A computational view of the brain plasticity at rest

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Chapter 6

Impaired functional connectivity in patients with psychosis and visual hallucinations

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ABSTRACT

More than one-third of patients with psychosis experience visual hallucinations. Its pathomechanism however remains largely unknown. Schizophrenia is related to altered brain functional connectivity, yet, it is unknown how altered connectivity could predispose patients to experience visual hallucinations. Previous work suggested that this predisposition is caused by alterations in vision-related networks, including the Visual Network, with possibly a special focus on the Ventral Attention Network (Shine et al. 2014). This network responds to salient stimuli from the Visual Network and operates as a switch between the internally-focused Default Mode Network and the outside-world focused Dorsal Attention Network. Our study investigates the role of these networks in 3 groups: 14 patients with a psychotic disorder and visual hallucinations, 15 patients with a psychotic disorder without visual hallucinations, and 16 healthy participants. All patients underwent resting-state functional Magnetic Resonance Imaging after which we determined the intra- and inter-network functional connectivity of these networks in all participants. Moreover, we used fast Eigenvector Centrality Mapping to determine the most central, meaning the most functionally communicating, regions within these networks. Compared to healthy controls, patients with visual hallucinations had both lower intra- and inter-network functional connectivity in all vision-related networks, with this decrease being most prominent for the Ventral Attention Network, and the Dorsal Attention Network for intra-network functional connectivity. Moreover, Eigenvector Centrality Mapping showed a severe decrease in functional communication within the Visual Network in the right intracalcarine sulcus, with a simultaneous increase in functional communication in the lateral part of the left middle occipital gyrus, a region involved in object recognition. Generally, results of patients without hallucinations were in between patients with visual hallucinations and healthy controls. In conclusion, widespread dysconnectivity of predominantly vision-related functional networks predispose patients with psychosis to generate visual hallucinations. Our results are in line with earlier models on hallucinations in psychosis stating that the processing deficits in the Visual Network may either result in or exacerbate inadequate co-functioning and switching between the Default Mode Network and Dorsal Attention Network, possibly due to impaired Ventral Attention Network functioning. This, in combination with impaired attending of visual signals by the DAN, may lead to inappropriate saliency processing and wrongly attributing an external origin to internally generated events and, consequently, to visual hallucinations. The mostly complex nature of the psychotic visual hallucinations may be explained by the more central role of object processing regions.

6.1 INTRODUCTION

Psychotic disorders are characterized by the occurrence of hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, and negative symptoms such as apathy (American Psychiatric Association 2013). The most common psychotic disorder is schizophrenia. Already in the 19th century, when schizophrenia was still called amentia or dementia praecox, it was thought to be caused by altered brain connectivity (Collin, Turk, and van den Heuvel 2016). Recent studies support this hypothesis, showing that in schizophrenia regions and networks throughout the whole-brain are less functionally connected to each other and that nodes within networks are less hierarchically organized as compared to healthy controls (Lynall et al. 2010; Bordier et al. 2018). However, it remains largely unknown how visual hallucinations (VH), occuring in 37% of patients with psychosis, are related to altered brain connectivity (van Ommen et al. 2016).

VH in schizophrenia are mostly complex, including people and animals (Blom 2013; van Ommen et al. 2019). Shine et al. hypothesized these complex VHs are caused by dysfunction both within and between the vision-related networks (Shine et al. 2014). These functional networks encompass the Visual Network (VIS), the Default Mode Network (DMN), the Dorsal Attention Network (DAN) and the Ventral Attention Network (VAN). The VAN, including the anterior insula and ventral frontal cortex, responds to salient stimuli as captured by the VIS. The VAN switches processing between the internally-focused DMN and the outside world-focused DAN (see Fig 1A). The DAN, including the frontal eye fields and dorsolateral prefrontal cortex, primes visual objects in the external world by focusing on them. Contrarily, the DMN mainly consists of medial cortical regions and is active when the brain is at rest or internally focused, such as during memory retrieval and when envisioning the future (Buckner and DiNicola 2019). Both the DMN and DAN interact with the VIS to elucidate the stimulus' content (Shine et al. 2014).

Functional connectivity within and between networks (intra-network FC and inter-network FC) can be assessed by resting state functional Magnetic Resonance Imaging (rs-fMRI) (Friston et al. 1993). Rs-fMRI is task-free, thereby placing minimal demands on participants and circumventing task-related confounding factors (Fox and Greicius 2010). It is therefore a useful method for clinical populations, such as patients with psychosis. Besides FC, on a smaller, sub-network scale, the functional organization of the brain can also be depicted as a graph, consisting of multiple 'nodes' (brain regions) and 'edges' (connections) (van den Heuvel and Sporns 2013). From these parameters the relative importance of a node within the overall architecture of a network can be calculated. A node occupying a central position in the overall

organization of a network is called a 'hub'. If we knew more about the hubs within networks, this would lead to more specific knowledge about what brain mechanisms play a role in the generation of VH. We therefore analysed fMRI data acquired during resting-state and determined the functional connectivity and most central brain regions ('hubs') in the vision-related functional networks in two groups of patients with a psychotic disorder, namely those with and without having experienced VH.

This study firstly compares whole brain FC in patients with a psychotic disorder with VH to those without VH and healthy controls. Secondly, both intra- and inter-network FC of vision-related networks will be compared between these 3 groups. Thirdly, the hubs within these networks will be determined for each group and compared between groups applying Eigenvector centrality mapping. We hypothesize a lower overall FC in patients with psychosis versus controls. Also, in patients with VH, we expect a lower FC intra-VIS, intra-VAN, and higher FC intra-DMN. Moreover, we hypothesize to find higher FC between VIS-DMN. Furthermore, we expect an important role for the VAN in patients with VH, reflected in more (prominent) intra- and/or inter-network FC changes or hubs within the VAN. Finally, as psychotic VH are mainly complex VH, we expected that patients with VH have more or more central hubs in higher visual areas compared to patients without VH. Our hypotheses are visualized in Fig. 1B.

