

# **Flicker light stimulation induces thalamocortical hyperconnectivity with LGN and higher-order thalamic nuclei**

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## 1 **Highlights**

- 2 • Flicker light stimulation (FLS) induces thalamocortical hyperconnectivity between the  
3 first-order thalamic LGN and early visual cortices, likely due to entrainment.
- 4 • Thalamocortical connectivity between LGN and upstream visual areas, but not V1, is  
5 associated with the intensity of visual hallucinations.
- 6 • Thalamocortical connectivity changes with higher-order thalamic nuclei, such as  
7 anterior and mediodorsal nuclei, show strongest modulation by flicker frequency,  
8 which corresponds to the intensity of visual hallucinations.

## 10 **Abstract**

11 The thalamus is primarily known as a relay for sensory information; however, it also critically  
12 contributes to higher-order cortical processing and coordination. Thalamocortical  
13 hyperconnectivity is associated with hallucinatory phenomena that occur in various  
14 psychopathologies (e.g., psychosis, migraine aura) and altered states of consciousness (ASC,  
15 e.g., induced by psychedelic drugs). However, the exact functional contribution of  
16 thalamocortical hyperconnectivity in forming hallucinatory experiences is unclear. Flicker  
17 light stimulation (FLS) can be used as an experimental tool to induce transient visual  
18 hallucinatory phenomena in healthy participants. Here, we use FLS in combination with fMRI  
19 to test how FLS modulates thalamocortical connectivity between specific thalamic nuclei and  
20 visual areas. We show that FLS induces thalamocortical hyperconnectivity between LGN, early  
21 visual areas and proximal upstream areas of ventral and dorsal visual streams (e.g., hV4, VO1,  
22 V3a). Further, an exploratory analysis indicates specific higher-order thalamic nuclei, such as  
23 anterior and mediodorsal nuclei, to be strongly affected by FLS. Here, the connectivity  
24 changes to upstream cortical visual areas directly reflect a frequency-dependent increase in  
25 experienced visual phenomena. Together these findings contribute to the identification of  
26 specific thalamocortical interactions in the emergence of visual hallucinations.

## 27 **Introduction**

28 The functional role of the thalamus goes beyond a relay for sensory information to the cortex.  
29 Indeed, no more than 20% of thalamic volume are primary sensory nuclei (Hádinger et al.,  
30 2023; Rovó et al., 2012). With complex connectivity throughout the neocortex, the thalamus  
31 contributes to higher-order processing, cognition and is also thought to coordinate  
32 information availability across cortices (Halassa and Sherman, 2019; Sherman and Guillery,  
33 2006). Correspondingly, thalamocortical hyperconnectivity has been related to various  
34 pathologies, such as psychosis (Avram et al., 2021; Ramsay, 2019), epilepsy (Chen et al., 2021;  
35 Kim et al., 2014) and migraine (Bolay, 2020; Martinelli et al., 2021; Tu et al., 2019), and during  
36 diverse altered states of consciousness (ASC; e.g., induced by psychoactive drugs (Carhart-  
37 Harris et al., 2016; Müller et al., 2017; Preller et al., 2019)), all of which involve hallucinatory  
38 experiences (consider also (Hirschfeld et al., 2023; Hirschfeld and Schmidt, 2021; Prugger et  
39 al., 2022; Schmidt and Majić, 2017)). However, the exact functional contributions of  
40 thalamocortical hyperconnectivity to the emergence of hallucinatory phenomena is unclear.  
41 Previous reports are limited in the specificity of distinct thalamic nuclei contributions. Here,  
42 we utilize flicker light stimulation (FLS) in combination with fMRI to induce transient visual  
43 hallucinations in healthy participants and test for the differential modulation of functional  
44 connectivity between thalamic nuclei and visual areas.

45  
46 The neural mechanisms of visual hallucinations are difficult to investigate empirically as their  
47 involvement in pathologies are spontaneous and co-exist with other neurophysiologic  
48 symptoms (Rogers et al., 2021). This makes it important to identify an experimental tool that  
49 can selectively induce visual hallucinatory phenomena in healthy participants. FLS applies  
50 stroboscopic light, primarily at alpha frequency (8-12 Hz), over closed eyes to elicit visual  
51 hallucinatory perception within seconds of stimulus onset. FLS-induced hallucinations include  
52 the perception of simple geometric patterns, motion and colours (Allefeld et al., 2011; Amaya  
53 et al., 2023; Bartossek et al., 2021; Montgomery et al., 2023), which hold close similarity to  
54 the content of visual hallucinations reported in migraine (Cowan, 2013; Panayiotopoulos,  
55 1994; Richards, 1971; Schott, 2007; Wilkinson, 2004), epilepsy (Panayiotopoulos, 1994),  
56 psychedelic experiences (Bartossek et al., 2021; Klüver, 1966; Lawrence et al., 2022), and  
57 Charles Bonnet Syndrome (Ffytche, 2005; Jan and Castillo, 2012). FLS rhythmicity, frequency

58 and brightness can be closely controlled in an experimental setting (Rogers et al., 2021),  
59 making it an optimal tool to investigate neural mechanisms of visual hallucinations.

60

61 By identifying which thalamic nuclei display altered connectivity with the cortex during visual  
62 hallucinations, the functional role of thalamocortical dysconnectivity can be indicated. The  
63 lateral geniculate nucleus (LGN) is the first-order thalamic nucleus for visual input and has  
64 bidirectional connections with V1. Here, feedforward thalamocortical projections relay visual  
65 information from the retina. Feedback corticogeniculate connections modulate activity of the  
66 LGN via inhibitory interneurons (Sherman and Guillery, 2006). These pathways determine  
67 LGN activity by streaming visual information (e.g., stimulus features (Andolina et al., 2007))  
68 and integrating extra-visual modulations (e.g., attentional (Reinhold et al., 2023)) (see (Briggs,  
69 2020) for review). The cortico-striato-thalamo-cortical (CSTC) model proposes that drug- and  
70 pathology-induced hallucinations arise from thalamocortical hyperconnectivity (Geyer and  
71 Vollenweider, 2008; Preller et al., 2019; Vollenweider and Geyer, 2001). With the perspective  
72 of the thalamus as a sensory gate, its contribution to hallucinations is mostly attributed to  
73 dysfunctional gating, leading to “sensory flooding” (Geyer and Vollenweider, 2008) and  
74 consequent cortical misinterpretation of sensory signals. In line with this suggestion, the LGN  
75 was found to have increased connectivity with the occipital cortex in patients with  
76 schizophrenia (Anticevic et al., 2014b) and during psychedelic experiences (Müller et al.,  
77 2018), which may reflect reduced thalamic gating capacities of the LGN to visual information  
78 passing to the cortex.

79

80 Recently, there has been more attention on the differential roles of first-order and higher-  
81 order thalamic nuclei in the generation of visual hallucinations (Vollenweider and Preller,  
82 2020), which is facilitated by methodological advances allowing for parcellation of thalamic  
83 nuclei (Iglehart et al., 2020; Johansen-Berg et al., 2005). Higher-order nuclei do not receive  
84 input from sensory organs, instead, they orchestrate cortico-cortical communication and  
85 modulate activity of other thalamic nuclei (Sherman, 2016; Sherman and Guillery, 2006). With  
86 regards to visual processing, the inferior and lateral pulvinar are a group of higher-order  
87 nuclei with pronounced bidirectional anatomic connections to V1, V2 and V4 (Gattass et al.,  
88 2014; Shipp, 2003; Soares et al., 2001), contributing to visual processing and attention (Adams  
89 et al., 2000; Benevento and Rezak, 1976; Gattass et al., 2017; Guedj and Vuilleumier, 2020;

90 Kaas and Lyon, 2007; Saalman et al., 2012). They are associated with the generation of  
91 hallucinatory phenomena as they show a reduction in volume, neuronal number, and  
92 neuronal size in individuals with schizophrenia (Byne et al., 2002; Danos et al., 2003) and  
93 dementia with Lewy Bodies (symptoms includes visual hallucination) (Erskine et al., 2017). In  
94 sum, the inferior and lateral pulvinar are candidate higher-order thalamic nuclei to contribute  
95 to the emergence of FLS-induced visual hallucinatory phenomena.

