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Resting-State Brain Activity in Schizophrenia and Major Depression: A Quantitative Meta-Analysis

Simone Kühn [*,1,2] **and Jürgen Gallinat**[2]

[1]Department of Experimental Psychology, Ghent Institute for Functional and Metabolic Imaging, Faculty of Psychology and Educational Sciences, Ghent University, Henri Dunantlaan 2, 9000 Gent, Belgium; [2]Clinic for Psychiatry and Psychotherapy, Charité University Medicine, St Hedwig-Krankenhaus, Berlin, Germany

*To whom correspondence should be addressed; tel: 0032-9-264-603; e-mail: simone.kuhn@ugent.be

Intrinsic activity of the brain during resting-state is not random and is currently discussed as a neural reflection of self-referential processing. Self-reference is typically reduced in schizophrenia as a disorder of the self while extensive self-attribution of, eg, negative thoughts is characteristic for major depression. However, a quantitative meta-analysis targeting the resting-state brain activity in both disorders is lacking. Here, we predict primarily abnormal resting-state activity in brain regions related to self-referential processing. By means of activation likelihood estimation (ALE) on functional magnetic resonance imaging and positron emission tomography studies, we investigated concurrence of hyperactivation and hypoactivation in resting-state measurements of schizophrenic and depressed patients compared with healthy controls. We found hypoactivation in ventromedial prefrontal cortex (vmPFC), left hippocampus, posterior cingulate cortex, lower precueus and the precuneus, and hyperactivation in bilateral lingual gyrus of schizophrenic patients. In major depression, we found hyperactivation in vmPFC, left ventral striatum, and left thalamus and hypoactivation in left postcentral gyrus, left fusiform gyrus, and left insula. An overall ALE analysis confirmed the proximity of hypoactivation in schizophrenia and hyperactivation in major depression in the vmPFC.The opposing resting-state activity in vmPFC for the 2 disorders is in line with the different expression of dysfunctional self-reference as core characteristics of schizophrenia and major depression. The vmPFC has previously been identified as a crucial area for self-referential processing and may represent a target to increase the diagnostic validity of resting-state activity for disorders with dysfunctions of the self.

Key words: resting-state/schizophrenia/major depression/meta-analysis/anatomical estimation likelihood

Introduction

When we engage in goal-directed behavior (of nonself-referential nature), a set of brain regions decreases their activity, whereas the same set of brain regions increase their activity when we are at rest or engage in self-referential tasks. The consistency with which this set of brain regions decreases its activity during tasks and increases it during resting has led to the notion of a so-called "default mode" network of the brain.[1] This network includes superior and inferior anterior medial frontal regions, lower precuneus, and posterior lateral parietal cortices. In order to measure the intrinsic activity of this network, subjects are typically asked to rest quietly with their eyes closed for several minutes while functional magnetic resonance imaging (fMRI) or positron emissions tomography (PET) is employed.

Within task-related studies, these default mode brain regions have been shown to be active, particularly during perspective taking of intentions, beliefs, and desires of others as well as remembering the past and planning the future, moral judgments, and perceiving pictures of oneself.[2] These functions have been subsumed under the term of self-referential processes[3,4] which has been shown to be altered in schizophrenia[5] as well as in major depression.[6]

A growing number of studies used neuroimaging techniques to study resting state dysfunctions in mental disorders. Atypical patterns of brain activity during resting-state are apparent in a number of psychiatric disorders and are have been characterized by dysfunction of introspective mental processes. Qualitative meta-analyses (eg, ref. [7]) have summarized the findings of resting-state studies, but a quantitative assessment of the default mode network activity in schizophrenia and major depression is lacking. Previous review articles pointed at hypoactivity in medial frontal cortex in schizophrenic patients[8] and hyperactivity in depressed patients.[9,10] The aim of the present

