Research Paper

Altered brain connectivity in patients with schizophrenia is consistent across cognitive contexts

Pierre Orban, PhD; Martin Desseilles, MD, PhD; Adrianna Mendrek, PhD; Josiane Bourque, MSc; Pierre Bellec, PhD; Emmanuel Stip, MD

Early-released on Apr. 19, 2016; subject to revision

Background: Schizophrenia has been defined as a dysconnection syndrome characterized by aberrant functional brain connectivity. Using task-based fMRI, we assessed to what extent the nature of the cognitive context may further modulate abnormal functional brain connectivity. **Methods:** We analyzed data matched for motion in patients with schizophrenia and healthy controls who performed 3 different tasks. Tasks 1 and 2 both involved emotional processing and only slighlty differed (incidental encoding v. memory recognition), while task 3 was a much different mental rotation task. We conducted a connectome-wide general linear model analysis aimed at identifying context-dependent and independent functional brain connectivity alterations in patients with schizophrenia. **Results:** After matching for motion, we included 30 patients with schizophrenia and 30 healthy controls in our study. Abnormal connectivity in patients with schizophrenia followed similar patterns regardless of the degree of similarity between cognitive tasks. Decreased connectivity was most notable in the medial prefrontal cortex, the anterior and posterior cingulate, the temporal lobe, the lobule IX of the cerebellum and the premotor cortex. **Limitations:** A more circumscribed yet significant context-dependent effect might be detected with larger sample sizes or cognitive domains other than emotional and visuomotor processing. **Conclusion:** The context-independence of functional brain dysconnectivity in patients with schizophrenia provides a good justification for pooling data from multiple experiments in order to identify connectivity biomarkers of this mental illness.

Introduction

Beyond abnormal activity of focal brain areas,[1] aberrant functional interactions between brain regions are thought to be a core feature of schizophrenia.[2–4] Among the current issues related to this influential idea is whether abnormal functional connectivity in patients with schizophrenia is context-dependent.[5] Resting-state fMRI characterizes intrinsic functional brain connectivity, which is guided by endogenous processes and spontaneous thoughts in the absence of any explicit task.[6] Resting-state functional brain imaging in patients with schizophrenia has revealed a widespread functional dysconnectivity between brain regions that are also known to exhibit abnormal levels of activation in relation to impairments in task performance and/or symptomatology.[7–11] However, a critical issue with the study of resting-state functional connectivity in patients with schizophrenia is the poor control over the cognitive state of these individuals, which may confound the interpretation of the results. Patients with schizophrenia experience pronounced disturbances of thoughts and differ from controls with regards to their internal mentations and cognitive states during rest.[12] The question of the context-independence of abnormal functional connectivity in patients with schizophrenia may thus be best adressed by characterizing such alterations using well-defined behavioural paradigms. To date, research has focused on determining whether alterations in brain connectivity were further modulated by task complexity in single cognitive domains.[13–15] However, to our knowledge, there is no sufficiently powered study that specifically examined commonalities and differences in dysconnectivity across distinct cognitive tasks.[16]

In the present work, we sought to assess whether the degree of cognitive similarity would impact the results by looking at 2 cognitive domains that strongly differ from one another, emotional versus visuomotor processing. We further distinguished the emotional processing task based on an additional embedded component, either incidental learning or recognition memory. These 3 paradigms were studied with a connectome-wide general linear model analysis. We characterized context-independent effects through commonalities in the main effects of abnormal functional connectivity across the 3 tasks. We evaluated context-dependent effects of abnormal connectivity using interaction analyses that looked for changes in functional connectivity between tasks in patients

Correspondence to: P. Orban, CRIUGM, Université de Montréal, 4545 Queen Mary, Montreal, QC H3W 1W5; pierre.orban@criugm.qc.ca

Submitted July 13, 2015; Revised Nov. 19, 2015; Accepted Jan. 5, 2016

DOI: 10.1503/jpn.150247

with schizophrenia that exceed those seen in healthy controls. We expected that the patterns of functional connectivity would be modulated by the cognitive context, and more so for highly dissimilar tasks, in both participants with schizophrenia and healthy controls. We hypothesized that, provided context-dependent effects would be observed superimposed on widespread context-independent dysconnectivity patterns in patients with schizophrenia, small versus large degrees of cognitive difference between tasks would be associated with context-dependent effects of different amplitudes.

Methods

Participants

We recruited stable patients with schizophrenia (i.e., no relapse within the last 2 months and no change in their antipsychotic medication within the month preceding the study) and healthy controls to participate in this study. Schizophrenia was diagnosed according to DSM-IV, and patients underwent full clinical assessment with the Positive and Negative Syndrome Scale (PANSS)[17] and the vocabulary, similarities and block design subtests of the Wechsler Adult Intelligence Scale (WAIS). These subtests are among those that define the general ability index, which is clinically useful as a measure of cognitive abilities that are less vulnerable to impairments of processing and working memory. Control participants were screened using the nonpatient edition of the Clinical Interview for DSM-IV (SCID). General exclusion criteria were age younger than 18 years or older than 45 years, past or present neurologic or Axis-I psychiatric disorder, alcoholism or drug abuse, noncompliance with testing procedures, or any contraindication for MRI (e.g., cardiac pacemaker, aneurysm clip).

The ethics committees of the Fernand-Seguin Research Centre, Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec approved our study protocol. In agreement with the Declaration of Helsinki, we obtained written informed consent from participants before the experiment. The ability of patients with schizophrenia to give informed consent was established using the guidelines of the Canadian Psychiatric Association.

Cognitive tasks

All participants performed 3 cognitive tasks administered during 1 fMRI scanning session. An in-depth description of the experimental tasks can be found elsewhere.[18–20] Data in these activation fMRI studies were drawn from the same sample.

Task 1[18] was an emotional processing task in which participants were passively exposed to blocks of emotionally positive, negative and neutral pictures selected from the International Affective Picture System (IAPS).[19] Because the series of images differed not only in valence, but also in arousal, there were 5 experimental conditions: positive content/high arousal, positive content/low arousal, negative content/high arousal, negative content/low arousal and neutral. Participants viewed 2 blocks of each condition, except for the neutral condition, which was viewed in 4 blocks. Experimental blocks lasted 40 s and were administered in a random order. They were each preceded by 3 s of instructions and were followed by 15-s rest periods, during which a black screen was displayed. Although participants were not explicitly instructed to try and remember the images, they were told that a recognition memory task would subsequently follow. Task 1 thus assessed incidental encoding in addition to evaluating emotional processing.