96

97 When aiming to identify the functional role of thalamocortical interactions in the emergence  
98 of visual hallucinations, it is relevant to test for differential contributions of visual stream  
99 areas with regards to their hierarchical organization. The visual cortex comprises of early  
100 visual cortices (EVC: V1-V3), which are typically defined by their retinotopic representation of  
101 the visual field (Engel et al., 1997; Sereno et al., 1995), and upstream visual areas, which show  
102 less pronounced retinotopy and are commonly described by their selective response to  
103 specific features of visual input, such as the activation preference for motion (hMT/V5; (Zeki  
104 et al., 1991)), shape (hV4/LO2; (Grill-Spector et al., 1998; Malach et al., 1995; Silson et al.,  
105 2013)), colour (hV4/VO1; (Persichetti et al., 2015)) and orientation (LO1; (Silson et al., 2013)).  
106 One previous EEG study indicated an increase in V4 activity during FLS (Ffytche, 2008), which  
107 may relate to the increased intensity of subjective experience of seeing shapes and colours.  
108 However, it is likely that altered processing in multiple visual areas relates to FLS-induced  
109 effects and the exact functional contributions of cortical areas along the visual hierarchy has  
110 not yet been reported.

111

112 In this study, we test whether FLS-induced visual hallucinations relate to altered  
113 thalamocortical connectivity, and which thalamic nuclei and visual areas are primarily  
114 modulated. We use constant light, 3 Hz FLS and 10 Hz FLS, expecting that 10 Hz FLS will induce  
115 stronger visual hallucinatory phenomena than 3 Hz FLS and constant light, as previously  
116 reported (See (Amaya et al., 2023; Bartossek et al., 2021)). We acquired resting state fMRI  
117 data and use the Automated Anatomical Labelling Atlas 3 (AAL3; (Rolls et al., 2020)) for  
118 thalamus parcellation and a volume-based maximum probability map (MPM) of visual  
119 topography (Wang et al., 2015) for parcellation of visual areas. We hypothesise that LGN will  
120 show hyperconnectivity with EVC for 3 Hz and 10 Hz FLS, as they receive excitatory signals  
121 from the retina and therefore synchronise to the periodic visual stimulus. For higher-order

122 visual regions, as well as higher-order thalamic nuclei (e.g., inferior and lateral pulvinar), we  
123 expect to find parametric modulation of connectivity by the experimental conditions, such  
124 that constant light will induce hypoconnectivity, as found in previous work (Schmidt et al.,  
125 2020), and FLS will induce frequency-dependent increases in connectivity, whereby 10 Hz  
126 produces the strongest coupling. Thereby, changes in connectivity should resemble the  
127 intensity of subjective hallucination experience.

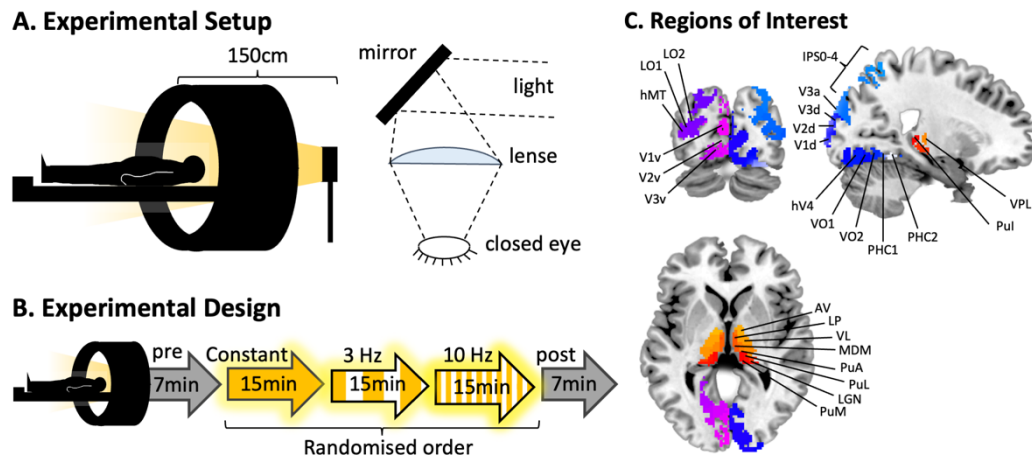
## 128 **Methods**

### 129 **Participants**

130 Twenty-four German speakers with no history of psychiatric or neurological disorders  
131 participated in the experiment (14 female; age range 20-41 years, mean (*M*) =  
132 28 years standard deviation (*SD*) = 5.7 years). All participants were right-handed according to  
133 the Edinburgh Handedness Inventory (Oldfield, 1971) (mean laterality quotient = 77.1). Social  
134 media and student mailing lists were used for recruitment. Participants were informed about  
135 the study aims and background, such as possible risks of FLS, before giving written consent.  
136 The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin  
137 (application number: EA4/143/18). All procedures were consistent with the guidelines  
138 included in the “Declaration of Helsinki – Ethical Principles for Medical Research Involving  
139 Human Subjects”.

### 140 **Flicker light stimulation**

141 For presentation of the light stimulation, we used the light device Lucia N°03 (Light  
142 Attendance GmbH, Innsbruck, Austria), which has been developed to evoke hypnagogic visual  
143 impressions by intermittent light stimulation. It is equipped with one halogen lamp that is  
144 used for constant light stimulation and eight LEDs to apply FLS with high precision in timing  
145 and luminance via a programmable interface. Three light stimulation conditions were used:  
146 (1) Constant light stimulation at full intensity through a halogen lamp; (2) 3 Hz; and (3) 10 Hz  
147 FLS as 50% ON/ 50% OFF times with LED light at maximum intensity, as previously applied  
148 (Bartossek et al., 2021; Schwartzman et al., 2019). To apply light stimulation inside the fMRI  
149 scanner, the light device was mounted on an aluminium stand close to the end of the gantry  
150 at  $150 \pm 2$  cm from the participants’ eyes. To make the light stimulation comparable to a  
151 previous phenomenological study, where the lamp was positioned 50 cm from the  
152 participants’ eyes (Bartossek et al., 2021), two lenses were introduced into the MRI-mirror  
153 system to collect and focus the light [Figure 1A] to deliver approximately the same amount of  
154 light to the eyes. To protect the light device from overheating (as the in-built ventilation did  
155 not work in the magnetic field), a custom-made air cooling was used that comprised of an  
156 industrial vacuum cleaner positioned outside of the shielded MRI room to deliver cold air via  
157 extension hose to the light device.



158

159 *Figure 1.* (A) Illustration of the setup inside the MRI scanner. FLS with the Lucia N°03 light  
160 device is optimized for stimulation from about 50 cm distance from the face. To obtain the  
161 same light intensity of stimulation inside of the scanner, the lamp was positioned at the end  
162 of the gantry at approximately 150 cm distance from the eyes and lenses were used to focus  
163 light onto the eyes to obtain the same amount of light as outside of the scanner. (B) The fMRI  
164 session comprised five closed-eye resting-state scans. The experimental conditions, constant  
165 light, 3 Hz and 10 Hz (15 minutes each) were presented in a randomised order, while the pre  
166 and post scans (7 minutes each) consisted of closed-eye rest for baseline measurements. (C)  
167 Regions of interest (ROIs) were extracted from AAL3 for thalamus parcellation (Rolls et al.,  
168 2020) and a volume-based MPM of visual topography (Wang et al., 2015). Thalamic ROIs, as  
169 labelled, are anteroventral (AV), lateroposterior (LP), ventrolateral (VL), mediodorsal medial  
170 (MDM), anterior pulvinar (PuA), lateral pulvinar (PuL), lateral geniculate nucleus (LGN), medial  
171 pulvinar (PuM), inferior pulvinar (PuI), and ventroposterolateral (VPL) nuclei. Additional  
172 thalamic ROIs not displayed are mediodorsal lateral (MDL), intralaminar (IL), ventroanterior  
173 (VA) and medial geniculate nuclei (MGN). Cortical ROIs of visual topography are split into the  
174 dorsal stream (V1d, V2d, V3d, V3a, V3b, LO1, LO2, hMT), ventral stream (V1v, V2v, V3v, hV4,  
175 VO1, VO2, PHC1, PHC2) and parietal stream (IPS0-4, SPL1, FEF). Cortical ROIs not displayed  
176 are V3b, SPL1 and FEF.



## 177 **Study Design and Procedure**

178 To minimize risk of aversive effects of FLS, all participants underwent a preliminary semi-  
179 structured video-interview with a psychologist to identify any acute mental disorders,  
180 consumption of psychotropic medication and/or pregnancy. Thereafter, participants were  
181 screened for indications of photosensitive epilepsy based on electroencephalography (EEG)  
182 and were shortly presented FLS of each experimental condition to be familiarized with the  
183 procedures and setup. All measurements were conducted at the Center for Cognitive  
184 Neuroscience Berlin (CCNB) at the Freie Universität Berlin.

