Multiple Network Dysconnectivity in Adolescents with Psychotic Experiences: a longitudinal population-based study

AUTHOR(S)

Aisling O'Neill, Eleanor Carey, Niamh Dooley, Colm Healy, Helen Coughlan, Clare Kelly, Thomas Frodl, Erik O'Hanlon, Mary Cannon

Multiple Network Dysconnectivity in Adolescents with Psychotic Experiences: a longitudinal population-based study

Aisling O'Neill[1,2]*, Eleanor Carey[1,2], Niamh Dooley[1,2], Colm Healy[1], Helen Coughlan[1], Clare Kelly[2], Thomas Frodl[2,3], Erik O'Hanlon[1,2]**, Mary Cannon[1,2]**

Running title: Connectivity and adolescent psychotic experiences

Word count abstract: 243

Word count article body: 3941

[1]Department of Psychiatry, Royal College of Surgeons Ireland, Dublin, Ireland

[2]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

[3]Department of Psychiatry and Psychotherapy, Otto von Guericke Universität Magdeburg, University Hospital Magdeburg, Germany

*Corresponding author: Dr Aisling O'Neill, Room 336, Trinity College Institute of Neuroscience, Lloyd Institute, Trinity College Dublin, Ireland.

Email: aoneill@rcsi.com

**Joint senior authors

ABSTRACT

Background: Functional dysconnectivity amongst neural networks is well established in psychosis, and has been implicated in the psychopathology associated with the disorder. However, little is known about functional connectivity (FC) in individuals, particularly adolescents, who experience sub-threshold psychotic experiences (PE), and their trajectory over time. Thus, the aim of this study was to investigate large and small-scale network FC in adolescents with PE.

Methods: A population-based case-control study of 24 adolescents (mean age 13.58) who met criteria for PE were drawn from a sample of 211 young people recruited for a neuroimaging study, followed up 2 years later (n=18, mean age = 15.78), and compared to matched controls drawn from the same sample. Functional seed networks included the default mode (DMN), salience (SN), central executive (CEN), motor (MN), and auditory networks (AN). Whole-brain FC analyses were performed using the CONN functional connectivity toolbox.

Results: At both timepoints, the PE group generally displayed significant hypoconnectivity, with specific instances of hyperconnectivity, compared to controls. At baseline, FC in the PE group was decreased between regions in the MN and DMN, and the AN and visual regions. At follow up, FC in the PE group was decreased between regions in the SN and DMN, the AN and visual regions, and also within the MN.

Conclusions: Significant hypoconnectivity across multiple networks reflects findings in established psychosis, supporting a prominent role for the default mode network in the dysfunctional information processing and integration thought to underlie psychotic experiences.

Key words: psychotic-like experiences; functional connectivity; salience; default mode; motor; auditory

Introduction

Abnormal functional connectivity (FC, which describes the temporal relationship between activation measured in distinct brain regions) is well established across the psychosis spectrum(Amico et al., 2017; Dong, Wang, Chang, Luo, & Yao, 2017; Du et al., 2018; Friston, 2011; Karcher, O'Brien, Kandala, & Barch, 2019; O'Neill, Mechelli, & Bhattacharyya, 2018; Pelletier-Baldelli, Andrews-Hanna, & Mittal, 2018). FC analyses of otherwise healthy individuals who report sub-threshold psychotic experiences (PE) are of specific interest in psychosis research, given the greater prevalence of these symptoms amongst the general population than the prevalence of psychotic disorders (5.8% and 3.0%, respectively)(McGrath et al., 2015; Perala et al., 2007). A meta-analysis observed a median PE of 7.5% in adolescents aged 13 to 18(Kelleher, Connor, et al., 2012), making investigation of PE in adolescence of distinct importance. Furthermore, PE have also been associated with a relatively increased risk for psychosis(Healy et al., 2019; Kaymaz et al., 2012), suicidality(Kelleher et al., 2014; Nishida et al., 2010); and neurocognitive impairment(Kelleher, Clarke, Rawdon, Murphy, & Cannon, 2013).

Connectivity studies in psychosis have focused on the resting-state FC of three large-scale networks; the default mode (DMN), the central executive (CEN), and the salience networks (SN). Recent meta-analyses of resting-state studies consistently describe network hypoconnectivity in established psychosis, primarily across the DMN and SN (Dong et al., 2017; O'Neill et al., 2018). The DMN is involved in internally directed thought processes (e.g. memory and perspective taking)(Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner, Andrews-Hanna, & Schacter, 2008); whilst CEN engagement is related to external, goal driven processes (e.g. executive task performance)(Littow et al., 2015). The SN is thought to modulate the engagement of the DMN and CEN as salient stimuli are detected(Menon, 2011), resulting in the allocation of attentional resources to the stimuli for further processing(Menon, 2015). Aberrant salience attribution, and the subsequent dysfunctional engagement of the DMN and CEN, has been proposed as an explanation

for the psychotic symptoms and cognitive impairments that characterise the disorder(Manoliu et al., 2014; Menon, 2011; Moran et al., 2013).

Increasingly, studies have investigated the relationships between abnormal FC in smaller networks, such as the auditory (AN) and motor networks (MN), and characteristic features of psychosis including auditory hallucinations and motor deficits(Alderson-Day et al., 2016; Bernard et al., 2014; Thoma et al., 2016). Of particular interest is the MN, with emerging evidence supporting a relationship between dysfunction of this network and the wider pathophysiology and aetiology of psychosis(Bernard, Goen, & Maldonado, 2017).

Less is known about FC in young people who report PEs, and importantly, the trajectories of FC abnormalities over time in this group. Findings from a preliminary cross-sectional analysis of a subsample of the current cohort (part of the "Adolescent Brain Development Study", ABD(Kelleher, Murtagh, et al., 2012)), demonstrated significant hypoconnectivity of the DMN, CEN, SN, and AN in the PE group, with the DMN displaying the most abnormalities(Amico et al., 2017), reflecting similar observations in established psychosis(O'Neill et al., 2018). Later cross-sectional studies involving subsamples of the same cohort identified additional functional, volumetric, and structural connectivity differences between the PE group and controls, across regions strongly implicated in psychosis(Jacobson et al., 2010; O'Hanlon et al., 2015), indicating significant multi-modal neural deficits associated with PE.

Two additional analyses involving participants of the ABD cohort who underwent neurocognitive testing demonstrated significant motor deficits amongst the PE participants during the Pegboard test of motor skills, at ages 11 to 13(Blanchard et al., 2010), and again at ages 17 to 21(Carey et al., 2019). However, the possible FC abnormalities underlying these motor deficits have not yet been investigated. Furthermore, the longitudinal changes in network FC related to PE in adolescence have also yet to be explore.

Therefore, given these previous findings, the likelihood of additional psychopathology following childhood PE, and the ongoing neural development associated with adolescence, the aim

of the current study was to investigate the longitudinal changes in FC of the DMN, CEN, and SN, and the AN, and MN, over two timepoints, in a sample of adolescents who met criteria for a PE at the initial visit, but prior to the onset of any formal psychotic disorder. We hypothesised that FC would be significantly decreased in the PE group compared to the control group at both baseline and follow-up, across all networks.