Task 2[20] (note: this task occurred third in the sequence) was a retrieval of emotional information (presented in task 1) using the same structure and type of visual emotional stimuli as in task 1. In this case, however, 50% of stimuli were new, and participants were asked to determine if each image had been presented earlier.

Task 3[21] was a mental rotation task in which participants had to determine whether 2 black and white drawings of 3-dimensional (3-D) shapes were identical or mirror images of each other.[22] This task was presented second in the sequence, between incidental encoding and subsequent retrieval of emotional information, and as such served as a distractor task to prevent mental rehearsal of emotional material. In the experimental condition, 1 shape was rotated along its vertical axis relative to the other shape. In half the trials, the figures were identical, whereas in the other half they were mirror images. In the control condition, participants viewed the unrotated identical or mirror 3-D drawings. Participants were presented with 4 blocks of each condition, with a different pair of shapes every 4.75 s, on average. Experimental blocks lasted 40 s and alternated with one another. They were each preceded by 3 s of instructions and were followed by 15-s rest periods, during which a black screen was displayed.

Functional MRI data acquisition

We acquired brain imaging data on a 3 T MRI scanner (Magnetom Tim Trio, Siemens). We recorded 273 functional volumes per participant during both task 1 and task 2 and 160 volumes during task 3. Functional T_2*-weighted images were obtained using a blood oxygen level–dependent (BOLD) sensitive, single-shot echo planar sequence (repetition time [TR] 3000 ms, echo time [TE] 30 ms, flip angle [FA] 90°, matrix size 64 × 64, voxel size 3.5 × 3.5 × 3.5 mm^3, 41 slices). The durations of data collection were 13.65, 13.65 and 8 min, respectively, for tasks 1, 2 and 3. Structural T_1*-weighted scans were acquired using a gradient recalled sequence (TR 19 ms, TE 4.92 ms, FA 25°, matrix size 256 × 256, voxel size 1 × 1 × 1 mm^3, 176 slices).

Functional MRI data preprocessing

The data sets were preprocessed and analyzed using the NeuroImaging Analysis Kit version 0.13.4 (NIAK; www.nitrc.org/projects/niak/), under CentOS with Octave version 3.6.1 (http://gnu.octave.org) and the Minc toolkit version 0.3.18 (www.bic.mni.mcgill.ca/ServicesSoftware/ServicesSoftwareMincToolKit). Analyses were executed in

parallel on the "Guillimin" supercomputer www.calculquebec.ca/en/resources/compute-servers/guillimin) using the pipeline system for Octave and Matlab (PSOM)[23] version 1.2.1.

A detailed description of the pipeline can be found on the NIAK website (http://niak.simexp-lab.org/pipe_preprocessing.html). Briefly, each fMRI data set was corrected for slice timing, and a rigid-body motion was then estimated for each time frame, both within and between runs, as well as between 1 fMRI run and the T_1 scan for each participant.[24] The T_1 scan itself was nonlinearly coregistered to the Montreal Neurological Institute (MNI) ICBM152 stereotaxic symmetric template[25] using the CIVET pipeline.[26] The rigid-body, fMRI-to-T_1 and T_1-to-stereotaxic transformations were all combined to resample the fMRI in MNI space at a 3 mm isotropic resolution. The following nuisance covariates were regressed out from fMRI time series: slow time drifts (basis of discrete cosines with a 0.01 Hz high-pass cut-off), average signals in conservative masks of the white matter and the lateral ventricles as well as the first principal components (typically around 4–6 components depending on the participant) accounting for 95% variance of the 6 rigid-body motion parameters and their squares.[27] The fMRI volumes were finally spatially smoothed with a 6 mm isotropic Gaussian blurring kernel.

There were large differences in head movement between patients with schizophrenia and controls. To minimize artifacts due to excessive motion, all volumes showing frame displacement (FD) greater than 0.5 mm were removed through a censoring method.[28] To overcome the confound of motion retained after scrubbing (residual FD [rFD]), we matched the samples from the 2 populations for levels of residual motion. Matching the participants balanced the groups with respect to rFD, the number of scrubbed volumes and the number of volumes left after scrubbing, which are used in subsequent steps of the analysis.

Functional brain parcellation

We sought to characterize the effect of schizophrenia on functional connectivity between pairs of functionally relevant, rather than anatomically defined, brain regions. To this end, we applied a bootstrap analysis of stable clusters (BASC)[29] to identify brain clusters that consistently exhibited similar BOLD fluctuations in individual participants and that were spatially stable across participants. The BASC replicates a hierarchical Ward clustering 1000 times and computes the probability that a pair of voxels fall in the same cluster, a measure called stability. The stability matrix is fed into a clustering procedure to derive consensus clusters, which are composed of voxels with a high average probability of being assigned to the same cluster across all replications. At the individual level, the clustering was applied to the similarity of regional time series, which was replicated using a circular block bootstrap. We applied consensus clustering to the average individual stability matrix to identify group clusters. The group clustering was replicated via bootstrapping of participants in the group. A consensus clustering was finally applied on the group stability matrix to generate group consensus clusters. We carried out the cluster procedure at a specific resolution, with 50 clusters, as this resolution has been suggested to have higher sensitivity for connectome-wide association analyses in our prior independent work using the same methodology.[30] These functional brain clusters, hereafter coined as regions, were generated using the concatenation of the 3 fMRI runs, thus encompassing all cognitive contexts as well as short rest epochs.

