Research Paper

Abnormal effective connectivity and psychopathological symptoms in the psychosis high-risk state

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Background: Recent evidence has revealed abnormal functional connectivity between the frontal and parietal brain regions during working memory processing in patients with schizophrenia and first-episode psychosis. However, it still remains unclear whether abnormal frontoparietal connectivity during working memory processing is already evident in the psychosis high-risk state and whether the connection strengths are related to psychopathological outcomes. **Methods:** Healthy controls and antipsychotic-naive individuals with an at-risk mental state (ARMS) performed an n-back working memory task while undergoing functional magnetic resonance imaging. Effective connectivity between frontal and parietal brain regions during working memory processing were characterized using dynamic causal modelling. **Results:** Our study included 19 controls and 27 individuals with an ARMS. In individuals with an ARMS, we found significantly lower task performances and reduced activity in the right superior parietal lobule and middle frontal gyrus than in controls. Furthermore, the working memory–induced modulation of the connectivity from the right middle frontal gyrus to the right superior parietal lobule was significantly reduced in individuals with an ARMS, while the extent of this connectivity was negatively related to the Brief Psychiatric Rating Scale total score. **Limitations:** The modest sample size precludes a meaningful subgroup analysis for participants with a later transition to psychosis. **Conclusion:** This study demonstrates that abnormal frontoparietal connectivity during working memory processing is already evident in individuals with an ARMS and is related to psychiatric symptoms. Thus, our results provide further insight into the pathophysiological mechanisms of the psychosis high-risk state by linking functional brain imaging, computational modelling and psychopathology.

Introduction

A key challenge in research on the early detection of psychosis is to find robust neural markers to characterize the brain mechanisms underlying the onset of psychosis. A fundamental problem in research in this area is then to identify a clinical risk syndrome — an "at-risk mental state" (ARMS) — that reflects a high-risk predisposition to psychosis.[1] The ARMS is defined by the presence of 1 or more of the following criteria: attenuated psychotic symptoms, brief limited intermittent psychotic episodes, trait vulnerability and a marked decline in psychosocial functioning and unspecified prodromal symptoms.[1] Individuals with an ARMS have an increased probability of transition to psychosis within the first years of follow-up.[2] A recent study showed that the highest risk for transition was within the first 2 years of follow-up, while the overall rate of transition was estimated to be 34.9% over a 10-year period.[3]

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Working memory deficits are considered to be a central manifestation of the pathophysiology of schizophrenia.[4] The psychosis high-risk state has also been associated with prominent impairments in working memory.[5] Individuals with an ARMS can be separated from healthy controls on the basis of their impaired working memory performance,[6] whereby working memory functioning at baseline provides valuable predictions about the longitudinal development of psychosis in these individuals.[7] Consistent with these findings, a recent meta-analysis has suggested that it is possible to differentiate between clinical high-risk individuals who transition or do not transition to psychosis with respect to working memory.[8] Functional magnetic resonance imaging (fMRI) studies have shown that working memory deficits in individuals with an ARMS are accompanied by reduced activation in frontal and parietal brain regions.[9–11] Moreover, the reduced prefrontal activation in individuals with an ARMS during a working memory task is associated with a reduction in grey matter volume in the same area.[12] These changes are not attributable to effects of the illness or treatment and thus might reflect core neurobiological markers of increased vulnerability to psychosis.

It has been proposed that psychosis may be characterized not only by focal brain abnormalities, but also by abnormal integration of task-related brain regions.[13,14] During working memory processing as operationalized by the n-back task, prefrontal and parietal brain regions are robustly activated,[15] while these structures also exhibit anatomic connections that critically contribute to working memory performance.[16] Abnormal prefrontal–parietal interaction during working memory processing has been shown in patients with schizophrenia[17] and in individuals at high genetic risk for schizophrenia.[18] Moreover, the extent of this dysfunctional connectivity has often been linked to the severity of the psychotic symptoms,[19,20] providing a mechanistic link between the degree of functional network integrity and the development of psychotic symptoms.[14] Clinical studies have also reported abnormal effective prefrontal–parietal connectivity in patients with established schizophrenia,[21–23] as measured by dynamic causal modelling (DCM), a model-based approach to examine condition-specific causal interactions between different brain regions.[24] There is also evidence to suggest that vulnerability to psychosis is associated with the severity of dysfunctional effective connectivity during working memory processing. A very recent DCM study showed significantly reduced connection strengths in individuals at high genetic risk for schizophrenia who were experiencing psychotic symptoms compared with healthy controls.[25] Remarkably, individuals with psychotic symptoms exhibited a negative correlation between the individual connectivity strength and their propensity to delusion formation.

