

# Reduced parietofrontal effective connectivity during a working-memory task in people with high delusional ideation

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**Background:** Working-memory impairment is a core cognitive dysfunction in people with schizophrenia and people at mental high risk. Recent imaging studies on working memory have suggested that abnormalities in prefrontal activation and in connectivity between the frontal and parietal regions could be neural underpinnings of the different stages of psychosis. However, it remains to be explored whether comparable alterations are present in people with subclinical levels of psychosis, as experienced by a small proportion of the general population who neither seek help nor show constraints in daily functioning. **Methods:** We compared 24 people with subclinical high delusional ideation and 24 people with low delusional ideation. Both groups performed an n-back working-memory task during functional magnetic resonance imaging. We characterized frontoparietal effective connectivity using dynamic causal modelling. **Results:** Compared to people who had low delusional ideation, people with high delusional ideation showed a significant increase in dorsolateral prefrontal activation during the working-memory task, as well as reduced working-memory-dependent parietofrontal effective connectivity in the left hemisphere. Group differences were not evident at the behavioural level. **Limitations:** The current experimental design did not distinguish among the working-memory subprocesses; it remains unexplored whether differences in connectivity exist at that level. **Conclusion:** These findings suggest that alterations in the working-memory network are also present in a nonclinical population with psychotic experiences who do not display cognitive deficits. They also suggest that alterations in working-memory-dependent connectivity show a putative continuity along the spectrum of psychotic symptoms.

## Introduction

Working memory is associated with neural activation of the parietal and dorsolateral prefrontal regions.<sup>1</sup> The tight functional coupling of these spatially separate regions in the frontoparietal network is indispensable for the efficient processing of working memory.<sup>2</sup> Altered activation of these regions<sup>3-5</sup> and disruptions in frontoparietal connectivity pathways are considered crucial to the development of working-memory impairment across the psychosis continuum.<sup>6-9</sup>

Although research has provided valuable insights into the neural mechanisms of working-memory deficits in schizophrenia, it remains unclear whether such neural alterations are also associated with nonclinical psychosis-like experiences. Of the general population, 5% to 8% report occasional psychotic experiences,<sup>10</sup> such as suspiciousness, thought insertion/broadcasting, ideas of reference, grandiosity or perceptual abnormalities. Epidemiological studies indicate that there are parallels between clinical and non-

clinical psychotic experiences: for example, similarities in thought content and in demographic and genetic risk factors.<sup>11</sup> On the other hand, nonclinical psychosis is mostly transitory<sup>12</sup> and does not necessarily cause distress, nor does it affect daily functioning. Moreover, in contrast to the well-established association between manifest psychotic disorders and neurocognitive impairment,<sup>13</sup> findings in the subclinical population are less consistent. While some studies have found no significant association between subclinical psychosis and neurocognitive impairments,<sup>14,15</sup> others have found that people transitioning to clinical psychosis showed significantly impaired neurocognitive function.<sup>16,17</sup> All of this suggests that impaired neurocognitive function, including working-memory deficits, may be a marker of disease vulnerability rather than of symptoms. In the general population, subclinical psychosis-like experiences can be assessed via self-report measures, such as the Peters Delusion Inventory (PDI),<sup>18</sup> which measures delusional ideation in healthy participants. Those who score

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high on the PDI show results similar to those with clinical schizophrenia, but they report these delusional experiences to be less distressing.<sup>18</sup> To date, little is known about whether people with high delusional ideation show neural alterations in working-memory processing similar to those of people with clinical psychosis.

Altered regional activation in frontoparietal areas has been observed in clinical psychosis,<sup>19,20</sup> but there is less agreement about the direction of these functional activation differences. Such discrepancies may be explained in part by working-memory load, which depends on task demands and a person's working-memory capacity.<sup>21</sup> The relationship between working-memory performance and dorsolateral prefrontal cortex (dlPFC) activation is best characterized by an inverted U-shaped function,<sup>22</sup> which describes individual behavioural differences in working-memory load as the independent variable for different levels of dlPFC activation.<sup>21</sup> In such studies, low-performing patients show hypoactivation of the dlPFC as a consequence of activation failure, while high-performing patients exhibit strong dlPFC activation that is thought to be less efficient than that of healthy people. Thus, cognitive performance depends on the efficiency of prefrontal activation, which appears to be reflected in a person's working-memory capacity. Increased regional activation of the dlPFC has also been observed in people at risk for psychosis.<sup>23,24</sup>

In addition to differences in regional activation, dysfunctional integration has also been proposed as an underlying pathophysiological mechanism of psychosis, known as the dysconnectivity hypothesis,<sup>25–27</sup> which suggests abnormal synaptic plasticity as a common pathophysiology of psychotic illnesses. Dynamic causal modelling (DCM) provides an elegant tool for estimating effective connectivity among distinct brain regions and experimentally induced modulatory influences on these connections.<sup>28</sup> It is thought to approximate context-dependent modulation of synaptic plasticity from neuroimaging data. This technique has given important insights into the underlying working-memory network dynamics of patients with schizophrenia, in particular showing aberrant connectivity between the frontal and parietal regions.<sup>6</sup> Recent connectivity studies have extended the profile of frontal dysfunction to prodromal people in terms of both brain activation and connectivity strengths, and they have identified symptom-related functional changes in a wide spectrum of people with psychosis. For example, Schmidt and colleagues<sup>7</sup> demonstrated a progressive reduction in frontoparietal connectivity that was most pronounced in people with first-episode psychosis compared with healthy controls (people in an at-risk mental state took an an intermediate position). This progressive pattern may reflect a putative dynamic trajectory of disrupted frontal integration that emerges before psychosis onset and proceeds with ongoing illness.<sup>8</sup> Configuration of the frontoparietal network has been reported to vary with the persistence of psychotic symptoms.<sup>29</sup> However, effective connectivity in the frontoparietal network has not been investigated in people with current subclinical delusional ideation.