185 The scanning session comprised of five scans: pre and post scans, each lasting seven minutes  
186 and consisting of closed-eye rest in darkness, and three light stimulation scans lasting fifteen  
187 minutes each [Figure 1B]. After every scan, the participants were asked six questions about  
188 their subjective experiences (see below) and verbally responded via the speaker system of  
189 the scanner. An anatomical scan was performed before participants were released from the  
190 scanner and experiment.

## 191 **FLS-induced phenomenology**

192 Phenomenological aspects of the FLS-induced state were retrospectively assessed using six  
193 questions of the Altered States of Consciousness Rating Scale (ASC-R; (Dittrich, 1998)), which  
194 were previously identified as most characteristic of the subjective experience (Bartossek et  
195 al., 2021). The questions were applied in German, taken from original version of the 5D-ASC  
196 (Dittrich, 1998) and participants were asked to rate by verbally naming a value from 0-100%  
197 for how much the following statements apply: (1) *Ich fühlte mich schläfrig* English: *I felt sleepy*,  
198 (2) *Ich fühlte mich körperlos* English: *I had the impression I was out of my body*, (3) *Wie im*  
199 *Traum waren Raum und Zeitgefühl verändert* English: *My sense of time and space was altered*  
200 *as if I was dreaming*, (4) *Ich fühlte mich wie in einer wunderbaren anderen Welt* English: *I felt*  
201 *I was in a wonderful other world* (5) *Ich sah regelmäßige Muster*, English: *I saw regular*  
202 *patterns* (Note: In the original version the statement continues as: ... *with closed eyes or in*  
203 *complete darkness*) (6) *Ich sah Farben vor mir* English: *I saw colors* (Note: In the original  
204 version the statement continues as: ... *with closed eyes or in complete darkness*). We ran one-  
205 way repeated-measures ANOVAs to test the effect of experimental condition on ASC-R  
206 questionnaire ratings using the *rstatix* package in Rstudio (v2022.07.2). As distribution of  
207 ratings had a tendency for skewedness (e.g., positive skew for pre and post scans), significant  
208 ANOVA results were additionally confirmed using non-parametric Kruskal-Wallis testing.

## 209 **fMRI Scanning**

210 Participants were scanned using a 3T Siemens Tim Trio MRI scanner equipped with a 32-  
211 channel head coil (Siemens Medical, Erlangen, Germany). For resting-state fMRI images, a  
212 T2\*-weighted echo planar imaging (EPI) sequence was used (37 axial slices acquired  
213 interleaved, in-plane resolution is 3mm<sup>2</sup>, slice thickness = 3 mm, flip angle (FA) = 70°, 20% gap  
214 between slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms). A structural image  
215 was acquired for each participant using a T1-weighted image acquired with Magnetisation  
216 prepared rapid gradient-echo (MPRAGE) sequence (TR = 1900 ms, inversion time = 900 ms,  
217 TE = 2.52 ms, FA = 9°, voxel size 1mm<sup>3</sup>). Head motion was minimized using cushioned supports  
218 to restrict movement.

## 219 **MRI data pre-processing**

220 Data were pre-processed and analysed using a custom-built resting-state data analysis  
221 pipeline within SPM12 ([www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)). The anatomical T1-images were  
222 normalized to MNI152 space using the segmentation approach, by estimating a nonlinear  
223 transformation field, which is then applied to the functional images. Slice time correction and  
224 realignment was applied to the functional data before spatial normalisation to MNI152 space  
225 using unified segmentation in SPM12, which includes reslicing to an isometric 2 mm voxel size  
226 (Ashburner and Friston, 2005). The frame-wise displacement (FD) was calculated for each  
227 scan using BRAMILA tools (Power et al., 2012). Volumes that exceeded a threshold of 0.4 mm  
228 were masked during following analysis steps (*“scrubbing”*). Principal component analysis  
229 (CompCor) was done using the DPABI toolbox (toolbox for Data Processing & Analysis of Brain  
230 Imaging, <http://rfmri.org/dpabi>) within the CSF/white matter mask on the resting-state data  
231 to estimate nuisance signals (Behzadi et al., 2007). Anatomical masks for CSF, white and grey  
232 matter were derived from tissue-probability maps provided in SPM12. Smoothing was  
233 performed with a 3 mm FWHM Gaussian kernel, to retain high spatial specificity of small ROIs  
234 within the thalamus. The first five principal components of the CompCor analysis, six head  
235 motion parameters, linear and quadratic trends as well as the global signal were used as  
236 nuisance signals to regress out associated variance. The removal of global signal changes has  
237 been controversially discussed in resting-state fMRI literature with arguments for and against  
238 (see (Murphy and Fox, 2017) for overview). It has been particularly discussed for  
239 pharmacological studies (e.g., (Carhart-Harris et al., 2012; Vollenweider and Preller, 2020)),  
240 in which changes in blood flow, blood pressure, breathing rate and other physiologic

241 parameters might account for some aspects of ROI-to-ROI correlations. Until conclusive  
242 interpretations of such differences are revealed, it is suggested to report data with and  
243 without global signal regression (Vollenweider and Preller, 2020). Therefore, we additionally  
244 report all analyses without GSR in the Supplement. Finally, the toolbox REST  
245 ([www.restfmri.net](http://www.restfmri.net)) was used for temporal band-pass filtering (0.01-0.08 Hz).

#### 246 **ROI-to-ROI correlation analysis**

247 We used the AAL3 (Rolls et al., 2020) to define anatomical ROIs for thalamus parcellation (14  
248 thalamic nuclei for each hemisphere) and a volume-based MPM of visual topography for  
249 cortical parcellation (23 visual areas for each hemisphere; see Figure 1C) (Wang et al., 2015).  
250 Using probability maps of V1 and V2, overlapping ROIs at the midline were resolved by  
251 assigning voxels to the region with highest probability. Of thalamic ROIs, the Reuniens nucleus  
252 is only 8mm<sup>3</sup> and was not included in our analyses.

253 For each ROI, mean BOLD time courses were extracted and temporal ROI-to-ROI correlations  
254 calculated. For all ROI-to-ROI pairs, we averaged the correlation coefficients of pre and post  
255 scans and then computed differences with experimental conditions via subtraction of  
256 matrices. We took the mean of correlation coefficients for ipsilateral connections (e.g., left  
257 LGN and left V1v averaged with right LGN and right V1v) to give one bilateral functional  
258 correlation coefficient for each pair of ROIs. Lilliefors test of normality showed that at least  
259 90% of ROI-to-ROI correlation coefficients were Gaussian distributed across participants for  
260 each condition. Therefore, to test for specific changes within thalamus and visual areas, we  
261 ran repeated-measures ANOVAs with condition as a fixed effect and connectivity changes as  
262 the dependent variable. We selected 16 visual areas to test: 8 within the ventral stream (V1v,  
263 V2v, V3v, hV4, VO1, VO2, PHC1, PHC2) and 8 within the dorsal stream (V1d, V2d, V3d, V3a,  
264 V3b, LO1, LO2, hMT), as classified by Wang *et al.* (2015). We conducted the analyses for LGN,  
265 inferior and lateral pulvinar. We Bonferroni-corrected the alpha threshold to .003 (.05/16) to  
266 correct for 16 repeated-measures ANOVAs for every thalamic nucleus. When tests were  
267 significant, post-hoc t-tests were used to determine the differences between condition  
268 groups. Thereafter, we further explored the ROI-to-ROI connectivity matrices of all thalamic  
269 and visual ROIs to identify if functional connectivity with any other thalamic nuclei or visual  
270 areas appeared to be modulated by FLS.

271

#### 272 **Testing the relationship between subjective experience and connectivity changes**

273 To test for the relationship between subjective experience and connectivity changes, we  
274 selected ratings of “I saw regular patterns” and “I saw colours” to reflect the intensity of visual  
275 phenomena. Using paired t-tests, we tested whether the distribution of ratings between the  
276 two items were different for each condition. As these tests were nonsignificant, we took the  
277 average of seeing patterns and seeing colours for each participant as the measure for  
278 occurrence of visual hallucinations. We subtracted the average of pre and post ratings from  
279 those of each experimental condition. From here, we ran linear mixed effects models with  
280 change in subjective ratings as a fixed effect and change in functional connectivity as the  
281 dependent variable. Participants were included as a random effect. Models with random  
282 intercept only had better fit (i.e., lower Akaike Information Criterion values) than random  
283 intercept and random slope models, and therefore models were run with random intercepts  
284 only. Following our hypotheses, we ran this test for connectivity changes between LGN,  
285 inferior pulvinar, lateral pulvinar and 16 visual subregions, thus Bonferroni-correcting the  
286 alpha threshold to .003. The analyses were conducted using the *lme4* package in Rstudio  
287 (v2022.07.2). Underlying assumptions of linear mixed modelling (e.g., equal variance of  
288 residuals, Gaussian-distributed dependent variable) were tested and met.