We have previously shown that individuals with an ARMS and patients with first-episode psychosis had reduced activation during n-back working memory processing in the middle frontal gyrus (MFG) and superior parietal lobule (SPL) compared with healthy controls,[25] suggesting differences in the underlying brain connectivity. Indeed, the working memory–induced modulation of connectivity from the right MFG to the SPL was gradually reduced from healthy controls to individuals with an ARMS and further to nontreated patients with first-episode psychosis,[27] even though the difference between healthy controls and individuals with an ARMS did not reach statistical significance owing to the small number of individuals included in the ARMS group. We have therefore used DCM to examine whether abnormal frontoparietal connectivity during working memory processing is already evident in the psychosis high-risk state, and we included a larger sample of individuals with an ARMS than we had in our previous study.[27] Furthermore, we also investigated whether the connection strengths in individuals with an ARMS were related to the severity of psychiatric symptoms and to deficits in global functioning. We hypothesized that individuals with an ARMS would exhibit significantly altered connectivity strengths between the MFG and SPL compared with healthy controls and that the strengths of connectivity in individuals with an ARMS would be related to the manifestation of psychiatric symptoms.

Methods

Participants

We recruited patients with an ARMS in the FePsy (Früherkennung von Psychosen) clinic using the Basel Screening Instrument for Psychosis (BSIP),[28] which is based on the personal assessment and crisis evaluation criteria.[29] All participants provided written informed consent and the study was approved by the research ethics committee.

Inclusion in the study required 1 or more of the following criteria: attenuated psychotic-like symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) or a first- or second-degree relative with a psychotic disorder plus at least 2 further risk factors for — or indicators of — the initial stages of psychosis according to the BSIP. Inclusion because of attenuated psychotic symptoms required that the change in mental state had to be present at least several times a week and for a duration of more than 1 week (a score of 2 or 3 on the Brief Psychiatric Rating Scale [BPRS] hallucination item or a score of 3 or 4 on BPRS items for unusual thought content or suspiciousness). Inclusion because of BLIPS required scores of 4 or above on the hallucination item or score of 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously. A more detailed description of these ARMS criteria can be found in our previous study.[1] In addition, we assessed (pre)psychotic and negative symptoms using the BPRS and the Scale for the Assessment of Negative Symptoms (SANS) in combination with the BSIP.

We excluded individuals who were taking antipsychotics (we did not exclude those taking antidepressants); had a history of previous psychotic disorders; had psychotic symptomatology secondary to an "organic" disorder; met the International Classification of Diseases, Tenth Revision criteria for substance abuse; had psychotic symptomatology associated with an affective psychosis or a borderline personality disorder;

were younger than 18 years; had inadequate knowledge of the German language; and had an IQ less than 70, as measured with the multiple choice vocabulary test.

We recruited healthy controls from the same geographical area as the individuals with an ARMS. Inclusion criteria for the control group were no current psychiatric disorder; no history of psychiatric illness, head trauma, neurologic illness, serious medical or surgical illness or substance abuse; and no family history of any psychiatric disorder, as assessed by an experienced psychiatrist (J.A., A.R-R. or S.J.B.) in a detailed clinical semi-structured interview.

N-back task

During the n-back task,[10,26] all participants saw series of letters with an interstimulus interval of 2 seconds. Each stimulus was presented for 1 second. During a baseline (0-back) condition, participants were required to press the button with the right hand when the letter "X" appeared. During 1-back and 2-back conditions, participants were instructed to press the button if the currently presented letter was the same as that presented 1 (1-back condition) or 2 trials previously (2-back condition). The 3 conditions were presented in 10 alternating 30 second blocks ($2 \times$ 1-back, $3 \times$ 2-back and $5 \times$ 0-back), matched for the number of target letters per block (i.e., 2 or 3), in a pseudorandom order. Task performance was expressed by the sensitivity index d', using the formula $d' = z(\text{Hits}) - z(\text{FA})$, where FA reflects false alarms.[30] Hit and false alarm rates of zero or 1 were adjusted as previously described.[31] The d' values were subjected to 1-way analysis of variance (ANOVA).

Functional MRI

We performed fMRI using a 3 T scanner (Siemens Magnetom Verio, Siemens Healthcare) with an echo planar sequence with a repetition time of 2.5 s, echo time of 28 ms, matrix 76×76, 126 volumes and 38 slices with 0.5 mm interslice gap, providing a resolution of $3 \times 3 \times 3$ mm^3 and a field of view 228×228 cm^2.

