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Altered thalamocortical connectivity induced by flicker light stimulation

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INTRODUCTION

Perceptual disturbances, such as visual hallucinations, occur similarly during various psychopathologies (e.g., Charles Bonnet Syndrome, migraine aura), hinting towards a shared underlying mechanism. However, the specific neural mechanisms remain unclear up to today. Induction methods for altered experiences (e.g., psychedelic drugs, flicker light stimulation (FLS)) are experimentally utilized to search for the neural correlates of visual hallucinations, which have since revealed a link with thalamocortical dysconnectivity (see Avram et al., 2021 for review). Here, we use FLS to test whether visual hallucinations relate to altered thalamocortical connectivity, and which thalamic and visual cortical subregions are primarily modulated. We expect that, as FLS stimulates the visual pathway, the Lateral Geniculate Nucleus (LGN; first-order nuclei for visual input) will show changes in coupling with early visual cortices (EVC), while the ventrolateral (VL) nucleus, which plays a role in synesthesia (Ro et al., 2007) and perceptual disturbances (Avram et al., 2021), will show changes in coupling with higher-order visual cortices (HVC).

METHODS

24 German speakers with no history of neurological disorders participated in the experiment (14 female; 10 male; age range 20-41 years, M = 28.0, SD = 5.7). Participants were scanned using a 3T Siemens Tim Trio MRI scanner equipped with a 32-channel head coil (Siemens Medical, Erlangen, Germany) at the Center for Cognitive Neuroscience Berlin, Freie Universität Berlin. To apply light stimulation inside the MRI scanner, the Lucia N°03 stroboscope (Light Attendance GmbH, Innsbruck, Austria) was mounted on a stand close to the end of the gantry at 150±2cm from the eyes [Fig 1A]. The scanning session involved seven-minute pre- and post-scans and three fifteen-minute light stimulation scans consisting of (1) constant light (2) 3 Hz and (3) 10 Hz FLS in a randomized order [Fig 1B]. After each scan, the participants were asked six questions from the Altered States of Consciousness Rating scale (ASC-R; Dittrich et al., 1998) and responded via the MRI speaker system.

Fig. 1

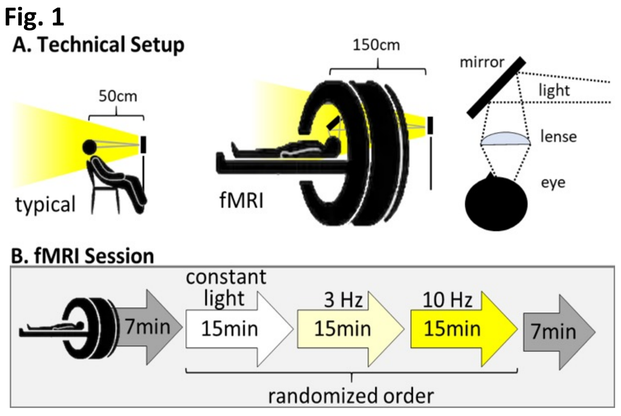
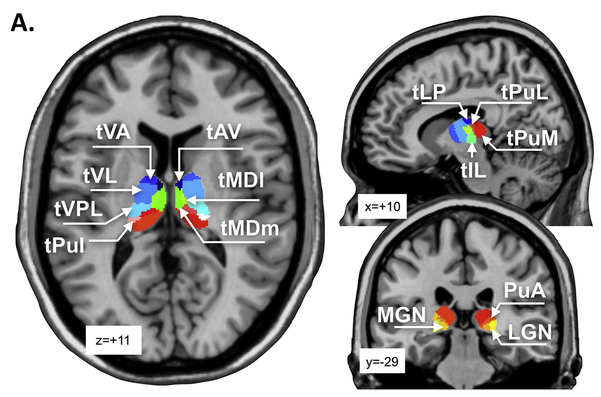
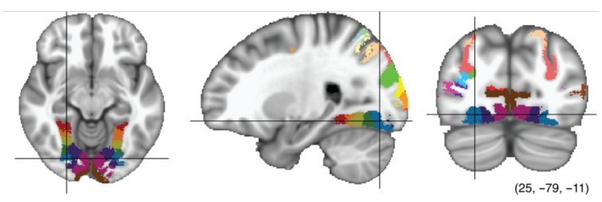