Connectome-wide association analysis

For each task and each pair of distinct regions at resolution 50, we measured the between-regions connectivity using the Fisher transform of the Pearson correlation between the average time series of the clusters. The within-region connectivity was the Fisher transform of the average correlation between time series inside the region. An individual connectome was thus a 50×50 matrix (see Appendix 1, Fig. S2A and B, available at jpn.ca, for an illustration of a parcellation and associated connectome). Such task-specific connectomes were used to detect group differences associated with each task and then to look for commonalities across task on such main group effects (context-independent effect). We further derived the difference in connectomes between any pair of tasks to assess group × task interaction effects (context-dependent effect). In the main model, a group-level general linear model was estimated for each inter-/intraregion connection with intercept, schizophrenia, age and sex values for the task(s) included as covariates in the analysis, the latter 2 being entered in the model as confounding variables (Appendix 1, Fig. S2C). In secondary models, we included either the average scores on the WAIS tests, the positive scores of the PANSS or the negative scores of the PANSS, again with age and sex as confounding variables. We used these models to test for associations between these variables and functional connectivity in patients with schizophrenia only. The parameters of the models were estimated through minimum least-square, and we used a t test with an associated p value derived under a Gaussian, independent and identically distributed assumption on the residuals. With 50 regions, there were $1225 = (50(50–1))/2$ tests for interregion connectivity and 50 tests for intraregion connectivity. In order to correct for multiple comparisons, we relied on a Benjamini–Hochberg false discovery rate (FDR) correction.[31] In the absence of any true effect, the FDR controls for the family-wise error (FWE; i.e., the probabilty to have 1 or more findings across all connections), and we ensured that significant findings at qFDR < 0.05 were found at least minimally for all tasks. However, because we aimed to mitigate type 2 errors (i.e., false negatives) in the context of a conjunction analysis, we report findings at qFDR < 0.01. Besides, we applied the FDR control to each contrast separately. In the presence of true discoveries that are strong and widespread, it has been argued[32] and supported based on simulations[30] that the FDR scales well across contrasts, as it controls for a proportion, even in the presence of positive dependencies across contrasts (as in the repeated-measures scenario explored here).

Results

Participants

We recruited 41 patients with schizophrenia (22 men, 19 women, mean age 32.07 ± 6.95 yr) and 46 healthy controls (21 men, 25 women, mean age 29.85 ± 8.55 yr) for participation in this study, but only 30 in each group were included in the analyses after being matched for motion levels. There were large differences in head movement between patients with schizophrenia and controls (run averaged FD 0.32 ± 0.20 v. 0.19 ± 0.08, $p < 0.001$). The volumes retained after scrubbing remained higher in patients with schizophrenia than in controls (0.18 ± 0.06 v. 0.14 ± 0.03, $p < 0.01$). Matching the participants by keeping 30 patients with schizophrenia with minimal rFD and keeping 30 controls with maximal rFD balanced the groups with respect to rFD (0.15 ± 0.04 v. 0.16 ± 0.03), the number of scrubbed volumes (45 ± 31 v. 41 ± 27) and the number of volumes left after scrubbing (190 ± 31 v. 194 ± 27; (Appendix 1, Fig. S1).

Patients' mean scores on the PANSS were 79.83 ± 20.18 for the total score, 18.66 ± 6.71 on the positive scale, 20.41 ± 6.82 on the negative scale and 40.76 ± 9.82 on the general scale. The age at onset of schizophrenia was 22.33 ± 5.39 years, and the mean disease duration was 9.55 ± 6.71 years. Patients with schizophrenia presented significant cognitive alterations compared with healthy controls on the vocabulary (9.39 ± 3.07 v. 12 ± 3.34), similarities (7.11 ± 2.29 v. 11.47 ± 2.69) and block design (6.16 ± 2.56 v. 10.42 ± 2.29) subtests of the WAIS. All patients were receiving treatment with at least 1 atypical antipsychotic medication (clozapine, olanzapine, quetiapine, risperidone, and/or ziprasidone) at the time of study. The average chlorpromazine equivalent dose was 579.92 ± 349.38.

Functional MRI results

Because a connectome-wide analysis generates a large quantity of results, we used a 3-step procedure to narrow down the exploration of the findings. First, summary statistics (percentage of discoveries) indicated the overall proportion of connections with a significant effect for a given contrast (e.g., patients with schizophrenia v. healthy controls in task 1 only). Second, for the contrasts with significant discoveries, percentage of discovery maps showed which regions had the highest proportion of their connections with a significant effect. Third, we expored the functional connectivity maps for these highly affected brain regions to examine the direction of the effects (i.e., increases v. decreases in connectivity). Results are hereafter reported following this approach.

Percentages of discoveries

Within-group comparisons of task 1 or task 2 (emotional stimuli) against task 3 (visuomotor stimuli) yielded a high number of significant discoveries both in controls (60% and 55% of the brain connections with a significant effect) and patients with schizophrenia (54% and 47%). By contrast, the comparison of tasks 1 and 2, which only slighlty differ in terms of their memory components, revealed a smaller effect in controls (14%) and patients with schizophrenia (10%). In line with the aim of the present research, the similar tasks 1 and 2 are thus characterized by reduced variations in functional connectivity as opposed to the dissimilar task 3, both in controls and patients with schizophrenia. This result underscores that the cognitive context does importantly modulate functional connectivity patterns, and more so for dissimilar tasks. It is thus not garanteed that putative differences in connectivity between the 2 populations would remain unchanged in these distinct connectivity contexts. In patients with schizophrenia, no significant association was found with either the severity of their cognitive deficits on the WAIS tests or the severity of their clinical symptoms on the positive and negative subscales of the PANSS.

Between-group comparisons showed that each experimental task was significantly associated with altered functional connectivity in patients with schizophrenia relative to controls. In total, 27%, 14% and 6% of the connections showed a significant effect of schizophrenia in tasks 1, 2 and 3, respectively. By contrast, comparisons between tasks did not yield any significant interaction effect with schizophrenia on functional connectivity. The former result does not indicate a context-independent effect at this stage, as there is no guarantee that the same brain networks were affected in a similar fashion across tasks. However, the latter result already indicates that there is no evidence of a significant context-dependent functional dysconnectivity in patients with schizophrenia.

Spatial distribution of significant discoveries

Discovery percentage maps revealed which brain regions were associated with the largest amount of discoveries, and more specifically the proportion of significant connections for any given region. Maps are shown in Figure 1 for all types of within- and between-group contrasts along with the functional brain parcellation seen at resolution 50. Within-group maps showed that many regions changed their connectivity with more than 50% of the other regions when comparing the emotional tasks 1 and 2 with the visuomotor task 3, both in patients with schizophrenia and controls (Fig. 1A and B). Such regions covered the medial prefrontal cortex, precuneus, medial temporal lobe, and visual and motor areas. Of note, the same regions had maximal between-task effects in both patients with schizophrenia and healthy controls.