## 289 **Results**

### 290 **FLS-induced subjective experience**

291 We assessed the subjective experience following each scanning session (including pre/post  
292 scans) to test whether reported effects induced by the experimental conditions were  
293 comparable to previous findings where FLS was applied outside of the MRI (Amaya et al., 2023;  
294 Bartossek et al., 2021). Using ASC-R scores from each session, we ran 5x1 repeated-measures  
295 ANOVAs to test the effect of condition on ASC ratings. The results are presented in Figure 2.  
296 We found a significant effect of experimental condition on ratings of “I felt I was in a  
297 wonderful other world” ( $F(4, 92) = 9.83, p < .001$ ), “My sense of time and space was altered  
298 as if I was dreaming” ( $F(4, 92) = 7.12, p < .001$ ), and “I had the impression I was out of my  
299 body” ( $F(4, 92) = 5.37, p < .001$ ), where post-hoc paired t-tests revealed that 10 Hz elicited  
300 significantly higher ratings than pre and post resting scans ( $p < .05$ ). Further, there was a  
301 significant effect of experimental condition on ratings of “I saw patterns” ( $F(2.09, 48.03) =$   
302  $104.53, p < .001$ ) and “I saw colours” ( $F(2.2, 50.71) = 88.78, p < .001$ ), where post-hoc paired  
303 t-tests showed that all experimental conditions were significantly different from each other  
304 and 10 Hz generated the highest ratings ( $p < .001$ ) [Figure 2]. Non-parametric Kruskal-Wallis  
305 testing confirmed all ANOVA results (Out of body:  $H(4) = 14.23, p = .006$ ; Altered time and  
306 space:  $H(4) = 15.88, p = .003$ ; Wonderful other world:  $H(4) = 16.79, p = .002$ ; Patterns:  $H(4) =$   
307  $87.61, p < .001$ ; Colours:  $H(4) = 87.84, p < .001$ ), together showing that FLS inside the MRI  
308 scanner robustly induced hallucinatory experiences in all participants, with 10 Hz stimulation  
309 eliciting the highest intensity of subjective experience

310

### 311 **Changes in functional connectivity between LGN and visual areas**

312 We tested for effects of FLS (3 Hz, 10 Hz) and constant light on connectivity changes from  
313 baseline between LGN nuclei and 16 visual areas using repeated-measures 3x1 ANOVAs (note  
314 that for every participant we averaged connectivity changes across ipsilateral connections;  
315 see methods). Alpha is Bonferroni corrected to .003 (.05/16). We found an increase in  
316 connectivity strength for 3 Hz and 10 Hz compared to baseline (average of pre and post scans),  
317 however 3 Hz and 10 Hz were not different from each other [Figure 3]. Specifically, there was  
318 a significant effect of experimental condition on connectivity changes between LGN and V1v  
319 ( $F(2, 46) = 17.75, p < .001$ ), V1d,  $F(2, 46) = 20.64, p < .001$ ), V2v ( $F(2, 46) = 26.91, p < .001$ ),  
320 V2d ( $F(2, 46) = 27.17, p < .001$ ), V3v ( $F(2, 46) = 20.73, p < .001$ ), V3d ( $F(2, 46) = 16.39, p < .001$ ),

321 which encompasses all early visual areas. In addition, there was a significant effect of  
322 experimental condition on connectivity changes with hV4 ( $F(2, 46) = 13.15, p < .001$ ), VO1 ( $F(2,$   
323  $46) = 7.40, p = .002$ ) and V3a ( $F(2, 46) = 7.85, p = .001$ ), whereby 10 Hz FLS induces the  
324 strongest coupling, followed by 3 Hz while constant light induced a weak decoupling.

325

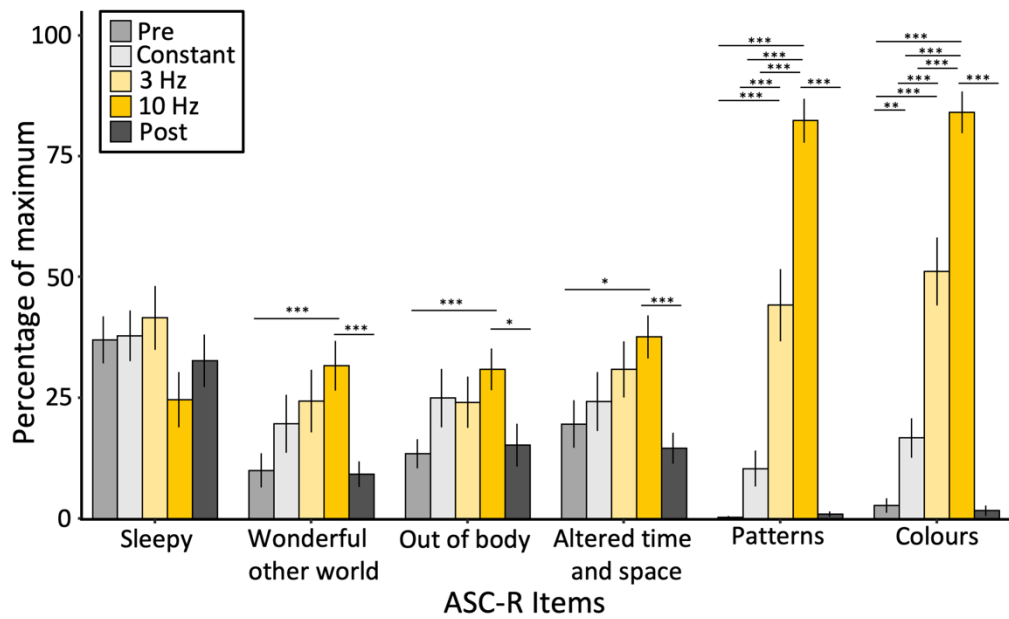
### 326 **Changes in functional connectivity between pulvinar and visual areas**

327 Using the same treatment of data as for the LGN, we tested for effects of experimental  
328 condition on connectivity changes between inferior and lateral divisions of the pulvinar and  
329 16 subregions of the visual cortex. Using repeated-measures 3x1 ANOVAs, we found no  
330 significant effects of condition on connectivity changes with inferior pulvinar across all tested  
331 visual areas, which is evident in Figure 3. For the lateral pulvinar, a significant effect of  
332 condition was revealed for connectivity changes with V1d ( $F(2,46) = 7.13, p = .002$ ) and V2v  
333 ( $F(2,46) = 7.47, p = .002$ ), whereby post-hoc t-tests showed that 10 Hz and 3 Hz induced  
334 stronger coupling than constant light ( $p < .05$ ) [Figure 3].

