS high spatial resolution in the parietal cortex, suggesting that factors like stimulation site, TMS parameters, and patient characteristics significantly influence TEPs. TEPs from frontal eye fields stimulation have been previously investigated by Torriero et al. (2019); however, their study focused on late components, therefore limiting a comparison with the early TEPs we studied.

TMS-evoked neuronal activation propagates via anatomical connections, preferentially to brain areas functionally connected to the stimulated areas, and, therefore, TEPs at the source level represent an index of effective connectivity of stimulated areas within their networks (Momi et al. 2021). Furthermore, TMS-EEG research has demonstrated that TMS applied over V1/V2, as well as over the intraparietal sulcus and frontal eye fields, respectively modulates visual perception and attention, while simultaneously affecting the associated EEG correlates (Taylor and Thut 2012). Thus, TMS-evoked cortical activation in our study reflects a behaviorally relevant measure of the effective connectivity of stimulated areas with their functional networks.

The finding that TMS-evoked VIS activation was similar in patients with and without VHs suggests that V1/V2 effective connectivity does not explain VHs. This result suggests that the early stages of bottom-up visual processing are likely unaffected in patients with VHs. Our findings expand previous reports on normal visual cortex excitability in DLB patients with VHs as measured by TMS-induced phosphenes (Taylor et al. 2011) and are in line with neuroimaging studies demonstrating normal activity in primary