Between-group comparisons looking at each task separately showed that some regions had more than 20% of their connections affected by schizophrenia (Fig. 1C). As previously indicated, no significant group × task interaction effect was observed. In order to select a series of regions of interest for further characterization, we computed a minimum discovery percentage map, which showed the minimal values of discoveries across the 3 tasks (Fig. 1D). Seven brain regions that showed the highest effects on this map were then selected for further exploration: the medial prefrontal cortex, anterior and posterior cingulate, temporal lobe, lobule IX of the cerebellum and premotor cortex.

Consistent decrease in functional connectivity across tasks

The discovery percentage maps did not characterize which specific connections were identified as significantly altered in patients with schizophrenia for each region, nor the direction of the effect (i.e., an increase v. a decrease in connectivity). Figure 2 reveals significant changes in connectivity for the 7 regions identified above that are commonly observed between patients with schizophrenia and controls for all 3 tasks. These significant context-independent effects took the form of a decrease in connectivity. A key brain region to be affected was the anterior cingulate, which showed decreased connectivity with the prefrontal cortex, temporal lobe and putamen. Other context-independent effects were also detected between the cerebellar lobule IX and temporal lobe, putamen and premotor cortex, or between the premotor cortex and temporal lobe and putamen.

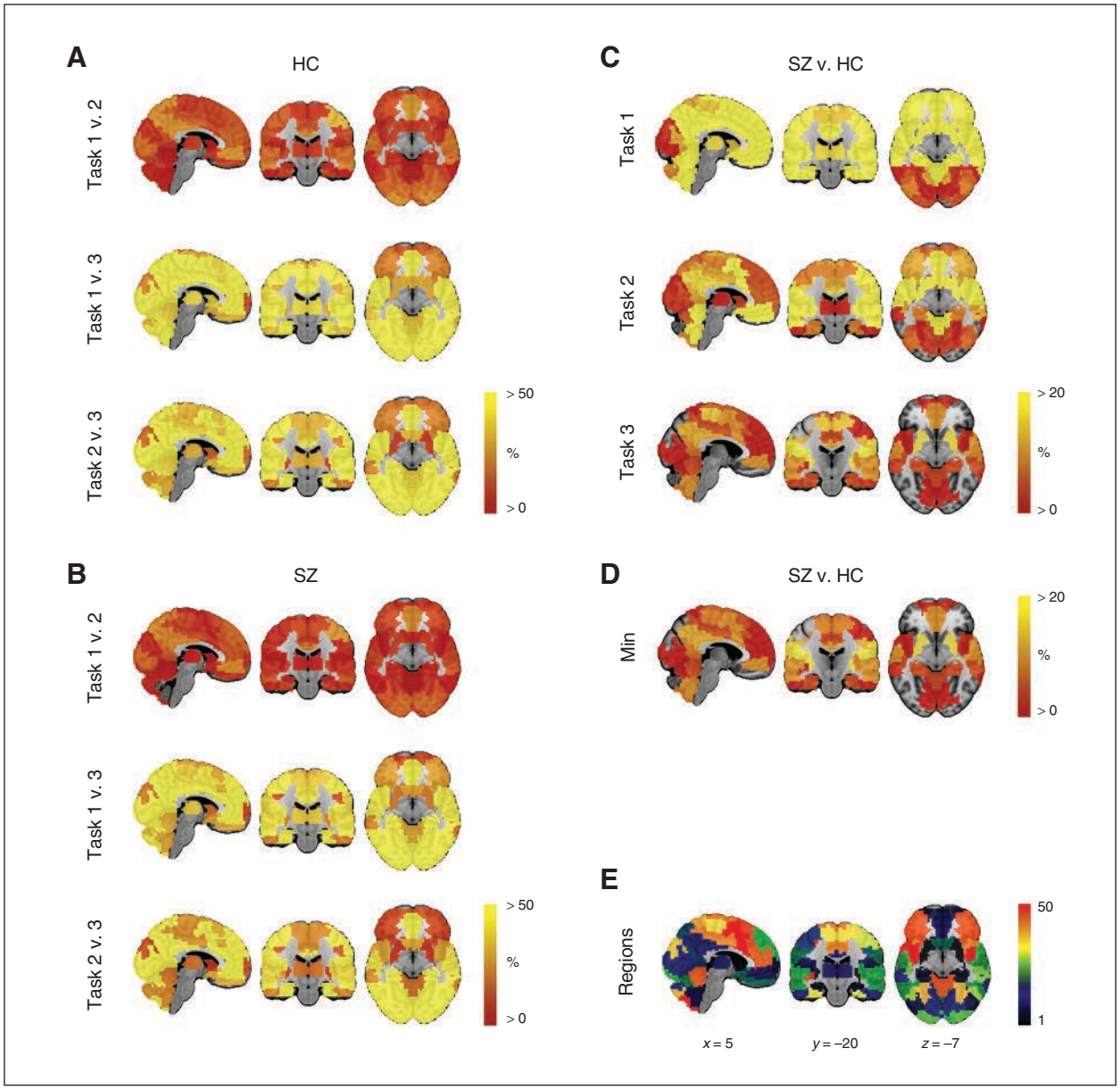

Fig. 1: Within-group discovery maps show at resolution 50 the percentages of connections for each region that are modulated by the type of task, separately for (**A**) healthy controls and (**B**) patients with schizophrenia. (**C**) Between-group discovery maps show the percentages of connections with a significant schizophrenia effect for single task contrasts. No group × task interaction effects were found to be significant for any pairwise comparison between tasks. (**D**) The minimum map shows the minimal discovery percentages observed across tasks 1, 2 and 3 for the between-group contrasts. (**E**) The regions map shows the functional brain parcellation at resolution 50. Montreal Neurological Institute coordinates are given for representative slices superimposed onto the MNI152 nonlinear template. HC = healthy controls, SZ = schizophrenia. Task 1 = emotional processing with incidental encoding, task 2 = emotional processing with memory retrieval, task 3 = visuomotor processing.