Fig. 2



Thalamus parcellation of AAL3 atlas (Rolls et al., 2020)



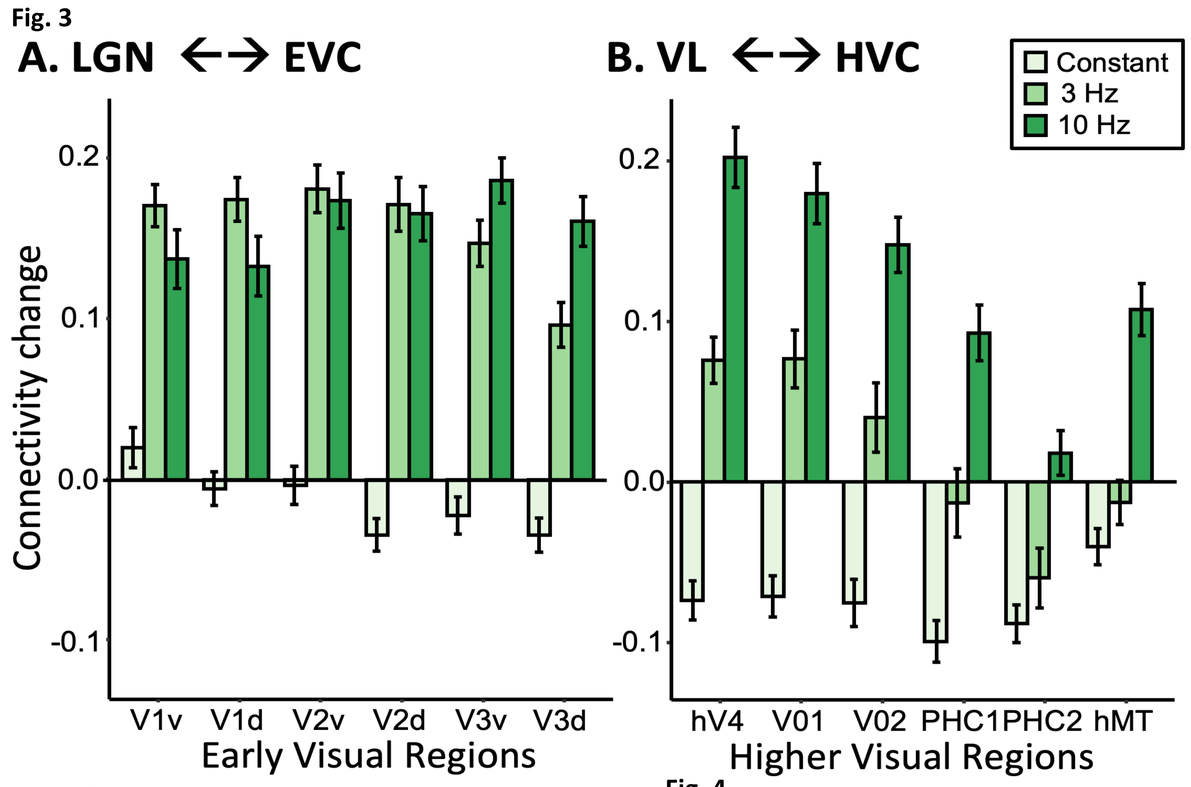
Volume-based maximum probability map of visual topographic regions (Wang et al., 2015)