Methods

2.1. Participants

A sample of 211 young people between the ages of 11 and 13 years old were initially recruited from primary schools in Dublin and Kildare, Ireland, as part of the ABD study(Kelleher, Murtagh, et al., 2012). All participants attended a diagnostic clinical interview with trained raters (recruitment and interview details outlined in Kelleher et al. (2011; 2012)). PE were assessed using the psychosis section of the Schedule for Affective disorders and Schizophrenia for School-Age Children (K-SADS)(Kaufman et al., 1997), and confirmed by a consensus committee (two psychiatrists and a psychologist) (further details in Supplementary Material).

A subsample of 100 participants with no contraindications to functional magnetic resonance imaging (fMRI) agreed to take part in a neuroimaging study that took place 1 to 3 years (mean 2 years) after the original interview, and again 2 years later. Of the 100 participants scanned, 26 met criteria for a PE in the original diagnostic interview. 25 of this PE group were scanned at timepoint 1 (TP1), and an additional participant scanned at timepoint 2 (TP2). One PE participant was removed during the analysis due to structural abnormalities. Apart from the participant only scanned at TP2, 17 PE participants who took part in TP1 returned for TP2. From the remaining participants, 25 individuals without PE were selected to match the PE group for gender, handedness, age (at each time of scanning), socioeconomic status, and number of scans, forming the control group – one of whom was added only at TP2. Overall, at TP1: PE=24, controls = 24; at TP2: PE=18, controls=18. Mean age of both groups was 13.58 years at TP1, and 15.78 years at TP2. None of the participants in

either group had any history of neurological disorder (e.g. epilepsy). Written parental consent and participant assent were obtained before the study began.

2.2. Resting-state data acquisition

Whole-brain fMRI data were acquired for each participant using a 3T magnetic resonance imaging system(Philips Achieva, Philips Medical Systems Netherland BV), in Trinity College Institute of Neuroscience, Dublin. During scanning, participants were presented with a fixed white cross in the centre of a black screen and were asked to look at this cross for the duration of the scan, while blinking normally. T2*-weighted images were acquired continuously using a gradient echo planar imaging over 5:26mins, with the following parameters: TR/TE = 2000/27ms; flip angle = 90°; 37 x 3.2mm slices acquired parallel to the anterior-posterior commissure plane; FoV = 240mm; matrix = 80 x 80. High resolution T1 weighted images were acquired with a turbo gradient echo 3-D sagittal sequence, using the following parameters: TE/TR = 8.4/3.9ms; flip angle = 8°; 256 x 256 matrix; 180 x 0.9mm slices; FoV = 230. Scan duration was 5:47 minutes.

2.3. Pre-processing of functional data

All data pre-processing and analysis were performed using the CONN functional connectivity toolbox (v18a)(Whitfield-Gabrieli & Nieto-Castanon, 2012), via the SPM12 platform (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). Briefly, pre-processing included functional realignment and unwarping, slice timing correction, structural segmentation of the data into typical tissue classes, normalisation to the Montreal Neurological Institute (MNI) template, resampled at $2mm^3$, functional normalization, Artifact Detection Tools (ART) based outlier identification/scrubbing, and smoothing using an 8mm full width at half maximum Gaussian filter (additional details in Supplementary Material).

2.4. Functional connectivity analysis

Whole-brain seed-to-voxel analyses were performed, using the CONN toolbox. The networks and seed regions of interest were as follows: 1) the DMN – seeds included the precuneus, ventral anterior cingulate cortex, and the parahippocampal gyrus cortex(Uddin, Kelly, Biswal, Castellanos, & Milham, 2009); 2) the SN – seeds included the dorsal anterior cingulate cortex, and the insula(Menon, 2011); and 3) the CEN – seeds included the dorsolateral prefrontal cortices (BA9 and BA46, separately)(Menon & Uddin, 2010). The additional networks included 4) the MN –seeds included the primary motor cortex M1, premotor cortex, and the anterior cerebellum (cerebellum IV-V)(Stoodley, Valera, & Schmahmann, 2012); and 5) the AN – seeds included the primary auditory cortex A1 (BA41, and BA42 separately), and the secondary auditory cortex A2(Allen, Laroi, McGuire, & Aleman, 2008; Ford et al., 2009).

Seed regions were identified via inbuilt CONN atlases (based on FSL Harvard-Oxford atlas cortical and subcortical areas(Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006), AAL atlas cerebellar areas(Tzourio-Mazoyer et al., 2002), and standard Brodmann areas(Whitfield-Gabrieli & Nieto-Castanon, 2012), and were all bilateral. The average BOLD signal time series over each of the seed regions were then extracted from each subject's brain space. Covarying for the movement and ART outlier artifacts identified during pre-processing, the strength and significance of the bivariate Pearson correlations between the time series of each seed region and the time course from all other brain voxels was then calculated within each subject's brain space, using General Linear Modelling.

Second level random-effects analyses were used to create group connectivity maps (i.e. for the PE group, and the control group), averaging the correlation coefficients resulting from the first level analysis across participants, and then to examine FC differences between groups.

Two-sample ANOVAs were used to identify cross-sectional differences in whole-brain seed-to-voxel FC between the PE group and the control group, at TP1, and TP2. Repeated measures ANOVAs were used to identify longitudinal FC differences within the groups, across timepoints (in these

cases, only participants present for both TP1 and TP2 were included, thus PE=17, and controls=17). Finally, mixed measures ANOVAs were used to assess group by time effects on FC (again, only participants present for both TP1 and TP2 were included). Results were initially thresholded at an FDR whole-brain corrected cluster-level of $P < 0.05$. P was then adjusted to 0.01, to correct for the number of networks being compared (5 networks).

Results

3.1. Demographics

Participant demographic information is summarised in eTable 1 (Supplementary Material). At TP2, 10 PE participants met criteria for the re-occurrence of PE.

3.2. Differences in whole brain seed to voxel functional connectivity between and within the PE and control groups

3.2.1. Triple network differences

Cross-sectional between group differences: At TP1, no group differences in FC survived the $P < 0.01$ significance threshold.

At TP2, the PE group displayed significantly decreased FC between the left insular cortex and the precuneus, and significantly increased FC between the right dorsolateral prefrontal cortex (BA46) and the right insular cortex, compared to controls (Figure 1, Table 1).

Longitudinal within group differences: The within group analyses revealed greater changes within the controls over time than in the PE group, with most of the changes occurring between the DMN and the SN (Supplementary material). Briefly, in the controls, FC within the DMN, and between the DMN and SN increased over time, with a few instances of increased FC between the CEN and the DMN. In the PE group, the majority of changes also occurred within the DMN, and between the SN

and the DMN, with two instances of FC changes between the CEN and the DMN, though the direction of these changes were more mixed than in the CON group (Supplementary material).