335

### 336 **Association of connectivity strength with subjective experience**

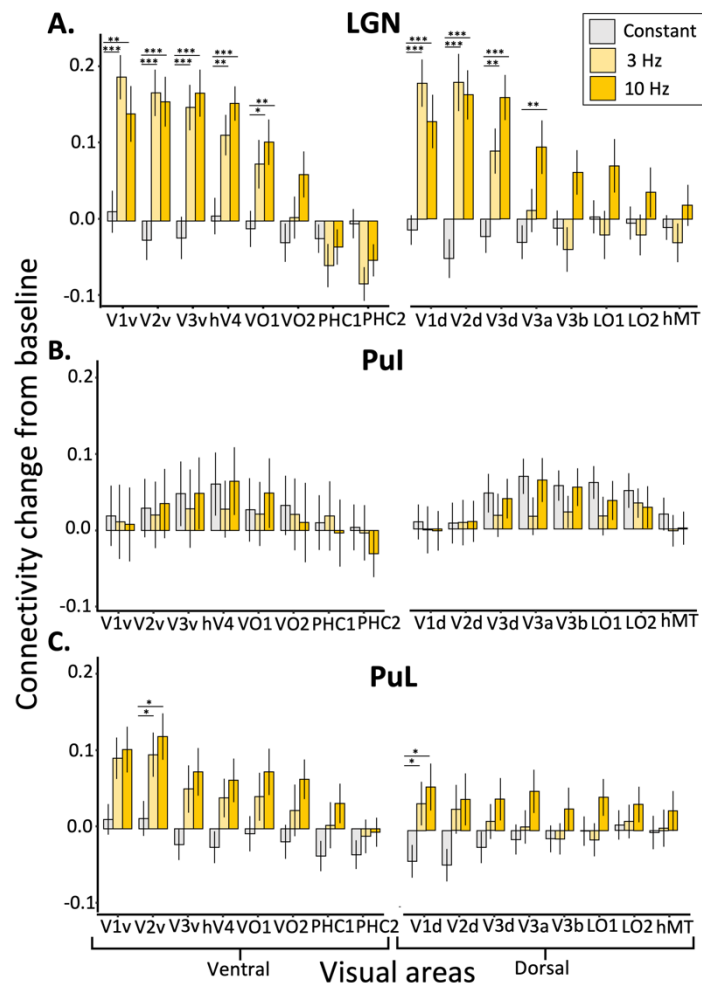
337 We ran linear mixed models with rating as a fixed effect and participant-specific random  
338 intercepts to determine if ASC-R mean ratings of experienced visual effects (i.e., mean of “I  
339 saw patterns” and “I saw colours”; see Methods) could predict changes in functional  
340 connectivity between ROIs. Alpha was Bonferroni-corrected to .003 to account for the  
341 comparison of 16 models for each group (i.e., 16 visual areas for LGN, lateral pulvinar and  
342 inferior pulvinar). We found that subjective ratings significantly predicted increases in  
343 connectivity between the LGN and V2v ( $p < .001; R^2m = 0.15; R^2c = 0.46$ ), V2d ( $p < .001; R^2m$   
344  $= 0.15; R^2c = 0.44$ ), V3v ( $p < .001; R^2m = 0.19, R^2c = 0.54$ ), V3d ( $p < .001; R^2m = 0.26, R^2c =$   
345  $0.59$ ), hV4 ( $p < .001; R^2m = 0.22, R^2c = 0.50$ ), VO1 ( $p = .002; R^2m = 0.12, R^2c = 0.55$ ), VO2 ( $p$   
346  $= .001; R^2m = 0.10, R^2c = 0.48$ ), V3a ( $p < .001; R^2m = 0.16, R^2c = 0.58$ ) and V3b ( $p = .001; R^2m$   
347  $= 0.10, R^2c = 0.46$ ). Furthermore, subjective ratings significantly predicted connectivity  
348 increases between lateral pulvinar and V1d ( $p < .001; R^2m = 0.10; R^2c = 0.56$ ). Together, this  
349 shows that the subjective ratings associate moreso with LGN interactions with upstream  
350 visual areas beyond V1, while connectivity between V1 and lateral pulvinar are significantly  
351 associated with subjective ratings.



352

353

354 *Figure 2.* Mean scores of ASC-R items for each experimental condition, indicating no  
355 differences on wakefulness across conditions, minor parametric effects on general ASC  
356 phenomena and a strong modulation of visual phenomena. Effects tested via one-way  
357 repeated-measures ANOVAs; post-hoc paired t-test significance represented by \*  $p < .05$ , \*\*  
358  $p < .01$ , \*\*\*  $p < .001$ . Standard error is depicted by error bars.



359

360 *Figure 3.* Effects of FLS on functional connectivity changes compared to baseline (average of  
 361 pre and post scans) between visual areas and (A) LGN, (B) inferior pulvinar (Pul) and (C) lateral  
 362 pulvinar (PuL). Visual areas are grouped into ventral and dorsal visual streams, as presented  
 363 by Wang *et al.* (2015). Of the repeated-measures ANOVAs that returned significant effects of  
 364 condition on connectivity change from baseline ( $\alpha = .003$ ), post-hoc paired t-tests indicate  
 365 differences between conditions, where significance is represented by \*  $p < .05$ , \*\*  $p < .01$ , \*\*\*  
 366  $p < .001$ . There is a strong modulation of condition on connectivity increases between LGN and  
 367 EVC, and proximal upstream visual areas of dorsal (V3a) and ventral (hV4, VO1) streams. 3 Hz  
 368 and 10 Hz induce LGN hyperconnectivity to the same degree for EVC, however for higher  
 369 areas of the dorsal stream (V3a, V3b, LO1), LGN hyperconnectivity is only apparent during 10  
 370 Hz FLS. There is no significant effect of light stimulation on connectivity changes between  
 371 inferior pulvinar and visual areas, while lateral pulvinar shows a similar pattern of connectivity  
 372 changes as LGN with visual areas, albeit less strong.



### 373 **Exploratory analysis of thalamocortical connectivity**

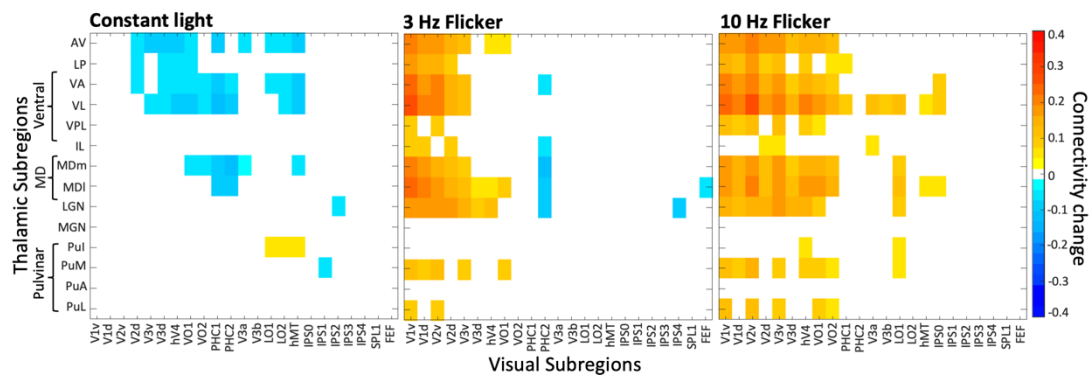
374 To explore the whole connectivity profiles of thalamic nuclei, we plotted connectivity  
375 matrices with 14 thalamic ROIs from the AAL3 atlas (Rolls et al., 2020) and 23 cortical ROIs  
376 from the Wang *et al.* maximum probability map of visual topography (Wang et al., 2015).  
377 Figure 4 displays the ROI-to-ROI correlation coefficients of the experimental conditions  
378 subtracted by the averaged pre and post scans, thus showing the connectivity change induced  
379 by the conditions. We see strong hyperconnectivity between AV, ventral and MD thalamic  
380 nuclei and cortical visual regions. Connectivity with higher-order cortical visual regions, such  
381 as hV4, VO1 and LO1, show more frequency-dependent effects (i.e., 10 Hz induces more  
382 coupling than 3 Hz) than EVC. We note that, as ventral nuclei (i.e., VA, VPL and VL nuclei) show  
383 similar changes in connectivity patterns and have anatomical proximity, we consider their  
384 effects collectively as a ventral group. Likewise, MDM and MDL are divisions of MD nuclei  
385 showing similar connectivity patterns and are therefore considered together as the MD region.  
386 The changes in connectivity induced by 10 Hz FLS are additionally represented in Figure 6.

387

### 388 **Exploratory analysis of visual area and thalamic interconnectivity**

389 To explore interconnectivity profiles of visual and thalamic areas, we plotted masked  
390 interconnectivity matrices of 23 cortical and 14 thalamic visual ROIs, where only connectivity  
391 changes that were significantly different from baseline ( $\alpha = .01$ ) are displayed [Figure 5].  
392 Figure 5A shows that 3 Hz and 10 Hz FLS leads to hyperconnectivity within EVC (i.e., V1-V2)  
393 but hypoconnectivity between EVC and higher visual areas of both the ventral (e.g., LO2/1)  
394 and dorsal (e.g., V3a/b, IPS) streams. Meanwhile, higher visual areas show increased coupling  
395 to each other (e.g., LO2/1 and IPS). Interconnectivity matrices of thalamic ROIs display few  
396 changes in connectivity amongst thalamic nuclei, especially at 10 Hz FLS [Figure 5B].