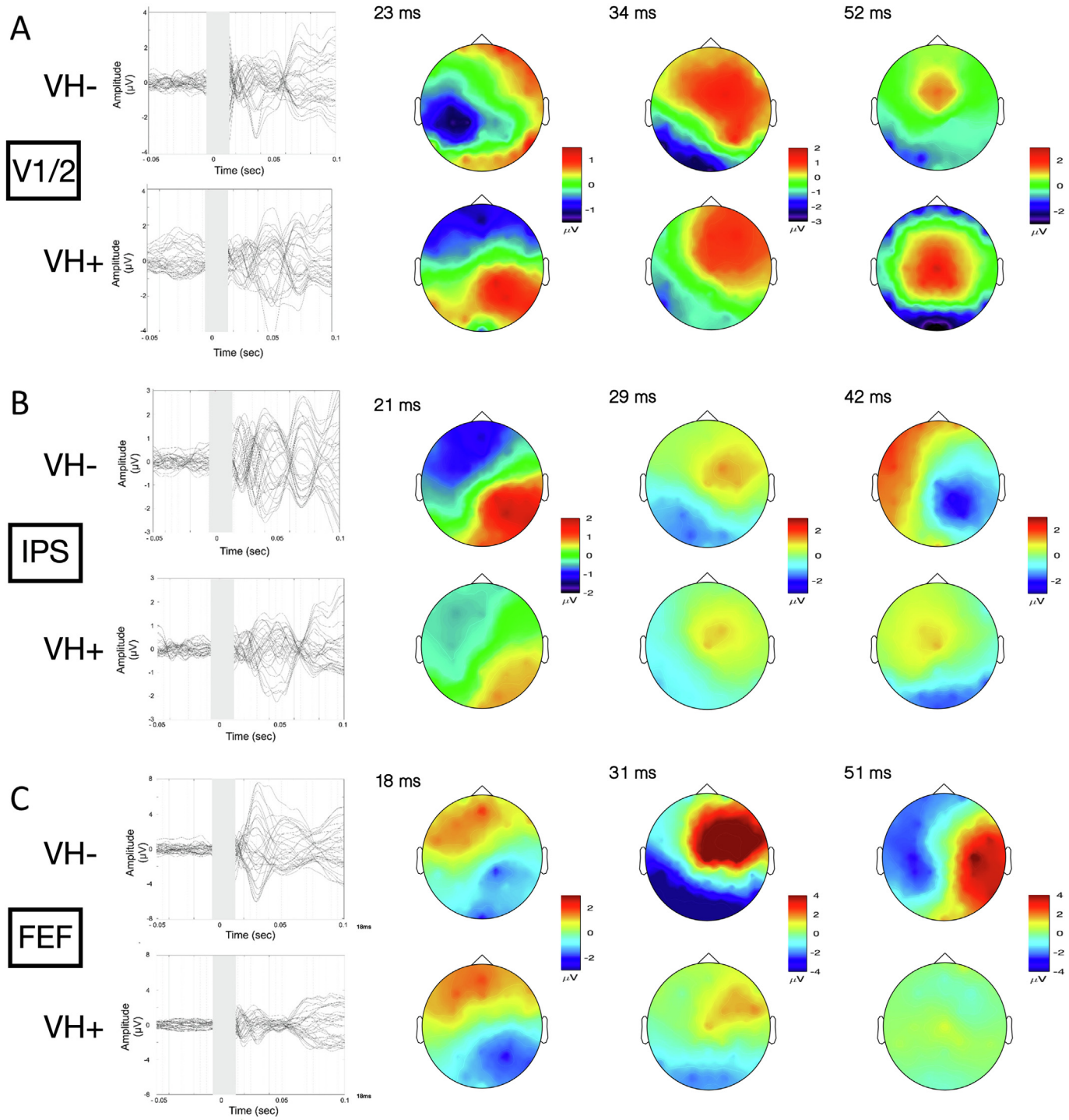

Fig. 2. Scalp topographies of TMS-evoked potentials (TEPs) at sensor level resulting from stimulation of the three nodes, primary/secondary visual cortex V1/2(A), intraparietal sulcus (IPS) (B) and frontal eye fields (FEF) in patients with visual hallucinations (VH+) and patients without (VH−) (C). For each stimulated point the butterfly plots of the evoked response are represented on the left (top VH−, bottom VH+), while the scalp topographies of the identified TEP peaks within the time of interest are represented on the right. Each peak was identified by visually inspecting the butterfly plots of the average TEPs between groups (VH− and VH+) for each condition. See results for further comment on TEPs topographies. *To be reproduced in color on the Web (free of charge) and in black-and-white in print.*

and secondary visual areas in PD and DLB patients with VH (Shine et al., 2015).

In our study TMS stimulation of the FEF and IPS produced less activation of the DAN in patients with VHs. Hypoactivation and altered functional connectivity within the DAN have been observed in previous neuroimaging studies in PD and DLB patients with VHs (Shine et al., 2013; Shine et al., 2015; Bejr-Kasem et al., 2019; Diez-Cirarda et al., 2023). The results of the present study thus lend further support to recent pathophysiological models, suggesting that VHs in PD and DLB might be due to a defective DAN-exerted top-down attentional control rather than primary changes in the bottom-up visual processing (Shine et al., 2011; Shine et al., 2014; McKeith et al. 2017; Muller et al. 2014). By exploiting the perturbation-based approach provided by our TMS-EEG paradigm,