In the current study, we recruited participants with subclinical high delusional ideation based on the PDI from a

large group of healthy people. We compared working memory in participants with high PDI scores versus a control group with low PDI scores, measuring performance, regional neural activation and effective connectivity in frontoparietal networks. We tested for altered local dlPFC activation and hypothesized that the group with high delusional ideation would have reduced working-memory-dependent effective connectivity in the frontoparietal pathway, based on previous studies of the psychosis spectrum.<sup>6,7,9</sup>

## Methods

### *Participants and instruments*

We recruited participants from a university mailing list. To identify the group with subclinical high delusional ideation, we collected delusion scores from 1059 people who completed the 21-item version of the PDI online (mean  $\pm$  standard deviation [SD] total PDI score  $6.75 \pm 3.57$ ).<sup>30</sup> People who scored in the upper quartile of the total population (corresponding to a total PDI score  $> 9$ ) were contacted and screened, and those who were free of past or present psychiatric or neurologic disorders were included in the high delusional ideation group. Participants drawn from the lower end of the PDI distribution were included in the low delusional ideation group. Exclusion criteria were a current or past psychiatric Axis I disorder according to the Structured Clinical Interview for DSM-IV,<sup>31</sup> current or past substance abuse; and severe medical conditions. In total, 24 people with high delusional ideation (PDI score mean  $\pm$  SD  $12.33 \pm 1.99$ ) and 24 people with low delusional ideation (PDI score mean  $\pm$  SD  $2.08 \pm 2.10$ ) participated in the current study.

Both groups were matched for age and sex. Participants were characterized for sociodemographic status (years of education), handedness (Edinburgh Handedness Inventory<sup>32</sup>) and schizotypy (Schizotypal Personality Questionnaire<sup>33</sup>). We also collected neurocognitive measures, including the Digit-Span Test for verbal working memory, Trail Making Tests A and B for attention and cognitive flexibility, and a vocabulary test for verbal intelligence.<sup>34</sup>

The study was approved by the Ethics Committee of Charité–Universitätsmedizin Berlin. Participants gave informed consent and received compensation. Data from the current subclinical sample have been published in the context of reversal learning<sup>35</sup> and self-referential processing.<sup>36</sup>

### *Working memory task*

All 48 participants underwent functional MRI (fMRI) while performing a numeric n-back working-memory task, which consisted of 2 conditions (similar to Deserno and colleagues<sup>6</sup> and Schlagenhaut and colleagues<sup>37</sup>): “2-back” (working-memory condition) and “0-back” (control condition). For a detailed description, see Appendix 1, available at [jpn.ca/180043-a1](http://jpn.ca/180043-a1). One block consisted of 22 digits with 3 targets. In total, we alternated 6 “2-back” and 6 “0-back” conditions in the experiment, for a total duration of 10 minutes.

### Behavioural data analysis

We tested for differences in task performance using the sensitivity index  $d'$ , which provides a measure of a person's task performance by including the number of correct hits and false alarms for each condition (for details, see Appendix 1). We used a repeated-measures analysis of variance (ANOVA), with condition (2-back v. 0-back) as the within-participants factor and group (low delusional ideation v. high delusional ideation) as the between-participants factor. To reveal the direction of possible effects, we conducted post hoc  $t$  tests. Effects at a threshold of  $p < 0.05$  were reported as significant.

### Functional MRI

We performed fMRI on a 3 T Siemens Trio scanner with a 12-channel head coil using gradient-echo-planar imaging (36 slices, repetition time 2190 ms, echo time 30 ms, flip angle 90°, matrix  $64 \times 64$ , voxel size  $3 \times 3 \times 3.75$  mm<sup>3</sup>). Volumes with slices parallel to the anterior–posterior commissure line covered the whole cortex and were collected in descending order, for a total of 293 volumes.

### fMRI data analysis

We analyzed fMRI data using statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience; www.fil.ion.ucl.ac.uk/spm) in MATLAB 2009b.

All scans were preprocessed using a standard protocol (see Appendix 1). For statistical analysis of blood oxygen level-dependent (BOLD) responses, we used the general linear model approach as implemented in SPM8 (for details, see Appendix 1).<sup>38</sup> We computed individual contrast images for 2-back versus baseline and 0-back versus baseline. At the group level, we performed a flexible factorial ANOVA with condition (2-back v. 0-back) as the within-participants factor and group (people with low delusional ideation/people with high delusional ideation) as the between-participants factor. We reported the main effects of task and task  $\times$  group interaction, as well as post hoc  $t$  tests.

We reported the main effect of working-memory-related activation at  $p < 0.05$  (family-wise error [FWE]–corrected) at the voxel level across the whole brain. Based on our a priori hypothesis concerning dlPFC alterations in the psychosis spectrum, we applied small-volume correction (SVC) using literature-based unilateral masks of the dlPFC for the differences between the groups with high and low delusional ideation (for details on the computation of literature-based probabilistic regions of interest, see Heinzl and colleagues<sup>39</sup>).

### Dynamic causal modelling

We used DCM to analyze the influence of the working-memory task on effective connectivity between working-memory-related regions and to investigate whether these modulatory effects on connectivity strengths differed between groups. For this, we extracted time series from 3 predefined regions (see below) and specified the assumed connections

between them. We analyzed the interregional coupling that was independent of the experimental condition (intrinsic connectivity) and, as our primary outcome measure, the modulation of connectivity strength by our experimental condition. We specified the influence of task stimuli on the sensory input region as driving input. We used deterministic DCM 10 as implemented in SPM8 (r4010).