Resting-state data processing

The following preprocessing steps were performed: (1) Slice time correction (2) Spatial realignment (3) Coregistration (4) Normalization (5) Scrubbing (volume interpolation) (6) Smoothing (7) Nuissance regression (White matter, CSF fluid, motion parameters, linear and quadric trend, global signal) (8) Band-pass filtering (0.01-0.08 Hz). We extracted regions of interest (ROIs) from the AAL3 atlas for thalamus parcellation (15 thalamic regions for each hemisphere; Rolls et al., 2020) [see Fig 2A] and from a probability map of visual topographic areas (23 cortical regions for each hemisphere; Wang et al., 2015) [see Fig 2B] to calculate ROI-to-ROI correlation coefficients. Differences between the average of pre/post scans and the experimental conditions were computed to indicate changes in functional connectivity. We tested for differences in connectivity between LGN and EVC, and VL nuclei and HVC using t-tests. In the AAL3 atlas, the LGN is 234mm^3 and the VL nucleus is 2096 mm^3. We set the alpha threshold at 0.017 (0.05/3) to correct for three comparisons for every family of t-tests. We ran one-way ANOVAs to test the effect of experimental condition on ASC-R questionnaire ratings. In addition, we plotted correlation matrices between thalamic and visual regions to explore overall changes in functional connectivity for all thalamic and visual cortical pairs across experimental conditions.

RESULTS

Fig. 3



Thalamocortical connectivity

We tested the effects of FLS on thalamocortical connectivity between LGN and EVC and VL nuclei and HVC. We found that 3 Hz and 10 Hz FLS significantly increased coupling between the LGN and EVC (ventral and dorsal V1, V2, V3) compared to constant light ($p<.001$) [Fig 3A]. We also found a parametric modulation of flicker frequency for increased connectivity between VL nuclei and HVC, specifically for V4 and medial temporal areas ($p<.01$) [Fig 3B]. Exploratory correlation matrices are shown in Fig 4. Flicker frequency also affected participant ratings of seeing patterns and colours ($F(4) = 88.95$, $p<.001$; $F(4) = 88.03$, $p<.001$), such that 10 Hz FLS generated the highest ratings [Fig 5].

Fig. 4

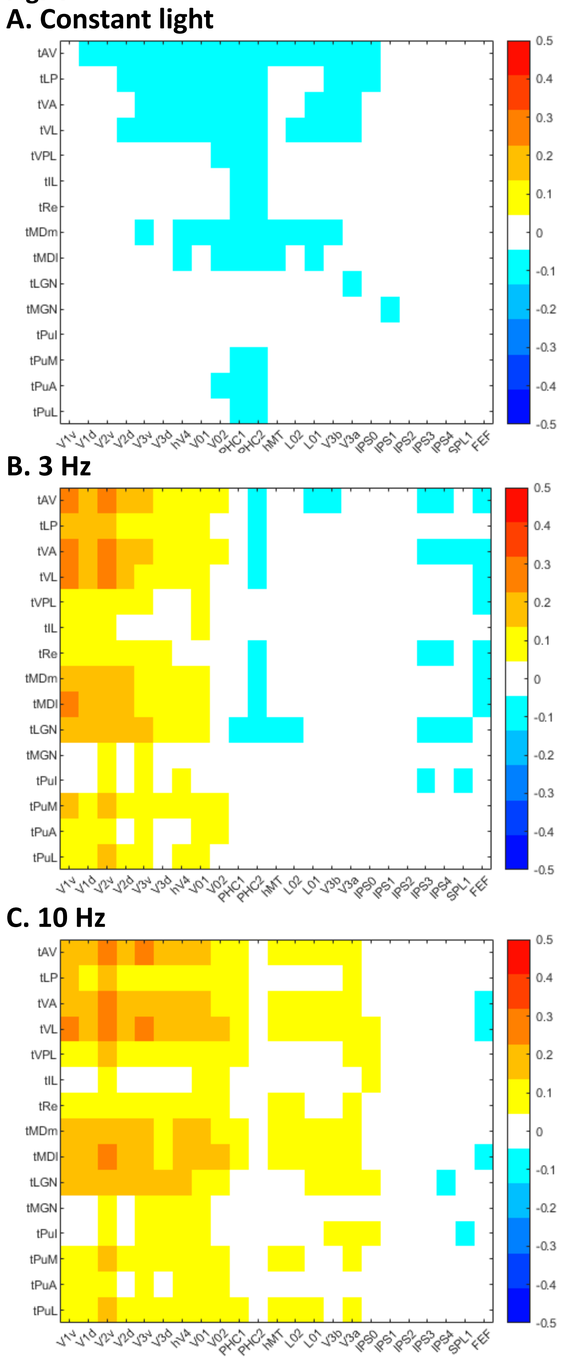
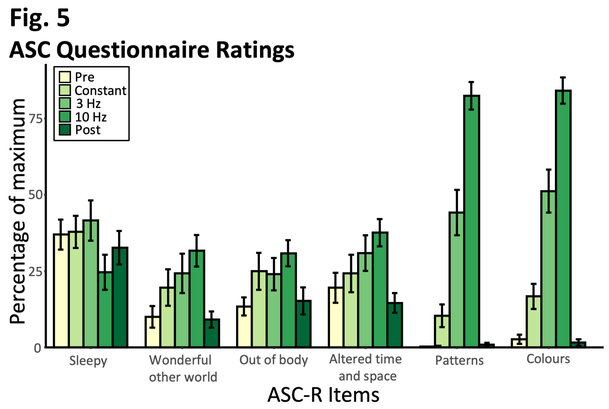