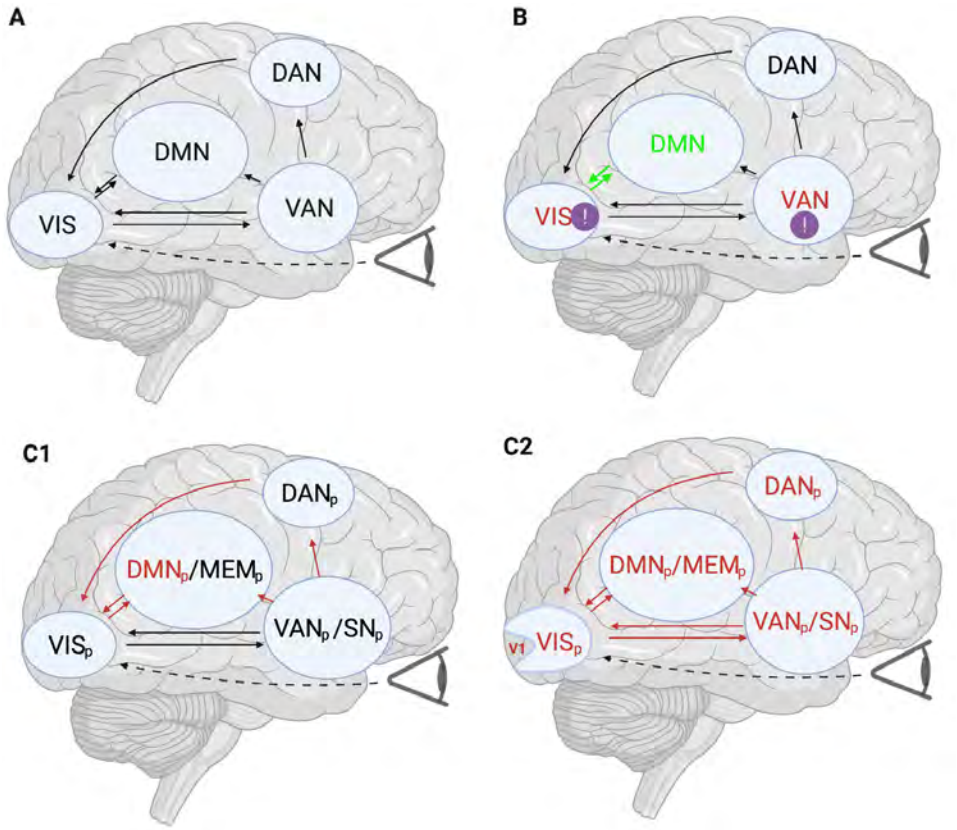

Figure 1. Visualization of visual processing, our hypothesis and a summary of the results. **A:** The networks involved with normal visual processing, based on (1), with the author's permission. The networks involved with visual processing are the visual system (VIS), the Default Mode Network (DMN), the Dorsal Attention Network (DAN) and the Ventral Attention Network (VAN). The VAN responds to salient stimuli as captured by the VIS: it switches activation away from the inner-focused DMN, to the outer-focused DAN. The DAN primes visual stimuli in the external world. The DAN and DMN themselves also interact with VIS to elucidate the stimulus' content. **B:** Our hypothesis. Mostly based on (1), with the author's permission, but also on (10). Altered functional connectivity both within and between vision-related networks would predispose some patients with psychosis to generate VH, via erroneous interpretation (having an origin in the external world) of ambiguous signals. The VAN is thought to play a key role in psychotic VH generation, by constantly generating superfluous neural responses to both externally and internally evoked signals. Moreover, impaired processing in the VIS, the DAN's inability to appropriately prime stimuli, and hyperactivity and -connectivity of the DMN would contribute to VH. VH in schizophrenia are also related to higher white matter connectivity between the hippocampus (DMN) and visual areas (10). Thus, previous studies suggest altered functional connectivity both within and between vision-related networks, which predisposes some patients with psychosis to generate VH. Green letters: higher intra-network functional connectivity. Red letters: lower intra-network functional connectivity. Green arrows: higher intra-network functional connectivity. Red arrows: lower inter-network functional connectivity. Exclamation mark: important role. **C1:** Results of comparisons between PSVH- (patients with a psychotic disorder without visual hallucinations) and HC (healthy controls). Green letters: higher intra-network functional connectivity. Red letters: lower intra-network functional connectivity. Green arrows: higher intra-network functional connectivity. Red arrows: lower inter-network functional connectivity. PSVH- have lower intra-network FC compared to

HC for the DMN_p, and lower inter-network FC than for VIS_p-DAN_p, VIS_p-DMN_p, VAN_p-DAN_p, SN_p-DAN_p, VAN_p-DMN_p, DAN_p-DMN_p. PSVH- and HC do not differentiate regarding the distribution of eigenvector values. **C2:** Results of comparisons between PSVH+ (patients with a psychotic disorder with visual hallucinations) and HC (healthy controls without visual hallucinations). PSVH+ have lower intra-network FC than HC for VIS_p, VAN_p, SN_p, DAN_p and DMN_p, and lower inter-network FC compared to HC for the following combinations: VIS_p-SN_p, VIS_p-DAN_p, VIS_p-DMN_p, SN_p-VAN_p, SN_p-DAN_p, SN_p-DMN_p, VAN_p-DAN_p, VAN_p-DMN_p, and the DAN_p-DMN_p. ECM: PSVH+ has lower ECM values for the right ICalc than HC, lying closely to H0. PSVH+ have lower ECM values for the left MTGo than HC, and a strong trend towards higher left MOGl values than HC. Green letters: higher intra-network functional connectivity. Red letters: lower intra-network functional connectivity. Green arrows: higher intra-network functional connectivity. Red arrows: lower inter-network functional connectivity. V1: lack of communication.

6.2 METHODS

6.2.1 Participants

This study is part of the INZICHT study, which goal is to gain insight into VH in psychosis. It involves a cognitive part (INZICHT1, https://www.trialregister.nl/trial/4858), and an fMRI part (INZICHT2; including this study, https://www.trialregister.nl/trial/6685). Participants for INZICHT2 were recruited via: 1) INZICHT 1, 2) the GROUP study, a multi-site longitudinal observational study focused on gene-environment interaction, 3) the Department of Psychotic Disorders, University Medical Center Groningen (UMCG), 4) Lentis Center for Mental Health Groningen and Winschoten; 5) the patients association of psychotic disorders Anoiksis. Participants fulfilled the following criteria: 1) age between 18-55; 2) speaking Dutch fluently; 3) being able to give informed consent. In addition, patients met DSM-IV-TR criteria (or the DSM 5 equivalent) for schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder Not Otherwise Specified (NOS) (American Psychiatric Association 2000). Participants affected with schizophrenia either had VH more than a couple of times in the last month (belonging to the patient group with VH, PSVH+) or (almost) never had VH (PSVH-). All PSVH- participants never had experienced VH, however, one PSVH- participant experienced VH once around 7 years ago, another PSVH- participant twice 8 years ago. In case of psychiatric comorbidity, the psychotic disorder had to be predominating. Moreover, the VH had to be related to the primary psychotic disorder. Their own psychiatrist evaluated the last two conditions. Exclusion criteria were: 1) the psychiatric disorders mental retardation, amnesia, delirium, current substance dependence (excluding nicotine and caffeine), dissociative disorders, borderline personality disorder; 2) the neurological disorders dementia, degenerative, demyelinating or inflammatory diseases of the central nervous system, other non-congenital anatomical cerebral abnormalities such as tumors and infarcts, epilepsy, congenital brain injury, brain surgery, current (mild) traumatic brain injury or a medical history of more severe traumatic brain injury; 3) visual acuity <0.5 (assessed by a chart with

sentences at a reading distance); 4) visual field defects (Donders technique); 5) cognitive impairment (Mini-Mental State Examination (MMSE) score <26 (Folstein, Folstein, and McHugh 1975); 6) fMRI incompatibility. Furthermore, HC were excluded if they had experienced a psychotic episode or VH, or if a first degree family member has (a history of) psychosis. Participants received a 50 euro coupon for participating in INZICHT2.

The ethics board of the University Medical Center Groningen (UMCG) approved the study protocol. All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

6.2.2 Symptom assessment

Trained researchers interviewed participants about psychotic symptoms using the Dutch version of the Questionnaire for Psychotic Experiences (QPE; http://qpeinterview.com/home/, (Rossell et al. 2019)) and the validated Positive and Negative Syndrome Scale (PANSS; (Kay, Fiszbein, and Opler 1987)).

6.2.3 MRI and fMRI data acquisition

Participants underwent a 10-minutes' fMRI scan, during which they were instructed to keep their eyes closed, relax and think of nothing in particular, yet to stay awake. The lights in the scanner room were dimmed during scanning. Data was collected using a 3T Philips Magnetic Resonance system with a standard 64-channel SENSE head coil (Intera, Philips Medical Systems, Best, The Netherlands). Echo-planar images (EPI) were acquired, anterior-posterior, with the following parameters: TR 2 s, TE 30 ms, voxel size 3 mm isotropic, flip angle 90° (FOV 192x117x192), 39 slices per volume, without slice gap. A T1 weighted scan was acquired for anatomical reference (160 slices, voxel size 1 mm isotropic, FOV 256x160x224 mm). Directly after scanning participants were asked if they experienced hallucinations in any sensory domain. If so, we interviewed them about hallucination characteristics.