### Model space

Based on previous studies of working-memory processing in the 3 regions of interest, we included the parietal cortex, the dlPFC and the visual cortex in the model space. We defined 3 families of models according to the direction of the modulatory working-memory effect on frontoparietal connectivity: bidirectional, forward and backward. We also extended the model space to further models that considered unidirectional and bidirectional experimental effects on connections between the primary visual cortex, the dlPFC and the parietal cortex, respectively, resulting in 16 models for each model family (for details, see Fig. 1 and Appendix 1). We estimated model parameters using one-state, bilinear, deterministic DCM. We corrected for differences in slice time acquisition between the 3 areas according to Kiebel and colleagues.<sup>40</sup>

### Bayesian model selection

To find the most likely model for the measured hemodynamic response, we performed Bayesian model selection using a random-model effects approach.<sup>41</sup> We compared model evidence using exceedance probabilities (EPs) for the 3 model families.<sup>42</sup> We also reported EPs for all 48 models, as well as protected EPs.<sup>42</sup>

### Bayesian model averaging

For statistical group comparison of the model parameters, we performed Bayesian model averaging. This approach provides averages of DCM parameters for the entire model space, weighted by the posterior model probabilities for each model.<sup>43</sup> In this way, models with low posterior probability contributed less to estimation of the marginal posterior. We extracted the posterior means from the averaged DCM parameters to test for group differences in modulatory parameters and in intrinsic connections. We performed 1-sample  $t$  tests for within-group effects and 2-sample  $t$  tests for group comparisons. We reported results at a statistical threshold of  $p < 0.05$  based on our a priori hypotheses of reduced working-memory-dependent modulation of frontoparietal<sup>6–8</sup> and/or parietofrontal<sup>9</sup> connection in the working-memory network.

## Results

### Sociodemographic characteristics

People with high delusional ideation scored significantly higher on the Schizotypal Personality Questionnaire than those with low delusional ideation ( $t = -3.81$ ,  $p < 0.001$ ). The 2 groups did not differ with respect to any neurocognitive measures (Table 1).

*Behavioural performance*

Repeated-measures ANOVA with  $d'$  revealed a significant main effect of task ( $F = 211.0, p < 0.001$ ), no significant effect of group ( $F = 1.8, p = 0.19$ ) and no significant task  $\times$  group interaction ( $F = 0.42, p = 0.52$ ). Both groups performed significantly better in the control condition than in the working-memory condition (post hoc paired  $t$  test:  $t = 13.38, p < 0.001$ ).

*fMRI: regional activation*

We observed a significant main effect of condition in multiple regions that have previously been related to the working-memory network (Table 2).<sup>1</sup> In the left dlPFC, we observed a marginal effect of the group  $\times$  task interaction ( $F = 15.73, p_{FWE, SVC} = 0.051; x = -52, y = 12, z = 34$ ). The post hoc  $t$  test showed that people with high delusional ideation showed a higher BOLD response in the left dlPFC than people with low delusional ideation for the 2-back > 0-back contrast ( $t = 3.97, p_{FWE, SVC} = 0.026; x = -52, y = 12, z = 34$ ) due to higher activation during the 2-back condition but not the 0-back condition (Fig. 2).