We analyzed fMRI data using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). All volumes were realigned to the first volume, corrected for motion artifacts, mean adjusted by proportional scaling, normalized into standard stereotactic space (Montreal Neurological Institute; MNI) and smoothed using an 8 mm full-width at half-maximum Gaussian kernel. We convolved the onset times for each condition (0-back, 1-back and 2-back) with a canonical hemodynamic response function. Serial correlations were removed using a first-order autoregressive model, and we applied a high-pass filter (128 s) to remove low-frequency noise. Six movement parameters were also entered as nuisance covariates to control for movement. We focused our analysis on the 2-back > 0-back contrast (main effect of task) to capture the highest possible working memory load during the n-back in accordance with a previous n-back fMRI study in patients with schizophrenia.[21] We evaluated between-group differences using a second 2-sample *t* test. As groups differed in terms of education and antidepressant medication, these variables were added as covariates in the second-level model. We assessed statistical significance at the cluster-level using the nonstationary random field theory.[32] The first step of this cluster-level inference strategy consisted of identifying spatially contiguous voxels at a threshold of $p < 0.001$, without correction (cluster-forming threshold).[33] Finally, a family-wise error–corrected cluster-extent threshold of $p < 0.05$ was defined to infer statistical significance.

Dynamic causal modelling

We used DCM10, as implemented in SPM8 (revision number 4290), to analyze effective connectivity. In DCM for fMRI, regional time series derived from a general linear model analysis are used to analyze connectivity and its modulation by experimental conditions. This method models hidden neuronal dynamics and the influence that one neuronal system exerts over another.[24] In DCM, the modelled neuronal dynamics need to be transformed into a measured response (i.e., the blood oxygen level–dependent signal) by using a hemodynamic forward model.[34,35] The DCM method allows modelling of the endogenous coupling between 2 regions, which is independent of context ("intrinsic connections"). The impact of experimental stimuli can be modelled directly on specific regions ("driving inputs") or on the strength of coupling between 2 regions ("modulatory input"). Here, we explicitly examined how the coupling strengths between the parietal and frontal regions were changed by the 2-back condition (modulatory effect).

Regions of interest and time series extraction

The regions of interest of our anatomic network were selected on the basis of the previously published second-level SPM analysis of these data,[26] a previous meta-analysis emphasizing the importance of frontoparietal activation during the n-back task[15] and previous DCM studies of n-back working memory tasks in patients with psychosis.[21,36] The conventional second-level SPM analysis had revealed significant activation in the bilateral SPL and MFG in both groups, whereas individuals with an ARMS had reduced right SPL activations for the 2-back > 0-back contrast compared with healthy controls,[26] suggesting differences in brain connectivity between the SPL and MFG. To test this hypothesis, we created an anatomic mask comprising the SPL and MFG taken from the automated Talairach atlas in the Wake Forest University Pick Atlas toolbox.[37]

Regional time series within the bilateral SPL and MFG were extracted from spherical volumes of interest of 12 mm in diameter centred on the group maxima of the 2-back > 0-back contrast within the anatomic mask (Fig. 1A) using the first eigenvariate of voxels above a subject-specific threshold of $p < 0.001$, uncorrected. When a participant had no voxel above threshold at the group maxima (see the Appendix, Table S1, available at jpn.ca), we selected the nearest suprathreshold voxel within the mask. Participants who had no activated voxels under these criteria were excluded from further analyses.

Model architecture

Across all models tested, we assumed the same network layout of connections between the right and left SPL and MFG.

Specifically, SPL and MFG were reciprocally connected within both hemispheres, with additional interhemispheric connections among all regions. As in a recent DCM study of working memory,[38] the visual input (driving) entered the SPL bilaterally.[39,40] Starting from this basic layout, a factorially structured model space was derived by considering where the modulatory effect of the 2-back working memory condition might be expressed (Fig. 2A). We contrasted models in which the 2-back working memory condition was allowed to modulate, within both hemispheres, the parietofrontal connections, the frontoparietal connections or both (first, second and third row of Fig. 2A, respectively). These 3 intrahemispheric options were crossed with 4 possibilities in which interhemispheric connections might be modulated by the 2-back working memory condition (i.e., none, the interhemispheric connections between parietal areas [second column of Fig. 2A], the interhemispheric connections between frontal areas [third column of Fig. 2A], or both [fourth column of Fig. 2A]). As a result, our model space consisted of 12 alternative models, each of which was fitted to the data from each individual participant.

Bayesian model selection and averaging

We first used Bayesian model selection (BMS) to determine the plausibility of the models considered. The BMS method rests on comparing the (log) evidence of a predefined set of models (see the model architecture section). The model evidence is the probability of observing the empirical data, given a model, and represents a principled measure of model quality derived from probability theory.[41] Concretely, it represents the average predicted data under random sampling from the model's priors or, alternatively, the difference between the accuracy (fit) of a model and its complexity. We used a random-effects BMS approach for group studies, which is capable of quantifying the degree of heterogeneity in a population while being extremely robust to detect potential outliers.[42] A common way to summarize the results of