6.2.4 Data analyses

Image preprocessing, FC analysis and statistical analyses were performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK), fastECM toolbox (Wink et al. 2012), MarsBaR ROI toolbox (http://marsbar.sourceforge.net/) and customized scripts, implemented in Matlab 2016b (The Mathworks Inc., Natick, Massachusetts).

6.2.4.1 Image preprocessing

For each subject, the structural MR image was co-registered and normalized to the Montreal Neurological Institute (MNI) template and segmented in order to obtain white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) probability maps in MNI space.

FMRI data were spatially realigned, co-registered to the MNI-152 EPI template, and subsequently normalized utilizing the segmentation option for EPI images in SPM. All normalized data were denoised using ICA-AROMA (Pruim et al. 2015) and resampled to a 3 mm isotropic voxel resolution. Additionally, spatial smoothing was applied (8 mm) to fMRI. No global signal regression was applied.

6.2.4.2 Pre-whitening

To facilitate statistical inference, data were "pre-whitened" by removing the estimated autocorrelation structure in a two-step GLM procedure (Monti 2011; Bright and Murphy 2015). In the first step, the raw data were filtered against the 6 motion parameters (3 translations and 3 rotations). Using the resulting residuals, the autocorrelation structures present in the data were estimated using an Auto-Regressive model of order 1 (AR(1)) and then removed from the raw data. Next, the realignment parameters, white matter (WM) and cerebrospinal fluid (CSF) signals were removed as confounders on the whitened data.

6.2.4.3 ROI and functional network definitions

Based on the Power atlas coordinates (Power et al. 2011), 11 functional networks and associated 232 regions of interest (ROI) were defined (5 mm radius) using the MarsBar ROI toolbox for SPM12 (Brett et al. n.d.). For each ROI, a time-series was extracted by averaging across voxels per time point. Because the network definition in Shine and Power use similar terminology, we indicate the Power definition by the subscript "$_p$" when applicable. In all other cases, we refer to the Shine nomenclature. Our hypothesis involved the DAN, VAN, VIS and the DMN, as defined by Shine et al (Shine et al. 2014). In the Power atlas this results in a combination of the Memory Retrieval Network (MEM_p) and DMN_p creating the equivalent of the DMN, and in a combination of the Salience Network (SN_p) and the VAN_p creating the VAN. Connectivity results for the other networks can be found in the supplementary material. Due to their related function, the Sensory/somatomotor Hand and Mouth networks were combined into one network. We excluded the Cerebellar and Uncertain networks.

6.2.4.4 Functional connectivity analysis

For each subject, the pairwise temporal Pearson correlation between ROIs was calculated and a Fisher's z-transformed was applied. The ROI's z-values (hereafter: FC values) were averaged across subjects. Then, the median group FC-values were used for the whole-brain analysis. While we computed the median group FC-value per single Power's NWs and then, used to perform the intra- and inter-network analyses.
For whole brain, intra- and inter-networks analyses, the median group FC-values were compared between groups using a family-wise error corrected (FWE) permutation test. Permuting the subject's group labels were repeated 10000 times per subject, $p \leq 0.05$ was considered statistically significant. In order to determine to which alterations

VH related most, effect sizes (ES) for both intra- and inter-network FC were ranked.

6.2.4.5 Fast Eigenvector Centrality Mapping

To determine the most important hubs of the predefined networks, fast ECM (Wink et al. 2012) was performed on the defined ROI time course data per subject. The ECM method builds on the concept of node centrality, which characterizes functional networks active over time and attributes a voxel-wise centrality value to each ROI. Such a value is strictly dependent on the sum of centrality properties of the direct neighbor nodes within a functional network. In the fast ECM toolbox (Wink et al. 2012), ECM is estimated from the adjacency matrix, which contains the pairwise correlation between the ROIs. To obtain real-valued ECM value, we added +1 to the values in the adjacency matrix. Several ECM values can be attributed to a given node, but only the eigenvector with the highest eigenvalue (EV) will be used for further analyses. The highest EV values were averaged across subjects at group level. Based on these values, influential ROIs, i.e. the hubs (van den Heuvel and Sporns 2011; Mišić et al. 2015; Betzel et al. 2016), can then be identified. As for the FC analyses, we identified these hubs only for our NW of interest (VIS_p, VAN_p, SN_p, DAN_p, DMN_p, MEM_p), based on Power's definition. Per group, only the ROI's with the 5% highest ECM coefficients (hubs) were considered in subsequent analysis (see Suppl. Fig. 1 for the highest 10%).

To address group differences for the most influential hubs, mean group ECM coefficients were compared between groups. FWE correction was applied for the number of group level comparisons, but not for the total number of ROIs analyzed. Again, permuted labels were repeated 10000 times, $p \leq 0.05$ was considered statistically significant.

In addition, a proxy distribution for the null hypothesis (H0) was obtained by generating 1000 times surrogate BOLD time series using the iterative amplitude adjusted Fourier transform method (iAAFT) (Räth and Monetti 2009; Schreiber and Schmitz 1996). In this way, correlations between ROIs were removed; the null distribution represents the amount of centrality obtained when no functional communication is present in the brain. Note that the null distribution of the ECM is not centered at zero, as ECM values are forced to be positive real-valued. To define the confidence intervals of each ECM value estimated per ROI, a bootstrap technique (across time-point) was used at group level in parallel to resample the filtered fMRI data. To support visualization, a Gaussian distribution was fitted to both bootstrap and surrogate distributions.

6.2.4.6 Data and code availability

Data will be made available via the open source platform https://dataverse.nl/dataverse/RUGFMScUMCG. A toolbox containing the codes will be made available via the website www.visualneuroscience.nl.

6.3 RESULTS

Forty-eight participants were initially included: 15 PSVH+, 16 PSVH-, and 17 HC. One PSVH+ participant was excluded because the scan was not saved correctly. Moreover, one PSVH- was excluded due to excessive motion (>3mm) and one HC due to a structural brain abnormality. This led to 14 PSVH+, 15 PSVH- and 16 HC participants being included in the further analyses. Table 1 shows the demographic and illness characteristics. The mean age of all participants was 34.7 years (SD 10.1); 71.1% (n=32) was male. The groups were matched for age, gender, and cognitive profile (all participants had a MMSE score>25). Most patients were diagnosed with schizophrenia (55.2%); 20.7% with schizoaffective disorder; 24.1% with psychotic disorder NOS. The mean disease duration of PSVH+ was 11.1 years (SD 9.0) and of PSVH- 15.1 years (SD 12.6) (not significantly different). Patients had significantly higher scores compared to HC on all items assessing psychotic symptoms (PANSS, QPE). PSVH+ had the highest scores. PSVH+ scored significantly higher compared to PSVH- on the PANSS total positive symptoms and the QPE items on VH and the total hallucination score. Most patients used antipsychotics (PSVH+ 71.4%, PSVH- 86.7%), generally an atypical antipsychotic (PSVH+ 60.0%, PSVH- 69.2%). Seven PSVH+ and three PSVH- experienced hallucinations during scanning. One PSVH+ experienced seeing ongoing flashes of lights, another occasionally people and spaceships, the third PSVH+ experienced seeing a dog or donkey 10 times for 1 second. Two of them also experienced (almost) continuous auditory hallucinations (AH). One PSVH+ experienced (almost) continuous both AH and tactile hallucinations (TH). Two PSVH+ only experienced TH: one continuously, the other one experienced one short-lasting TH. An other PSVH+ reported AH which lasted 2 minutes in total. One PSVH- participant experienced (almost) continuous AH, and occasional TH. One PSVH- participant experienced one short-lasting AH. Last, one PSVH- experienced continuous TH.

6.3.1 Whole brain functional connectivity

Fig. 2 depicts whole brain FC matrices averaged per group as well as the FC distributions per group. Both PSVH+ and PSVH- had a lower overall FC than HC (HC versus PSVH+ $p<0.041$, HC versus PSVH- $p<0.044$). The overall FC scores of PSVH+ and PSVH- were very similar.