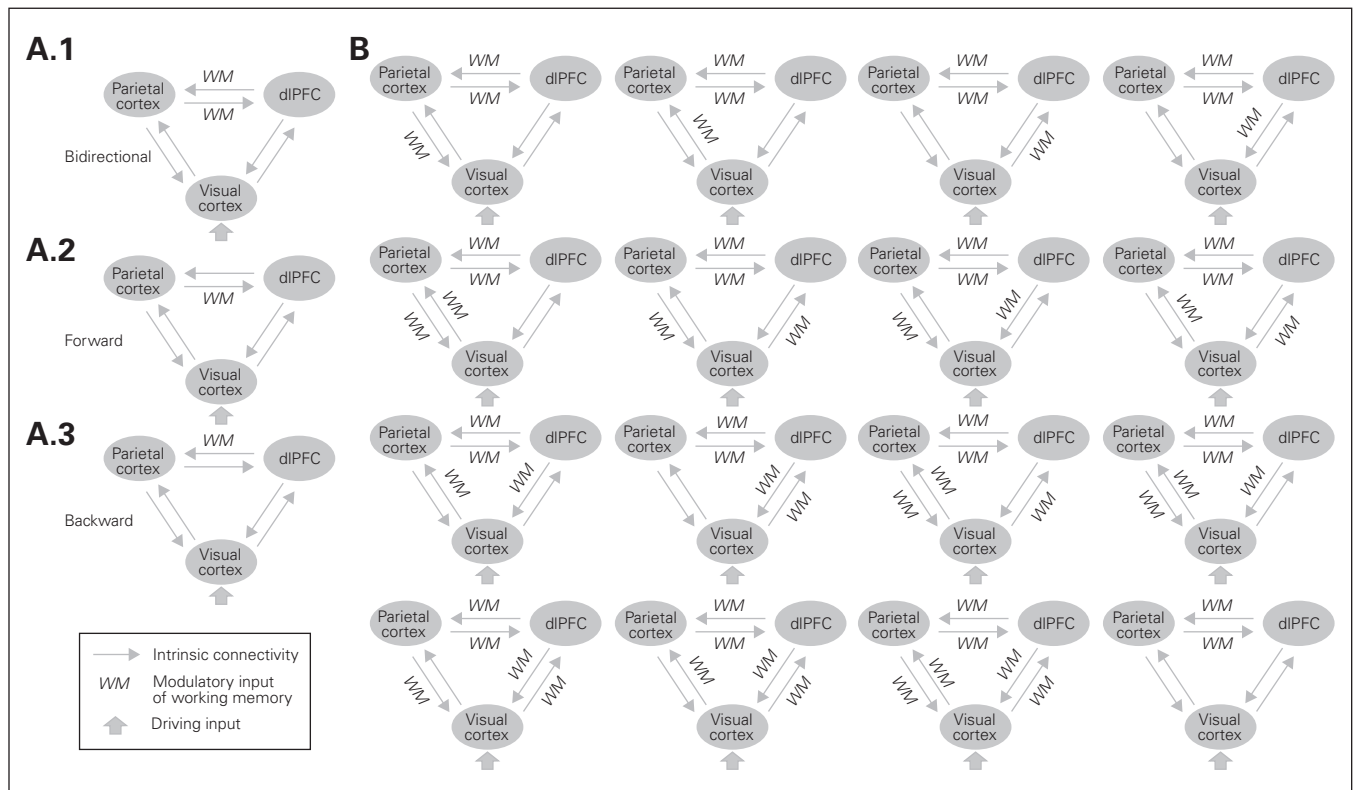
*Dynamic causal modelling*

Across all participants, a comparison of model evidence between the 3 families showed that the family with the forward modulation of frontoparietal connections provided the best

model fit for the left hemisphere (EP = 66%), while the backward model family clearly dominated for the right hemisphere (EP > 90%; Fig. 3). Separate Bayesian model selection for each group revealed that in people with low delusional ideation, the forward model family provided the best fit for the left hemisphere (EP = 68%) and the backward model family provided the best fit for the right hemisphere (EP = 82%). In people with high delusional ideation, the backward model family clearly dominated in the right hemisphere (EP = 90%), similar to those with low delusional ideation, but both the forward and the backward families explained the data in the left hemisphere equally (forward EP = 36%; backward EP = 39%). See Appendix 1, Figure S1, for information on which (subspace) models drove the effects at the family level. Using protected EPs, model comparison for all individual models across the 3 model families revealed no winning model.

*Group differences on DCM parameters*

Because the 2 groups differed descriptively in evidence regarding the model family (Fig. 3), we performed Bayesian model averaging over the whole model space (see Appendix 1, Table S1). We observed group differences in 3 connectivity parameters for the left hemisphere (Fig. 4). First, people with high delusional ideation showed a reduction in modulatory connectivity from the parietal cortex to the dlPFC ( $t = 2.850, p = 0.007$ ). Second, the modulatory connectivity from the



**Fig. 1:** Model space adapted from Deserno and colleagues.<sup>6</sup> (A) The 3 model families based on frontoparietal connectivity with (1) bidirectional, (2) forward and (3) backward modulation. (B) A 16-model subspace with additional modulations of the connections from the visual cortex to the dlPFC and the parietal cortex (example shown for the bidirectional family only). dlPFC = dorsolateral prefrontal cortex; WM = working memory.

**Table 1: Sociodemographic characteristics of the imaging sample**

Characteristic	Low delusional ideation* (n = 24)	High delusional ideation* (n = 24)	t value	p value
Age, yr	25.29 ± 4.77 (19/42)	23.54 ± 5.35 (18/40)	$t_{46} = 1.196$	0.24
Sex, M/F	16/8	16/8	—	0.77
Verbal IQ score	104.38 ± 6.14 (90/115)	105.62 ± 6.65 (85/115)	$t_{46} = -0.677$	0.50
Education, yr	16.46 ± 2.41 (13/20.5)	16.05 ± 3.55 (12/23)	$t_{31} = 0.365$	0.72
Trail Making Test A score	22.67 ± 8.71 (0/40)	26.42 ± 6.98 (17/40)	$t_{46} = -1.646$	0.11
Trail Making Test B score	51.79 ± 23.93 (0/110)	49.96 ± 12.01 (32/72)	$t_{46} = 0.335$	0.74
Digit Span test score	7.33 ± 2.24 (5/13)	8.375 ± 2.18 (5/12)	$t_{46} = -1.632$	0.11
PDI score, total	2.08 ± 2.10 (0/6)	12.33 ± 1.99 (10/17)	$t_{46} = -17.327$	< 0.001
PDI score, distress	4.17 ± 4.27 (0/13)	31.75 ± 11.04 (13/64)	$t_{46} = -11.421$	< 0.001
PDI score, preoccupation	4.38 ± 5.19 (0/17)	31.38 ± 7.131 (17/44)	$t_{46} = -14.997$	< 0.001
PDI score, conviction	6.33 ± 7.56 (0/23)	35.83 ± 10.76 (18/67)	$t_{46} = -10.991$	< 0.001
SPQ score	9.48 ± 9.15 (0/41)	23.70 ± 14.67 (5/73)	$t_{42} = -3.813$	< 0.001
d', 0-back	6.31 ± 0.82 (4.48/6.81)	5.73 ± 1.23 (3.13/6.81)	$t_{46} = 1.938$	0.06
d', 2-back	3.00 ± 1.01 (1.76/5.47)	3.10 ± 1.04 (0.92/5.47)	$t_{46} = -0.324$	0.75
Reaction time, 0-back, ms	453.17 ± 105.93 (309/725)	475.72 ± 107.16 (321/648)	$t_{46} = -0.733$	0.47
Reaction time, 2-back, ms	626.45 ± 125.74 (452/941)	628.69 ± 117.46 (438/879)	$t_{46} = -0.064$	0.95

F = female; M = male; PDI = Peters Delusion Inventory; SPQ = Schizotypal Personality Questionnaire.

\*Data are presented as mean ± standard deviation (minimum/maximum).