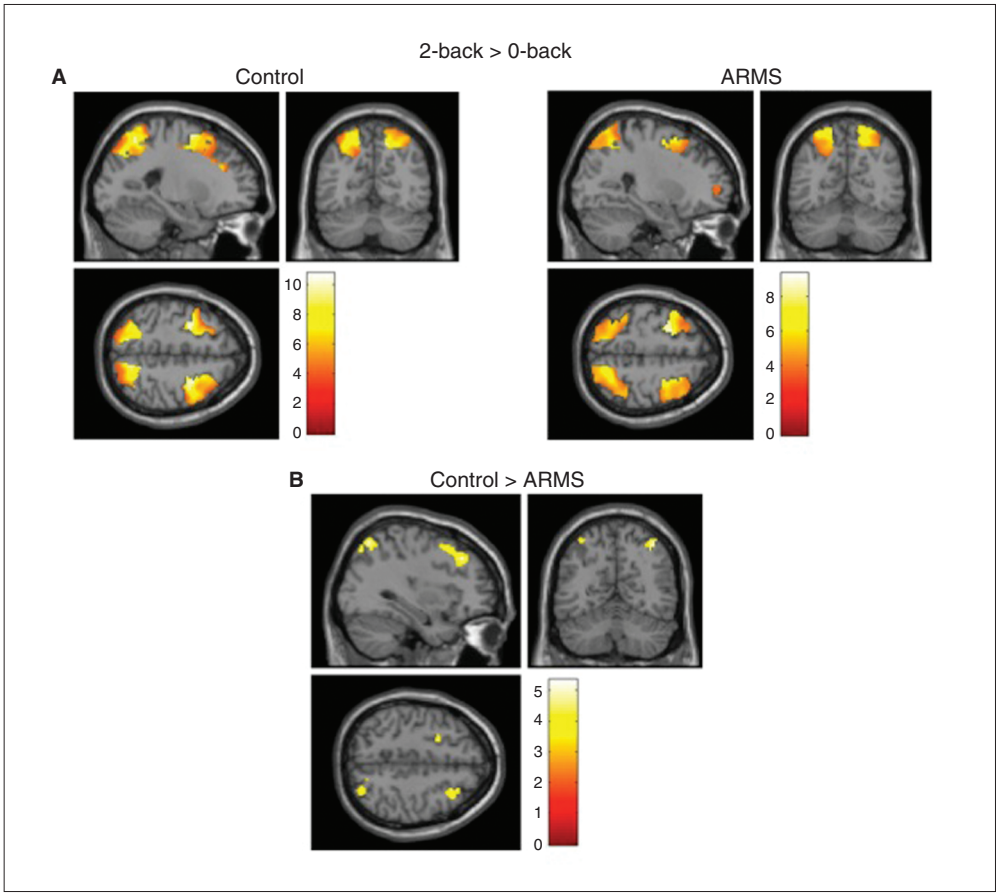

Fig. 1: (A) Significant activity in the bilateral superior parietal lobule (SPL) and middle frontal gyrus (MFG) during working memory processing (2-back > 0-back) within the anatomic mask for healthy controls and participants with an at-risk mental state (ARMS; family-wise error [FWE] cluster-level corrected at $p < 0.001$) **(B)** Significant difference in right SPL (Montreal Neurological Institute [MNI] coordinates $x, y, z = 38, –64, 58$; cluster size 304) and MFG activity (MNI coordinates $x, y, z = 34, 30, 40$; cluster size 291) between the control and ARMS groups during working memory processing (FWE cluster-level corrected at $p < 0.05$).

random-effects BMS is to report the exceedance probability of each model (i.e., the probability that this model is more likely than any other of the models tested to generate the given group data).[42] As data from the groups may be generated by different mechanisms and thus different models may explain the group-wise data best,[21] we performed BMS for each group separately.

Statistical comparison of model parameter estimates across groups is only valid if those estimates stem from the same model. Given that different models may be found to be optimal across groups, Bayesian model averaging (BMA) has been recommended as standard approach for clinical DCM studies.[43] The BMA method averages posterior parameter estimates over models, weighted by the posterior model probabilities.[44] Thus, models with a low posterior probability contribute little to the estimation of the marginal posterior.

Group statistics of DCM parameters

After BMA, we used the resulting posterior means from the averaged DCM to examine differences between groups. In this article, we focus on working memory-induced changes in connectivity. Thus, we tested for group differences in the modulatory parameters only. We then used 1-way ANOVA to test which of the connectivity parameters differed across groups.