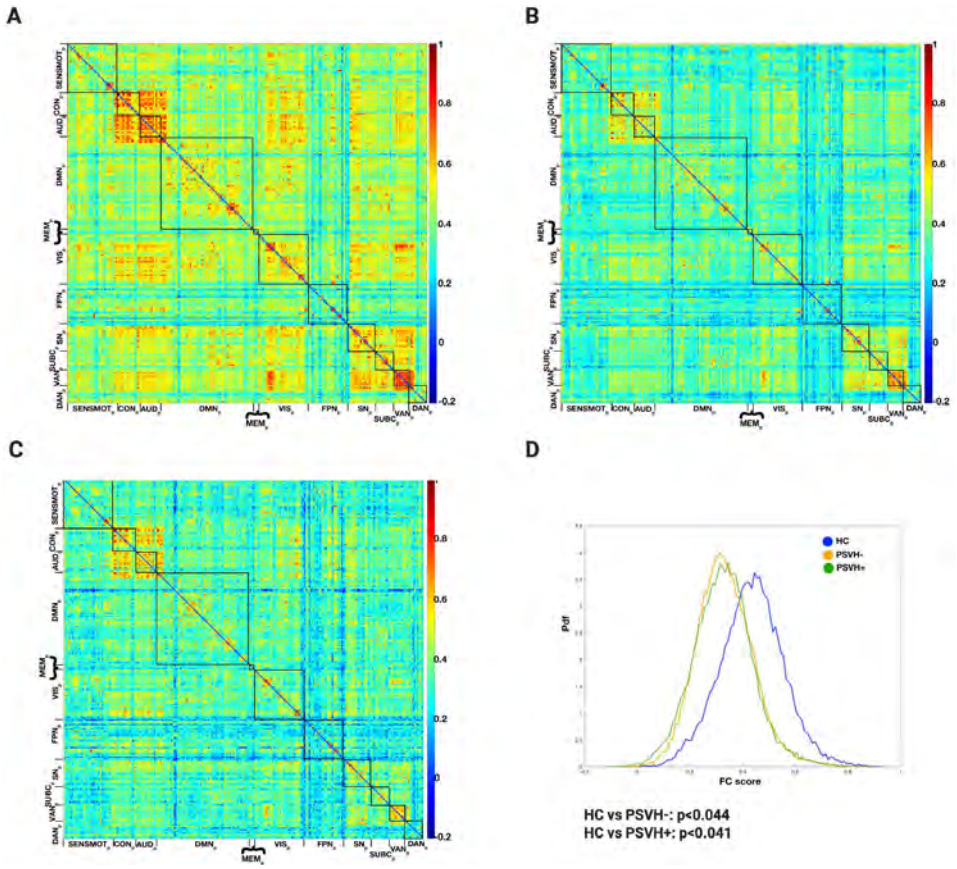

Figure 2. Whole brain functional connectivity per group, based on the Power atlas. $SENSMOT_p$: Sensory/somatomotor Hand and Mouth Networks, CON_p: Cingulo-opercular Task Control Network, AUD_p: Auditory Network, DMN_p: Default Mode Network, MEM_p: Memory Retrieval Network, VIS_p: Visual Network, FPN_p: Fronto-parietal Task Control Network, SN_p: Salience Network, $SUBC_p$: Subcortical Network, VAN_p: Ventral Attention Network, DAN_p: Dorsal Attention Network. A: healthy controls (HC), B: patients with a psychotic disorder without visual hallucinations (PSVH-), C: patients with a psychotic disorder with visual hallucinations (PSVH+), D: functional connectivity distributions per group and significant ($p \leq 0.05$) group comparisons.

6.3.2 Intra-network functional connectivity

Fig. 3 shows the intra-network FC for the 6 predefined networks (see Suppl. Fig. 2 for the results for the other networks. Median and 95% confidence interval values per group, covering all networks can be found in Suppl. Table 1). PSVH+ had a lower intra-network FC than HC for VIS_p (p=.011), VAN_p (p=.01), SN_p (p=.016), DAN_p (p=.014) and DMN_p (p=.037). PSVH- had a lower intra-network FC compared to HC for only the DMN_p (p=.037). None of the networks showed a higher intra-network FC in PSVH+ and/or PSVH- compared to HC. No significant differences between PSVH+ and PSVH-

were found either. In order to identify the most affected networks, Table 2 depicts their rank based on the ES when comparing the 3 groups. Noteworthy, the DAN and the VAN_p are affected most in PSVH+, compared to both HC and PSVH-.

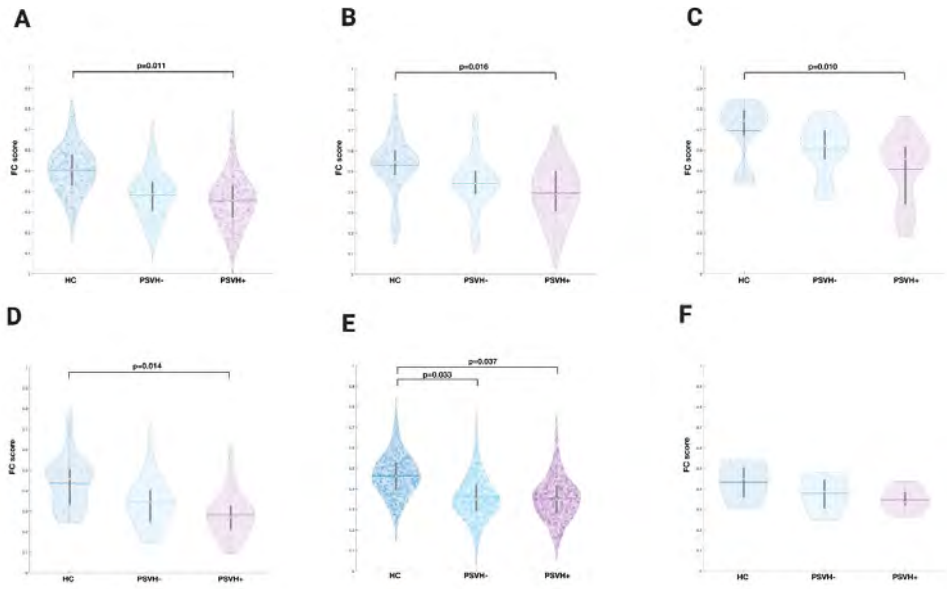

Figure 3. Intra-network functional connectivity, per group and group comparisons.
A: VIS_p, Visual Network, B: VAN_p, Ventral Attention Network, C: SN_p, Salience Network, D: DAN_p, Dorsal Attention Network, E: DMN_p, Default Mode Network, F: MEM_p, MEmory retrieval Network PSVH+: patients with a psychotic disorder with visual hallucinations, PSVH-: patients with a psychotic disorder without visual hallucinations, HC: healthy controls. Violin plots: white dot: median, horizontal stripe: mean.

6.3.3 Inter-network functional connectivity

Fig. 4 displays inter-network FC for the 6 predefined networks (see Suppl. Fig 3 for the other networks). PSVH+ showed a lower inter-network FC compared to HC for the following combinations: VIS_p-SN_p, VIS_p-DAN_p, VIS_p-DMN_p, SN_p-VAN_p, SN_p-DAN_p, SN_p-DMN_p, VAN_p-DAN_p, VAN_p-DMN_p, and the DAN_p-DMN_p. PSVH- had lower inter-network FC than HC for VIS_p-DAN_p, VIS_p-DMN_p, VAN_p-DAN_p, SN_p-DAN_p, VAN_p-DMN_p and the DAN_p-DMN_p. No network showed a higher inter-network FC in PSVH+ and/or PSVH- than HC. PSVH+ and PSVH- did not significantly differ. Table 3 depicts the ranking of the most affected networks inter-network wise, based on ES. The VAN_p and SN_p are the most affected networks in PSVH+, compared to both HC and PSVH-.