**Table 2: Regions that showed significant activation during working-memory processing for both groups\***

Region	MNI coordinates x, y, z	Cluster size, voxels	F value
Middle frontal gyrus	-38, 52, 13	588	79.79
Middle frontal gyrus	30, 4, 58	10472	240.52
Middle frontal gyrus	-52, 12, 34		170.89
Middle cingulate gyrus	-4, 20, 42		247.30
Inferior frontal gyrus	-44, 4, 32		147.37
Precentral gyrus	-42, 0, 40		140.23
Middle frontal gyrus	44, 34, 34		160.03
Anterior cingulate gyrus	6, 36, -6	2455	117.22
Anterior cingulate gyrus	-5, 38, -5		102.87
Superior frontal gyrus (medial segment)	-8, 48, -8		112.35
Superior frontal gyrus (medial segment)	-4, 62, 16		83.92
Superior frontal gyrus (medial segment)	2, 48, 34		79.69
Medial frontal gyrus	-4, 58, -4		77.87
Superior frontal gyrus (medial segment)	4, 60, 16		74.11
Anterior cingulate gyrus	-4, 26, -6		69.25
Middle cingulate gyrus	-4, 10, 26	10	46.84
Middle cingulate gyrus	6, 6, 28	7	40.07
Superior frontal gyrus	16, 40, 48	2	34.69
Inferior frontal gyrus	-44, 16, 4	747	71.50
Inferior parietal sulcus	-36, -46, 40	6533	256.19
Inferior parietal sulcus	38, -48, 44		183.17
Superior parietal lobule	-12, -68, 52		123.48
Superior temporal gyrus	56, -4, -12	2256	51.66
Superior temporal gyrus	50, -40, 10	2	34.17
Inferior temporal gyrus	-44, -58, -10	37	40.25
Cerebellum, declive	-30, -64, -28	1483	216.50
Cerebellum, declive	32, -50, -28		155.40
Cerebellum, uvula	-8, -75, -25		192.14

FWE = family-wise error; MNI = Montreal Neurological Institute; WBC = whole-brain corrected.

\*Indicated by the main effect of condition ( $p_{FWE, WBC} < 0.05$ ).

dIPFC to the visual cortex differed between groups: people with low delusional ideation displayed a stronger negative modulation than people with high delusional ideation ( $t = -2.246$ ,  $p = 0.031$ ). Third, intrinsic connectivity from the dIPFC to the visual cortex was increased in people with high delusional ideation ( $t = -2.501$ ,  $p = 0.016$ ). We observed no group differences in connectivity parameters for the right hemisphere. Driving input did not differ between groups for either hemisphere. For correlational analyses between PDI and DCM parameters, see Appendix 1, Table S2.