Table 1. List of Included Studies on Resting-State in Schizophrenia

Study	Modality/ Method of Analysis	Resting-State	*N* (SCZ/HC)	Foci	Reported Contrasts	Patient Details	Drug Status
Andreasen et al[62]	PET	No information	17/17	13 12	HC > SCZ SCZ > HC	First-episode SCZ	Unmedicated
Camchong et a[63]	fMRI/ICA	6 min, eyes closed	29/29	1	HC > SCZ	Chronic SCZ	Medicated
Hoptman et al[19]	fMRI/ALFF	6 min, eyes closed	29/26	15 8	HC > SCZ SCZ > HC	Chronic SCZ	Medicated
Huang et al[20]	fMRI/ALFF	6.7 min	66/66	1 2	HC > SCZ SCZ > HC	First-episode SCZ	Unmedicated
Liu et al[21]	fMRI/ReHo	6 min, eyes closed	18/18	28	HC > SCZ	First-episode SCZ	> 6-h medication washout
Malaspina et al[22]	SPECT	20 min, eyes open	16/9	11 3	HC > SCZ SCZ > HC	Chronic SCZ	Mixed
Mannell et al[23]	fMRI/ICA	Several blocks of 3-min rest in-between task, eyes open	16/16	7	HC > SCZ	Chronic SCZ	Medicated
Öngür et al[24]	fMRI/ICA	10 min, eyes open	14/15	1 9	HC > SCZ SCZ > HC	Chronic SCZ with acute psychosis	Medicated
Park et al[25]	FDG PET	15 min, eyes closed	29/21	6 8	HC > SCZ SCZ > HC	Chronic SCZ	Medicated
Salvador et al[26]	fMRI/whole brain but subdivided into ROIs	8.9 min, eyes open	40/40	1	SCZ > HC	Chronic SCZ	Medicated
Scheef et al[27]	ASL	6 min, eyes closed	11/25	8 6	HC > SCZ SCZ > HC	8 first-episode SCZ, 3 chronic SCZ	Unmedicated

Note: SCZ, schizophrenia; HC, healthy controls; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; ASL, arterial spin labeling; SPECT, single photon emission computed tomography; ICA, independent component analysis; ALFF, amplitude of low frequency fluctuations; ReHo, regional homogeneity; ROIs, regions of interest.

study was to perform a quantitative meta-analysis to assess the correspondence of resting-state alterations across multiple neuroimaging studies using the activation likelihood estimation (ALE) approach[11,12] with a particular focus on the medial prefrontal cortex due to its crucial role in self-referential processing. Dysfunctions of self-reference are prototypical for major depression and schizophrenia but have distinct manifestations. Major depression is characterized by recurrent series of negative thoughts, which are typically and extensively attributed to the self.[13] In schizophrenia, self-attribution is reduced and has been viewed as a characteristic symptom of a disease, which is determined by a fundamental dysfunction of the self.[14]

Methods

Selection of Studies

Studies were selected using a systematic search process. Peer-reviewed articles published in English until February 2011 were selected from the search results of 2 separate databases (Pubmed, ISI Web of Knowledge). Keyword searches were conducted using the following search terms: (1) "neuroimaging" <OR> "fMRI" <OR> "PET," (2) "resting-state" <OR> "default network" and (3) the terms "schizophrenia" <OR> "depression" <OR> "mood disorder." From the resulting articles, we selected those that compared resting-state in patients with resting-state of healthy controls on a whole-brain level. The reference lists of the selected articles were searched for additional studies that fit these criteria. We included all studies of which we were able to obtain Montreal Neurological Institute (MNI) or Talairach[15] coordinates of the whole-brain contrast comparing patients and control subjects. We included coordinates resulting from analyses computed across the whole brain and not restricted using partial coverage, regions of interest (ROIs), or small volume correction. Furthermore, we excluded studies using seed-voxel-based analysis procedures because their results are highly dependent on the positioning of this seed voxel. Of studies containing multiple independent patient samples, the appropriate coordinates were included as separate studies.[16] In accordance with many previous ALE meta-analyses, we included coordinates resulting from fMRI as well as from PET data.[17,18] We included data from fMRI and PET studies and different data analysis techniques despite the fact that they have a different physiological basis and different theoretical assumptions because both methods have