Group x time: The group x time analyses revealed significant interaction effects between the precuneus seed and clusters with peaks in the right insular cortex, and in the left anterior supramarginal gyrus. In both instances, a cross-over interaction effect was observed, with FC decreasing over time in the PE group, and increasing over time in the controls. Significant cross-over interactions were also observed for the SN, with FC between the left insular cortex and left frontal pole increasing in the PE group, and decreasing in the controls over time, whilst FC between the left insula and right precuneus decreased in the PE group, and increased in the controls over time. Where the right insular cortex was the seed, FC with the left cerebellum VI increased in the PE group and decreased in the controls over time, whilst FC with the right precuneus again decreased in the PE group, and increased in the controls over time (Figure 1, Table 1).

3.2.2. Motor network differences

Cross-sectional between group differences: At TP1, the MN displayed significantly decreased FC between the right M1 seed and the right lateral occipital cortex extending into the angular gyrus; between the left cerebellum IV-V seed and the precuneus; and also between the right cerebellum IV-V and the bilateral superior lateral occipital cortex, in the PE group compared to controls. Significantly increased FC was observed between the right cerebellum IV-V and the left parietal operculum/insular cortex, in the PE group compared to controls (Figure 2, Table 2).

At TP2, FC was significantly decreased within the PE group compared to controls between the left M1 seed and the left occipital pole, and the bilateral precentral gyrus; and between the right M1 seed and the left precentral gyrus. FC was significantly increased in the PE group at TP2 between the left M1 seed and the frontal operculum/insular cortex, and between the right M1 seed and the left superior frontal gyrus, and left frontal pole (Figure 2, Table 2).

Longitudinal within group differences: No significant differences in FC across the timepoints were observed within the PE group. In contrast, the control group displayed largely increased FC between the bilateral motor cortices and other regions within the MN, bilaterally (Supplementary material).

Group x time: No significant group x time interactions were observed.

3.2.3. Auditory network differences

Cross-sectional between group differences: At TP1, significantly decreased FC was observed in the PE group compared to controls between the right A1 (BA41) seed and the inferior temporal gyrus, and between the left A2 seed and the bilateral lingual gyrus (Table 3).

At TP2, FC was significantly decreased in the PE group compared to controls between the left A2 seed and a cluster with a peak in the superior lateral occipital cortex (Table 3).

Longitudinal within group differences: Within group analyses largely revealed increases in FC in the PE group between the auditory seeds and frontal regions including the middle frontal gyrus and the frontal pole, whilst the control group displayed a decrease in FC between the left A2 seed and the cerebellar vermis IV-V region (Supplementary material).

Group x time: No significant group x time interactions were observed.

Discussion

In keeping with the hypotheses, we observed significantly altered resting-state FC across the, motor, auditory, default mode, salience, and central executive networks in the PE group, compared to controls, at both the baseline and 2 year follow up. Specifically, the PE group largely displayed hypoconnectivity, evident at both timepoints. Localised instances of hyperconnectivity were observed between the motor and salience networks at baseline and follow up, between the central executive and salience networks at baseline, and between the motor and central executive networks at follow up. Furthermore, though the controls displayed more significant within group changes

across all the networks over time (primarily increases in connectivity), the mixed measures analyses did not identify any significantly greater changes in FC between the groups over time for any of the networks.

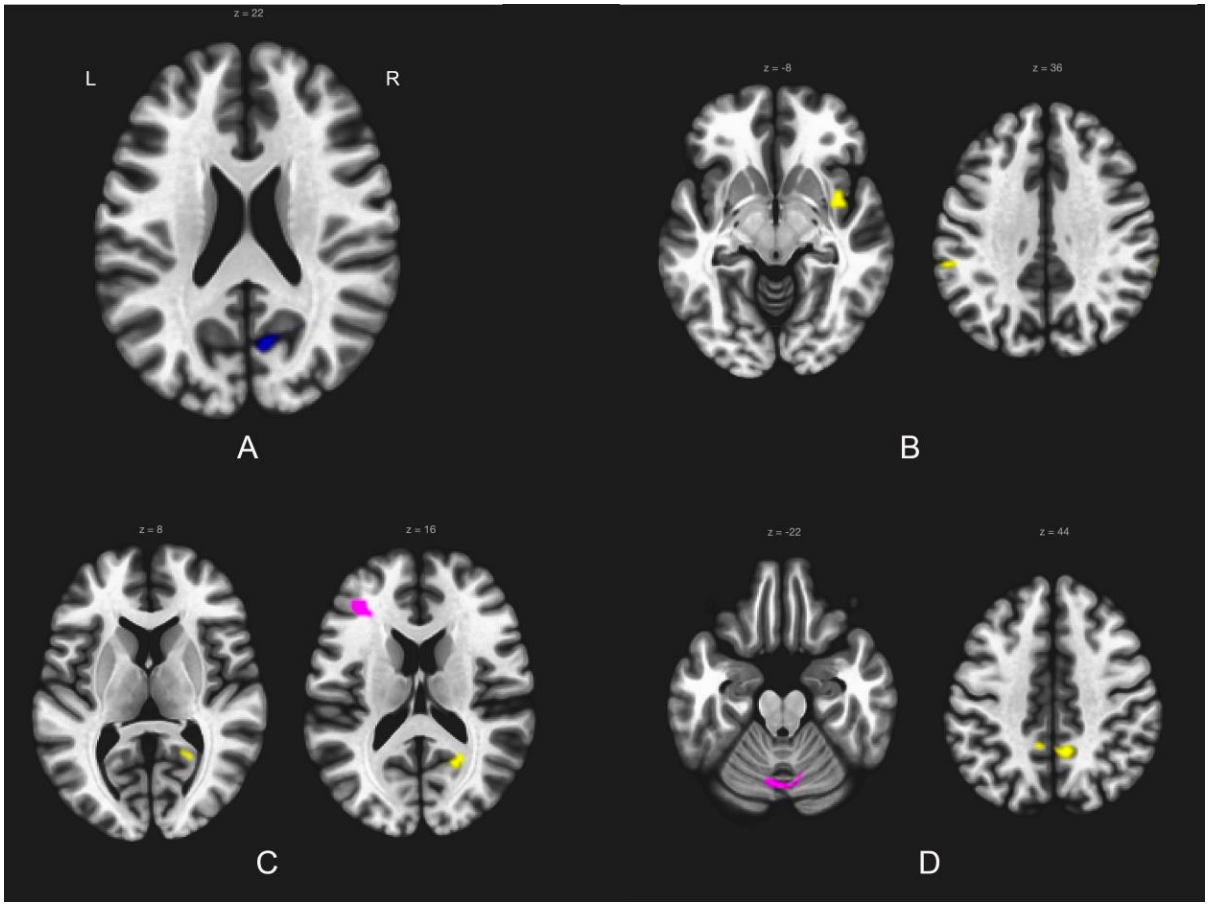
Default mode, salience, and central executive networks: No significant within or between network group differences were observed for the DMN, SN, and CEN at baseline. At follow-up, the PE group displayed decreased FC between the SN and the precuneus (DMN), and increased FC between the CEN and insula (SN), compared to controls. The most prominent finding of the mixed measures analysis is of consistent cross-over effects between the SN and DMN. In the majority of instances, FC increased in the controls over time, and decreased in the PE group. Both the between groups and mixed measures findings are consistent with the literature relating to established psychosis, which generally describes hypoconnectivity within the DMN, and between the DMN and SN(Dong et al., 2017; O'Neill et al., 2018; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011), and supports the key roles for the SN and DMN proposed by the large-scale network model of psychopathology(Menon, 2011). A limitation of FC analyses generally is that they cannot determine the directionality or causality of the functional connections – in this case, between the activation in the SN and the activation in the DMN and CEN – known as effective connectivity. A recent study by Palaniyappan et al. identified distinct patterns of DMN, CEN, and SN effective connectivity between patients with schizophrenia spectrum disorders and patients with psychotic bipolar disorder(Palaniyappan et al., 2018). Effective connectivity should be considered in future studies of PE groups, as it may be useful in determining prognostic biomarkers.