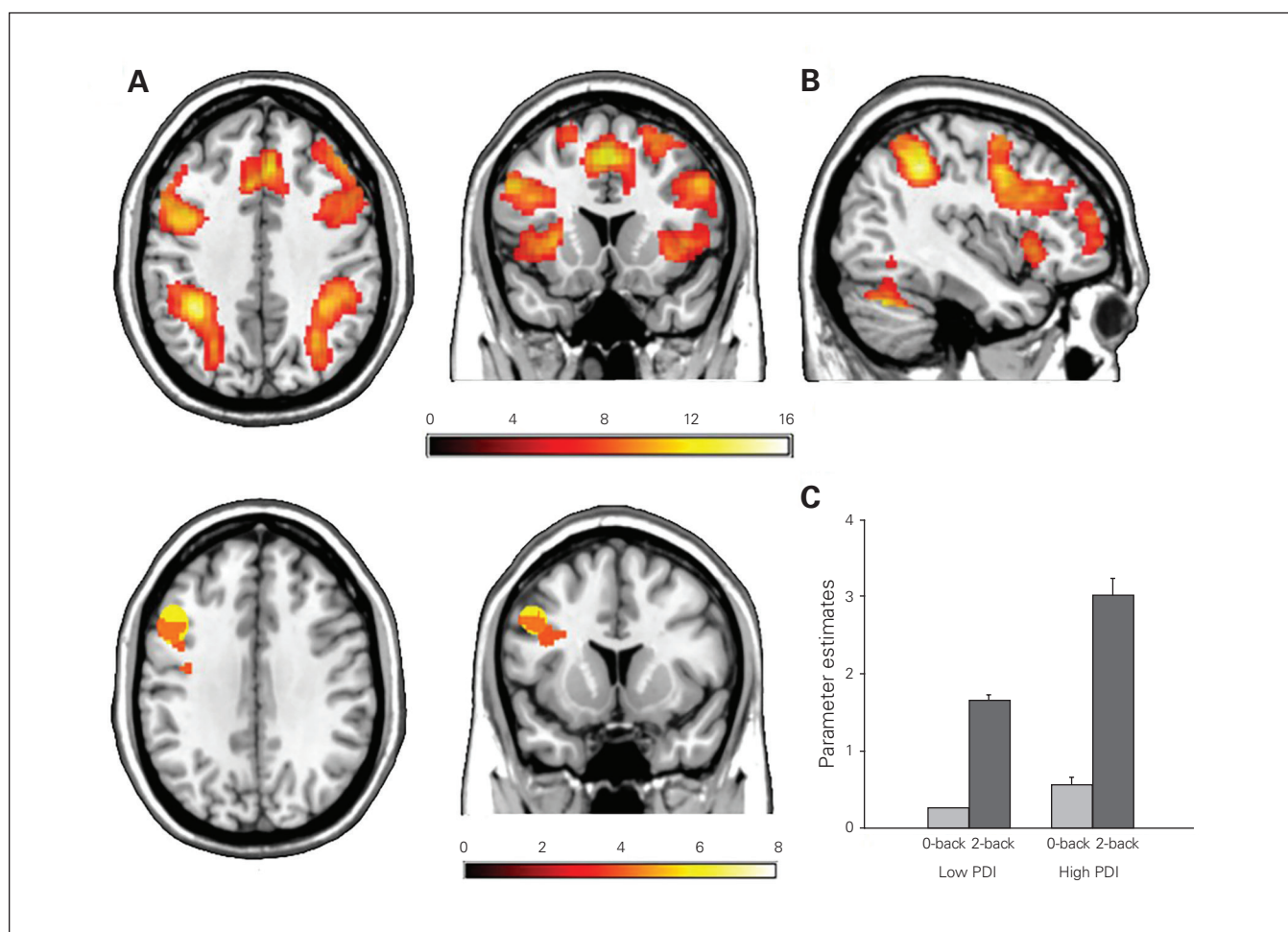
## Discussion

In the current study, people with high delusional ideation showed intact working-memory performance but increased dIPFC activation and reduced effective connectivity in the frontoparietal network during working-memory processing. This finding broadens our knowledge of effective

connectivity changes in the working-memory network in the psychosis spectrum, and it extends it to people with subclinical delusional ideation.

### *Increased dIPFC response in people with high delusional ideation*

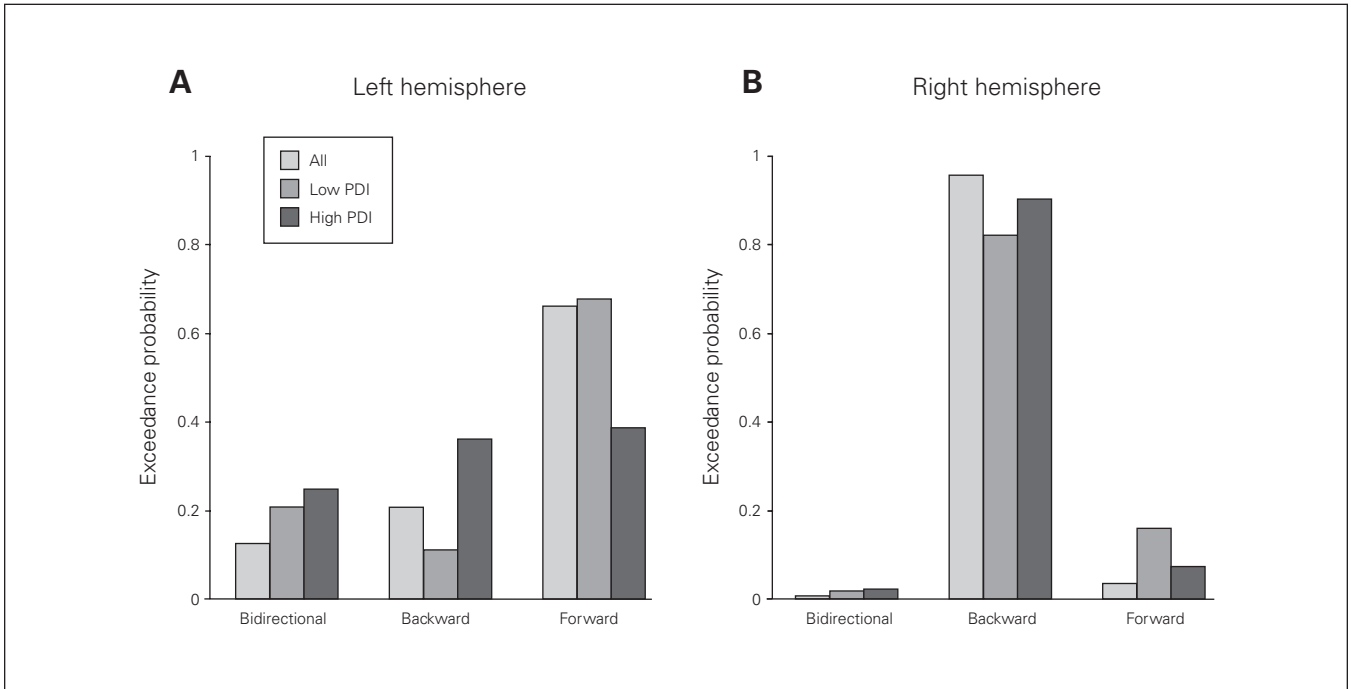
People with high delusional ideation exhibited stronger dIPFC response in the left hemisphere during working-memory processing than those with low delusional ideation, but group differences were not apparent at the behavioural level. This elevated activation in people with high delusional ideation can be interpreted in terms of an inverted U-shape relationship between neural activation and performance.<sup>22</sup> In this framework, performance-dependent neural activation is constrained by the person's cognitive load. That is, people with high delusional ideation may require additional recruitment of the frontal area to achieve working-memory