Table 2. List of Included Studies on Resting-State in Major Depression

Study	Modality/Method of Analysis	Resting-State	*N* (MD/HC)	Foci	Reported Contrasts	Patient Details	Drug Status
Brody et al[28]	FDG PET	40 min	13/24	1 1	HC > MD MD > HC		> 4-wk medication washout
Drevets et al[29]	PET[10]O	40 s, eyes closed	13/33	5 8	HC > MD MD > HC	MD with first-degree relatives with history of MD	> 3-wk medication washout
Duhameau et al[30]	ASL	~4 min	6/6	9	MD > HC	Treatment-resistant MD	Medicated
Grecius et al[31]	fMRI/ICA	5 min, eyes closed	28/20	4	MD > HC	MD with and without psychosis	Medicated
Kennedy et al[32]	FDG PET	40 min, eyes open	13/24	1 1	HC > MD MD > HC		> 4-wk medication washout
Liu et al[33]	fMRI/ReHo	3.7 min, eyes closed	15/15	7 4	HC > MD MD > HC	First-episode MD	Unmedicated
Saxena et al[34]	FDG PET	40 min, eyes open	27/17	2	MD > HC		Unmedicated
Veer et al[35]	fMRI/ICA	7.7 min, eyes closed	19/19	4 1	HC > MD MD > HC	first-episode MD	Unmedicated
Videbech et al[36]	PET[15]O	16 min	42/48	2	MD > HC	MD with and without psychosis	Medicated
Wu et al[16]	fMRI/ReHo	6.7 min, eyes closed	22/22	1 2	HC > MD MD > HC	First-episode, treatment responding MD	Medicated
Wu et al[16]	fMRI/ReHo	6.7 min, eyes closed	22/22	5 5	HC > MD MD > HC	First-episode, treatment refractory MD	Medicated
Yao et al[37]	fMRI/ReHo	6.7 min, eyes closed	22/22	7	HC > MD	Single episode and recurrent MD	> 2-wk medication washout

Note: MD = major depression. Abbreviations are explained in the first footnote of table 1.

been used to identify differences between the neural intrinsic functioning of the brain in patients compared with controls. The rationale was to provide an all-embracing overview over the attempts to identify resting-state abnormalities in schizophrenia and major depression. For the meta-analysis on resting-state alterations in schizophrenia, 11 studies reporting 140 foci of altogether 567 participants (table 1); for the second meta-analysis on major depression 11, studies with 70 foci of altogether 470 participants (table 2) were included. Each of the 2 meta-analyses explores the 2 directions of abnormality separately: resting-state decreases and increases in patients compared with healthy controls.

In order to investigate the similarity of the medial prefrontal location of abnormalities in schizophrenia and major depression, we performed a joint ALE meta-analysis comprising coordinates from both contrast schizophrenic patients < healthy controls and depressed patients > healthy controls.

Creation of ALE Maps

The ALE method provides a voxel-based meta-analytic technique for neuroimaging data.[11] By means of the software Brainmap GingerALE 2.0 (http://brainmap.org/ale/), statistically significant concordance in the pattern of brain activity among several independent experiments was computed. ALE maps display regions in the brain that comprise statistically significant peak activation locations from multiple studies. We converted coordinates reported in Talairach to MNI space using Lancaster et al[40] (tal2icbm). In the approach taken by ALE, localization probability distributions for all foci are modeled as the center of 3D Gaussian functions. The Gaussian distributions are summed across the experiments to generate a map of interstudy consistencies that estimates the likelihood of activation for each voxel, the ALE statistic, as determined by the entire set of studies. The false discovery rate method was employed to correct for multiple comparisons at a significance threshold of $P < .05$ and a cluster threshold of 100.