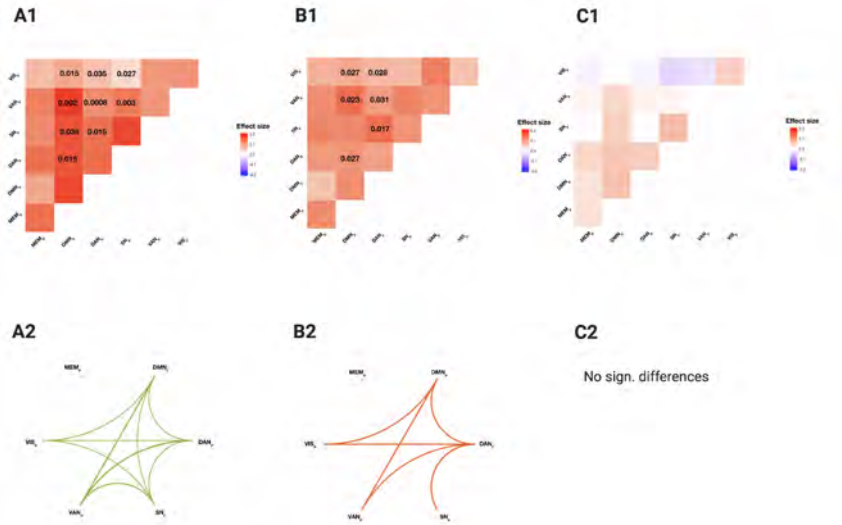

Figure 4. Inter-network functional connectivity: group comparisons.
A: healthy controls (HC) versus patients with a psychotic disorder with visual hallucinations (PSVH+), B: healthy controls (HC) versus patients with a psychotic disorder without visual hallucinations (PSVH-), C: patients with a psychotic disorder without visual hallucinations (PSVH-) versus patients with a psychotic disorder with visual hallucinations (PSVH+). 1: effect sizes of significant ($p \leq 0.05$) inter-network FC comparisons, 2: display of these significant differences. VIS_p: Visual Network, VAN_p: Ventral Attention Network, SN_p: Salience Network, DAN_p: Dorsal Attention Network, DMN_p: Default Mode Network, MEM_p: MEmory retrieval Network

6.3.4 Eigenvector Centrality Mapping

Fig. 5 A-C displays the ROIs with the 5% highest centrality value per group. For all groups, this includes ROIs from the DMN_p, VIS_p and VAN_p/SN_p. The ROIs with the 10% highest centrality value per group (Suppl. Fig. 1) belong to the same networks. Back to the 5% cut off, Fig. 5 D depicts the mean ECM values per group of the ROIs that significantly differ between groups. Three ROIs showed differences between PSVH+ and HC, being the the right intracalcarine cortex (ICalc, VIS), the left middle temporal gyrus temporo-occipitally (MTGo, VAN_p) and a trend for the lateral part of the left middle occipital gyrus (MOGl, VIS_p). PSVH+ had lower ECM values for the right ICalc and left MTGo than HC, and a strong trend towards higher left MOGl values compared to HC. The ECM value of the right ICalc in PSVH+ is close to the null distribution. The ECM values were not significantly different between PSVH+ and PSVH-, and between HC and PSVH-. Suppl. Fig 4. displays the mean ECM values of the ROIs within the highest 5 percentile, but that do not significantly differ between groups.

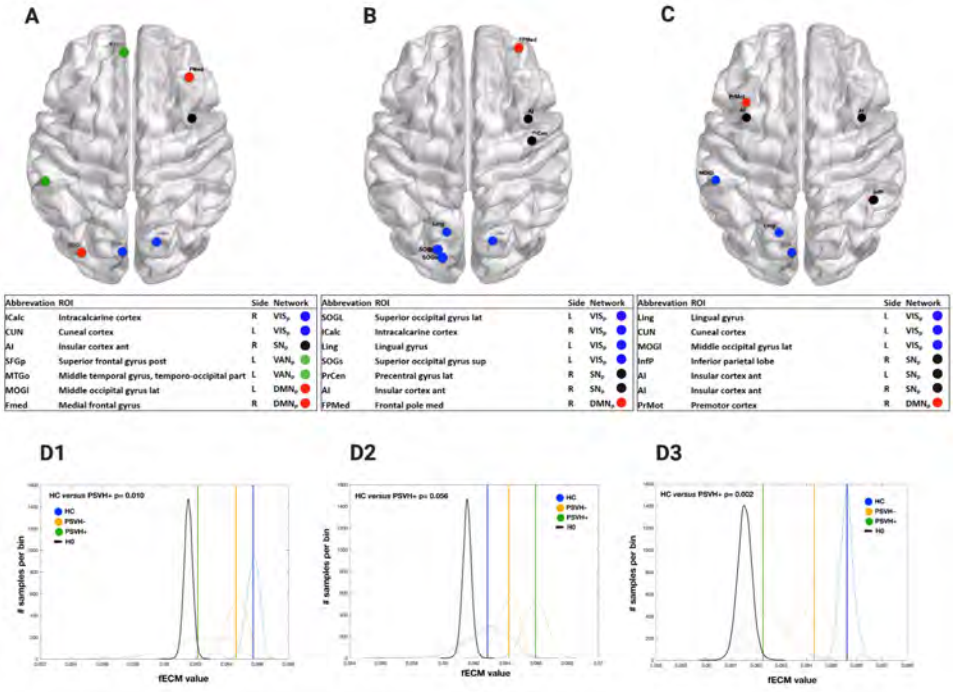

Figure 5 .ROIs with 5% highest centrality value per group, and group differences.
A: healthy controls (HC), B: patients with a psychotic disorder with visual hallucinations (PSVH+), C: patients with a psychotic disorder without visual hallucinations (PSVH-), D: mean ECM values per group of the ROIs that significantly ($p \leq 0.05$) differ between groups: 1: the right intracalcarine cortex (ICalc, VIS), 2: a trend for the left middle occipital gyrus lat (MOGl VIS_p), and 3: the left middle temporal gyrus temporo-occipital part (MTGo, VAN_p). Note that the null distribution of the ECM is not centered at zero, as ECM values were positive real-valued. To define the confidence intervals of each ECM value estimated per ROI, a bootstrap technique (across time-point) was used at group level in parallel to resample the filtered fMRI data. To support visualization, a Gaussian distribution was fitted to both bootstrap and surrogate distributions.

6.4 DISCUSSION

Our first finding is that overall FC in patients was lower than in HC. Second, we found reduced intra- and inter-network FC of all the vision-related functional networks in PSVH+, the VAN being most affected. Last, we found decreased centrality in the right intracalcarine cortex and increased centrality in the lateral part of the left middle occipital gyrus in PSVH+. Overall, our study corroborates to the notion that the symptoms of schizophrenia do not result from focal pathology, but primarily from disconnectivity between brain regions and networks (Collin, Turk, and van den Heuvel 2016). Below, we discuss these results and the implications for understanding VH in psychosis in more detail. See Fig. 1 for an overview of the results (C1 and C2)

together with an overview of vision-related networks (A) and the hypothesis (B).

6.4.1 Lower whole brain functional connectivity in patients with psychosis

As hypothesized, PSVH+ and PSVH- had lower overall FC than HC (van den Heuvel and Fornito 2014; Lynall et al. 2010). Our data confirms other rs-fMRI studies, which also found generally lower cerebral FC in schizophrenia than in controls (Lynall et al. 2010; Liang et al. 2006). However, other studies found higher FC in schizophrenia, involving the prefrontal cortex, inferior parietal lobe, medial regions, frontal and temporal lobe (Anticevic et al. 2015), cingulate gyrus and thalamus (Skudlarski et al. 2010). This suggests a more complex picture of the generation of schizophrenia symptoms. In line with this, Venkataraman et al (Venkataraman et al. 2012) found coexisting FC patterns in schizophrenia: lower FC between parietal and temporal regions, and between the temporal cortices, related to positive symptoms, whereas higher FC between parietal and frontal regions was associated with negative and general symptoms.