Fig. 5



CONCLUSION

Our results support that changes in thalamocortical connectivity may crucially underlie altered perceptual processing. Specifically, increased connectivity between VL nuclei and HVC is likely associated with intensity of visual hallucinations. As 10 Hz FLS increased ratings of seeing patterns and colours, which is in line with recent work (Amaya et al., 2023) and increased coupling between VL nuclei and HVC, it suggests that thalamocortical feedback loops higher in the visual hierarchy may be more important for generating visual hallucinations than feedforward/ feedback connections between LGN and EVC. Overall, our work extends previous research by identifying a differential pattern of thalamic and visual cortical subregion connectivity induced by FLS, which catalyses progress to establish the role of thalamocortical dysconnectivity in perceptual disturbances.

Amaya, I., Behrens, N., Schwartzman, D. J., Hewitt, T., & Schmidt, T. T. (2023). Effect of frequency and rhythmicity on flicker light-induced hallucinatory phenomena. https://doi.org/10.31234/osf.io/zbqc2.
Avram, M., Rogg, H., Korda, A., Andreou, C., Müller, F., Borgwardt, S. (2021). Bridging the Gap? Altered Thalamocortical Connectivity in Psychotic and Psychedelic States. *Frontiers in Psychiatry* 12: 706017. doi: 10.3389/fpsyt.2021.706017.
Dittrich A. The Standardized Psychometric Assessment of Altered States of Consciousness (ASCs) in Humans. Pharmacopsychiatry. 1998;31: 80–84. doi:10.1055/s-2007-979351
Ro, T., Farnè, A., Johnson, R.M., Wedeen, V., Chu, Z., Wang, Z.J., Hunter, J.V., Beauchamp, M.S. (2007). Feeling sounds after a thalamic lesion. Ann Neurol. 62(5):433-41. doi: 10.1002/ana.21219. PMID: 17893864.
Rolls, E.T., Huang C., Lin C., Feng J., Joliot, M., Automated anatomical labelling atlas 3 (2020). *NeuroImage* 206: 116189 doi: 10.1016/j.neuroimage.2019.116189.
Wang, L., Mruczek, R.E., Arcaro, M.J., Kastner, S. (2015). Probabilistic Maps of Visual Topography in Human Cortex. *Cereb Cortex.* 25(10):3911-31. doi: 10.1093/cercor/bhu277.

Acknowledgements
We thank the Light Attendance GmbH for providing a Lucia N°03 stroboscope free of charge.