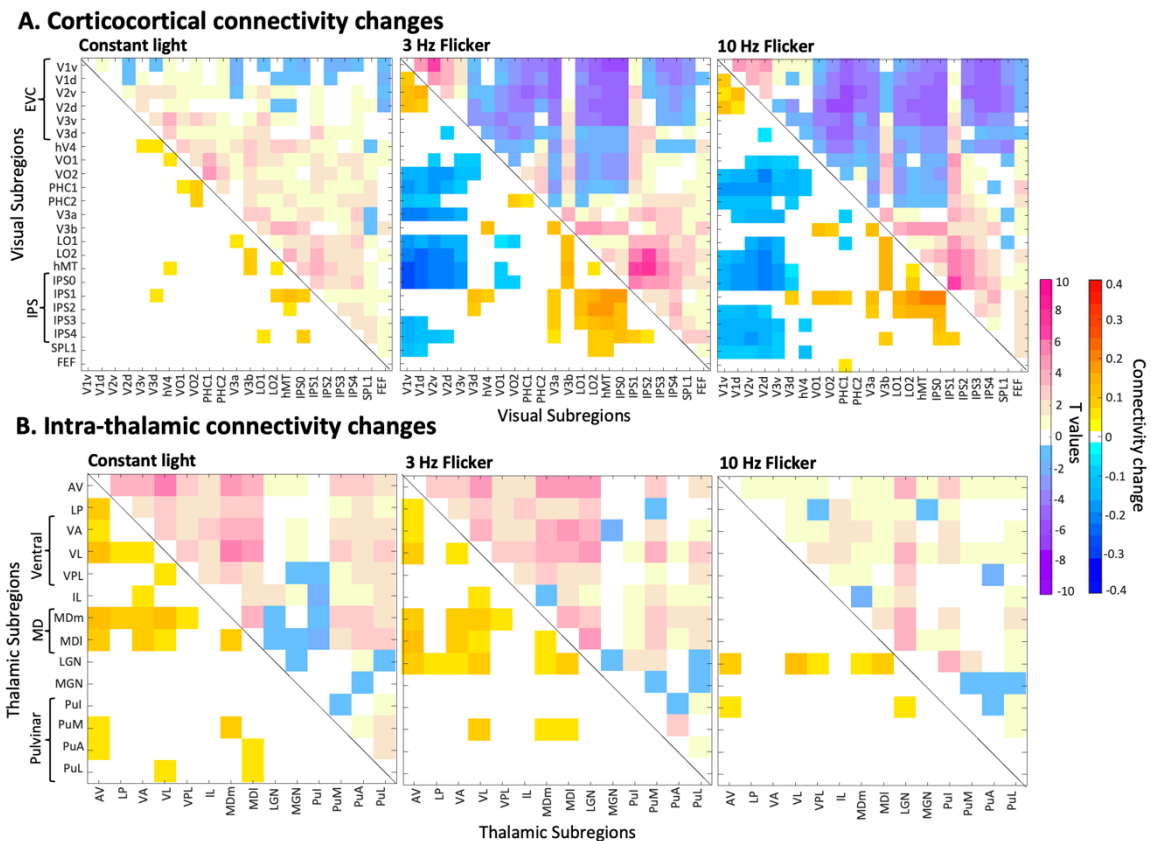
397



398

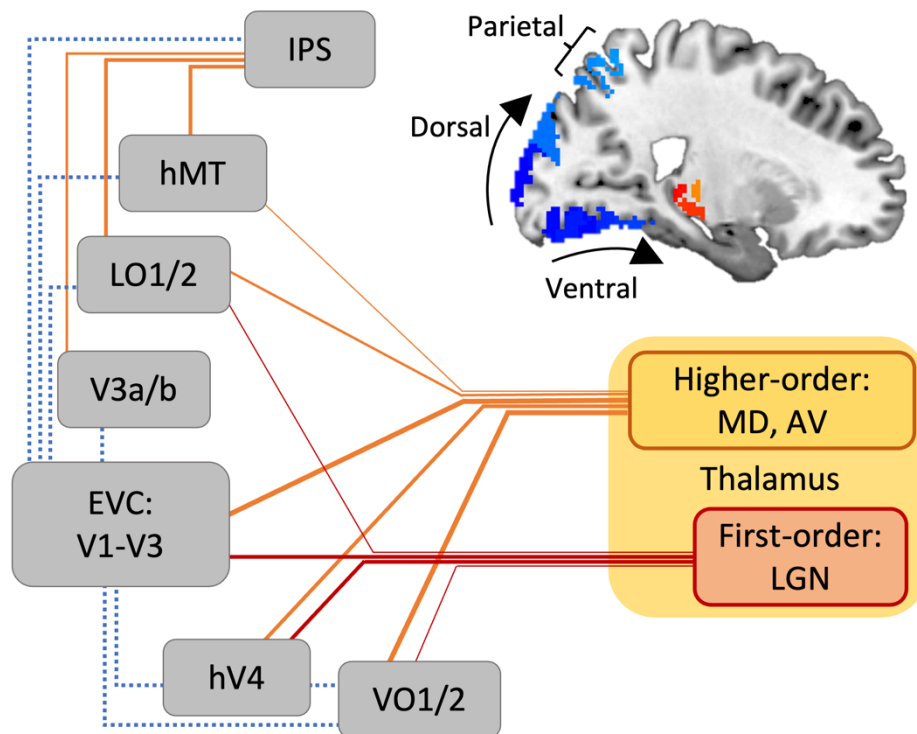
399 *Figure 4.* Connectivity matrices for all visual areas and thalamic nuclei during constant light, 3  
400 Hz and 10 Hz FLS, subtracted by the average of pre and post scans (closed-eye rest) to  
401 represent the connectivity change induced by the experimental conditions. A mask has been  
402 applied where only significant connectivity changes compared to baseline are shown, as  
403 determined by paired t-tests ( $\alpha=.01$ ). All divisions of ventral nuclei form a cluster as they  
404 display similar connectivity patterns. Likewise, medial and lateral divisions of MD nuclei show  
405 similar connectivity patterns and can be collectively considered as the MD region. With this  
406 clustering, we observe that AV, ventral and MD thalamic regions display the greatest  
407 frequency-dependent effects of FLS on connectivity changes with visual areas, in that 10 Hz  
408 induces the strongest coupling that is additionally evident in upstream visual areas of both  
409 ventral (e.g., VO2) and dorsal (e.g., hMT, V3a) visual streams. Meanwhile, we see overall  
410 hypoconnectivity in the constant light condition.

411



412

413 *Figure 5. (A) Connectivity changes between visual areas during constant light, 3 Hz and 10 Hz*  
 414 *FLS, as compared pre and post scans. Upper half of matrices show t values of paired t-tests;*  
 415 *lower half show connectivity changes (masked at  $p < .01$ , where paired t-tests revealed a*  
 416 *significant difference between connectivity in experimental condition versus baseline). There*  
 417 *are two groups of hyperconnectivity: within EVC and between upstream visual areas (e.g.,*  
 418 *LO1, hMT) and IPS, while these groups are decoupled from each other. (B) Connectivity*  
 419 *changes within the thalamus. The connectivity changes in the 10 Hz condition are confined to*  
 420 *relevant areas (i.e., LGN, AV, ventral and MD nuclei), which supports that the applied*  
 421 *parcellation yields region-specific effects. If ROIs were to reflect the same underlying signals,*  
 422 *one would expect an overall increase in connectivity between thalamic subfields. Thalamo-*  
 423 *cortico-thalamic connections likely drive increased LGN connectivity with other thalamic*  
 424 *nuclei (i.e., AV, ventral and MD nuclei), such that the signal passes from LGN via visual cortices*  
 425 *to higher-order thalamic nuclei.*



426

427 *Figure 6.* Summary of thalamocortical and corticocortical functional connections changes  
428 during 10 Hz FLS. Orange lines represent functional hyperconnectivity compared to baseline,  
429 while blue dashed lines represent hypoconnectivity. For display purposes, red and orange are  
430 used to distinguish between first-order (sensory) and higher-order (non-sensory) thalamic  
431 regions. The strength of correlation change is depicted by line thickness. During FLS, the LGN  
432 shows connectivity increases to early visual cortices (EVC; V1-V3) and proximal upstream  
433 areas of the ventral stream (i.e., hV4, VO1). We found that AV and MD higher-order thalamic  
434 nuclei display increased coupling with visual areas along ventral and dorsal visual streams.  
435 (Note: ventral nuclei also displayed a comparable connectivity profile, while their  
436 contributions as higher-order nucleus are less clear). Connectivity changes of higher-order  
437 nuclei with ventral areas are notably stronger than LGN coupling. As these nuclei do not  
438 receive direct driving retinal inputs, they are most likely driven by inputs from EVC. While the  
439 directionality of effects in higher-order regions are speculative, our findings may indicate that  
440 AV and MD nuclei take an orchestrating role for information flow across cortical regions, such  
441 as eliciting the observed hypoconnectivity between EVC and upstream cortical areas.