Motor network: Increasingly, interest has grown in the contribution of abnormal motor circuits to psychosis symptoms, beyond their overt role in motor dysfunction(Bernard, Goen, et al., 2017; Mittal & Walther, 2018). This is supported by longitudinal studies describing associations between delayed neuromotor development during infancy and childhood, and increased incidence of psychotic disorders in adulthood(Cannon et al., 2002; Clarke et al., 2011). In the current study, we demonstrated extensive FC abnormalities of the MN, at both baseline and follow-up. Specifically,

connectivity in the PE group at baseline was decreased between bilateral motor regions and the lateral occipital cortex into the angular gyrus and the precuneus (the posterior DMN), with one instance of increased FC occurring between the MN and the parietal operculum extending into the insula and putamen (SN), compared to the controls. Little has been reported on resting-state dysconnectivity between the MN and the DMN, SN, and CEN, across the psychosis spectrum. This is particularly true for the MN, and the SN and CEN. However, it is worth noting that the few instances of hyperconnectivity occurred between these three networks. Studies of Parkinson's and Huntington's diseases, both neurodegenerative disorders characterized in part by dopamine related motor dysfunction, have described abnormal connectivity between the DMN and the primary motor cortex(Bazan, Biazoli, Sato, & Amaro, 2015; Koenig et al., 2014). These studies suggested that such dysconnectivity may lead to deficits in motor related mental imagery, integration of visuomotor information, and executive control of movement(Bazan et al., 2015; Koenig et al., 2014). As this subsample of the overall cohort did not perform the Pegboard motor skills test, it was not possible to investigate the relationship between DMN–MN connectivity and motor performance. Nevertheless, it stands to reason that the abnormal DMN-MN connectivity in the PE group at baseline may lead to deficits similar to those described in Parkinson's and Huntington's diseases. These deficits could in turn underlie the impairments in motor function, and possibly those in cognitive function, observed in PE groups and groups at high risk for psychosis(Bernard et al., 2014; Bernard, Orr, & Mittal, 2017; Blanchard et al., 2010; Carey et al., 2019). Furthermore, as abnormal FC of the DMN has been linked to primary aspects of psychosis psychopathology(Hare et al., 2018; Mingoia et al., 2012; Scheinost, Tokoglu, Hampson, Hoffman, & Constable, 2019; Whitfield-Gabrieli & Ford, 2012), it is possible that the proposed relationship between motor circuit dysfunction and wider psychosis psychopathology may be mediated via functional connections with the integrative hubs of the large scale DMN. To explore this further, future studies should investigate any effects of DMN–MN connectivity on cognitive-motor functioning across the psychosis spectrum, and how this may vary over time.

At follow-up, hypoconnectivity within the MN became more prominent, in keeping with the findings of a recent meta-analysis of resting-state FC in schizophrenia exploring a range of networks(Waltmann et al., 2019). Within MN hypoconnectivity may be indicative of a neural inefficiency related to psychosis vulnerability, as previous longitudinal studies in individuals who are at risk for psychosis have demonstrated associations between dysconnectivity of motor regions, and transition to psychosis(Anticevic et al., 2015; Bernard, Orr, et al., 2017).

Auditory network: We observed decreased connectivity in the PE group between the auditory seeds and regions involved in visual processing at both baseline (the inferior temporal gyrus, involved in discriminating colours and shapes), and follow up (the lateral occipital cortex, involved in visual association)(Blumberg & Kreiman, 2010; Grill-Spector, Kourtzi, & Kanwisher, 2001). It is generally assumed that different sensory modalities are processed by largely independent pathways, though some integration between these specialized sensory networks is required to interpret different signals that arise from common events or objects(Macaluso & Driver, 2005; Majka et al., 2019). Though speculative, it is possible that reduced integration between the



itory and visual networks observed in the PE group could underlie a misattribution as to the source of different sensory stimuli, ultimately contributing to hallucinatory experiences.

Longitudinal within group findings: The typically developing control group demonstrated greater changes in FC over time than the PE group. This reflects previous findings in childhood and early adolescent development, describing delays in neurocognitive growth for individuals with psychotic symptoms(Gur et al., 2014), and in white matter growth for siblings of patients with childhood-onset schizophrenia(Gogtay et al., 2012), compared to controls. This could suggest that the dysconnectivity observed here is underpinned by a delay in FC development in groups that are vulnerable to psychosis, adding a dimension to the neurodevelopmental hypothesis of psychosis. Furthermore, in the study involving siblings of patients, the lag in white matter development was found to normalise with age (i.e. >14 years). Age-based normalisation in groups who meet criteria for PE should be explored in future studies.

These findings should be considered in view of certain limitations. Primarily, it was not possible in the current analyses to distinguish between frequency in psychotic experiences (i.e. those who experienced a handful of discrete events, compared to those whose experiences occurred several times a week for several years). It is possible that FC abnormalities may occur in a continuum, reflecting the full spectrum of psychotic experiences and psychotic disorders. However, dividing the sample would result in power issues. Due to the sample size, it was also impossible to explore transient versus persistent PEs. Notably, 8 of the returning participants who met criteria for a PE at baseline had no re-occurrence of PEs by follow-up. Where possible, future studies should address these gaps by exploring sub-group differences amongst individuals with PE.

In conclusion, in keeping with our hypotheses, we identified hypoconnectivity across the DMN, SN, AN, and MN, across two timepoints, reflecting findings in established psychosis. These findings may provide age-based markers for PE during adolescence, and provide insight into the impaired neural development in adolescents with PE.

Funding

This research was funded by the European Research Council (ERC 724809 to M.C.) and the Irish Health Research Board (HRA-PHR-2015-1323 to M.C.).