Results

We recruited 31 individuals with an ARMS and 20 healthy controls for participation in our study. Five participants (1 in the control group and 4 in the ARMS group) were excluded because they had no activated voxels in the regions of interest, leaving 27 individuals with an ARMS and 19 controls available for our analyses. The groups were well matched for age, sex, handedness, premorbid IQ and cannabis consumption. The demographic and clinical characteristics of participants are summarized in Table 1. As expected, controls had

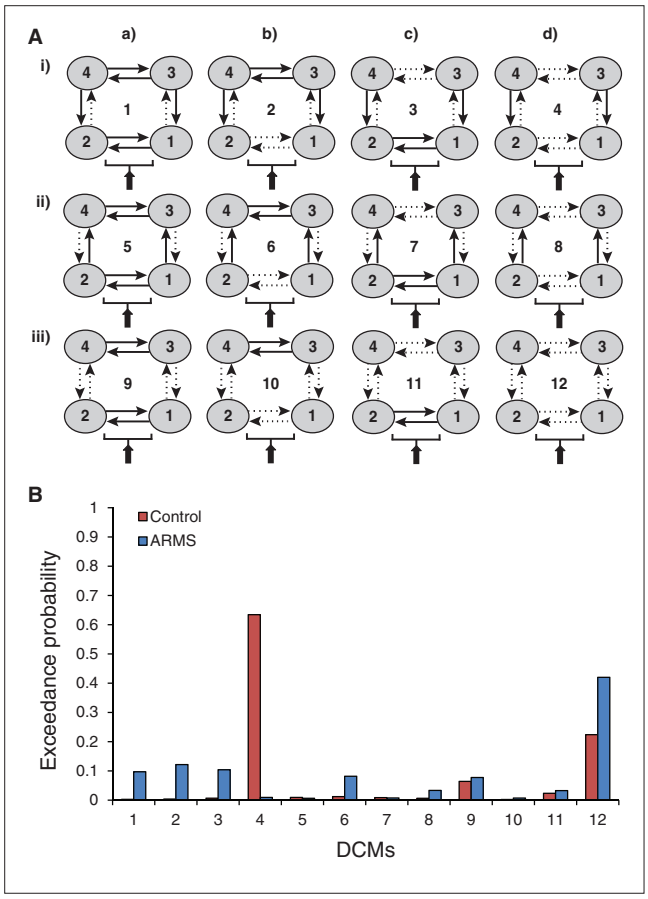

Fig. 2: (A) Model space tested in this study. Abbreviations: 1, right superior parietal lobule; 2, left SPL; 3, right middle frontal gyrus (MFG); 4: left MFG. **(B)** Bayesian model selection (BMS) among all 12 dynamic causal models (DCMs) over healthy controls and individuals with an at-risk mental state (ARMS). The BMS results are reported in terms of exceedance probabilities.

Table 1: Demographic and clinical characteristics of study groups

Characteristic	Group; mean ± SD*		Statistic	*p* value
	Control, *n* = 19	ARMS, *n* = 27		
Age, yr	26.5 ± 4.0	25.04 ± 5.0	$F_{1,45} = 0.628$	0.43
Sex, no. male	10	20	$\chi^2 = 2.26$	0.13
No. right-handed	18	27	$\chi^2 = 1.45$	0.23
Education, yr	16.38 ± 2.96	13.22 ± 2.3	$F_{1,45} = 15.00$	< 0.001
IQ	114 ± 9.8	108.13 ± 12.8	$F_{1,45} = 2.29$	0.14
BPRS total score	24.50 ± 1.15	35.93 ± 8.46	$F_{1,45} = 34.50$	< 0.001
APS score	0	7.07 ± 3.11	$F_{1,45} = 97.5$	< 0.001
SANS total score	0	17.81 ± 15.09	$F_{1,45} = 26.30$	< 0.001
GAF total score	88.50 ± 4.44	66 ± 15.69	$F_{1,45} = 37.31$	< 0.001
Antidepressant use, no.	0	11	$\chi^2 = 10.17$	0.001
Cannabis use, no.	3	6	$\chi^2 = 1.78$	0.18

APS = attenuated psychotic-like symptoms; ARMS = at-risk mental state; BPRS = Brief Psychiatric Rating Scale; GAF = Global Assessment of Functioning; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation.
*Unless otherwise indicated.

significantly lower scores on the BPRS, SANS and APS, but significantly higher Global Assessment of Functioning (GAF) scores than individuals with an ARMS. All participants in the ARMS group were antipsychotic-naïve, and 11 received antidepressants; no controls took antidepressants. Finally, formal education differed significantly between the groups.

Task performance

The sensitivity index d′ differed significantly between the control and the ARMS groups (mean 3.28 ± 1.36 v. 2.40 ± 0.95, $F_{1,45} = 6.70$, $p = 0.013$; see the Appendix, Fig. S1).

Between-group differences on brain activity

We observed significantly higher activation in the right SPL and MFG in controls than in individuals with an ARMS (Fig. 1B).