## 442 **Discussion**

443 We tested the effects of FLS on functional connectivity between anatomically specified  
444 thalamic nuclei and visual areas. We found that FLS induced hyperconnectivity between the  
445 LGN and early visual cortices (EVC: V1-V3), independent of flicker frequency. Meanwhile,  
446 upstream visual areas show a differential effect of flicker frequency on LGN connectivity, in  
447 that coupling was strongest for 10 Hz. Similarly, FLS induced a frequency-dependent increase  
448 in participant ratings of visual hallucinations (“I saw colours” and “I saw patterns”), which  
449 replicates previous findings (Amaya et al., 2023; Bartossek et al., 2021). The intensity of visual  
450 phenomena was associated with the strength of connectivity changes between LGN and  
451 higher visual areas, especially for V3 and hV4, suggesting that effects are not only driven by a  
452 simple feedforward mechanism from LGN to V1, but rather arise from a modulation of  
453 upstream visual areas. FLS additionally induced weak thalamocortical hyperconnectivity with  
454 the lateral pulvinar but had no effect on the inferior pulvinar. Hyperconnectivity between  
455 lateral pulvinar and V1 was associated with subjective ratings, which may correspond to a  
456 top-down modulatory influence of the pulvinar on V1. When exploring connectivity changes  
457 across all thalamic nuclei of the AAL3 atlas, we found stronger frequency-dependent  
458 modulations of connectivity between AV, ventral and MD thalamic nuclei and visual areas.  
459 Moreover, we explored corticocortical connectivity changes between visual areas and  
460 observed two groups of hyperconnectivity: (1) within EVC and (2) between upstream visual  
461 areas and intraparietal sulcus (IPS), while these groups were decoupled from each other.  
462 Overall, we identify that hyperconnectivity between upstream visual areas, LGN and other  
463 thalamic regions, such as AV, ventral and MD nuclei, may be most relevant for the emergence  
464 of visual hallucinations.

465

### 466 **Thalamocortical connectivity with LGN**

467 FLS significantly increased connectivity between LGN and EVC, hV4, VO1 and V3a. This  
468 expected finding supports that rhythmic retinal activation propagate along dorsal (i.e., V3a)  
469 and ventral (i.e., hV4, VO1) visual streams. It is likely that driving inputs from the retina cause  
470 synchronisation with LGN and subsequent visual areas via excitatory feedforward signalling,  
471 which manifests as an increase in functional connectivity, in the sense of entrainment. EEG  
472 studies have shown that periodic visual flicker at alpha frequency increases neural  
473 entrainment at that frequency (Adrian and Matthews, 1934; Mathewson et al., 2012;

474 Notbohm et al., 2016; Notbohm and Herrmann, 2016; Schwartzman et al., 2019), which  
475 coincides with findings that subjectively experienced FLS-effects are strongest in the alpha-  
476 frequency range (Amaya et al., 2023).

477

478 As there are rich feedback connections between visual cortices and thalamic nuclei (Budd,  
479 2004; Murphy et al., 1999), an increase in functional connectivity likely encapsulates both  
480 feedforward and feedback processes. Indeed, it was recently shown that visual flicker induced  
481 phase-locking in LGN and cortical layers 4 and 5 of V1 (Schneider et al., 2023), which are  
482 involved in feedforward and feedback processes, respectively. The corticogeniculate inputs  
483 may refine the feedforward signals, possibly through enhancing response precision and  
484 synchronising LGN action potentials (Andolina et al., 2007; Briggs, 2020; Sillito et al., 1994),  
485 leading to the development of specific geometric patterns and distinct colours. While our data  
486 may represent changes to both feedforward and feedback interactions during FLS, future  
487 research should assess the weighting of these contributions to the resulting thalamocortical  
488 hyperconnectivity.

489

#### 490 **Thalamocortical connectivity with pulvinar**

491 Due to the involvement of the pulvinar as a higher-order thalamic nucleus in visual processing  
492 (Adams et al., 2000; Benevento and Rezak, 1976; Guedj and Vuilleumier, 2020; Kaas and Lyon,  
493 2007), we expected to find effects of FLS on thalamocortical connectivity with the inferior and  
494 lateral pulvinar. The lateral pulvinar demonstrated increased coupling with EVC, which was  
495 more apparent for ventral visual areas compared to dorsal (see Figure 3). This reflects the  
496 major contribution of the lateral pulvinar to the ventral visual stream (Kaas and Lyon, 2007),  
497 which is responsible for shape and colour recognition (Ungerleider and Haxby, 1994), possibly  
498 relating to the hallucinatory perception of patterns and colours, although tests of this  
499 association did not survive conservative Bonferroni correction. Additionally, there were no  
500 effects of FLS on inferior pulvinar connectivity, together showing that the effects of FLS on  
501 pulvinar connectivity were smaller than expected, especially when compared to other  
502 thalamic nuclei (see below). It is possible that the observed effects on the pulvinar can be  
503 assigned to contributions to visual attention (Gattass et al., 2017; Saalmann et al., 2012),  
504 rather than the subjective experience of visual hallucinatory phenomena.

505

## 506 **Further thalamic nuclei displaying altered thalamocortical connectivity**

507 Exploratory analyses of ROI-to-ROI connectivity highlighted three further thalamic subregions  
508 whose connectivity to visual areas seem to be modulated by FLS: (1) anterior nuclei, where  
509 all divisions of anterior nuclei are included in the AV region of the AAL3 atlas. (2) the ventral  
510 nuclei group, which includes VA, VPL and VL nuclei, and (3) MD nuclei. All these thalamic  
511 regions showed hyperconnectivity with EVC during 3 Hz and 10 Hz FLS and hyperconnectivity  
512 with further upstream visual areas (e.g., V3a, VO2) for 10 Hz FLS only.

513 Anterior nuclei are critically involved in spatial navigation and memory (Roy et al., 2022; Safari  
514 et al., 2020). For example, they receive head direction signals through vestibular sensory  
515 inputs (Peyrache et al., 2019; Sharp et al., 2001; Taube, 2007). Within the anterior division,  
516 AV nuclei are linked to the visual cortex via connections to the retrosplinal cortex (Lomi et al.,  
517 2023), which is thought to contribute to spatial organization in imagination (Botzung et al.,  
518 2008; D'Argembeau et al., 2008; Hassabis et al., 2007; Szpunar et al., 2007). Furthermore, a  
519 post-mortem study of patients with schizophrenia found fewer thalamocortical projections in  
520 the AV nucleus bilaterally (Danos et al., 1998), suggesting a potential role in pathologic altered  
521 perceptual processing.

522 Within the ventral group, the VL nucleus has been associated with auditory-tactile  
523 synaesthesia (Ro et al., 2007), despite being primarily known as a first-order relay for motor  
524 inputs (Percheron et al., 1996). The ventral thalamic group were found to be hyperconnected  
525 with sensorimotor networks within psychosis (Avram et al., 2018) and following LSD  
526 administration (Avram et al., 2022), together indicating an contribution to altered perceptual  
527 processing. VL nuclei were further found to be functionally connected to the lateral visual  
528 network (Kumar et al., 2022), which is involved in motion and shape perception (Smith et al.,  
529 2009). Here, despite being known as first-order nuclei, we speculate that ventral thalamic  
530 regions may serve higher-order, integrative functions within visual processing, as it was found  
531 that first-order nuclei can also form a hub for interactions with multiple functional networks  
532 (Hwang et al., 2017).

533 MD nuclei have extensive connections with the prefrontal cortex (Haber and Mcfarland, 2001)  
534 and are primarily involved in executive cognitive function (Parnaudeau et al., 2017). For  
535 patients with psychotic disorders, MD nuclei were functionally hypoconnected with  
536 prefrontal areas (Avram et al., 2018; Woodward and Heckers, 2016) while being  
537 hyperconnected with sensorimotor areas (Anticevic et al., 2014). Further, in a healthy



538 population, MD nuclei were activated during perception of fused versus non-fused colour  
539 (indicative of hallucinatory perception; (Seo et al., 2022)). Ventral and MD nuclei were also  
540 highlighted in recent reviews of relevant thalamic regions contributing to drug- and  
541 pathology-related hallucinatory phenomena (Avram et al., 2021; Doss et al., 2021).  
542 Together, these thalamic regions (AV, ventral, MD) show a similar thalamocortical  
543 hyperconnectivity pattern with visual cortices as recently reported in patients with chronic  
544 schizophrenia (Rolls et al., 2021), suggesting that the observed hyperconnectivity could be  
545 associated with hallucinatory experiences. However, the sparsity of literature linking these  
546 thalamic regions to the visual system makes it difficult to infer how exactly they contribute  
547 mechanistically to the emergence of visual hallucinations. This calls for further research into  
548 the functional involvement of higher-order nuclei in visual processing and consequently in  
549 hallucinatory experiences.