Conflicts of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

Alderson-Day, B., Diederen, K., Fernyhough, C., Ford, J. M., Horga, G., Margulies, D. S., . . . Jardri, R. (2016). Auditory Hallucinations and the Brain's Resting-State Networks: Findings and Methodological Observations. *Schizophr Bull, 42*(5), 1110-1123. doi:10.1093/schbul/sbw078

Allen, P., Laroi, F., McGuire, P. K., & Aleman, A. (2008). The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev, 32*(1), 175-191. doi:10.1016/j.neubiorev.2007.07.012

Amico, F., O'Hanlon, E., Kraft, D., Oertel-Knöchel, V., Clarke, M., Kelleher, I., . . . Cannon, M. (2017). Functional connectivity anomalies in adolescents with psychotic symptoms. *PLoS One, 12*(1). Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2017-05116-001&site=ehost-live

marycannon@rcsi.ie

amicof@gmail.com

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann N Y Acad Sci, 1316*, 29-52. doi:10.1111/nyas.12360

Anticevic, A., Haut, K., Murray, J. D., Repovs, G., Yang, G. J., Diehl, C., . . . Cannon, T. D. (2015). Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. *JAMA Psychiatry, 72*(9), 882-891. doi:10.1001/jamapsychiatry.2015.0566

Bazan, P. R., Biazoli, C. E., Jr., Sato, J. R., & Amaro, E., Jr. (2015). Motor Readiness Increases Brain Connectivity Between Default-Mode Network and Motor Cortex: Impact on Sampling Resting Periods from fMRI Event-Related Studies. *Brain Connect, 5*(10), 631-640. doi:10.1089/brain.2014.0332

Bernard, J. A., Dean, D. J., Kent, J. S., Orr, J. M., Pelletier-Baldelli, A., Lunsford-Avery, J. R., . . . Mittal, V. A. (2014). Cerebellar networks in individuals at ultra high-risk of psychosis: Impact on postural sway and symptom severity. *Hum Brain Mapp, 35*(8), 4064-4078. doi:10.1002/hbm.22458

Bernard, J. A., Goen, J. R. M., & Maldonado, T. (2017). A case for motor network contributions to schizophrenia symptoms: Evidence from resting-state connectivity. *Hum Brain Mapp, 38*(9), 4535-4545. doi:10.1002/hbm.23680

Bernard, J. A., Orr, J. M., & Mittal, V. A. (2017). Cerebello-thalamo-cortical networks predict positive symptom progression in individuals at ultra-high risk for psychosis. *Neuroimage Clin, 14*, 622-628. doi:10.1016/j.nicl.2017.03.001

Blanchard, M. M., Jacobson, S., Clarke, M. C., Connor, D., Kelleher, I., Garavan, H., . . . Cannon, M. (2010). Language, motor and speed of processing deficits in adolescents with subclinical psychotic symptoms. *Schizophr Res, 123*(1), 71-76. doi:10.1016/j.schres.2010.05.028

Blumberg, J., & Kreiman, G. (2010). How cortical neurons help us see: visual recognition in the human brain. *J Clin Invest, 120*(9), 3054-3063. doi:10.1172/JCI42161

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi:10.1196/annals.1440.011

Cannon, M., Caspi, A., Moffitt, T. E., Harrington, H., Taylor, A., Murray, R. M., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry, 59*(5), 449-456. doi:10.1001/archpsyc.59.5.449

Carey, E., Dooley, N., Gillan, D., Healy, C., Coughlan, H., Clarke, M., . . . Cannon, M. (2019). Fine motor skill and processing speed deficits in young people with psychotic experiences: A longitudinal study. *Schizophr Res, 204*, 127-132. doi:10.1016/j.schres.2018.08.014

Clarke, M. C., Tanskanen, A., Huttunen, M., Leon, D. A., Murray, R. M., Jones, P. B., & Cannon, M. (2011). Increased risk of schizophrenia from additive interaction between infant motor developmental delay and obstetric complications: evidence from a population-based longitudinal study. *Am J Psychiatry, 168*(12), 1295-1302. doi:10.1176/appi.ajp.2011.11010011

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980. doi:10.1016/j.neuroimage.2006.01.021

Dong, D., Wang, Y., Chang, X., Luo, C., & Yao, D. (2017). Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity. *Schizophr Bull*. doi:10.1093/schbul/sbx034

Du, Y., Fryer, S. L., Fu, Z., Lin, D., Sui, J., Chen, J., . . . Calhoun, V. D. (2018). Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. *Neuroimage, 180*(Part B), 632-645. doi:10.1016/j.neuroimage.2017.10.022

Ford, J. M., Roach, B. J., Jorgensen, K. W., Turner, J. A., Brown, G. G., Notestine, R., . . . Mathalon, D. H. (2009). Tuning in to the voices: a multisite FMRI study of auditory hallucinations. *Schizophr Bull, 35*(1), 58-66. doi:10.1093/schbul/sbn140

Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., . . . Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *Am J Psychiatry, 162*(7), 1256-1265. doi:10.1176/appi.ajp.162.7.1256

Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain Connect, 1*(1), 13-36. doi:10.1089/brain.2011.0008

Gogtay, N., Hua, X., Stidd, R., Boyle, C. P., Lee, S., Weisinger, B., . . . Thompson, P. M. (2012). Delayed white matter growth trajectory in young nonpsychotic siblings of patients with childhood-onset schizophrenia. *Arch Gen Psychiatry, 69*(9), 875-884. doi:10.1001/archgenpsychiatry.2011.2084

Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr., . . . Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biol Psychiatry, 61*(8), 935-945. doi:10.1016/j.biopsych.2006.06.027

Grill-Spector, K., Kourtzi, Z., & Kanwisher, N. (2001). The lateral occipital complex and its role in object recognition. *Vision Res, 41*(10-11), 1409-1422. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11322983

Gur, R. C., Calkins, M. E., Satterthwaite, T. D., Ruparel, K., Bilker, W. B., Moore, T. M., . . . Gur, R. E. (2014). Neurocognitive growth charting in psychosis spectrum youths. *JAMA Psychiatry, 71*(4), 366-374. doi:10.1001/jamapsychiatry.2013.4190

Hare, S. M., Ford, J. M., Mathalon, D. H., Damaraju, E., Bustillo, J., Belger, A., . . . Turner, J. A. (2018). Salience-Default Mode Functional Network Connectivity Linked to Positive and Negative Symptoms of Schizophrenia. *Schizophr Bull*. doi:10.1093/schbul/sby112

Healy, C., Brannigan, R., Dooley, N., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychol Med, 49*(10), 1589-1599. doi:10.1017/S0033291719000485

Jacobson, S., Kelleher, I., Harley, M., Murtagh, A., Clarke, M., Blanchard, M., . . . Cannon, M. (2010). Structural and functional brain correlates of subclinical psychotic symptoms in 11-13 year old schoolchildren. *Neuroimage, 49*(2), 1875-1885. doi:10.1016/j.neuroimage.2009.09.015

Karcher, N. R., O'Brien, K. J., Kandala, S., & Barch, D. M. (2019). Resting-State Functional Connectivity and Psychotic-like Experiences in Childhood: Results From the Adolescent Brain Cognitive Development Study. *Biol Psychiatry*. doi:10.1016/j.biopsych.2019.01.013

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version

(K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry, 36*(7), 980-988. doi:10.1097/00004583-199707000-00021

Kaymaz, N., Drukker, M., Lieb, R., Wittchen, H. U., Werbeloff, N., Weiser, M., . . . van Os, J. (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychol Med, 42*(11), 2239-2253. doi:10.1017/S0033291711002911

Kelleher, I., Clarke, M. C., Rawdon, C., Murphy, J., & Cannon, M. (2013). Neurocognition in the extended psychosis phenotype: performance of a community sample of adolescents with psychotic symptoms on the MATRICS neurocognitive battery. *Schizophr Bull, 39*(5), 1018-1026. doi:10.1093/schbul/sbs086