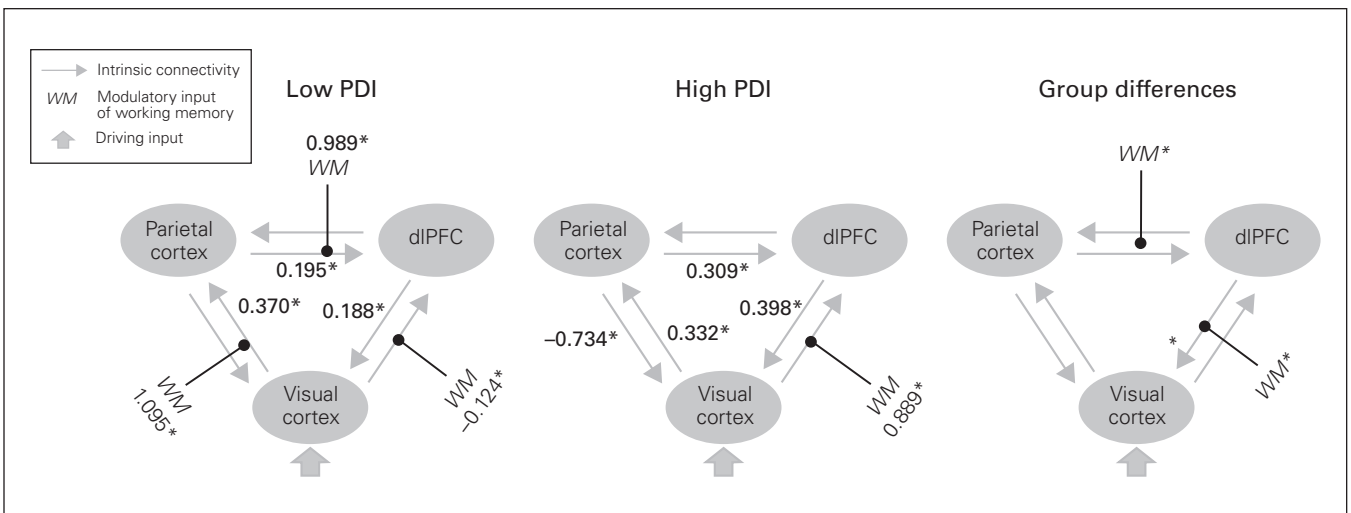
**Fig. 2:** Local activation during working memory. (A) Frontoparietal activation during working-memory performance in participants with high and low delusional ideation taken together (displayed at  $p_{\text{FWE, WBC}} < 0.05$  for the 2-back > 0-back contrast;  $x, y, z = -40, 15, 36$ ). (B) Higher left dIPFC activation in people with high versus low delusional ideation for the 2-back > 0-back contrast ( $t = 3.97$ ,  $p_{\text{FWE, SVC}} = 0.026$ ;  $x, y, z = -52, 34, 12$ ). Literature-based dIPFC mask displayed in yellow. (C) Plot of parameter estimates extracted from peak voxels of the task  $\times$  group interaction effect. dIPFC = dorsolateral prefrontal cortex; FWE = family-wise-error-corrected; PDI = Peters Delusion Inventory; SVC = small-volume-corrected; WBC = whole-brain-corrected.

performance comparable to those without delusions. In line with our findings, a similar pattern of heightened dlPFC activation without working-memory performance deficit has been observed in first-degree relatives of patients with

schizophrenia,<sup>44</sup> in people in an at-risk mental state<sup>24</sup> and in high-performing patients with schizophrenia.<sup>45</sup> Moreover, inefficient recruitment of frontal regions has also been reported in cognitive aging (where older people exhibit



**Fig. 3:** Results of Bayesian model selection for each hemisphere across all participants taken together, as well as separately for people with low and high delusional ideation (low PDI and high PDI, respectively). The measure of relative model evidence is given as exceedance probability. Family selection of bidirectional, forward or backward modulation of frontoparietal connectivity for the left and right hemisphere, respectively. PDI = Peters Delusion Inventory.



**Fig. 4:** Parameter estimates from Bayesian model averaging over the entire model space (i.e., 48 models). Within-group results for people with low and high delusional ideation (low PDI and high PDI, respectively). Group differences were found for 3 dynamic causal modelling parameters: working-memory-induced (modulatory) parietofrontal connectivity was reduced in people with high delusional ideation compared to those with low delusional ideation; people with high delusional ideation showed enhanced intrinsic frontovisual connectivity; and we observed a group difference in the modulatory influence on frontovisual connectivity. All effects were observed in the left hemisphere. \*Significant at  $p < 0.05$ . dlPFC = dorsolateral prefrontal cortex; PDI = Peters Delusion Inventory; WM = working memory.

stronger prefrontal activation than adolescents when exposed to the same cognitive load)<sup>46</sup> and in alcohol dependence.<sup>47</sup> Additional prefrontal activation may depict a common mechanism employed to maintain cognitive performance.

#### *Reduced working-memory-dependent modulation of parietofrontal effective connectivity*

In the current study, people with high delusional ideation showed a significant reduction in working-memory-induced modulatory connectivity from the left parietal cortex to the left dlPFC compared with people who had low delusional ideation. This finding was in line with those of Nielsen and colleagues,<sup>9</sup> who observed reduced modulatory influence from the left parietal cortex to the left dlPFC in patients with first-episode psychosis — interpreted in terms of the dysconnectivity hypothesis as the “inability to modulate synaptic efficacy of the network.” Reduced effective connectivity in people with high delusional ideation could indicate a diminished ability to modulate prefrontal sensitivity by ascending parietal afferents during the working-memory task. The coupling between the parietal and prefrontal cortices is crucial for the encoding, storage and recall of information for working memory,<sup>48</sup> so a reduction in these parameters reflects aberrant functional integration in the working-memory network. In particular, it has been suggested that the parietofrontal connection is involved in the encoding and maintenance of sensory input, here of visually presented numbers.<sup>49</sup> Thus, because the parietal cortex is implicated in number representation,<sup>50</sup> people with high delusional ideation might display inefficient top-down control and attention allocation during number encoding, potentially related to weaker stimulus updating during working-memory processing.