We further explored the dysconnectivity patterns observed across tasks in patients with schizophrenia by looking at unthresholded connectivity maps (Fig. 3A). Pairwise comparisons of a schizophrenia effect between tasks revealed a high degree of similarity in terms of Pearson correlations between connectivity maps. For the 7 selected regions, the average correlation between tasks was 0.78 ± 0.14. However, the comparisons between dissimilar tasks (tasks 1 or 2 with task 3: 0.77 ± 0.17 and 0.74 ± 0.14) appeared less highly correlated than the comparisons between the similar tasks 1 and 2 (0.86 ± 0.07; Fig. 3B).The comparisons between tasks 1 or 2 with task 3 (0.67 ± 0.21 and 0.66 ± 0.19) were also less highly correlated than the comparisons between tasks 1 and 2 (0.79 ± 0.13) when including all 50 regions (i.e., including even those that showed no significant effects; Fig. 3C). The fact that similar tasks are associated with higher similar patterns of dysconnectivity may be some indication that discrete context-dependent effects remained undetected in our main analysis. Yet, these findings highlight the high consistency of the change in connectivity in patients with schizophrenia, even for tasks that are distinct from one another.

Discussion

Our overall findings speak for the context-independence of functional dysconnectivity in patients with schizophrenia, with the patterns of abnormal connectivity in these patients persisting over the reorganization of brain dynamics that

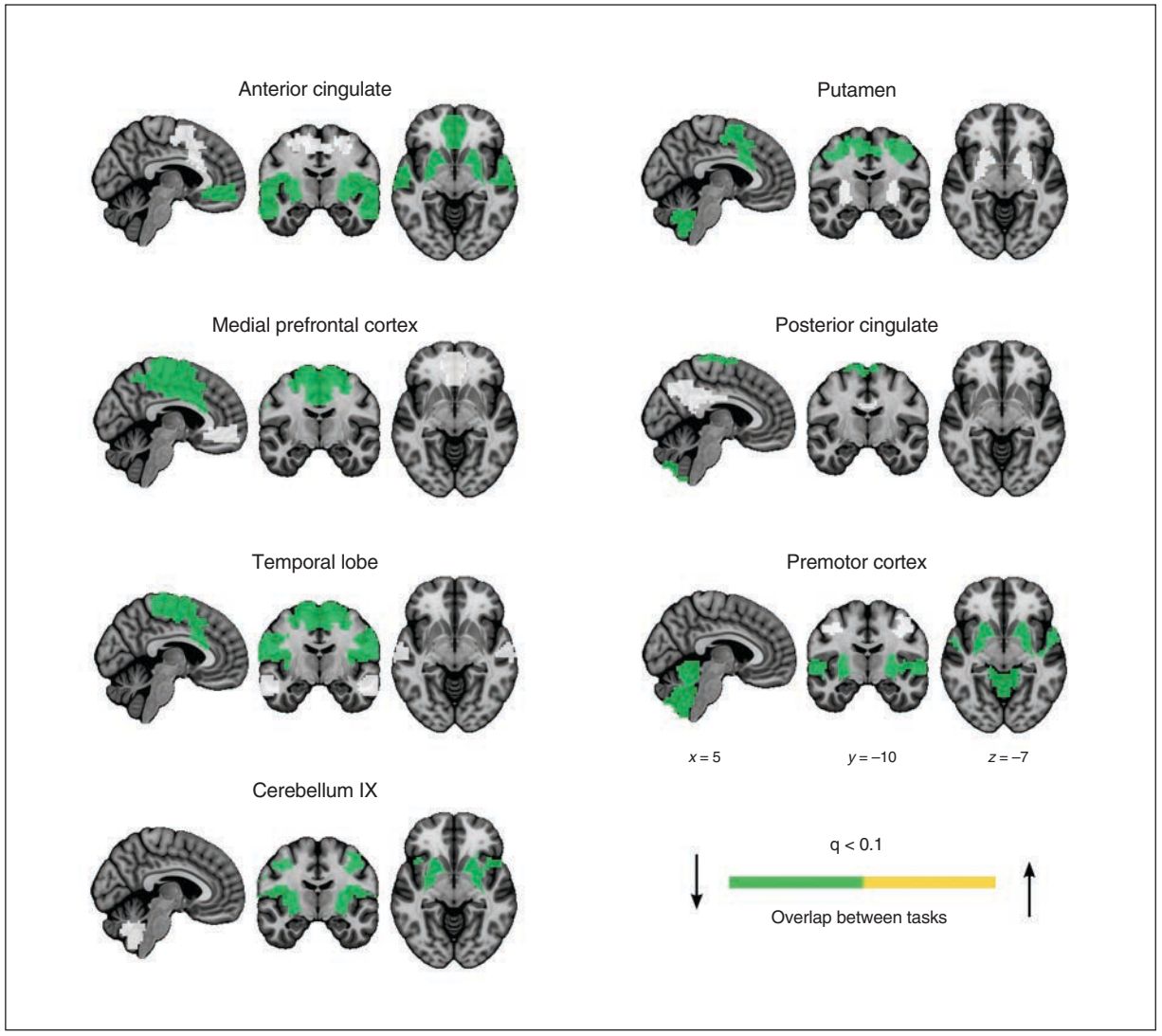

Fig. 2: Significant context-independent decreased functional connectivity in patients with schizophrenia versus healthy controls. Seven seed brain regions, shown in white, were selected because they showed significant changes in connectivity between patients with schizophrenia and healthy controls in all 3 tasks. For each seed region, the overlap in functional connectivity alterations across tasks is shown at a false-discovery rate < 0.1. These context-independent effects are observed only as decreases. Montreal Neurological Institute coordinates are given for representative axial slices superimposed onto the MNI152 nonlinear template.

otherwise occurs in response to specific environmental stimulations. The task paradigms[18,20,21] either differed from one another in major ways (emotional processing v. visuomotor task) or were distinguishable based only on minor characteristics (to promote incidental encoding v. retrieval processes in the context of emotional processing). Our objective was to