Results

Schizophrenic patients showed decreases in resting-state compared with healthy controls in ventromedial

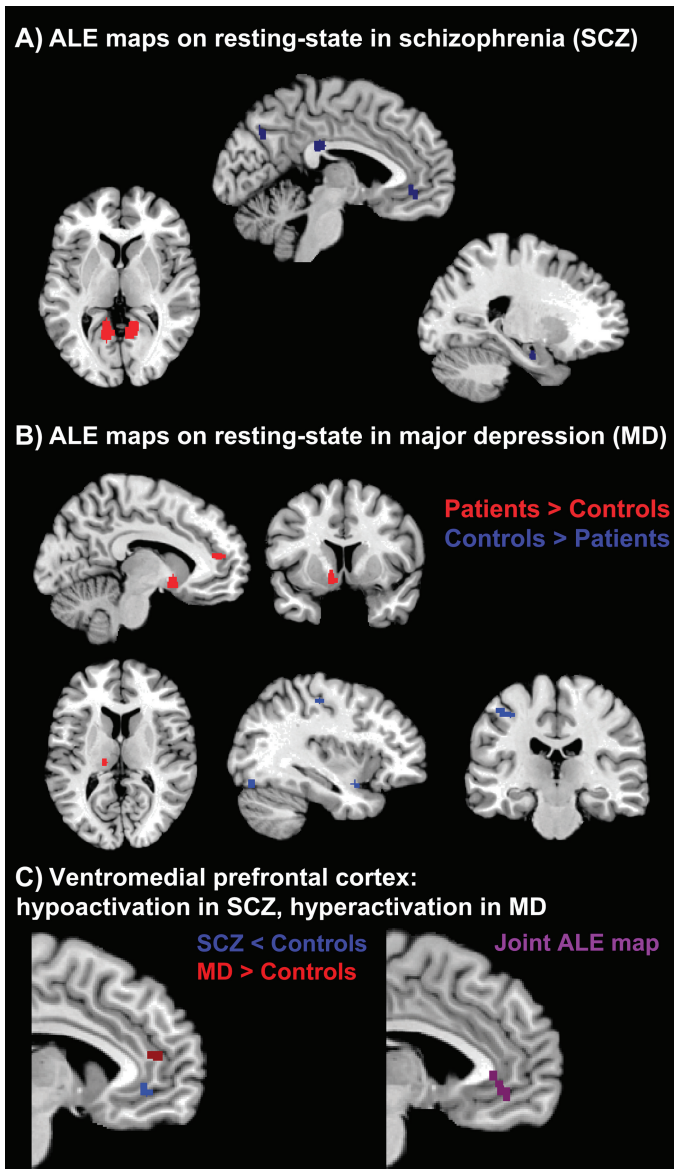

Fig. 1. Activation likelihood estimation (ALE) meta-analysis maps on differences in resting-state (A) between schizophrenic patients (SCZ) and healthy controls, (B) between patients with major depression (MD) and healthy controls ($P < .05$, false discovery rate [FDR] corrected). (C) On the left, the proximity of hypoactivity in schizophrenic patients and hyperactivity in depressive patients within the ventromedial prefrontal cortex (vmPFC); on the right, the results of a joint ALE map comprising coordinates of the contrast SCZ < controls and MD > controls ($P < .05$, FDR corrected).

prefrontal cortex (vmPFC), left hippocampus, posterior cingulate cortex, lower precueus, and the precuneus. Furthermore, the analysis revealed that schizophrenic patients have increases in resting-state activity in bilateral lingual gyrus (figure 1A; table 3).

In studies focusing on resting-state in major depression patients showed higher resting-state activation in vmPFC, the left ventral striatum, and left thalamus but displayed reduced brain activity in left postcentral gyrus, left fusiform gyrus, and left insula relative to controls (figure 1B; table 3).