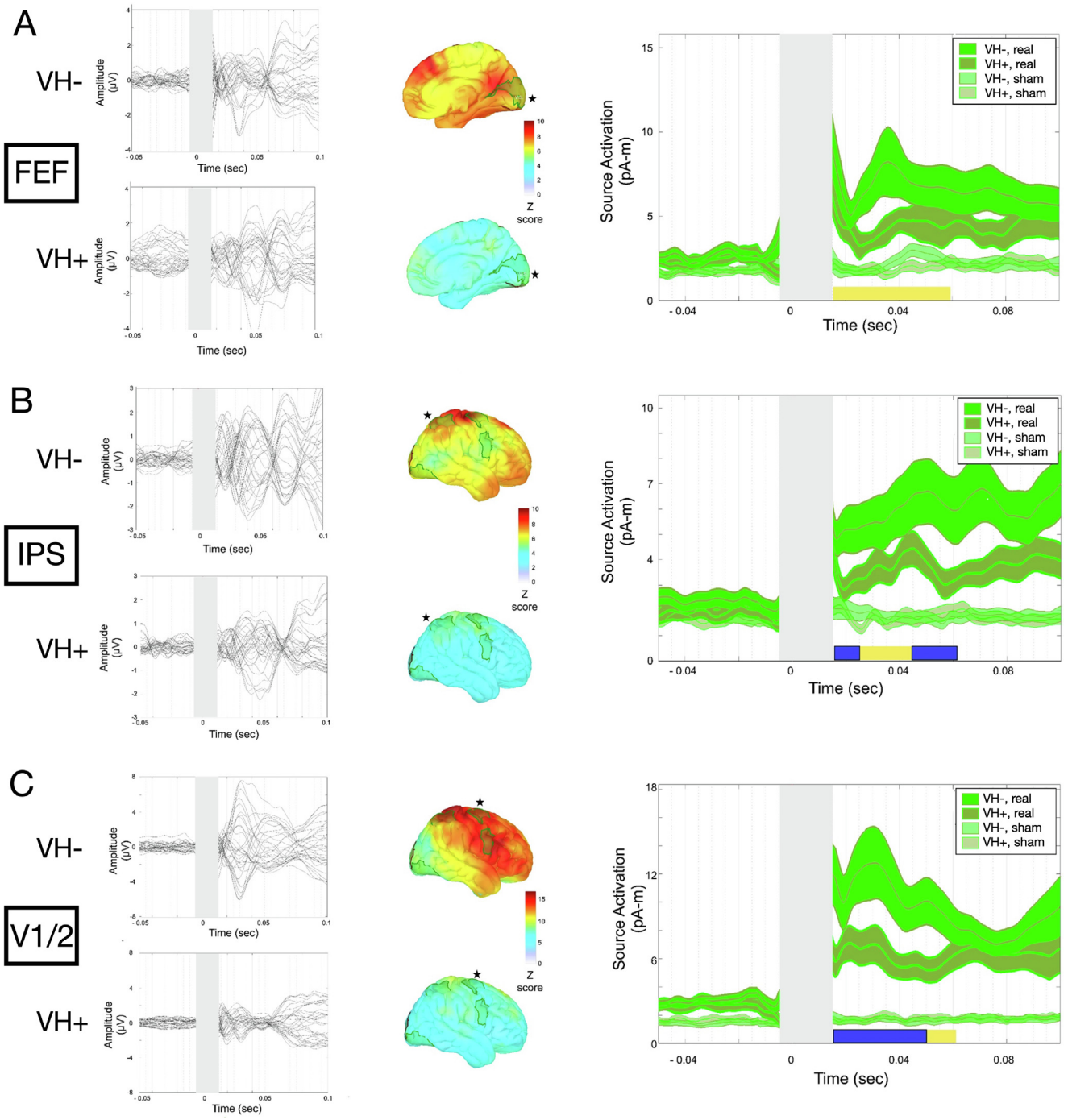

Fig. 3. Stimulated networks results. Grand-average transcranial magnetic stimulation-electroencephalography (TMS-EEG) responses from primary/secondary visual cortex (V1/2) (A), intraparietal sulcus (IPS) (B), and frontal eye fields (FEF) (C) showed as cortical source activation overlaid with a region of interests (ROIs) of the stimulated network (left; activation at 30 ms for V1/2, 50 ms for IPS and 30 ms for FEF; star: stimulation point), and source activation time series extracted for the ROIs (right). The yellow bar represents the time of interest (TOI). The blue bar represents time points of significant difference between patients with (VH+) and without (VH−) visual hallucination in real stimulation conditions. *To be reproduced in color on the Web (free of charge) and in black-and-white in print.*

we could better disentangle the specific contributions of frontal eye fields and intraparietal sulcus in the context of DAN dysfunction in patients with VHs. Specifically, the finding that patients with VHs displayed reduced DAN activation following intraparietal sulcus stimulation suggests that VHs are associated with right intraparietal sulcus reduced effective connectivity within the DAN. The intraparietal sulcus is a fundamental node in the cortical network subserving goal-directed attention (Asplund et al., 2010). Structural alterations in the parietal lobule have been previously observed in PD and DLB patients with VH (Ramirez-Ruiz et al., 2007; Delli Pizzi et al., 2014). The effective connectivity of the frontal eye fields within the DAN was also reduced in patients with VH. When considering only patients with dementia, no significant differences in TMS-evoked activity from frontal eye fields stimulation were found between patients with and without VH. Therefore, degeneration of frontal regions observed in cognitively impaired patients with DLB and PDD cannot explain our results (Oppedal et al., 2019; Burton et al., 2004; Chung et al., 2019). Conversely,