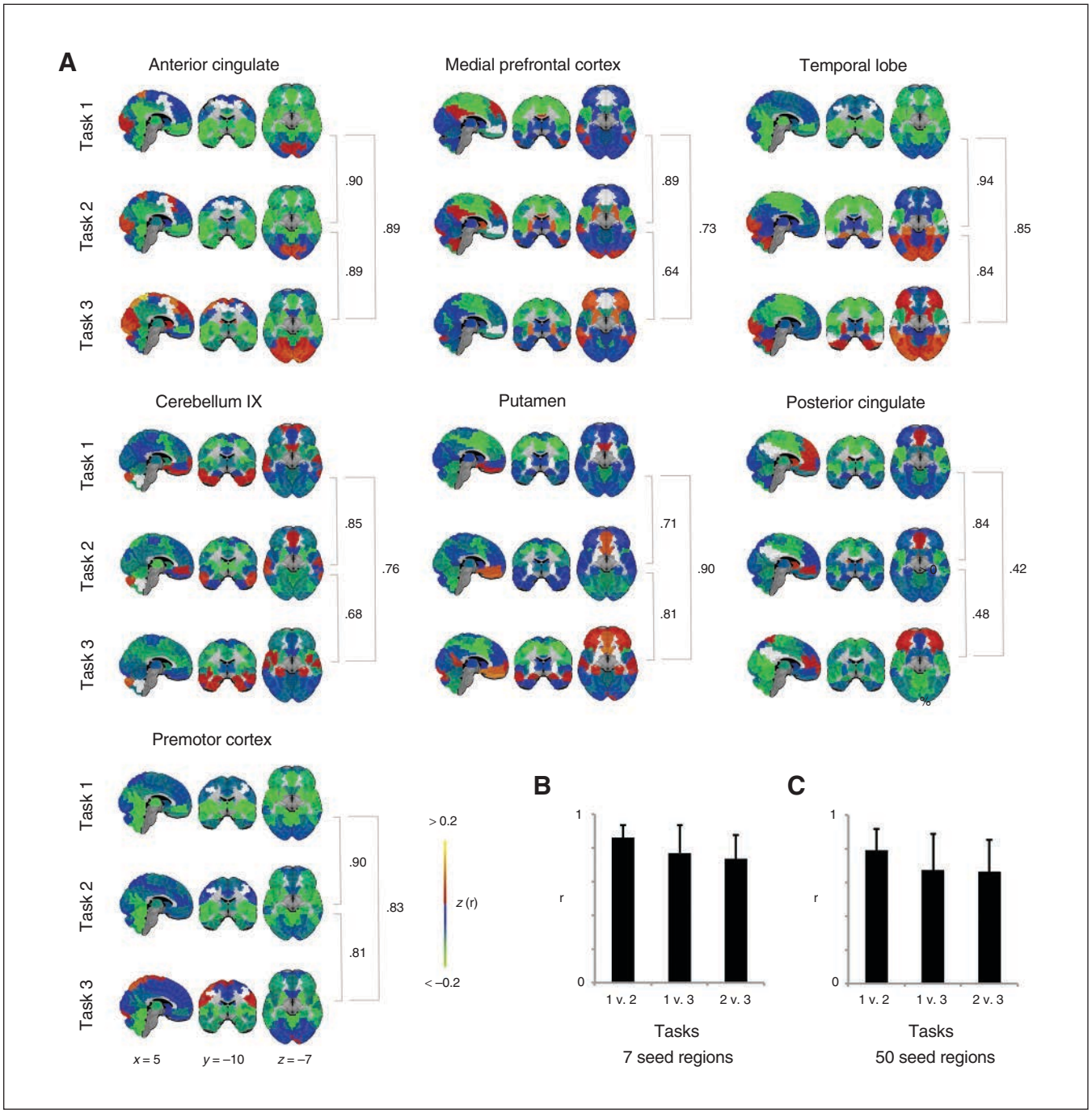

Fig. 3: Unthresholded alterations in functional connectivity in patients with schizophrenia versus healthy controls. Seven seed brain regions were selected because they showed significant changes in connectivity between patients with schizophrenia and healthy controls in all 3 tasks. (**A**) For each seed region, maps show the changes in functional connectivity (z(*r*) = Fisher z-transformed Pearson correlation *r*) between patients with schizophrenia and healthy controls, independently for each task. Between-task pairwise correlations of functional connectivity maps are given (Pearson correlation coefficients). Higher degree of similarity in functional connectivity between tasks 1 and 2 than between either of them and task 3 for (**B**) the 7 selected regions and (**C**) for the 50 regions included in the analysis. Montreal Neurological Institue coordinates are given for representative slices superimposed onto the MNI152 nonlinear template. Task 1 = emotional processing with incidental encoding, task 2 = emotional processing with memory retrieval, task 3 = visuomotor processing.

determine whether small versus large degrees of cognitive difference between tasks would lead to putative context-dependent effects of different amplitudes. Rather, there were large commonalities in the observed functional connectivity deficits across paradigms, irrespective of the characteristics of the tasks. One study reported task-specific alterations in connectivity between tasks of different cognitive domains, namely a verb-generation task and a working memory n-back task.[16] However, the significance of this work is hampered by several methodological confounds, such as the very small sample sizes. Three other studies have evaluated whether alterations in connectivity were further modulated by task complexity in the context of a single experimental paradigm, either in terms of different levels of memory load in a working memory n-back task (0-back, 1-back, 2-back)[13,15] or varying levels of sensory load in a sensory-processing task (from auditory sensory gating to multisensory processing).[14] The 2 former studies reported only stable abnormalities across task levels, whereas the latter found that task complexity also modulated altered connectivity. These studies and ours all agree in highlighting a largely consistent profile of dysconnectivity across distinct tasks or their levels of complexity. However, the discrepency regarding the presence of more circumscribed context-dependent effects needs to be resolved. First, the nonevidence of such effects may be explained by low statistical power. Second, future studies should carefully compare multiple other paradigms associated or not with the pathophysiology of schizophrenia.