Bayesian model selection results

The BMS revealed that model 4 had the greatest model evidence in controls (exceedance probability 63.43%), while model 12 was the second best (exceedance probability 22.41%). In individuals with an ARMS, model 12 was clearly superior to all other models (exceedance probability 42.01%; Fig. 2B).

Between-group differences on effective connectivity

Indivduals with an ARMS exhibited significantly lower connectivity strengths from the right MFG to the right SPL than controls ($F_{1,45} = 8.19$, $p = 0.006$, Bonferroni-corrected; Fig. 3A and Table 2). Notably, there was no significant correlation between the modulation of connectivity from the right MFG to the right SPL and d′ ($r = 0.082$; $p = 0.59$), and there was no significant relation to educational level ($F_{1,45} = 2.51$, $p = 0.12$) or antidepressant use ($F_{1,45} = 1.23$, $p = 0.27$).

Relation of effective connectivity and symptoms

Finally, we related the working memory–induced connectivity from the right MFG to the right SPL to the BPRS, SANS and GAF scores in the ARMS group. Using a backward linear regression, our results showed that working memory–induced modulation of connectivity strength from the right MFG to the right SPL was explained by the BPRS total score (see the Appendix, Table S2). The working memory–induced modulation of connectivity from the right MFG to the right SPL was negatively correlated to BPRS scores in the ARMS group ($r = –0.523$, $p = 0.005$; Fig. 3B).

Discussion

The present study demonstrates that working memory–induced modulation of frontoparietal connectivity in participants within the psychosis high-risk state is reduced relative to healthy controls. These findings generally support the disconnection hypothesis, which proposes that altered functional integration is a key mechanism in the pathophysiology of cognitive impairments in individuals with schizophrenia.[13,14] In particular, the findings confirm previous evidence that abnormal effective connectivity is already evident in the high-risk state for psychosis.[25,36] Moreover, the findings provide evidence for a mechanistic relation between the degree of functional network integrity and psychopathology by showing that working memory–induced modulation of connectivity from the right MFG to the right SPL was related to the BPRS score in patients with an ARMS.

The working memory performance was operationalized by the sensitivity index, which provides an objective measure independent of participants' response bias, and was significantly reduced in individuals with an ARMS relative to healthy controls. Although previous n-back studies in ARMS samples found no difference in task performance relative to controls or only a statistical trend in terms of accuracy and reaction time,[11,12] behavioural studies in larger samples have indicated clear neuropsychological deficits in high-risk populations,[45,46] including individuals at genetic risk for schizophrenia,[47] confirming that these deficits may be a cognitive marker of increased vulnerability to disease. This is in line with previous studies reporting working memory deficits in the early course of the illness[6] and with a recent meta-analysis demonstrating that the psychosis high-risk state is characterized by prominent impairments in working memory.[5] Cognitive impairments are of great clinical relevance, given their potential in predicting the transition from the high-risk state to psychosis[7] and their relation to the persistence of psychotic symptoms.[48]

The conventional fMRI analysis of our data revealed that the ARMS group had significantly less activity in the right SPL than healthy controls during working memory processing. This finding corresponds to those of previous fMRI studies showing that individuals with an ARMS failed to activate parietal areas, including the SPL, when the working memory task became increasingly difficult.[9] Our finding of reduced right MFG activity in the ARMS group compared with the control group is also consistent with findings of previous n-back studies of ARMS samples.[11,12,49] Interestingly, the altered function in the MFG during the task was associated with volumetric abnormalities in the same area[12] and subcortical dopamine synthesis capacity.[11] These findings are consistent with neuroimaging and neuropsychological evidence that the ARMS is associated with neurofunctional abnormalities that are qualitatively similar to but less severe than those seen in patients with schizophrenia,[50,51] suggesting that the functional abnormalities they displayed might reflect a correlate of their increased vulnerability to psychosis.

Furthermore, our model selection results indicated that the most likely model in the ARMS group contains working memory–induced modulation of both parietofrontal and frontoparietal connectivity. This finding corresponds with the results of a recent study showing high functional connectivity strength during the n-back task within typical working memory-related regions, including the middle frontal and parietal cortices.[52] The n-back task comprises continuous encoding of incoming visual letters on the one hand and rule updating on the other. Specifically, it has been suggested that connections from the parietal to the frontal cortex may contribute to the encoding of incoming stimuli,[53] while

Table 2: Analysis of variance results for the between-group comparison of connectivity estimates

Connectivity group	*F*	*p* value
Left to right superior frontal gyrus	0.237	0.63
Left parietofrontal	0.301	0.59
Right to left parietal	0.435	0.51
Right parietofrontal	1.030	0.32
Left frontoparietal	0.081	0.78
Left to right frontal	3.216	0.08
Right frontoparietal	8.19	0.006*
Right to left frontal	0.000	0.98

*Bonferroni-corrected group differences for multiple comparisons.