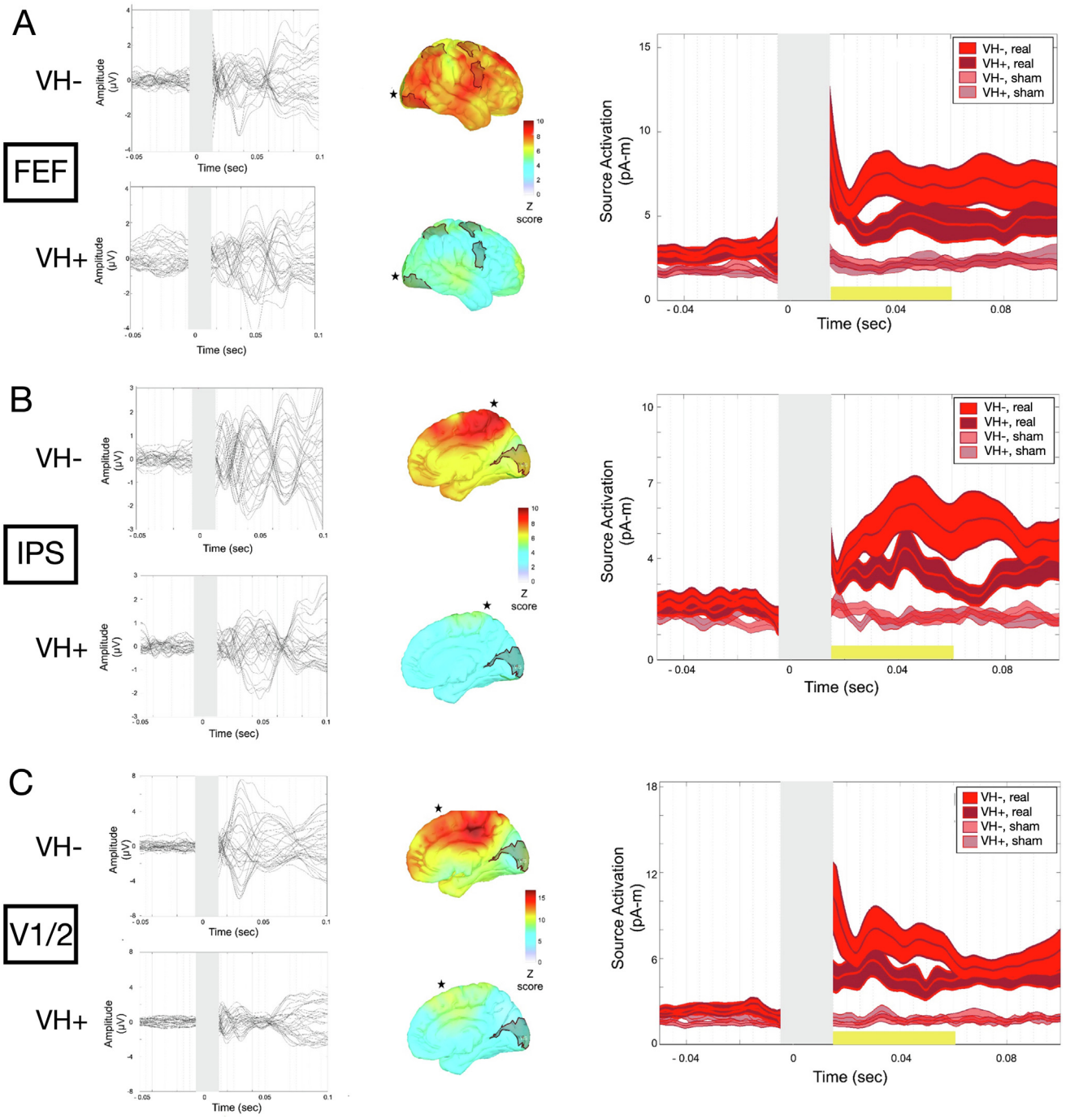

Fig. 4. Non-Stimulated network results (control). Grand-average transcranial magnetic stimulation-electroencephalography (TMS-EEG) responses from primary/secondary visual cortex (V1/2) (A), intraparietal sulcus (IPS) (B), and frontal eye fields (FEF) (C) showed as cortical source activation overlaid with non-stimulated network region of interests (ROIs) (left; activation at 30 ms for V1/2, 50 ms for IPS and 30 ms for FEF; star: stimulation point), and as source activation time series extracted for the non-stimulated network ROIs (right). The yellow bar represents the time of interest (TOI). VH+: patients with visual hallucination; VH−: patients without visual hallucination.

when considering only patients with dementia, we still found a significant reduction in intraparietal sulcus effective connectivity in patients with and without VHs, confirming that this region plays a crucial node in the DAN dynamics underlying VHs irrespective of the cognitive status.

