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Neuroimaging Biomarkers for Early Drug Development in Schizophrenia

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Abstract

Given the relative inability of currently available antipsychotic treatments to adequately provide sustained recovery and improve quality of life for patients with schizophrenia, new treatment strategies are urgently needed. One way to improve the therapeutic development process may be an increased use of biomarkers in early clinical trials. Reliable biomarkers that reflect aspects of disease pathophysiology can be used to determine if potential treatment strategies are engaging their desired biological targets. This review evaluates three potential neuroimaging biomarkers: hippocampal hyperactivity, gamma-band deficits and default network abnormalities. These deficits have been widely replicated in the illness, correlate with measures of positive symptoms, are consistent with models of disease pathology, and have shown initial promise as biomarkers of biological response in early studies of potential treatment strategies. Two key features of these deficits, and a guiding rationale for the focus of this review, is that the deficits are not dependent upon patients' performance of specific cognitive tasks, and have analogues in animal models of schizophrenia, greatly increasing their appeal for use as biomarkers. Using neuroimaging biomarkers such as those proposed here to establish early in the therapeutic development process if treatment strategies are having their intended biological effect in humans may facilitate development of new treatments for schizophrenia.

Keywords

schizophrenia; neuroimaging; biomarkers; hippocampus; gamma-band; default network

Introduction

Management and treatment of the symptoms of schizophrenia may be the greatest unmet need in psychiatry. Negative and cognitive symptoms are the most poorly treated, with no intervention having yet earned a federal indication for cognitive symptoms in the illness.

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While more responsive to antipsychotic medications, treatment of positive symptoms is also less than ideal, with up to 30% of patients relapsing the first year (1). Considering the tremendous scale of suffering caused by an illness affecting an estimated 28 million people worldwide (2), it is disheartening that almost every major pharmaceutical company is substantially reducing or eliminating research into novel mechanisms to treat schizophrenia and other psychiatric illnesses (3).

A key factor in the lack of progress in treatment development is the unavailability of reliable biomarkers that can be used to determine if therapeutic candidates elicit their targeted biological effects. The use of endophenotypes or intermediate phenotypes for diagnosis and prognosis remains an unmet goal, due not only to the large heterogeneity of findings within patients, but also because findings often also are observed in relatives or individuals at risk for schizophrenia (4). In the context of this review, the term biomarker is used as an indicator of neuronal function, hypothesized to be involved in the pathology of schizophrenia, that can serve as immediate and objective measures of the biological effects of therapeutic candidates. Used in this sense, biomarkers can be more distal than intermediate phenotypes from disease symptoms, but more proximal to hypothesized pathological mechanisms. This use of biomarkers holds excellent promise for therapeutic development, particularly with recent advances in functional neuroimaging.

Accordingly, the potential utility of neuronal biomarkers for therapeutic development is a topic of much recent interest (see (5) for review). This interest is reflected in endeavors such as the recent Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative, funded by the National Institute of Mental Health to develop imaging biomarkers to enhance translational research (6). Findings from the initiative, which focuses on developing imaging biomarkers associated with cognitive deficits thought to be central to the pathology of schizophrenia, will likely contribute greatly to biomarker use in drug development.

The goal of this review is to examine candidate biomarkers of neuronal function that are not specific to particular cognitive tasks, but rather may reflect fundamental neurobiological deficits in schizophrenia. Measures specific to certain cognitive tasks are useful because they can be used to directly associate neuronal activity with behavior, and as such can have high interpretability. Their use as biomarkers often is hampered, however, due to the large variability in reported results. For example, multiple studies have shown prefrontal hypoactivity during working memory in patients, but an equal number of studies have observed the opposite effect (reviewed by (7)). These discrepancies likely stem from variability in subject performance and cognitive strategies, task demands and other task differences, including differences in baseline or comparison conditions. An additional important limitation of task-based imaging approaches is that they have limited translational applicability, as they cannot be functionally imaged in rodents, and are not suitable for all subject populations, including infants or individuals with substantial cognitive deficits. This review therefore focuses on measures that can be examined not only during tasks but also in the task-free, “resting” state. The three main topics discussed are: hippocampal hyperactivity, gamma-band deficits and default network abnormalities. All three deficits have been widely replicated, often correlate with positive symptom measures, and, as

discussed below, merit consideration as biomarkers for therapeutic development. The sections below discuss each aspect of brain function in terms of previous findings, the possible neurobiological underpinnings, and their use to date in studies of existing and novel treatments.