6.4.2 VH in psychosis relate to widespread lower intra- and inter-network connectivity in vision-related networks

Mainly based on the model by Shine, we hypothesized that VHs in psychosis relate to lower intra-VIS, intra-VAN and intra-DMN FC, with higher inter-VIS-DMN FC (Shine et al. 2014; Amad et al. 2014). Our results partially confirm this hypothesis, since we found lower instead of higher inter-VIS_p-DMN_p FC. Moreover, our results indicate that widespread FC impairments in vision-related networks is associated with the occurrence of psychosis-related VH. Whereas PSVH- only showed lower intra-DMN_p FC compared to HC, PSVH+ showed a decrease in almost all the vision-related networks (VIS_p, VAN_p, SN_p, DAN_p and DMN_p). Similarly, PSVH- showed reduced inter-network FC for various network pairs compared to HC. However, PSVH+ even showed more reductions, mainly involving the VAN. Generally, PSVH- FC values seemed to lie in between PSVH+ and HC. Corresponding to our results, multiple studies in schizophrenia have shown widespread altered FC. A recent meta-analysis found reduced intra-network FC for the DMN, affective network, VAN, thalamus network and the somatosensory network in schizophrenia (Dong et al. 2018). Additionally, inter-network FC was also found to be lower in VAN-TN, VAN-DMN, VAN-FrontoParietal central executive Network (FPN, see below), FPN-thalamus network, FPN-DMN, and higher for VAN-affective network. Accordingly, early-stage schizophrenia was related to reduced inter-network FC between the somatomotor-limbic system, somatomotor system-DMN, DAN-DMN, VAN-limbic system, and VAN-DMN (Hummer et al. 2020). Wang et al. more specifically determined the intra- and inter-network FC between large-scale networks belonging to Menon's 'triple-network model' for positive symptoms in schizophrenia (Menon 2011; Wang et al. 2016; Supekar et al. 2019). It includes the SN (which corresponds to Shine et al's VAN (Shine et al. 2014)), DMN,

and the FPN (Wang et al. 2016). The FPN is, like the DAN, a task-positive network. It includes the dorsolateral prefrontal and posterior parietal cortices, involving goal directed higher order cognition such as attention, working memory and decision making (Chand, Hajjar, and Qiu 2018). Deficits in the engagement and disengagement of these three core neurocognitive networks play a key role in schizophrenia (Menon 2011). Accordingly, patients with schizophrenia had a reduced inter-network FC for SN-DMN, SN-FPN and FPN-DMN (Wang et al. 2016). An important aspect of this model is the inappropriate assignment of saliency to external and internal stimuli by the SN (Menon 2011). Aberrant SN activity causes dysfunctional switching between the DMN and FPN. Accordingly, intra-SN FC was reduced (Wang et al. 2016). Overall, our results corroborate the models proposed by both Shine et al. and Menon (Shine et al. 2014; Menon 2011). Note that Shine et al.'s model in schizophrenia is partially based on auditory hallucinations, whilst Menon's model has been developed for positive symptoms in schizophrenia. Here, we focus on VH. Both our PSVH+ and PSVH- participants showed a high prevalence of auditory hallucinations, therefore an auditory component in our results can not be ruled out completely. As patients with psychosis with VH mostly also have auditory hallucinations (53), it is difficult to disentangle their mechanisms. On the other hand, this fact suggests a partially shared underlying mechanism.

6.4.3 The Ventral Attentional Network and its role in psychosis-related VH

Both the model proposed by Shine et al. (Shine et al. 2014) and the triple brain network model in schizophrenia (Menon) indicate that the VAN is most affected in VH and schizophrenia (Menon 2011). Our data support the VAN_p being the most impaired network according to our inter-network analysis in PSVH+. Moreover, it was the second most impaired network resulting from the intra-network analysis, and its left MTGo showed less communication compared to HC as assessed by the Eigenvector analyses. The MTGo is involved in saliency processing by detecting changes in the visual environment in colour, shape, orientation and motion (Vossel et al. 2009; Downar et al. 2000; Born and Bradley 2005). PSVH+ showed the highest impairment of intra-network FC in the DAN_p. A previous study also found lower intra-DAN FC during rs-fMRI compared to controls (Woodward, Rogers, and Heckers 2011). However, other studies found higher intra-DAN FC and higher DAN-activity during a target detection task in schizophrenia (Jimenez et al. 2016; Kraguljac et al. 2016). Menon et al. suggested that suboptimal functioning of the VAN (which includes the SN), together with inadequate switching between the DMN and DAN could lead to impaired salience mapping and, consequently, confusion between stimuli from the internal and external world, causing VH (Menon 2011). Moreover, the DAN's inability to appropriately prime salient phenomena would contribute to the impaired interpretation of visual stimuli (Shine et al. 2014). Although the current study does not address causality, our findings seem to support these models. Interestingly, multiple

studies point towards a SN dysfunction as the root of the impaired inter-network FC. In schizophrenia, intra-SN variation negatively predicts the FC between the three networks, which is mediated by intra-SN connectivity (Wang et al. 2016). Moreover, in schizophrenia also the SN-FPN and SN-DMN interactions were weaker, and the switches between these networks were more frequent (Supekar et al. 2019). These alterations correlated positively with positive symptoms, including hallucinations. In further agreement, graph theory and causal reasoning found that the independent components with the most influential roles in producing auditory hallucinations-related activity were those within the SN (Looijestijn et al. 2018). Future studies could use similar methodologies to explore whether a similar causal mechanism (with a key role for the VAN) underlies VH in psychosis.

6.4.4 VH in psychosis are related to impaired functional communication within the occipital cortex

Corresponding to Shine's model, the intra-VIS FC in PSVH+ was reduced. This indicates that VHs in psychosis are related to impaired communication between visual areas additional to the impairments described above. Furthermore, the ECM value for the right ICalc was close to the null distribution in PSVH+. At the same time, the left MOGl in PSVH+ was more central compared to in the HC. This change in centrality can be interpreted as a decrease and increase in information transfer (communication) by the ICalc and MOGl, respectively. Note that the ICalc definition used in this paper includes V1 (Horton and Hoyt 1991), while the MOGl is part of the lateral occipital complex (LOC), a higher visual area, mainly involved with processing of faces (Kanwisher and Yovel 2006), animals (Cichy, Chen, and Haynes 2011) and objects (Grill-Spector, Kourtzi, and Kanwisher 2001). Based on our data, we conclude that VHs are related to a severely reduced communication between V1 and other brain areas, and at the same time to an increased communication between the LOC and other areas, except V1. Other studies also found occipital functional segregation in schizophrenia (Bordier et al. 2018; Lynall et al. 2010). Because PSVH- did not differentiate from HC, our study suggests that this higher occipital segregation is more specifically related to VH, instead of being related to schizophrenia in general. This suggests that VH in psychotic patients are related to deficits in the early stages of visual processing, which contributes very likely to the impaired salience detection by the VAN. The increased central role of the LOC corresponds with the predominantly complex nature of VH in psychosis (Blom 2013; van Ommen et al. 2019; Ffytche, Blom, and Catani 2010; Santhouse, Howard, and Ffytche 2000).