In this paper, for TMS targeting we used fixed average coordinates on a reconstructed brain template as described in previous studies (Capotosto et al., 2009, 2012; He et al., 2007). Despite the proven millimetric accuracy of this approach (Carducci and Brusco 2012) and the relative stability of the stimulated regions within their networks (Smith et al., 2023, Seitzman BA et al., 2019), we acknowledge that this method's precision in targeting the DAN in every participant may be limited due to inter-individual variability (Mueller et al., 2013). The coordinates we used were based on a meta-analysis by He et al. (2007) involving exclusively young and healthy subjects. While there is no established evidence indicating that network nodes shift location due to aging or neurodegeneration, we acknowledge the possibility that these two factors could potentially impact the accuracy of our stimulation.

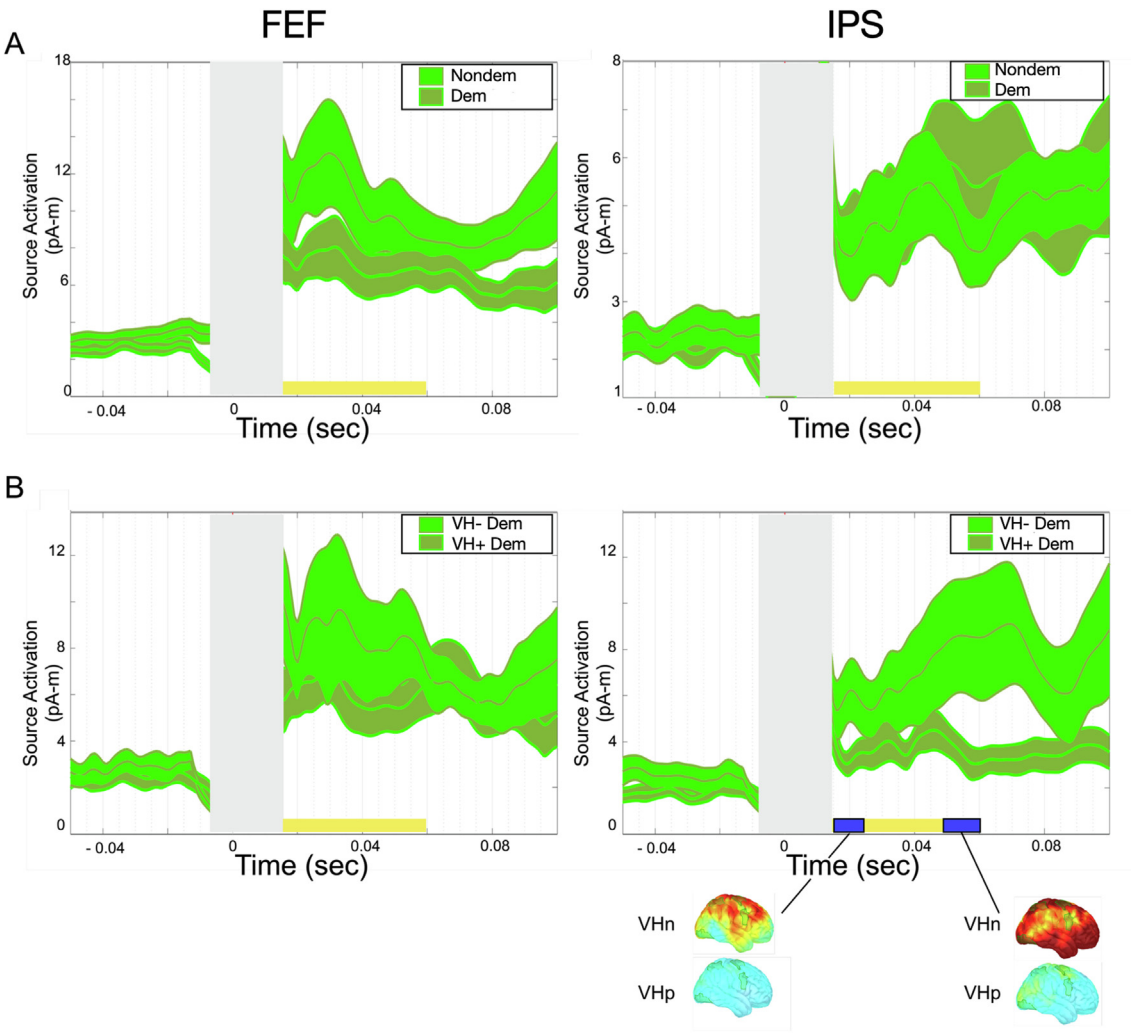

Fig. 5. Controlling for factor Dementia. A. Dorsal attention network (DAN) source level activation in demented vs. non-demented patients following frontal eye fields (FEF) and intraparietal sulcus (IPS) stimulation. B Comparison in DAN activation following FEF (left) and IPS (right) stimulation in patients with dementia between those with and without visual hallucinations (VHs). Only IPS stimulation resulted in reduced DAN activation in patients with and without VHs among the group with dementia; blue bars (17–22 ms and 51–59 ms) represent time points of significant difference between patients with (VH+) and without (VH−) visual hallucination; source activation depicted at 23 and 55 ms. The yellow bar represents the time of interest (TOI).

Similarly, the coordinates were identified during task execution in the reference study (He et al. 2007), while our data were collected at rest. However, recent evidence supports the stability of the node topography we stimulated across different states of network activity (Seitzman BA et al., 2019). In our study, we opted for a methodological approach that prioritizes reproducibility by using an average DAN mask derived from Shine et al. (2015), who examined alterations in the VIS and DAN in a similar patient population. Although this methodological choice strengthens the reproducibility and comparability of our findings, extracting source-reconstructed signals from a template DAN mask may be subject to localization errors and potential loss of signal components due to inter-individual variability. Unfortunately, individual-level reconstruction was not possible due to the lack of single-subject functional MRI scans. While the intraparietal sulcus was our parietal TMS target based on studies showing effects on visuospatial attention (Capotosto et al., 2009, 2012; Rushworth et al. 2006; Sack et al. 2002), we acknowledge that gyral crowns belonging to superior and inferior parietal lobule were also being stimulated (Siebner et al., 2022). As a result, it is plausible that the responses we observed also reflect activation of these superficial posterior parietal areas. However, despite these