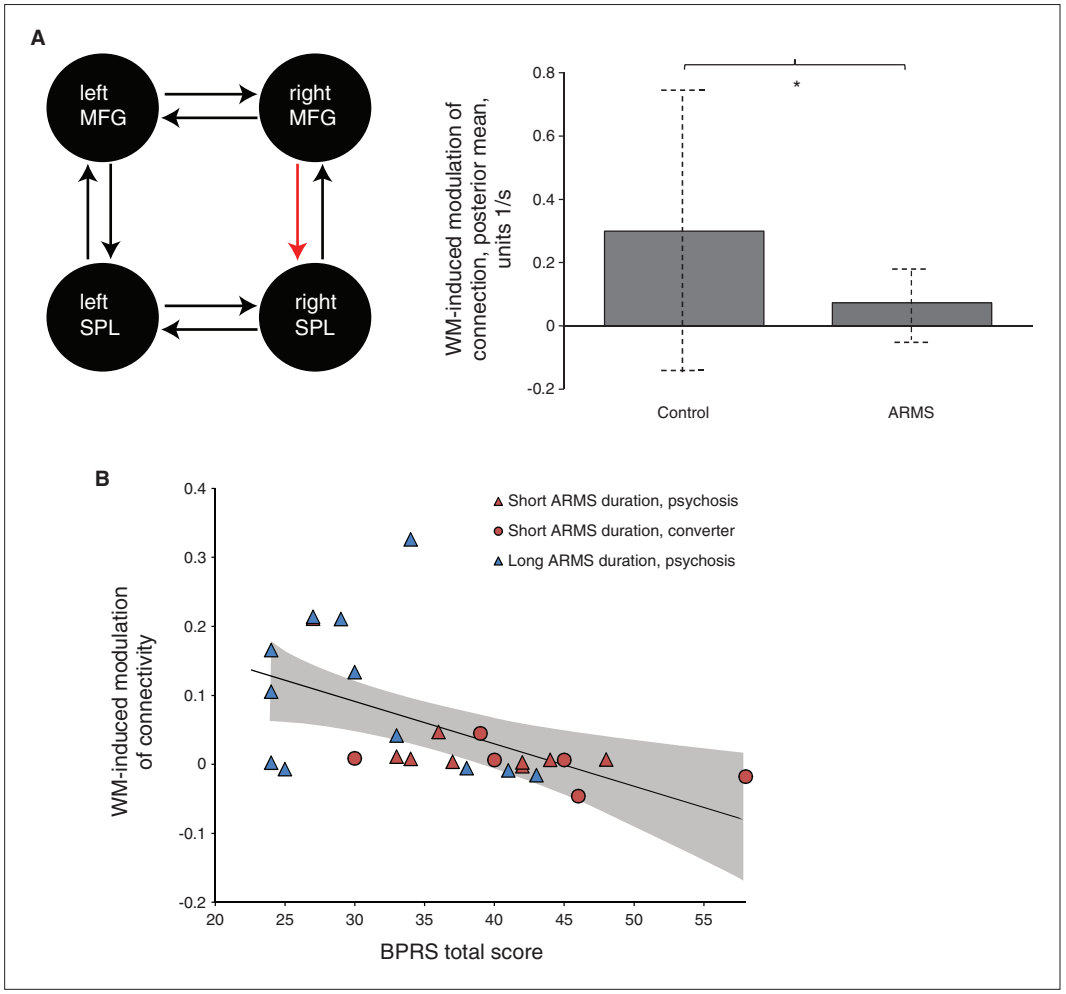

Fig. 3: (A) The modulatory effect of the 2-back working memory condition on the connectivity from the right middle frontal gyrus (MFG) to the right superior parietal lobule (SPL) in the control group (n = 19) and the at-risk mental state (ARMS) group (n = 27). The y axis denotes the average over all participants and all 12 dynamic causal models (DCMs; using Bayesian model averaging) with regard to the posterior mean of the modulatory effect; this encodes changes in connection strength induced by the 2-back working memory condition. *p = 0.006, Bonferroni-corrected. Importantly, the connectivity estimates for controls differed significantly from zero (p = 0.008). **(B)** Significant negative correlation between the working memory–induced modulation of connectivity from the right MFG to the right SPL and Brief Psychiatric Rating Scale (BPRS) scores in the ARMS group (r = –0.523, p = 0.005). Participants with a long ARMS duration are marked in blue (n = 12), whereas those with a short ARMS duration are represented in red (n = 15); participants who transitioned to psychosis (n = 6) are represented with circles and those who did not transition to psychosis (n = 21) are represented with triangles. WM = working memory.