Our meta-analysis demonstrated "hypoactivity" in schizophrenic patients and "hyperactivity" in patients with major depression within the vmPFC (figure 1C, left). In order to test the similarity of the vmPFC location of hypoactivity as well as hyperactivity in more detail, we performed a joint ALE meta-analysis comprising coordinates of the contrast schizophrenic patients < healthy controls and depressed patients > healthy controls (figure 1C,right). The concurrence to which both psychiatric disorders contributed—though with the opposite signature—was located in the vmPFC (MNI coordinate: −4, 39, −7).

In order to illuminate the effects of medication, we preformed separate exploratory analyses on medicated and unmedicated patients. Within the schizophrenic patients, we found concurrence for the reduction of resting-state activity within the vmPFC only in unmedicated (4 studies) not in medicated (7 studies) patients. In depressed patients on the other hand, concurrence for increases of vmPFC resting-state activity was found in medicated (4 studies) rather than unmedicated (7 studies) patients.

Discussion

The present quantitative meta-analyses on resting-state studies in schizophrenia and major depression assess the strength of evidence for a core set of brain regions that show alterations during rest. An analysis on coordinates of reduced resting-state activation in schizophrenia showed hypoactivation in vmPFC, left hippocampus, posterior cingulate cortex, lower precueus, and the precuneus. Concurrence for hyperactivation in schizophrenic patients was found in bilateral lingual gyrus. In major depression on the other hand, we found several areas with resting-state hyperactivation including the vmPFC, left ventral striatum, and left thalamus. Resting-state hypoactivation was observed in left postcentral gyrus, left fusiform gyrus, and left insula. In order to provide evidence for the close regional proximity of hypoactivation in schizophrenia and hyperactivation in major depression within the vmPFC, we conducted a joint meta-analysis in which we exclusively found a cluster of concurrence in vmPFC. fMRI as well as PET studies were considered despite the fact that they have a different physiological basis because both methods have been used to identify differences between resting-state activity of the brain in patients compared with controls.

The brain regions within the resting-state network, in particular the vmPFC and the precuneus, have been shown to play an essential role in self-referential processing. Notably, activity in these regions is also elicited by tasks assessing mentalizing,[41,42] as well as tasks requiring retrospective and prospective memory for self-relevant information.[43] The medial prefrontal cortex in particular has been associated with online self-evaluations,[44] retrieval of self-generated vs externally presented words,[45]

Table 3. Statistical Concurrence Observed Across Studies Alterations of Resting-State in Schizophrenia and Major Depression

Anatomical Region	Brodmann Area	Coordinates (MNI)			Volume (mm^3)
		x	*y*	*z*	
Healthy controls > schizophrenic patients					
Precuneus	7	3	−44	69	528
Lower precuneus	7	−6	−70	35	488
Posterior cingulate	23	−1	−29	26	384
Ventromedial prefrontal cortex (vmPFC)	32/10/11	−10	48	−20	312
vmPFC	24/32	−4	40	−9	272
Left hippocampus		−21	−10	−24	264
Lower precuneus	23	10	−42	28	248
Schizophrenic patients > healthy controls					
Left lingual gyrus	19	−11	−57	2	1296
Right lingual gyrus	19	11	−55	2	1200
Healthy controls > depressed patients					
Left fusiform gyrus	19	−33	−78	−18	480
Left postcentral gyrus	40/2/3	−42	−22	50	368
Left insula	13	−40	6	−20	208
Depressed patients > healthy controls					
Left ventral striatum		−9	8	−11	488
vmPFC	32/9	−9	46	12	249
Left thalamus		−17	−22	10	224

and the self-reference effect of memory.[46] The hypoactivity of schizophrenic patients in vmPFC during resting-state could be related their deficits in self-referential source memory. Memory studies on healthy subjects have shown that stimuli processed with reference to the self are better remembered than other stimuli. In contrast, schizophrenia patients demonstrate significantly lower source memory for self-generated items (self-referential source memory) relative to healthy controls but show intact external source memory.[47] The notion that a disorder of the self is a core feature of schizophrenia has existed since the early days of schizophrenia research and is still a topic of debate.[48,49] Several neurobiological models of self-disturbance[50,51] share the assumption that the fundamental disturbance causing psychotic symptoms is the difficulty to distinguish between the origins of endogenously and exogenously generated stimuli. A recent meta-analysis on studies addressing self-reflection in healthy subjects implicated the importance of vmPFC in the process of tagging information as relevant for the self.[5] The autors assume that deficits in medial prefrontal cortex could be causally related to the lack of insight that is widely recognized in psychotic patients.[52]