Kelleher, I., Connor, D., Clarke, M. C., Devlin, N., Harley, M., & Cannon, M. (2012). Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychol Med, 42*(9), 1857-1863. doi:10.1017/S0033291711002960

Kelleher, I., Devlin, N., Wigman, J. T., Kehoe, A., Murtagh, A., Fitzpatrick, C., & Cannon, M. (2014). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychol Med, 44*(8), 1615-1624. doi:10.1017/S0033291713002122

Kelleher, I., Harley, M., Murtagh, A., & Cannon, M. (2011). Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophr Bull, 37*(2), 362-369. doi:10.1093/schbul/sbp057

Kelleher, I., Murtagh, A., Molloy, C., Roddy, S., Clarke, M. C., Harley, M., & Cannon, M. (2012). Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. *Schizophr Bull, 38*(2), 239-246. doi:10.1093/schbul/sbr164

Koenig, K. A., Lowe, M. J., Harrington, D. L., Lin, J., Durgerian, S., Mourany, L., . . . Group, P.-H. I. o. t. H. S. (2014). Functional connectivity of primary motor cortex is dependent on genetic burden in prodromal Huntington disease. *Brain Connect, 4*(7), 535-546. doi:10.1089/brain.2014.0271

Littow, H., Huossa, V., Karjalainen, S., Jaaskelainen, E., Haapea, M., Miettunen, J., . . . Kiviniemi, V. J. (2015). Aberrant Functional Connectivity in the Default Mode and Central Executive Networks in Subjects with Schizophrenia - A Whole-Brain Resting-State ICA Study. *Front Psychiatry, 6*, 26. doi:10.3389/fpsyt.2015.00026

Macaluso, E., & Driver, J. (2005). Multisensory spatial interactions: a window onto functional integration in the human brain. *Trends Neurosci, 28*(5), 264-271. doi:10.1016/j.tins.2005.03.008

Majka, P., Rosa, M. G. P., Bai, S., Chan, J. M., Huo, B. X., Jermakow, N., . . . Mitra, P. P. (2019). Unidirectional monosynaptic connections from auditory areas to the primary visual cortex in the marmoset monkey. *Brain Struct Funct, 224*(1), 111-131. doi:10.1007/s00429-018-1764-4

Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., . . . Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophr Res, 83*(2-3), 155-171. doi:10.1016/j.schres.2005.11.020

Manoliu, A., Riedl, V., Zherdin, A., Muhlau, M., Schwerthoffer, D., Scherr, M., . . . Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophr Bull, 40*(2), 428-437. doi:10.1093/schbul/sbt037

McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., . . . Kessler, R. C. (2015). Psychotic Experiences in the General Population: A Cross-National Analysis Based on 31,261 Respondents From 18 Countries. *JAMA Psychiatry, 72*(7), 697-705. doi:10.1001/jamapsychiatry.2015.0575

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci, 15*(10), 483-506. doi:10.1016/j.tics.2011.08.003

Menon, V. (2015). Salience Network. In A. W. Toga (Ed.), *Brain Mapping: An Encyclopedic Reference* (Vol. 2, pp. 597-611). Academic Press: Elsevier.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct, 214*(5-6), 655-667. doi:10.1007/s00429-010-0262-0

Mingoia, G., Wagner, G., Langbein, K., Maitra, R., Smesny, S., Dietzek, M., . . . Nenadic, I. (2012). Default mode network activity in schizophrenia studied at resting state using probabilistic ICA. *Schizophr Res, 138*(2-3), 143-149. doi:10.1016/j.schres.2012.01.036

Mittal, V. A., & Walther, S. (2018). As Motor System Pathophysiology Returns to the Forefront of Psychosis Research, Clinical Implications Should Hold Center Stage. *Schizophr Bull*. doi:10.1093/schbul/sby176

Moran, L. V., Tagamets, M. A., Sampath, H., O'Donnell, A., Stein, E. A., Kochunov, P., & Hong, L. E. (2013). Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biol Psychiatry, 74*(6), 467-474. doi:10.1016/j.biopsych.2013.02.029

Nishida, A., Sasaki, T., Nishimura, Y., Tanii, H., Hara, N., Inoue, K., . . . Okazaki, Y. (2010). Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in

adolescents aged 12-15 years. *Acta Psychiatr Scand, 121*(4), 301-307. doi:10.1111/j.1600-0447.2009.01439.x

O'Hanlon, E., Leemans, A., Kelleher, I., Clarke, M. C., Roddy, S., Coughlan, H., . . . Cannon, M. (2015). White matter differences among adolescents reporting psychotic experiences: A population-based diffusion magnetic resonance imaging study. *JAMA Psychiatry, 72*(7), 668-677. doi:10.1001/jamapsychiatry.2015.0137

O'Neill, A., Mechelli, A., & Bhattacharyya, S. (2018). Dysconnectivity of Large-Scale Functional Networks in Early Psychosis: A Meta-analysis. *Schizophr Bull*. doi:10.1093/schbul/sby094

Palaniyappan, L., Deshpande, G., Lanka, P., Rangaprakash, D., Iwabuchi, S., Francis, S., & Liddle, P. F. (2018). Effective connectivity within a triple network brain system discriminates schizophrenia spectrum disorders from psychotic bipolar disorder at the single-subject level. *Schizophr Res*. doi:10.1016/j.schres.2018.01.006

Pelletier-Baldelli, A., Andrews-Hanna, J. R., & Mittal, V. A. (2018). Resting state connectivity dynamics in individuals at risk for psychosis. *Journal of Abnormal Psychology, 127*(3), 314-325. doi:10.1037/abn0000330

10.1037/abn0000330.supp (Supplemental)

Perala, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., . . . Lonnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry, 64*(1), 19-28. doi:10.1001/archpsyc.64.1.19

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: Where are we now? *Neuroscience and Biobehavioral Reviews, 35*(5), 1110-1124. doi:10.1016/j.neubiorev.2010.11.004

Scheinost, D., Tokoglu, F., Hampson, M., Hoffman, R., & Constable, R. T. (2019). Data-Driven Analysis of Functional Connectivity Reveals a Potential Auditory Verbal Hallucination Network. *Schizophr Bull, 45*(2), 415-424. doi:10.1093/schbul/sby039

Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *NeuroImage, 59*(2), 1560-1570. doi:10.1016/j.neuroimage.2011.08.065

Thoma, R. J., Chaze, C., Lewine, J. D., Calhoun, V. D., Clark, V. P., Bustillo, J., . . . Turner, J. A. (2016). Functional MRI Evaluation of Multiple Neural Networks Underlying Auditory Verbal Hallucinations in Schizophrenia Spectrum Disorders. *Front Psychiatry, 7*, 39. doi:10.3389/fpsyt.2016.00039

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic

anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978

Uddin, L. Q., Kelly, A. M., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Hum Brain Mapp, 30*(2), 625-637. doi:10.1002/hbm.20531

