Brain networks responsible for visual hallucinations in Parkinson's Disease and Dementia with Lewy bodies: a combined TMS-EEG study

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Abstract

Visual hallucinations (VH) are particularly frequent in Parkinson's disease (PD), PD with dementia (PDD) and Dementia with Lewy bodies (DLB). Beside parkinsonism, the clinical features of PDD and DLB crucially include visual hallucinations and cognitive impairment. VH in PD, PDD and DLB typically progress along a clinical spectrum ranging from vivid dreams to frank psychosis, which is associated with the development of dementia and institutionalization. Understanding mechanisms of VH is crucial in detecting new targets for novel therapeutic approaches in patients with VH. The brain mechanisms underlying VH in PD, PDD and DLB are largely unclear. VH might reflect a failure in recruiting the dorsal attentional network (DAN) during periods of conflict resolution in visual processing. The DAN is composed of widespread neural circuits including regions within the frontal eye fields (FEF), and the intraparietal sulcus (IPS) in the right hemisphere. Transcranial magnetic stimulation (TMS) is a neurostimulation technique able to assess brain functions and disease-associated dysfunction. Recently introduced combined TMS-EEG approaches would provide an interesting window in the investigation of abnormal brain dynamics responsible for VH. In this study, we will use TMS-EEG to investigate excitability and connectivity abnormalities in each of the single nodes within the DAN (FEF and IPS) and the visual cortex, in patients with VH and in age-matched healthy subjects. Finally, given the pathophysiological role of decreased cortical cholinergic transmission in patients with VH, we will also assess the link between changes in the DAN network connectivity and changes in short-afferent inhibition (SAI), a non-invasive TMS measure of the cortical cholinergic tone.

Background

Visual hallucinations (VH) are particularly frequent in neurodegenerative disorders with Lewy bodies including Parkinson's disease (PD), Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) (Aersland et al., 2001). Morphologically, these conditions are mainly characterized by cortical and subcortical alpha-synuclein deposition leading to Lewy bodies (LB). PD manifests with a parkinsonian syndrome characterized by bradykinesia, resting tremor and rigidity (Berardelli et al., 2013). Beside a parkinsonian syndrome, the clinical features of DLB and PDD include cognitive impairment, visual hallucinations, and fluctuating attention. DLB and PD show considerable clinical overlap, in particular when dementia is present (PDD) (Jellinger et al., 2017). Visual misperception in PD, PDD and DLB typically progress along a clinical spectrum from vivid dreams, visual misperception, and hallucinations to frank psychosis, which is commonly associated with the development of dementia (Goetzet al., 2010; Hely et al., 2008). Currently available treatments offer only limited symptomatic benefit, and the development of these features signifies a major risk for nursing home placement. Therefore, understanding mechanisms of VH is crucial in individualized specific target for new therapeutic approach. The brain mechanisms underlying VH in PD, PDD and DLB are not fully understood. A review of functional MRI (fMRI) suggest that dysfunction rather than degeneration in the primary visual cortex occurs in PD, PDD and DLB patients with VH (Shine et al., 2014). Hence, VH are proposed to be the result of combined attentional (top-down) and

visual perceptual (bottom-up) impairment interacting with scene representations to produce the activation of incorrect but environmentally expected perceptual proto-objects (Collerton et al., 2005). This theoretical model has received support from experimental studies demonstrating the presence of attentional deficits and reduced perception (Koerts et al., 2010), as well as breakdown between large-scale attentional control networks across the brain in PD patients with VH (Shine et al., 2015). More specifically, VH would reflect a failure in recruiting the dorsal attentional network (DAN) during periods of conflict resolution in visual processing (Shine et al., 2015). The DAN is composed of widespread neural including regions within the frontal eye fields (FEF), and the intraparietal sulcus (IPS) (Asplund et al., 2010). Given that VH are thought to reflect a cortical network disorder, possible approaches able to examine their pathophysiology include advanced non-invasive brain stimulation techniques. Transcranial magnetic stimulation (TMS) is a neurostimulation technique able to assess neural activity in relation to specific brain functions (cognition and behavior) and disease-associated dysfunction in neurologic and psychiatric disorders (Hallett et al., 2017). Studies using TMS-induced phosphenes as a marker of visual cortex excitability found correlation between visual cortex excitability and severity of VH in DLB patients (Taylor et al., 2011). However, phosphenes reporting may be difficult when investigating populations with dementia. Recent technical progresses have allowed the concomitant use of TMS and EEG providing an interesting window in the investigation of the cortical phenomena generated by TMS and possibly of several brain dynamics (Farzan et al., 2016). More specifically, in patients with VH TMS-EEG approach may uncover excitability and connectivity abnormalities in each of the single nodes within the DAN (FEF and IPS) and the visual cortex. Finally, several evidence pointed to abnormal cholinergic tone as a crucial step in the dysregulation of the bottom-up and top-down processing interaction underpinning VH in PD, PDD, and DLB (Collerton et al., 2005; Muller et al., 2013).