Hyperactivity during resting-state in major depression on the other hand might be related to rumination, namely the excessive mental occupation with a recurrent series of thoughts united by a common theme and an increase in self-focus. Previous studies have shown an association between individual differences in rumination and medial frontal cortex activation[53] and increases in activity in the medial frontal cortex while judging self- vs nonself-related traits in depressed patients.[55] Moreover, it has been suggested that the self-focus in depression emerges due to a lack of inhibition of the resting-state network in medial frontal cortex.[54]

An exploratory analysis on the effects of medication revealed concurrence for the reduction of resting-state activity within the vmPFC in particular in unmedicated schizophrenia patients and for increases of vmPFC resting-state activity in medicated depressed patients. These results should be treated with caution because they rely on concurrence across a limited number of studies. Further research should investigate resting-state activity differences in the vmPFC in unmedicated vs medicated patients. If these results are confirmed, one might conclude that the resting-state reduction in vmPFC in schizophrenia is related to the disorder itself, whereas the increase in depression could be considered as an effect of medication.

Apart from vmPFC where we hypothesized to find abnormalities in schizophrenia and major depression, we found hypoactivation in posterior cingulate cortex, lower precueus, and the precuneus in schizophrenia. These brain regions are part of the resting-state network[1] and have likewise been associated with social cognition[3,4] known to be decreased in schizophrenia.[56] The hippocampal hypoactivity might be in line with memory deficits observed in schizophrenic patients.[57] A ROI-based study showed that the hippocampus has reduced functional connectivity to brain regions that have been associated with episodic memory, such as posterior cingulate cortex, medial prefrontal cortex, and parahippocampal gyrus.[58] But the direction of the hippocampal effects is a matter of debate, and some studies highlight hippocampal overactivity instead of underactivity (for an overview[59]). Nevertheless, the presented evidence for concurrence of

hypoactivity in left hippocampus could be in accordance with volume reductions of the hippocampus.[60,61] In order to explore the functional meaning of the decrease in resting-state in the left hippocampus and increase in lingual gyrus in schizophrenic patients, future research should focus on correlations between resting-state abnormalities with psychopathology. Apart from our predicted vmPFC region, we found hyperactivity in left ventral striatum and left thalamus in the resting-state of depressed patients. The higher activity in the ventral striatum during rest could be viewed as in agreement with studies showing lower task-related activation during reward learning or processing of positive stimuli (eg, ref. [62]). The thalamus has been shown to decrease in metabolism as patients progressed from the acute to the remitted phase of the illness,[63] but more detailed research is needed to explore behavioral correlates of the observed hypoactivation and hyperactivation in the brain regions that were beyond our predictions.

A possible limitation of the present meta-analysis is the use of different statistical approaches such as independent component analysis, regional homogeneity, etc. to assess resting-state in the studies included. However, these various analysis methods have been employed to characterize the target activation within the so-called default network. As soon as more resting-state studies on schizophrenic and depressed patients are published, subanalyses should be performed including studies with the same statistical analysis approach.

Conclusions

Our meta-analysis on hypoactivation and hyperactivation in resting-state of schizophrenic and depressed patients revealed consistency across different studies. In line with our predictions, we found a region of concurrence in vmPFC to which both psychiatric disorders contributed though with the opposite signature. The decrease in resting-state activity in schizophrenia is consistent with reductions in self-referential processing that might underlie the lack of insight into the illness and the increase in major depression is compatible with excessive rumination and increased self-focus in this disorder.

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