Besides modulation of effective connectivity from the parietal to the frontal cortex, evidence for a reduction in working-memory-dependent connectivity from the right frontal to the right parietal cortex has been reported in prodromal participants,<sup>7</sup> as well as in medicated patients with schizophrenia.<sup>6</sup> Task-dependent connectivity from the right middle frontal gyrus to the right parietal lobule was reduced in participants in an at-risk mental state with behavioural working-memory impairment.<sup>8</sup> Furthermore, a progressive reduction of this modulatory connectivity from healthy controls to people with first-episode psychosis (people in an at-risk mental state took an intermediate position) was shown by Schmidt and colleagues,<sup>7</sup> while deficits in performance were found only in patients with first-episode psychosis. Similarly, right hemispheric frontoparietal modulation was reduced in a sample of patients with chronic schizophrenia and reduced performance.<sup>6</sup> Although the current literature shows reduced modulatory influence of working-memory context in the frontoparietal network in people with schizophrenia and participants in an at-risk mental state, there are still inconsistencies regarding the anatomic direction and laterality of group differences. Such inconsistent findings may arise due to clinical heterogeneity of the investigated samples, including stage of illness, medication status or psychopathology, as

well as differences in task demands and performance of the investigated samples.<sup>51</sup> For example, an increase in working-memory load seems to shift the information flow from a frontoparietal configuration toward a parietofrontal one.<sup>49,52</sup> Such subtle factors may influence the direction of effective connectivity within the frontoparietal pathway and demand further exploration of varying degrees of task demands in the psychosis continuum.

The modulatory impact on connectivity from the left dlPFC to the visual cortex differed significantly between groups. While people with low delusional ideation showed negative modulatory influence, there was no such effect in people with high delusional ideation. Moreover, people with high delusional ideation showed a stronger intrinsic connectivity from the dlPFC to the visual cortex than people with low delusional ideation. Because the dlPFC plays a critical role in controlling activity in task-related brain regions,<sup>53</sup> this weaker negative influence could indicate reduced context-dependent top-down signalling to primary sensory areas that would normally promote selective attention to task-related subcomponents. This context-dependent modulation was less pronounced in people with high delusional ideation, who showed stronger context-independent intrinsic connectivity from the dlPFC to the visual cortex.

#### *Altered working-memory-dependent effective connectivity along the psychosis spectrum*

Impairment of working-memory-modulated frontoparietal effective connectivity has been proposed as a mechanism underlying cognitive deficits in patients with schizophrenia.<sup>6</sup> Consistent findings of aberrant working-memory-related frontoparietal connectivity along the psychosis spectrum and a negative correlation between connectivity strength and the severity of psychotic symptoms in people in an at-risk mental state<sup>8,54</sup> have recently led to the hypothesis that abnormalities in this pathway might reflect vulnerability for emerging psychosis.<sup>55</sup> The presence of a similar reduction in modulatory effective connectivity in our nonclinical sample with subclinical delusion gives additional support for the latter notion. It is noteworthy that people with high delusional ideation did not differ in terms of working-memory performance. This might have been due to compensatory mechanisms that maintained cognitive stability. On the other hand, the lack of deficits might show that altered frontoparietal connectivity represents an intrinsic feature of people experiencing psychotic symptoms, rather than a vulnerability marker.

Whether and in which way prodromal stages of psychosis and subclinical delusions differ from one another and how they interact with neurocognitive ability is of particular interest for future research. These questions demand longitudinal studies to determine putative overlaps of frontoparietal effective connectivity in people with transient, attenuated delusions and in those who might develop clinically impairing delusions, possibly with concomitant working-memory deficits. In this way, specific characteristics of the content of psychotic experiences could differ in their value in



predicting the occurrence of a psychotic disorder.<sup>56</sup> Future research requires precise characterization of people with non-clinical psychosis and the content of their psychotic experiences, with clearer specifications of neurocognitive overlaps between these populations, to achieve a better understanding of how to allocate subclinical psychosis to the psychosis spectrum. To date, substantial variability in the use of diagnostic tools (self-report v. clinical interview; different questionnaires) has resulted in a heterogeneous group of people with psychotic-like experiences and limited the comparability of findings. As well, the range of “psychotic-like experiences” is broad,<sup>57</sup> and it is likely that there are differences in relationships between distinct psychotic-like phenomena and cognition. Investigating working-memory network connectivity in different samples that share specific phenomenological characteristics provides a promising approach for characterizing and classifying the phenomenology of psychosis. This concept fits with recent efforts in developing a data-driven classification system based on a dimensional approach to psychopathology (i.e., the incorporation of a “full range of variation, from normal to abnormal”).<sup>58</sup>

### Limitations

The block design of the current study did not distinguish among the different components of the working-memory processes (encoding, retrieval, information manipulation) shown in patients.<sup>59</sup> Therefore, it remains an open question whether distinct subprocesses are altered in people with high delusional ideation. As well, the current study intended to use a simplistic 3-node network underlying working-memory-dependent effective connectivity for reasons of parsimony and comparability with previous psychosis studies.<sup>6</sup> Nevertheless, in the existing connectivity work, there is diversity in the designed model space even within the framework of working-memory research<sup>6,8,29</sup> that makes the comparison of findings difficult (for example, with regard to laterality effects and interhemispheric connections).

### Conclusion

The current study shows that comparable alterations in working-memory-dependent modulation of connectivity in people with high delusional ideation resemble those previously described in a preclinical at-risk mental state and clinical schizophrenia samples. We observed no deficits in working-memory performance, but these people exhibited stronger dlPFC activation and a reduction in effective connectivity between the parietal and frontal regions. The increase in prefrontal activation might reflect compensatory (and thus inefficient) recruitment of this region in response to the dysfunctional connectivity in the working-memory network.<sup>21</sup> Thus, changes in frontoparietal connectivity patterns appear sensitive to cognitive tasks, even in healthy people, who differ only in terms of subclinical delusional ideation. Such differences might reflect subtle changes in the underlying temporal cortico-cortical dynamics along the psychosis spectrum and highlight the importance of studying cognitive

function in terms of connectivity to further specify potential differences between psychotic symptoms and nonclinical psychotic beliefs.

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