Waltmann, M., O'Daly, O., Egerton, A., McMullen, K., Kumari, V., Barker, G. J., . . . Modinos, G. (2019). Multi-echo fMRI, resting-state connectivity, and high psychometric schizotypy. *Neuroimage Clin, 21*, 101603. doi:10.1016/j.nicl.2018.11.013

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol, 8*, 49-76. doi:10.1146/annurev-clinpsy-032511-143049

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect, 2*(3), 125-141. doi:10.1089/brain.2012.0073

Tables

Table 1: Between group differences in FC between the DMN, CEN, and SN, and the rest of the whole brain at TP1 and TP2

	Seed network	Difference contrast	Seed	Effect anatomy	Cluster peak MNI coordinates			Cluster size	Cluster p_{FDR} value
					X	Y	Z		
TP2	SN	PE < controls	L. insular cortex (BA13)	**Precuneus cortex**, cuneal cortex, supracalcarine cortex	8	-66	22	181	0.0085
	CEN	PE > controls	R. dorsolateral prefrontal cortex (BA46)	**Insular cortex**, Heschl's gyrus, planum polare, central operular cortex	42	-14	8	225	0.0031
Group x Time	DMN	PE ↓ : controls ↑	Precuneus	Insular cortex, temporal pole	36	4	-8	245	0.00066
		PE ↓ : controls ↑		Supramarginal gyrus (anterior), parietal operculum cortex	-58	-36	36	158	0.0049
	SN	PE ↑ : controls ↓	L. insular cortex (BA13)	**Frontal pole**, middle frontal gyrus, inferior frontal gyrus (pars)	-32	32	16	224	0.002
		PE ↓ : controls ↑		**Precuneus cortex**, supracalcarine cortex	22	-54	8	203	0.002
		PE ↑ : controls ↓	R. insular cortex (BA13)	**Cerebellum VI**, Vermis VI, Vermis VII, Crus I	-10	-68	-22	214	0.0014
		PE ↓ : controls ↑		Precuneus cortex	8	-52	44	212	0.0014

TP1 = timepoint 1; TP2 = timepoint; PE = psychotic experiences group; MNI = Montreal Neurological Institute; Cluster size in voxels; cluster peaks are indicated in bold; FDR=false discovery rate corrected; L = left; R = right.

Table 2: Between group differences in FC between the motor network and the rest of the whole brain at TP1 and TP2

	Difference contrast	Seed	Effect anatomy	Cluster peak MNI coordinates			Cluster size	Cluster p_{FDR} value
				X	Y	Z		
TP1	PE < controls	R. Primary motor cortex	Lat. Occipital cortex (superior), angular gyrus, superior parietal lobule	44	-58	56	131	0.044
	PE < controls	L. Cerebellum IV-V	Precuneus, lateral occipital cortex (bilateral superior), superior parietal lobule	8	-68	66	241	0.0024
	PE < controls	R. Cerebellum IV-V	Lat. occipital cortex (superior), precuneus	8	-68	66	254	0.0013
	PE < controls		Lat. Occipital cortex (superior), superior parietal lobule	-18	-68	68	165	0.005
	PE > controls		Parietal operculum cortex, insular cortex, putamen	-28	-26	8	167	0.005
TP2	PE < controls	L. Primary motor cortex	Occipital pole	-20	-94	-6	279	0.0013
	PE > controls		Frontal operculum cortex, Insular cortex	38	22	8	226	0.0022
	PE < controls		Precentral gyrus, postcentral gyrus, superior frontal gyrus	42	-20	64	218	0.0022
	PE < controls		Precentral gyrus, Postcentral gyrus	-34	-22	70	167	0.0072
	PE > controls	R. Primary motor cortex	Superior frontal gyrus, middle frontal gyrus	-24	24	50	341	0.00018
	PE < controls		Precentral gyrus, postcentral gyrus	-30	-20	70	250	0.0009
	PE > controls		Frontal pole	-22	60	8	193	0.0029

TP1 = timepoint 1; TP2 = timepoint; PE = psychotic experiences group; MNI = Montreal Neurological Institute; Cluster size in voxels; cluster peaks are indicated in bold; FDR=false discovery rate corrected; L = left; R = right.

Table 3: Between group differences in FC between the auditory network and the rest of the whole brain at TP1 and TP2

	Difference contrast	Seed	Effect anatomy	Cluster peak MNI coordinates			Cluster size	Cluster p_{FDR} value
				X	Y	Z		
TP1	PE < controls	R. A1 (BA41)	Inferior temporal gyrus (temporooccipital), inferior temporal gyrus posterior), middle temporal gyrus	-56	-48	-20	303	0.00022
	PE < controls	L. A2 (BA22)	Lingual gyrus, cerebellum VI, occipital fusiform gyrus	14	-68	-10	192	0.0055
	PE < controls		Lingual gyrus, intracalcarine cortex	-8	-84	-4	149	0.0093
TP2	PE < controls	L. A2 (BA22)	Lat occipital cortex (superior), occipital pole	24	-90	30	218	0.0028

A1 = Primary auditory cortex; A2 = Secondary auditory cortex; TP1 = timepoint 1; TP2 = timepoint; PE = psychotic experiences group; MNI = Montreal Neurological Institute; Cluster size in voxels; cluster peaks are indicated in bold; FDR=false discovery rate corrected; L = left; R = right.