the connections from the frontal to the parietal cortex probably mediate the updating of rules (e.g., 2-back).[54,55] However, in healthy controls, the model with working memory–induced modulation of parietofrontal connectivity was identified as the most likely. This effect in healthy controls might result from higher attention during letter encoding, leading to stronger stimulus updating during working memory, as the parietal cortex is implicated in number representation.[56] Although both groups engaged a qualitatively similar working memory–related frontoparietal network (Fig. 1A), we found that the working memory–induced modulation of connectivity from the right MFG to the right SPL was significantly reduced in the ARMS compared with the control group. If the common interpretations of parietofrontal and frontoparietal connections during working memory processing are correct, we may speculate that this result would indicate a specific failure in rule updating in individuals with an ARMS. Abnormal brain connectivity in individuals with an ARMS during working memory processing has already been reported in previous DCM studies.[36] However, this work focused on task-independent connection strengths, so a direct comparison is precluded. Crossley and colleagues[36] found progressive left hemispheric alterations in the endogenous connection from the superior temporal gyrus to the MFG from individuals with an ARMS to patients with first-episode psychosis compared with healthy participants. We did not explore endogenous connections, but explicitly focused on task-induced brain connectivity, as the analysis of working memory–dependent modulation of connectivity may help to reveal a potential mechanism underlying cognitive deficits in patients with psychosis.[21] Our result is in line with that of a recent study in patients with schizophrenia, which also found reduced working memory–induced frontoparietal connectivity over the right hemisphere.[21] Thus, our results indicate that changes in working memory–induced frontoparietal connectivity during working memory processing might be not only apparent in patients with schizophrenia, but also in individuals at high risk for psychosis, suggesting a critical vulnerability threshold for later conversion into psychosis.

Furthermore, we demonstrated that the working memory–induced modulation of connectivity from the right MFG to the right SPL in individuals with an ARMS was negatively related to psychiatric symptoms, as indicated by the BPRS total score. This finding corresponds with recent evidence from a DCM study that showed a significant correlation between the individual connection strength and the formation of delusions in genetically high-risk participants[25] and with another fMRI study that found that participants with a high risk for psychosis showed reduced prefrontal functional connectivity in the default mode network that correlated with total and general scores on the Positive and Negative Syndrome Scale.[57] Together, these findings provide experimental evidence for a mechanistic relation between the degree of functional network integrity and state-related psychopathological symptoms. However, our finding is not specific for psychotic symptoms, as the BPRS subsumes a broad range of psychiatric symptoms. In this regard, working memory–related frontoparietal connectivity patterns at pretreatment baseline predicted the improvement in negative symptoms in antipsychotic-naive patients with schizophrenia.[58] Thus, further studies are needed to establish the specific relation between frontoparietal connectivity during working memory processing and symptom expression.

Although individuals with an ARMS have an increased probability of transition to psychosis, remission to a nonrisk state is more than 4-fold greater compared to individuals who do not transition to psychosis.[59] A recent study showed that nonconverting high-risk individuals showed significant improvement in attenuated positive symptoms, negative symptoms, and social and role functioning, but still remained at a lower level of functioning than nonpsychiatric controls.[60] Accordingly, individuals with a longer duration of an ARMS since their first presentation had significantly lower BPRS scores than individuals with a shorter duration of ARMS.[26] Interestingly, we observed that individuals with a longer ARMS duration had generally lower BPRS scores in association with higher frontoparietal connectivity (Fig. 3B). However, as our ARMS sample was already quite small, we decided against a subsequent analysis of the difference between short and long ARMS durations. Thus, the relation between the degree of abnormal effective connectivity and psychiatric symptom expression might provide further insight to characterize the continuum of the high-risk state and to estimate later transition tendencies, given that the highest risk for transition occurs within the first 2 years.[3]

Limitations

There are some limitations to be considered in the present study. Our analysis did not consider whether the connectivity parameters in individuals with and ARMS who later transitioned to psychosis differed from those who did not transition to psychosis; at the time of writing, only 6 participants had made this transition (Fig. 3B), precluding a meaningful subgroup analysis. The association between abnormal connectivity parameters, ARMS duration and conversion rates will be addressed in future studies. Although recent studies have demonstrated that parameter estimates[61] and model selection[62] are highly reproducible for deterministic DCM, replication studies are needed to support the use of DCM to explore connectivity differences between patients with psychosis and healthy controls.

Conclusion

This study extends recent evidence from patients with schizophrenia[21] and patients with first-episode psychosis[27] by demonstrating that dysfunctional working memory–induced modulation of frontoparietal connectivity is already evident in the high-risk state of psychosis. Moreover, to our knowledge, this is the first study showing that the extent of working memory–induced frontoparietal connectivity is related to the severity of psychiatric symptoms in individuals at high-risk for psychosis. Our results provide further insights into the pathophysiological mechanisms of the psychosis high-risk state by linking functional brain imaging, computational modelling and psychopathology.

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