Previous studies on schizophrenia have in some instances reported the superimposition of context-specific patterns of dysconnectivity when comparing rest and task states.[13,14,16,33] However, the interpretation of resting-state dysconnectivity in patients with schizophrenia may be biased by differences in thoughts and mind wandering during rest in patients with this mental illness.[12] We focused the present research on functional brain connectivity during task performance, as it offers a better control over the cognitive state of participants than rest. Yet, there is evidence that task-related versus task-unrelated effects can be disentangled within a single experimental paradigm.[34] These findings raise the question of the extent to which the spontaneous fluctuations seen at rest[6] may contribute to the dysconnectivity patterns observed during task performance. However, similarly pronounced differences in connectivity were detected between cognitive contexts both in patients with schizophrenia and healthy controls. Hence, irrespective of the common impact of intrinsic fluctuations across tasks, there is no guarantee that functional dysconnectivity in patients with schizophrenia would remain stable in these distinct connectivity contexts. The hidden contribution of task-unrelated, intrinsic activity should not diminish the ability to detect putative differences in task-related connectivity between tasks if these were present. In order to circumvent more uniquevocably the confound of intrinsic activity, a solution lies in the characterization of task-evoked connectivity networks[35] (i.e., brain networks defined by regions that present similar task-evoked responses). The nature of the association between connectivity versus activation deficits in this mental disorder is of great interest.[16] If functional brain dysconnectivity is context-independent, can it be inferred that it is also independent of task-induced brain activation? Future work should elucidate to what extent patterns of hypo- and hyperactivation in patients with schizophrenia, in the prefrontal cortex and beyond,[1] relate to the topography of abnormal functional connectivity in people with this mental illness.

Dysconnectivity patterns predominantly, yet not uniquely, took the form of a decrease in functional connectivity and were most strongly found in clinically relevant brain regions, in good agreement with previous studies.[3,4] The brain regions associated with dysconnectivity in this work are indeed components of brain networks that account for the psychiatric and cognitive symptoms of schizophrenia. Aberrant functional connectivity of the medial prefrontal cortex, together with the posterior cingulate cortex and other regions of the default mode network, may account for deficits in reality monitoring and self-referential processing.[36,37] Abnormal functional connectivity in the anterior cingulate cortex, which is part of the salience network, may account for impairments in cognitive control and detecting stimuli salience.[38,39] Functional dysconnectivity is known to be widespread in patients with schizophrenia, and our findings accordingly revealed alterations in the premotor cortex, basal ganglia[40,41] and cerebellum.[42,43] Deficient cerebellar function, for instance, has been associated with high-order cognitive deficits in patients with schizophrenia, as proposed in the "cognitive dysmetria" model of schizophrenia.[44,45] These interpretations, however, mainly consist of an exercise of reverse inference, as no direct association was found between functional dysconnectivity and the severity of either clinical symptoms or cognitive deficits in patients with schizophrenia.

Limitations

The rationale for the present study was that the genuine description of context-independent and context-dependent dysconnectivity in patients with schizophrenia can be obtained only through the direct comparison of multiple experimental paradigms.[5] Our conclusions are limited in this respect as we compared only 3 tasks,[18,20,21] which assessed 2 main cognitive domains: emotional and visuomotor processing. The study of abormal connectivity across distinct paradigms should be extended to other cognitive domains known to be affected in patients with schizophrenia (e.g., working memory[13]). The absence of a significant context-dependent effect in the present study might also be accounted for by insufficient statistical power. The benefits of investigating the whole functional brain connectome comes at the cost of a large increase in multiple comparisons needing correction. It is reasonnable to predict that a larger amount of significant effects would be detected with a larger sample, either as increased context-independent connectivity or as context-dependent changes in connectivity. For instance, the fact that there were trends toward hyperconnectivity between the medial prefrontal cortex and posterior cingulate cortex and putamen in all 3 tasks suggests this possibility. Finally, we cannot reject the possibility that treatment with atypical antipsychotic medication may have

impacted patterns of functional brain connectivity in patients with schizophrenia. Nonetheless, it is noteworthy that the medication type and dose had remained stable a month preceeding and throughout the research protocol.

Conclusion

These limitations might contribute to the absence of a significant context-dependent effect in the observed results. While we cannot exclude the existence of such circumscribed context-dependent effects, the present findings still provide compelling evidence that a large portion of altered functional brain connectivity in persons with schizophrenia is consistent across the 3 cognitive contexts that were studied. The study with task-based fMRI of functional brain connectivity dysfunction in patients with schizophrenia may thus benefit from pooling data from multiple experiments in order to identify reliable connectivity biomarkers of schizophrrenia.

Acknowledgments: This work was supported by grants from the Canadian Institutes of Health Research, Gender and Health Institute (grant number 200603MOP-158161-GSH-CFCA-130656 to A.M.), from the Natural Sciences and Engineering Research Council of Canada (grant number RN000028 to P.B.) and from investigator-initiated trials to E.S. (clinical trial number: NCT 00290121).

Affiliations: From the Department of Psychiatry, Université de Montréal, Montreal, Que., Canada (Orban); the Department of Psychology, Faculty of Medicine, University of Namur, Belgium (Desseilles); the Department of Psychology, Bishop's University, Sherbrooke, Que., Canada (Mendrek); the Department of Psychiatry, Université de Montréal, Montreal, Que., Canada (Bourque); the Department of Computer Sciences and Operational Research, Université de Montréal, Montreal, Que., Canada (Bellec); and the Department of Psychiatry, Université de Montréal, Montreal, Que., Canada (Stip).

Competing interests: P. Bellec declares being a member of an advisory board for Roche and is currently a part-time consultant for two contract research organizations, Biospective Inc. and NeuroRX research. E. Stip is on the scientific advisory boards for Janssen, Otsuka, Lundbeck, Sunovion and BMS. He has also received grants or research support from Roche. No other competing interests declared.

Contributors: P. Orban, A. Mendrek and E. Stip designed the study. A. Mendrek and J. Bourque acquired the data, which P. Orban, J. Bourque and P. Bellec analyzed. P. Orban, M. Desseilles, P. Bellec and E. Stip wrote the article, which all authors reviewed and approved for publication.