6.4.5 Limitations

Firstly, multiple (3) participants reported VH during scanning, which may have influenced our results. For example, during VH in psychosis the DMN showed lower activity than during periods without VH (Jardri et al. 2013). Secondly, medication may

have affected our results. For ethical reasons, participants were not taken off their medication. Antipsychotics however influence dopaminergic signalling, whereas dopamine plays an important role in coupling the explored networks (Dang, O'Neil, and Jagust 2012). Thirthly, in this study we focused on VH. Therefore, we only addressed 6 direct vision-related networks. Nonetheless, schizophrenia is known to be related to widespread dysconnectivity (see section 'VH in psychosis relates to widespread lower intra- and inter-network connectivity in vision-related networks' in the discussion). Note that the results for other networks are presented in Suppl. Fig. 2 and 3. These results may induce new research questions. For example, unexpectedly we found that PSVH+ have lower intra-NW FC of the subcortical areas compared to HC, and lower inter-network FC between subcortical areas and the VAN compared to PSVH-. This might suggest that subcortical areas and the interplay between subcortical areas and cortical networks might be an interesting topic for future research into VH in psychosis.

6.5 CONCLUSION

Concluding, widespread dysconnectivity of predominantly vision-related functional networks predisposes patients with psychosis to generate visual hallucinations. This decreased connectivity was most prominent for the Ventral Attention Network, and the Dorsal Attention Network in the intra-network analysis. Our results are therefore in line with earlier models on hallucinations in psychosis stating that the processing deficits in the Visual Network may either result in or exacerbate inadequate co-functioning and switching between the Default Mode Network and Dorsal Attention Network, possibly due to impaired Ventral Attention Network functioning. This, in combination with impaired attending of visual signals by the DAN, may lead to inappropriate saliency processing and wrongly attributing an external origin to internally generated events and, consequently, to VH. The mostly complex nature of the psychotic visual hallucinations may be explained by the more central role assumed by the LOC in visual processing, as observed during resting state activity.

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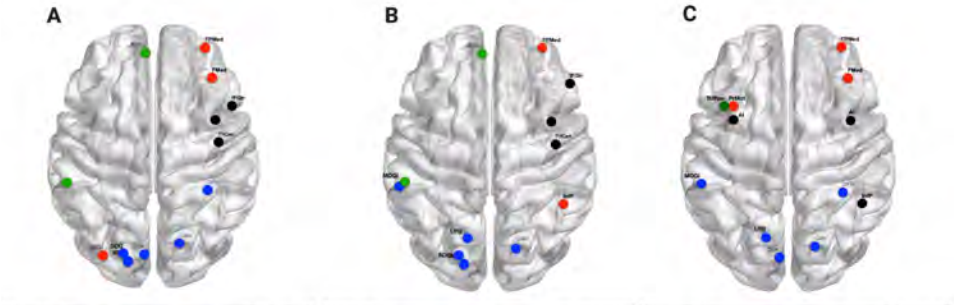
SUPPLEMENTARY FIGURES



Abbrevation	ROI	Side	Network
SOGl	Superior occipital gyrus lat	L	VIS_p
lCalc	Intracalcarine cortex	R	VIS_p
SOGs	Superior occipital gyrus sup	R	VIS_p
OFG	Occipital fusiform gyrus	R	VIS_p
CUN	Cuneal cortex	L	VIS_p
PrCen	Precentral gyrus lat	R	SN_p
IFGtr	Inferior frontal gyrus, pars triangularis	R	SN_p
AI	Insular cortex ant	R	SN_p
SFGp	Superior frontal gyrus post	L	VAN_p
MTGo	Middle temporal gyrus, temporo-occipital part	L	DMN_p
MOGl	Middle occipital gyrus lat	L	DMN_p
Fmed	Medial frontal gyrus	R	DMN_p
FPmed	Frontal pole med	R	DMN_p

Abbrevation	ROI	Side	Network
SOGl	Superior occipital gyrus lat	L	VIS_p
lCalc	Intracalcarine cortex	R	VIS_p
SOGl	Superior occipital gyrus lat	L	VIS_p
Ling	Lingual gyrus	L	VIS_p
SOGs	Superior occipital gyrus sup	L	VIS_p
MOGl	Middle occipital gyrus lat	L	VIS_p
IFGtr	Inferior frontal gyrus, pars triangularis	R	SN_p
AI	Insular cortex ant	R	SN_p
SFGp	Superior frontal gyrus post	L	VAN_p
MTGo	Middle temporal gyrus, temporo-occipital part	L	VAN_p
InfP	Inferior parietal lobe post	R	DMN_p
FPMed	Frontal pole med	R	DMN_p

Abbrevation	ROI	Side	Network
lCalc	Intracalcarine cortex	L	VIS_p
Ling	Lingual gyrus	L	VIS_p
OFG	Occipital fusiform gyrus	R	VIS_p
CUN	Cuneal cortex	L	VIS_p
MOGl	Middle occipital gyrus lat	L	VIS_p
InfP	Inferior parietal lobe	R	SN_p
AI	Insular cortex ant	L	SN_p
AI	Insular cortex ant	R	SN_p
TOFus	Temporal occipital fusiform cortex	L	DAN_p
FPMed	Frontal pole med	R	DMN_p
FMed	Medial frontal gyrus	R	DMN_p
PrMot	Premotor cortex	R	DMN_p
MTGp	Middle temporal gyrus post	L	DMN_p

Figure S1 .ROIs with 10% highest centrality value per group.
A: healthy controls (HC), B: patients with a psychotic disorder with visual hallucinations (PSVH+), C: patients with a psychotic disorder without visual hallucinations (PSVH-)

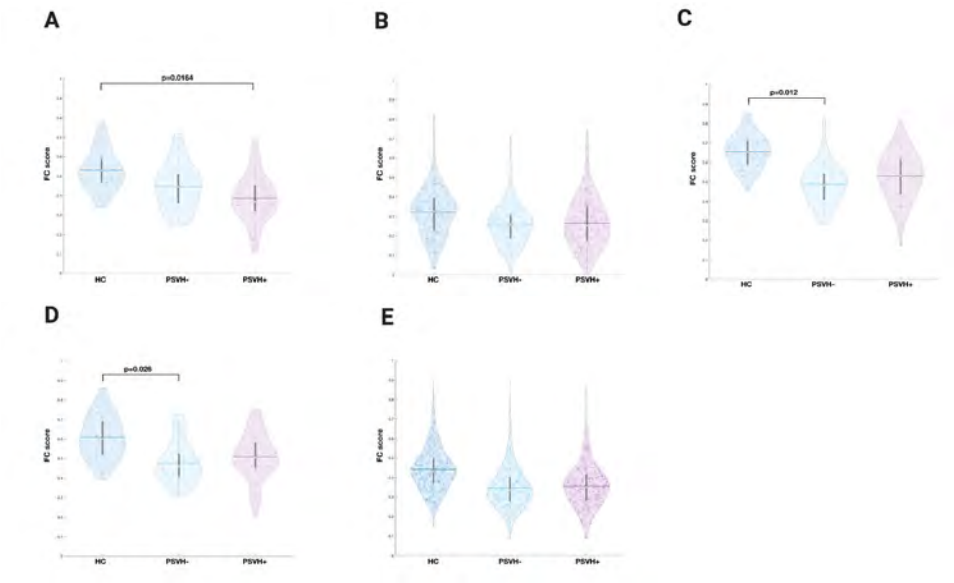


Figure S2. Intra-network functional connectivity of the remaining networks per groups, including group comparisons. A: Sensory/somatomotor Hand and Mouth Networks ($SENSMOT_p$), B: Cingulo-opercular Task Control Network (CON_p), C: Auditory Network (AUD_p), D: Fronto-parietal Task Control Network (FPN_p), E: Subcortical Network ($SUBC_p$). HC: healthy controls, PSVH+: patients with a psychotic disorder with visual hallucinations, PSVH-: patients with a psychotic disorder without visual hallucinationsViolin plots: white dot: median, horizontal stripe: mean.