methodological limitations, our findings align with the anticipated reduction, based on MRI findings, of DAN activation in patients with visual hallucinations. Finally in this study we only explored activity evoked from some key regions within the VIS and DAN. As such, we cannot exclude the possibility that other areas or other networks might contribute to the pathophysiology of VHs (Shine et al., 2015). We also acknowledge that our sample size is relatively small, limiting the generalizability of our findings. Future studies that involve more detailed clinical characterizations are needed to clarify the behavioral and clinical relevancy of changes in TMS-evoked DAN activation reported in the present study.

In conclusion, our study offers evidence for altered effective connectivity of the intraparietal sulcus within the DAN in patients with Lewy Body Disease. Our results suggest the need for future research aimed at further validating these findings through the use of more precise localization methods using individual MRI scans. Thus, TMS-EEG investigations (Leodori et al. 2020, 2022) may provide important insight in the pathophysiology of non-motor symptoms in patients with movement disorders and help developing possible targeted treatments.

Declaration of interest

None.

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Author contributions

GL, AF designed the study, collected the data, analyzed the data, and wrote the manuscript.

AS designed the study, examined the patients clinically, and reviewed and critiqued the manuscript.

MM collected the data, analyzed the data, reviewed, and critiqued the manuscript.

ST collected the data, and reviewed and critiqued the manuscript.

DB, AC, GF designed the study, examined the patients clinically, reviewed and critiqued the manuscript.

AB conceived and coordinated the study, and critically revised the manuscript.

All authors have approved the final article.

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CRediT Author Contribution Statement

Giorgio Leodori: Conceptualization, Investigation, Methodology, Visualization, Writing - original draft, Writing - review and editing. **Andrea Fabbrini:** Conceptualization, Investigation, Methodology, Visualization, Writing - original draft, Writing - review and editing. **Antonello Suppa:** Conceptualization, Validation, Writing - review and editing. **Marco Mancuso:** Data curation, Formal analysis, investigation, methodology, Software, Visualization, Writing - review and editing. **Sankalp Tikoo:** Investigation, Writing - review and editing. **Daniele Belvisi:** Conceptualization, Funding acquisition, Resources, Supervision, Writing - review and editing. **Antonella Conte:** Conceptualization, Funding acquisition, Resources, Supervision, Writing - review and editing. **Giovanni Fabbrini:** Conceptualization, Funding acquisition, Resources, Supervision, Writing - review and editing. **Alfredo Berardelli**: Conceptualization, Funding acquisition, Project Administration, Supervision, Writing - review and editing.

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