550

551 The role of higher-order thalamic nuclei in the formation of visual hallucinations may instead  
552 lie in their ability to orchestrate brain-wide cortical activity. AV, ventral and MD nuclei all  
553 display strong connector hub properties for cortical functional networks (Hwang et al., 2017),  
554 which suggests that these thalamic areas are not only functionally specific, but also contribute  
555 to domain-general, brain-wide function (Shine et al., 2023). For example, cross-frequency  
556 coupling (CFC) may be a mechanism underlying FLS-induced effects, whereby the thalamus  
557 and/or EVC are entrained to alpha frequency, which consequently modulates large-scale  
558 cortical excitability occurring in the gamma frequency range (Canolty and Knight, 2010;  
559 Klimesch et al., 2007; Kosciessa et al., 2021; Wang et al., 2012). Given the importance of the  
560 thalamus in coordinating brain-wide activity, thalamocortical pathways have become a  
561 central feature of multiple theories of consciousness (Alkire et al., 2008; Aru et al., 2019;  
562 Purpura and Schiff, 1997; Tononi and Edelman, 1998; Ward, 2011) e.g., Dynamic Core Theory  
563 ((Tononi and Edelman, 1998); from which Integrated Information Theory developed (Tononi,  
564 2011; Tononi et al., 2016)), where subjective experiences might partly depend on  
565 orchestrating roles of thalamocortical interactions. Further, Dendritic Integration Theory  
566 proposes that cortical layer 5p neurons, where dendritic signalling is under control of  
567 thalamocortical projections of higher-order nuclei, are critical for conscious experience (Aru  
568 et al., 2019). While our study does not directly address the neural mechanisms of conscious  
569 processing, it adds to an understanding regarding the role of thalamocortical interactions



570 within visual experiences in the context of hallucinatory perception. Future research should  
571 continue to integrate how thalamocortical interactions contribute to conscious awareness  
572 and phenomenal characteristics of subjective experience.

573

#### 574 **Connectivity within visual areas**

575 When exploring connectivity changes within the visual system, we found a consistent pattern  
576 of connectivity changes for 3 Hz and 10 Hz FLS. There was hyperconnectivity within two  
577 groups: (1) within EVC and (2) between upstream visual areas (e.g., LO1) and the IPS, while  
578 these two groups were decoupled from each other. Such altered corticocortical connectivity  
579 may have been mediated by the thalamus, which can sustain and modulate corticocortical  
580 functional connectivity (Schmitt et al., 2017). This connectivity pattern contrasts with effects  
581 on the visual system elicited by ASC pharmacological interventions, i.e., LSD, where a  
582 hypoconnectivity within EVC and within lateral visual regions (e.g., hV4/hMT) was found  
583 (Bedford et al., 2023; Carhart-Harris et al., 2016; Müller et al., 2018), however methodological  
584 differences in defining visual areas make it difficult to draw direct comparisons. Within our  
585 study, FLS-induced EVC hyperconnectivity likely reflects the visual sensory inputs that drive  
586 the consequent hallucinatory effects, while hallucinatory effects of LSD are mediated by  
587 serotonergic agonism (Aghajanian and Marek, 1999). It can be further speculated that EVC  
588 hyperconnectivity may evoke decoupling between EVC and upstream visual areas, which then  
589 become hyperconnected to further upstream areas (i.e., IPS) as a compensatory response.  
590 However, what the functional relevance of this would be is largely unclear, especially as  
591 similar corticocortical connectivity patterns for 3 Hz and 10 Hz FLS suggest that the altered  
592 connectivity does not correspond directly to the visual experience. Further research should  
593 explore in detail whether there is a phenomenal correlate of altered connectivity along the  
594 visual hierarchy and furthermore, whether a temporal sequence of connectivity changes can  
595 hint towards a causal link.

596

#### 597 **Limitations**

598 It must be acknowledged that not all thalamic nuclei are accounted for in the AAL3 atlas.  
599 Particularly, the thalamic reticular nucleus, which forms a thin sheet surrounding the  
600 thalamus (Pinault, 2004) is known to exert inhibitory control on other thalamic nuclei, such  
601 as the LGN (Halassa and Sherman, 2019). Therefore, it is possible that changes in connectivity

602 with thalamic regions may have been mediated by thalamic reticular activity. While future  
603 work could utilise other atlas parcellations of the thalamus that include reticular nuclei (e.g.,  
604 thalamic probabilistic atlas (Iglesias et al., 2018)), Rolls *et al.* (2020) purposely omitted this  
605 ROI from their atlas due to its difficult structure for automated parcellation. Accurate  
606 parcellation of the reticular nuclei may only be possible with a higher field MRI scanner (i.e.,  
607 7 Tesla) and thus higher resolution images.

608 Moreover, with the quantification of functional connectivity, interpreting the directionality of  
609 effects is highly limited. The well-described anatomy of retinal inputs to the thalamus allows  
610 to draw some inference on feedforward signalling from the LGN to the cortex. Furthermore,  
611 the lack of direct retinal inputs to higher-order nuclei suggests that these are most likely  
612 driven by corticothalamic signalling. However, an interpretation of directionality beyond  
613 these are speculative. Future investigations could employ effective connectivity analyses,  
614 such as regression Dynamic Causal Modelling (rDCM) (Frässle et al., 2021, 2017), as used in a  
615 recent LSD study (Bedford et al., 2023), which allows to test for directionality based on  
616 predefined network models of interacting regions. Thus, analyses such as rDCM could give  
617 more mechanistic insights into the sources of connectivity changes across thalamocortical  
618 and corticocortical loops. This may, in turn, shed further light on the functional roles of relay  
619 and higher-order thalamic nuclei in the generation of visual hallucinatory phenomena.

620

## 621 **Conclusions**

622 Overall, we show that FLS induces thalamocortical hyperconnectivity between LGN, EVC and  
623 proximal upstream areas of ventral and dorsal visual streams (i.e., hV4, VO1, V3a).  
624 Additionally, while only weak effects were found for the pulvinar, hyperconnectivity between  
625 other thalamic nuclei and visual areas were more apparent, i.e., mediodorsal, anterior and  
626 ventral nuclei. The hyperconnectivity between higher-order thalamic nuclei and upstream  
627 visual areas was only evident for 10 Hz FLS, which follows the parametric modulation of flicker  
628 frequency on subjective ratings of seeing patterns and colours. This suggests that, although  
629 thalamocortical hyperconnectivity with LGN may initially drive the FLS-induced effects, the  
630 subsequent cortical interactions with higher-order thalamic nuclei may be more relevant for  
631 the emergence of visual hallucinations. In sum, we identify, for the first time, the specific  
632 thalamic nuclei and visual areas that display altered connectivity during flicker-induced  
633 hallucinatory phenomena.

634

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637 system free of charge.

638

## 639 **Declaration of interest**

640 None

641

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645

## 646 **Data and code availability**

647 All data will be shared upon contact to I.A. (email: [ioanna.amaya@charite.de](mailto:ioanna.amaya@charite.de)). Code for MRI  
648 preprocessing and generating connectivity matrices will be made available at:  
649 <https://github.com/ioannaamaya/FLS-rsfMRI.git>. Any further information required to re-  
650 analyse the data presented in this article is available without restrictions upon request to I.A.

651

## 652 **Author contributions**

653 **Ioanna A. Amaya:** Formal analysis, Data curation, Methodology, Visualization, Writing –  
654 original draft. **Marianna E. Schmidt:** Data curation, Software. **Marie T. Bartossek:** Data  
655 curation. **Johanna Kemmerer:** Investigation, Data curation, Methodology. **Evgeniya Kirilina:**  
656 Methodology, Resources. **Till Nierhaus:** Methodology, Formal analysis, Software, Supervision,  
657 Writing – review & editing. **Timo T. Schmidt:** Conceptualisation, Investigation, Project  
658 administration, Resources, Methodology, Software, Supervision, Visualisation, Writing –  
659 original draft, Writing – review & editing.

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