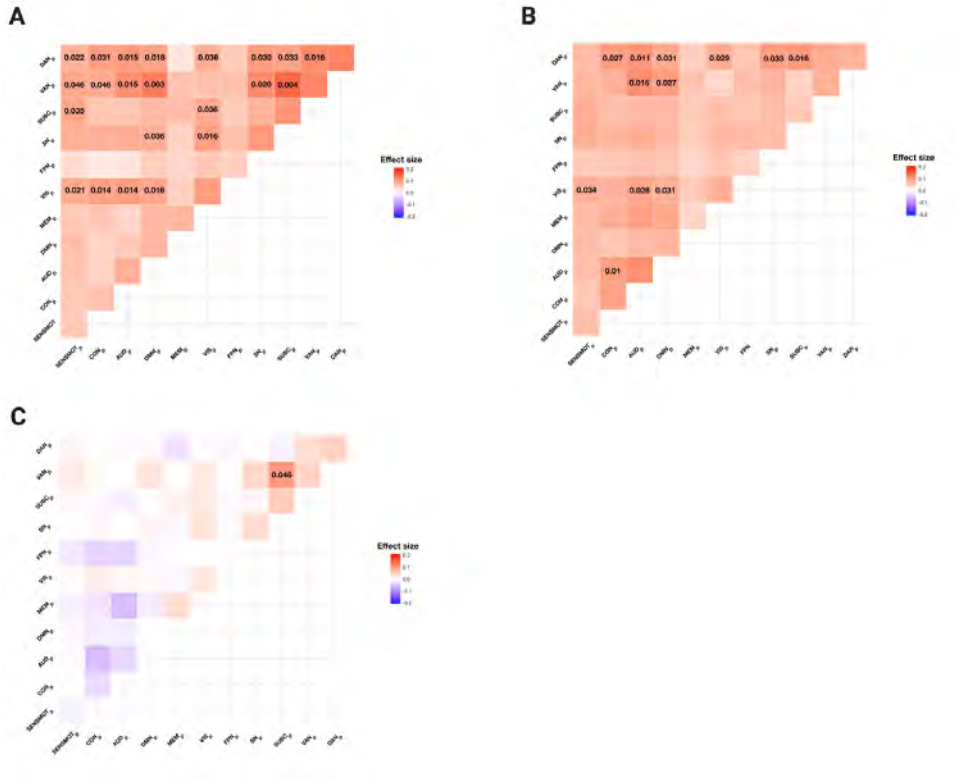


Figure S3. Inter-networks functional connectivity of all networks, group comparisons. $SENSMOT_p$: Sensory/somatomotor Hand and Mouth Networks, CON_p: Cingulo-opercular Task Control Network, AUD_p: Auditory Network, DMN_p: Default Mode Network, MEM_p: Memory Retrieval Network, VIS_p: Visual Network, FPN_p: Fronto-parietal Task Control Network, SN_p: Salience Network, $SUBC_p$: Subcortical Network, VAN_p: Ventral Attention Network, DAN_p: Dorsal Attention Network. HC: healthy controls, PSVH+: patients with a psychotic disorder with visual hallucinations, PSVH-: patients with a psychotic disorder without visual hallucinations

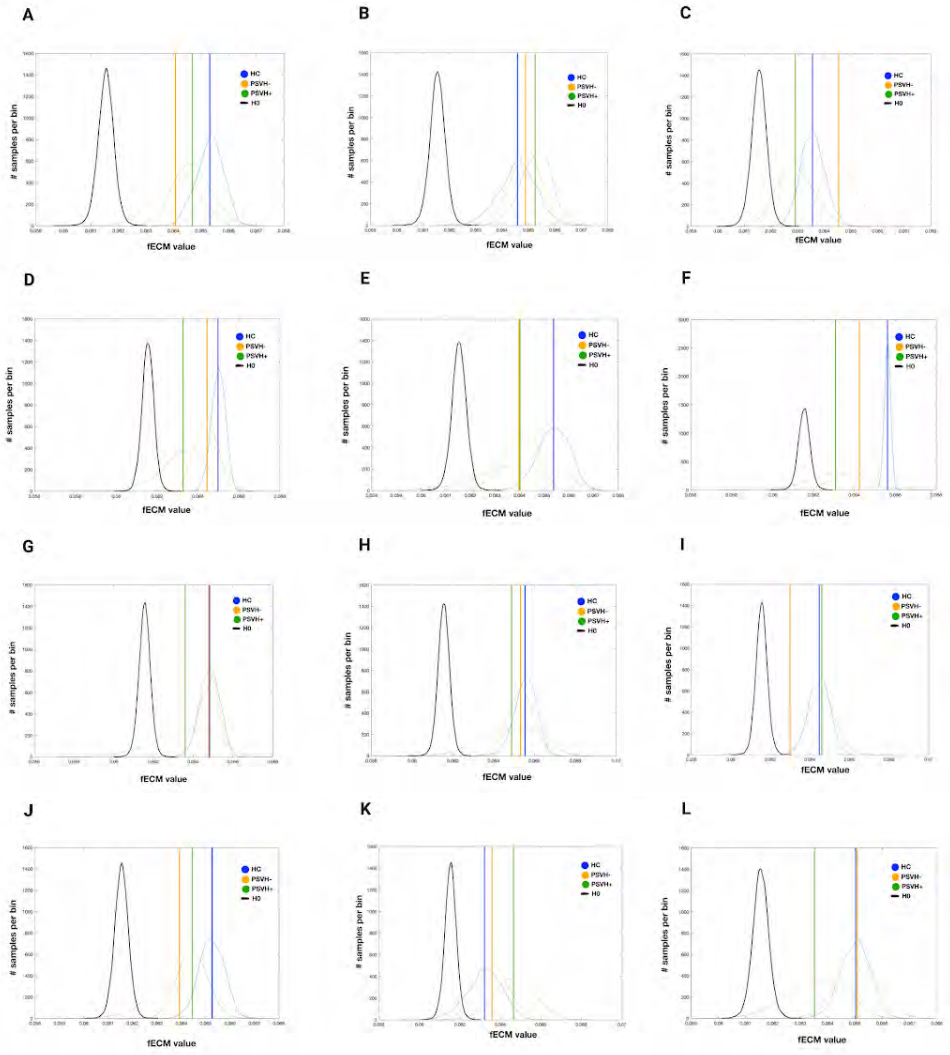


Figure 4. ROIs with 5% highest centrality value per group, non-significant group comparisons. Mean ECM values per group of the ROIs that do not significantly differ between groups. Note that the null distribution of the ECM is not centered at zero, as ECM values were positive real-valued. To define the confidence intervals of each ECM value estimated per ROI, a bootstrap technique (across time-point) was used at group level in parallel to resample the filtered fMRI data. To support visualization, a Gaussian distribution was fitted to both bootstrap and surrogate distributions. A: cuneal cortex (CUN) L, VIS_p; B: lingual gyrus (Ling) L, VIS_p; C: superior occipital gyrus sup (SOGs) L, VIS_p; D: superior occipital gyrus lat (SOGl) L, VIS_p; E: middle occipital gyrus lat (MOGl) L, VIS_p ; F: superior frontal gyrus post (SFGp) L, VAN_p; G: precentral gyrus lat (PrCen) R, SN_p; H: insular cortex ant (AI) R, SN_p; I: insular cortex ant (AI) L, SN_p; J: medial frontal gyrus (FMed) R,DMN_p; K: premotor cortex (PrMot) R, DMN_p; L: frontal pole med (FPMed) R, DMN_p.
HC: healthy controls, PSVH+: patients with a psychotic disorder with visual hallucinations, PSVH-: patients with a psychotic disorder without visual hallucinations.