Hippocampal Activity

Despite early suggestions of hippocampal involvement in schizophrenia (8, 9), widespread recognition of the region's contribution to disease mechanisms has been relatively recent. Structural and functional neuroimaging now provide strong evidence that hippocampal abnormalities likely are involved in the neurobiology of the illness. Meta-analyses based on early structural studies suggest that hippocampal volume is decreased in patients and in their unaffected first-degree relatives (10). The volume loss may also correlate with positive, negative and cognitive symptoms (11, 12). Although useful as evidence of localized pathology in schizophrenia, volumetric studies have limited utility as a biomarker because the time course for structural changes in the brain is longer than often can be used in a clinical trial. Functional measures may, however, be well-suited to serve as useful indicators of biological effects of therapeutic strategies.

Abnormalities in Hippocampal Function

Greater hippocampal regional cerebral blood flow in schizophrenia patients, relative to healthy comparison subjects, has been frequently reported (13-18). As summarized in Table 1, this hyperactivity is exacerbated in unmedicated patients and correlates with psychotic symptom severity (14, 17, 18). Cerebral blood volume (17) and blood flow (19) studies recently have replicated and extended this finding. Furthermore, Schobel and colleagues have shown that hippocampal basal blood volume correlates with both positive and negative symptoms in the prodromal state and predicts conversion to psychosis (17). Increased hippocampal blood flow and baseline activity have also been observed in animal models of schizophrenia, suggesting the phenotype has translational utility (20-22).

Functional magnetic imaging (fMRI) and positron emission tomography (PET) studies frequently report altered hippocampal response in schizophrenia. A theme of these findings is hippocampal hyperactivity during tasks requiring minimal or no cognitive load. These include fixation on a point (15, 23), passively viewing fearful faces (24), smooth pursuit eye movements (25), and passive listening to clicks (26), and to environmental noise (27). It is possible that hippocampal hyperactivity during rest or simple sensory processing tasks may reflect a generalized hypersensitivity to sensory input and/or inappropriate information processing, as discussed below.

In schizophrenia, a chronically hyperactive baseline state of hippocampal response may contribute to region's inability to be recruited during tasks in which it is thought to be required, such as memory encoding and pattern separation/completion (28). For example, diminished hippocampal recruitment has been observed in schizophrenia during image pair encoding (29), deep and shallow word encoding (30-32), novel word detection (33), and perceptual closure (34). Although reports of low-cognitive load tasks and hippocampal blood flow consistently suggest hyperactivity, studies involving tasks with substantial

hippocampal recruitment have been less consistent (35). This inconsistency could arise in part from variability in the baseline or control conditions used to isolate “task-relevant” activity.

Neurobiological Basis of Pathology: Hypotheses and Evidence

Increased basal perfusion and neuronal response during “passive” tasks is suggestive of generalized hippocampal hyperactivity in schizophrenia, which could be pharmacologically targeted. Tamminga and colleagues recently proposed a model that may explain hippocampal dysfunction in the disorder (28, 36). In this model, genetic factors and/or environmental insult(s) induce a prolonged hypoglutamatergic state in the dentate gyrus, the proximal hippocampal region in the excitatory “trisynaptic pathway.” This excitatory neurotransmission deficit induces compensatory long-term plasticity in its direct target, the CA3 hippocampal subfield. CA3 consequently reaches a hyperactive state in which it becomes highly sensitive to glutamatergic input. Coincident hypoactivation of the dentate gyrus, combined with CA3 hyperactivity, may result in diminished pattern separation and increased pattern completion, leading to spurious blending of associations that may contribute to delusions, as well as cognitive deficits.