Objectives and methods

TMS-induced cortical responses can be recorded with EEG as TMS-evoked potentials (TEPs). Several studies confirmed that TEPs reflect the state of the stimulated cortical circuits (Casarotto et al., 2010). A TEPs study on visual cortex showed that early negative local component (the N40) may serve as a new objective and non-invasive probe of visual cortex excitability (Herring et al., 2015). Functional connectivity between DAN nodes can be measured during resting state-EEG (rs-EEG) using phase lag index (PLI) (Stam CJ et al., 2007). By studying the propagation of the TEP across the scalp, it is possible to investigate the effective connectivity of the stimulated area (Massimini et al., 2005). Accumulating TMS-EEG evidence show that posterior alpha oscillations (8-14 Hz) (PAO) are informative of the visual system intrinsic state, and are subject to attention-related modulation from FEF and IPS (Taylor and Thut, 2012). PD, PDD and DLB patients show reduced PAO and increased posterior slow-wave activity (Peraza et al., 2018) and these abnormalities positively correlated with cognitive fluctuations in DLB (Bonanni et al., 2008). Given the possible pathophysiological role of cholinergic denervation in VH, it is important to probe the cholinergic tone non-invasively in patients with VH. Short afferent inhibition (SAI) is a paired-pulse TMS protocol suggested to be a biomarker of cholinergic function (Nardone et al., 2011). SAI was found reduced in non-demented PD patients with visual hallucinations compared to those without, and these changes were accompanied by selective deficits in attentional and visuospatial function (Manganelli et al., 2009; Celebi et al., 2012). Also, SAI was found abnormal in DLB compared to healthy controls (HC), and the abnormalities correlated with the presence of VH (Marra et al., 2012). In this study, we aim to investigate visual cortex excitability, and DAN-V1 connectivity in patients with PD without VH (VH-), PD, PDD and DLB with VH (VH+), and finally in a population of age-matched HC. Also, we will investigate possible relations between TMS-EEG variables and SAI to explore the pathophysiological link between DAN-V1 alterations and reduced cortical cholinergic tone in patients with VH. In more details, the study includes four objectives.

Objective 1: To investigate excitability in the visual cortex (V1), FEF, and IPS. Early TEP components (< 50 ms) have been related to local excitability (Komssi and Kähkönen, 2006). Accordingly, the amplitude of the early TEPs components elicited by TMS over the V1, FEF and IPS will be compared between our study populations (VH-, VH+, and HC). Our hypothesis is that TEP would uncover abnormal excitability in each node of the explored network (V1, FEF, IPS) in patients with VH.

Objective 2: To prove abnormal visual cortex inner state in patients with VH. We will compare PAO, and the relation between PAO power/phase and TEP amplitudes between our study populations (VH-, VH+, and HC). We expect abnormal PAO, and PAO-related TEPs modulation in patients with VH.

Objective 3: To prove abnormal DAN-V1 connectivity in patients with VH. We will investigate functional (PLI) and effective connectivity (TEP propagation) between FEF, IPS and V1 in our study populations (VH-, VH+, and HC). We hypothesize lower connectivity between FEF and IPS and V1, in patients with VH.

Objective 4: To assess correlation between SAI and DAN-V1 connectivity abnormalities, in patients with VH. Our hypothesis is that a cholinergic deregulation plays an important role in attentional network abnormalities responsible for VH. Thus, we expect SAI abnormalities to be prevalent in patients with VH and to correlate with connectivity changes in these patients.

Patients will be recruited from the movement disorders outpatient clinic, Department of Human Neuroscience, Sapienza University of Rome, Italy. The diagnosis of all neurodegenerative disorders will be achieved according to the most recent international diagnostic criteria. All patients will undergo a detailed motor and cognitive evaluation including: NPI-H, MMSE, MOCA, FAB, HAM-D, UPDRS, and H&Y.

TMS will be performed using a Magstim 200 stimulator with a 90 mm figure-of-eight coil (Magstim).TMS will be localized using a neuronavigational system (SofTaxic Optic) together with an optical tracking system (Nothern Digital). FEF, IPS and V1 coordinates will be calculated in the MNI space and fit of each participant's anatomical MRI (Apple et al., 2017) EEG will be recorded with a 32-channel elastic cuff via a TMS compatible system (Mega Electronics). EEG will be analysed using Matlab toolboxes (EEGLAB, Fieldtrip).

Novelty and prospects

The prevalence of VH in PD has been reported to range between 6% and 60% (Goetz et al. 2010). VH generally occur during the second half of the disease's course and have a persistent and progressive nature (Williams et al., 2005). The development of VH in PD commonly occurs in both demented and non-demented patients and leads to a high degree of burden on primary caregivers (Grossi et al., 2005; Aarsland et al., 2007). Moreover, VH usually heralds the development of dementia (Goetz CG, 2010; Hely MA 2008). The present study has been designed to uncover network dysfunctions specific of VH development in patients with PD, PDD and DLB. One of potential use of TMS-EEG might be in the identification of individuals in the prodromal phase, prior to the manifestation of significant VH. From a theoretical perspective EEG, as a functional marker of neuronal and synaptic integrity, may be sensitive to VH related subtle and early cortical excitability and connectivity changes that precede overt large-scale degenerative changes leading to dementia. In addition to the search for specific abnormalities of the presence of VH, the set of collected neurophysiological data could help to differentiate clinical conditions characterized by wide overlap such as PDD and DLB (disease biomarker). Furthermore, clarifying the relationship between cholinergic alterations and parameters of excitability and network functionality can provide objective indicators of therapeutic efficacy of drugs oriented to the regulation of cholinergic tone such as acetylcholinesterase inhibitors. This aspect is of particular relevance given the key role that cholinergic alterations also play in determining the therapeutic response to dopaminergic drugs, fundamental in the treatment of PD. Finally, the use of EEG neurophysiological biomarkers in PD, PDD and DLB patients might be the development of new therapeutic treatments. In fact, the study of the individual

nodes of the retentive network responsible for VH could identify the network node on which to apply invasive and / or non-invasive neurostimulation approaches able to improve the patient's symptoms. Today, in fact, we have advanced repetitive magnetic stimulation techniques known to induce long-term plasticity-like phenomena. Therefore the study is a fundamental prerequisite for a non-invasive neurostimulation intervention aimed at the symptomatic treatment of VH in patients with VH.

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