Figures

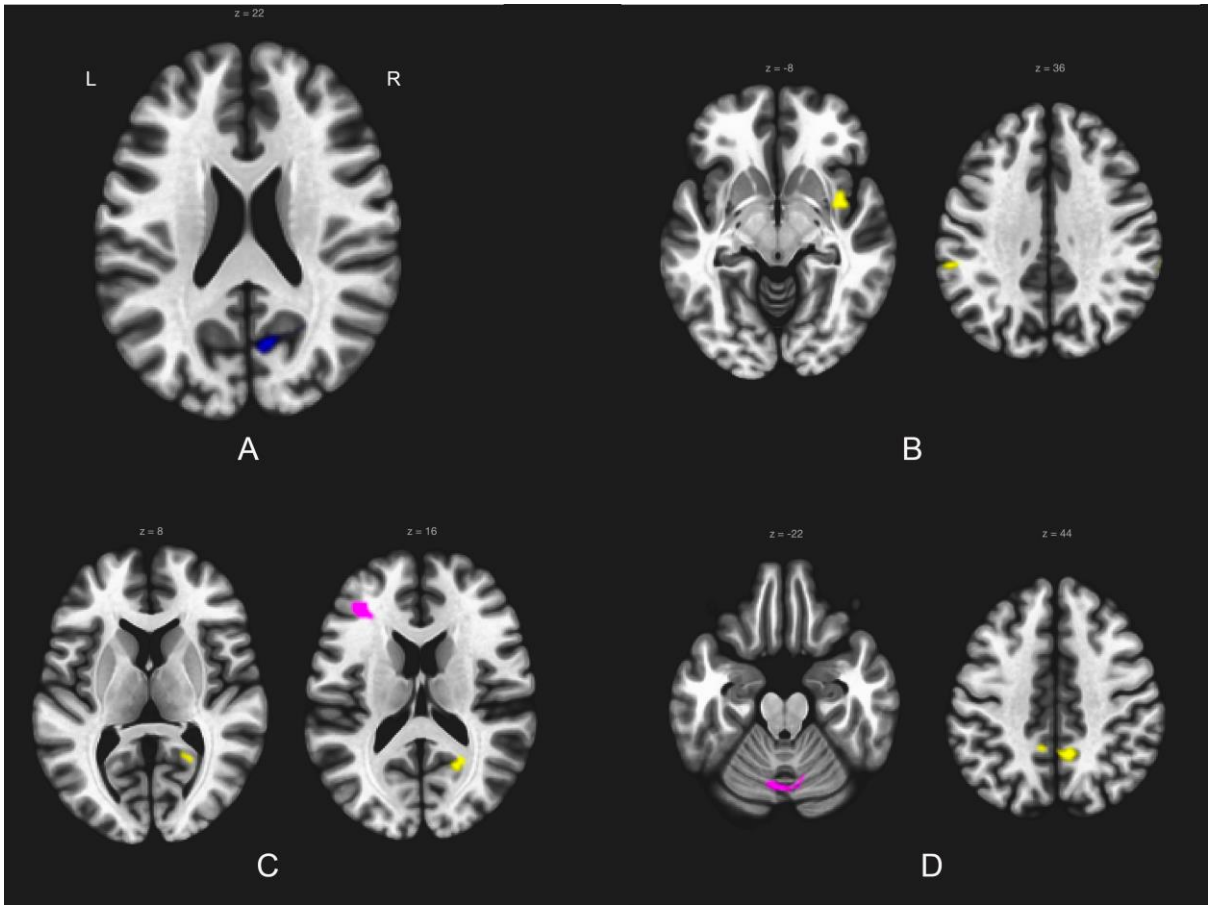


Figure 1: Triple network to whole-brain FC. A) TP2 left insula seed: precuneus (z=22); B) Group x Time precuneus seed: right insula (z=-8), left supramarginal gyrus (z=36); C) Group x Time left insula seed: right precuneus (z=8), left frontal pole (z=16); D) Group x Time right insula seed: left cerebellum VI (z=-22); right precuneus (z=44). MNI z coordinates are displayed above the figures. L=left, R=right. For TP2: Blue = PE<controls, Red = PE>controls. For Group x Time analyses: Yellow=regions where FC decreased in the PE group and increased in the controls, over time; Purple = regions where FC increased in the PE group and decreased in the controls, over time.

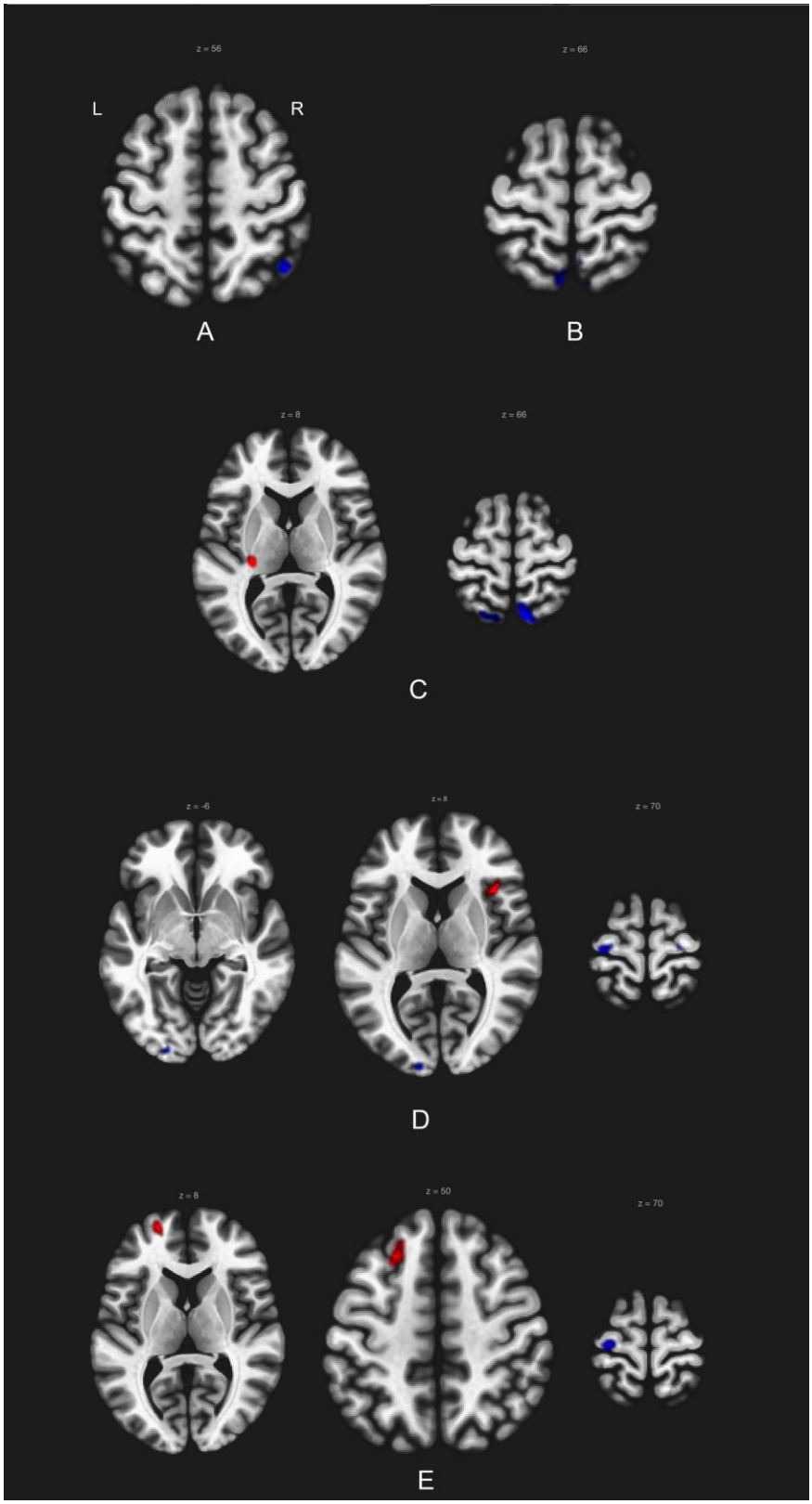


Figure 2: Motor network to whole-brain FC. A) TP1 right primary motor cortex seed: right lateral occipital cortex (z=56), B) TP1 left cerebellum IV-V seed: right precuneus (z=66); C) TP1 right cerebellum IV-V seed: left parietal operculum (z=8), right lateral occipital cortex (z=66), right lateral occipital cortex (z=66); D) TP2 left primary motor cortex seed: left occipital pole (z=-6), right frontal operculum (z=8), right precentral gyrus (z=70), left precentral gyrus (z=70), E) TP2 right primary motor cortex seed: left frontal pole (z=8), left superior frontal gyrus (z=50), left precentral gyrus (z=70). L=left, R=right. MNI z coordinates are displayed above the figures. Blue = PE<controls, Red = PE>controls.