References

1. Glahn DC, Ragland JD, Abramoff A, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp* 2005;25:60-9.
2. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci* 1995;3:89-97.
3. Pettersson-Yeo W, Allen P, Benetti S, et al. Dysconnectivity in schizophrenia: Where are we now? *Neurosci Biobehav Rev* 2011; 35:1110-24.
4. Jiang T, Zhou Y, Liu B, et al. Brainnetome-wide association studies in schizophrenia: the advances and future. *Neurosci Biobehav Rev* 2013;37:2818-35.
5. Fornito A, Zalesky A, Pantelis C, et al. Schizophrenia, neuroimaging and connectomics. *Neuroimage* 2012;62:2296-314.
6. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 2007;8:700-11.
7. Liang M, Zhou Y, Jiang T, et al. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. *Neuroreport* 2006;17:209-13.
8. Woodward ND, Rogers B, Heckers S. Functional resting-state networks are differentially affected in schizophrenia. *Schizophr Res* 2011;130:86-93.
9. Baker JT, Holmes AJ, Masters GA, et al. Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry* 2014;71:109-18.
10. Meda SA, Gill A, Stevens MC, et al. Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. *Biol Psychiatry* 2012;71:881-9.
11. Cheng W, Palaniyappan L, Li M, et al. Voxel-based, brain-wide association study of aberrant functional connectivity in schizophrenia implicates thalamocortical circuitry. *Npj Schizophrenia* 2015;1:SP-EP.
12. Shin D-J, Lee TY, Jung WH, et al. Away from home: the brain of the wandering mind as a model for schizophrenia. *Schizophr Res* 2015;165:83-9.
13. Repovš G, Barch DM. Working memory related brain network connectivity in individuals with schizophrenia and their siblings. *Front Hum Neurosci* 2012;6:137.
14. Çetin MS, Christensen F, Abbott CC, et al. Thalamus and posterior temporal lobe show greater inter-network connectivity at rest and across sensory paradigms in schizophrenia. *Neuroimage* 2014; 97:117-26.
15. Brandt CL, Kaufmann T, Agartz I, et al. Cognitive effort and schizophrenia modulate large-scale functional brain connectivity. *Schizophr Bull* 2015;41:1360-9.
16. Salomon R, Bleich-Cohen M, Hahamy-Dubossarsky A, et al. Global functional connectivity deficits in schizophrenia depend on behavioral state. *J Neurosci* 2011;31:12972-81.
17. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
18. Mendrek A, Bourque J, Dubé A, et al. Emotion processing in women with schizophrenia is menstrual cycle phase and affective valence dependent: an FMRI study. *ISRN Psychiatry* 2012;doi: 10.5402/2012/656274.
19. Lang PJ, Öhman A, Vaitl D. The International Affective Picture System (photographic slides). Center for Research in Psychophysiology, University of Florida. Gainesville, Florida; 1988.
20. Lakis N, Jiménez JA, Mancini-Marïe A, et al. Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal. *Psychiatry Res* 2011;194:245-56.
21. Jiménez JA, Mancini-Marïe A, Lakis N, et al. Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia. *Schizophr Res* 2010;122:53-62.
22. Shepard RN, Metzler J. Mental rotation of three-dimensional objects. *Science* 1971;171:701-3.
23. Bellec P, Lavoie-Courchesne S, Dickinson P, et al. The pipeline system for Octave and Matlab (PSOM): a lightweight scripting framework and execution engine for scientific workflows. *Front Neuroinform* 2012;6:7.
24. Collins DL, Evans AC. Animal: validation and applications of nonlinear registration-based segmentation. *Int J Pattern Recognit Artif Intell* 1997;11:1271-94.
25. Fonov V, Evans AC, Botteron K, et al. Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage* 2011;54:313-27.
26. Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *IEEE Trans Med Imaging* 2002;21:1280-91.
27. Giove F, Gili T, Iacovella V, et al. Images-based suppression of unwanted global signals in resting-state functional connectivity studies. *Magn Reson Imaging* 2009;27:1058-64.
28. Power JD, Barnes KA, Snyder AZ, et al. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012;59:2142-54.

29. Bellec P, Rosa-Neto P, Lyttelton OC, et al. Multi-level bootstrap analysis of stable clusters in resting-state fMRI. *Neuroimage* 2010; 51:1126-39.
30. Bellec P, Benhajali Y, Carbonell F, et al. Impact of the resolution of brain parcels on connectome-wide association studies in fMRI. *Neuroimage* 2015;123:212-28.
31. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57:289-300.
32. Efron B. Simultaneous inference: When should hypothesis testing problems be combined? *Ann Appl Stat* 2008;2:197-223.
33. Arbabshirani MR, Calhoun VD. Functional network connectivity during rest and task: comparison of healthy controls and schizophrenic patients. *Conf Proc IEEE Eng Med Biol Soc* 2011;2011:4418–21.
34. Fornito A, Yoon J, Zalesky A, et al. General and specific functional connectivity disturbances in first-episode schizophrenia during cognitive control performance. *Biol Psychiatry* 2011;70:64-72.
35. Orban P, Doyon J, Petrides M, et al. The richness of task-evoked hemodynamic responses defines a pseudohierarchy of functionally meaningful brain networks. *Cereb Cortex* 2015;25:2658-69.
36. Holt DJ, Cassidy BS, Andrews-Hanna JR, et al. An anterior-to-posterior shift in midline cortical activity in schizophrenia during self-reflection. *Biol Psychiatry* 2011;69:415-23.
37. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol* 2012;8:49-76.
38. White TP, Joseph V, Francis ST, et al. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophr Res* 2010;123:105-15.
39. Palaniyappan L, Simmonite M, White TP, et al. Neural primacy of the salience processing system in schizophrenia. *Neuron* 2013;79:814-28.
40. Woodward ND, Karbasforoushan H, Heckers S. Thalamocortical dysconnectivity in schizophrenia. *Am J Psychiatry* 2012;169:1092-9.
41. Anticevic A, Cole MW, Repovs G, et al. Characterizing thalamocortical disturbances in schizophrenia and bipolar illness. *Cereb Cortex* 2014;24:3116-30.
42. Collin G, Hulshoff Pol HE, Haijma SV, et al. Impaired cerebellar functional connectivity in schizophrenia patients and their healthy siblings. *Front Psychiatry* 2011;2:73.
43. Chen Y-L, Tu P-C, Lee Y-C, et al. Resting-state fMRI mapping of cerebellar functional dysconnections involving multiple large-scale networks in patients with schizophrenia. *Schizophr Res* 2013;149:26-34.
44. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. *Biol Psychiatry* 2008;64:81-8.
45. Lungu O, Barakat M, Laventure S, et al. The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature. *Schizophr Bull* 2013;39:797-806.