Other mechanisms also may contribute to the etiology of hippocampal hyperactivity in schizophrenia. In a postmortem study, Benes and colleagues observed a three-fold downregulation of glutamate decarboxylase 67 (GAD-67), an enzyme essential for the synthesis of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), in hippocampal CA3 in schizophrenia (37). Alterations to hippocampal GABAergic interneurons also may occur via altered $\alpha 7$ nicotinic acetylcholine receptor function (38). This receptor, which plays a key role in interneuron function, shows reduced expression in schizophrenia (39). Polymorphisms in *CHRNA7*, the $\alpha 7$ nicotinic receptor gene, that lead to reduced receptor expression, also confer susceptibility to sensory gating deficits, an endophenotypic marker for schizophrenia (40). Due to reduced expression of these receptors, CA3 interneurons are unable to be stimulated by cholinergic neurotransmitters. This inhibitory deficit may ultimately contribute to hippocampal hyperexcitability. Also, given recent findings of hippocampal CA1 alterations in schizophrenia, (17), the contribution of this subregion to hippocampal hyperexcitability merits future study.

Imaging Studies with Novel and Existing Treatments

Preliminary neuroimaging studies have reported significant effects of pharmacologic agents on the human hippocampus. Antipsychotic use is associated with lower hippocampal rCBF in schizophrenia (13, 41). The atypical antipsychotic clozapine also may normalize persistent abnormalities in hippocampal blood flow observed in patients previously treated with risperidone (42). Both haloperidol and olanzapine treatment have been associated with decreased hippocampal rCBF. This effect was associated with medication-induced reduction in positive symptoms after 6 weeks of treatment, suggesting that decreased hippocampal activity may predict clinical response to medication (43). Cholinergic modulation of hippocampal response has also been examined. Nicotine has been shown to reduce hippocampal hyperactivity during pursuit eye movements in schizophrenia patients (44). The $\alpha 7$ nicotinic receptor partial agonist 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-

A) also was shown to reduce hippocampal activity during pursuit eye movement in patients, an effect that correlated with plasma drug levels, and was dependent on the genotype of *CHRNA7*, the $\alpha 7$ nicotinic receptor (45, 46).

In summary, hippocampal hyperactivity is a feature of schizophrenia that can be targeted pharmacologically. The magnitude of hippocampal abnormalities often correlates with clinical symptoms (Table 1), and can predict clinical progression from a prodromal to psychotic state (17). Hippocampal dysfunction may thus represent a biomarker useful not only for determining if therapeutic strategies are producing their intended biological effects, but also as a useful early indicator to assess effects of potential treatment strategies on illness development.

Gamma Oscillations

Gamma oscillations, typically measured with magnetoencephalography (MEG) or electroencephalography (EEG), reflect high frequency (30-80 Hz) synchronized neuronal activity. The oscillations arise from the synchronous activity of multiple GABAergic interneurons that induce inhibitory postsynaptic potentials on excitatory pyramidal neurons. After GABA-mediated hyperpolarization has decayed, pyramidal neurons enter an excitable state which facilitates synchronous firing (47). This process is believed to play an important role in both early sensory processing and in higher cognitive functions as it facilitates coordination between specific populations of neurons (48, 49).

Abnormalities in Schizophrenia

In healthy individuals, relative to “rest,” increased gamma-band power is observed across a broad range of sensory evoked and cognitive processes (48). In contrast, during many of these processes, including auditory responses, visual and motor responses, working memory and selective attention paradigms, schizophrenia patients exhibit attenuated task-related increases in gamma power as well as impaired performance, compared to healthy individuals (48). While most reports of gamma-band activity are during cognitive task performance, alterations in high frequency power in patients also have been reported during “rest” (i.e. not task-driven), with several large-scale studies showing increased gamma or high beta (24-33 Hz) power (50-54). Some smaller studies have not found resting gamma differences (55), possibly due to sample size or methodology differences (e.g. EEG vs MEG). Elevated “pre-stimulus” baseline gamma also has been reported during auditory paradigms in schizophrenia (56, 57). Increased gamma-band power at rest and during pre-stimulus periods may underlie the relative inability of patients to increase gamma power during cognitive tasks and in response to sensory stimulation. Gamma-band deficits have been observed in first-degree unaffected relatives (58) and first-episode patients (59), suggesting gamma-band dysfunction may have a genetic component and does not result from antipsychotic treatment.

Associations have been reported between gamma abnormalities and both cognitive (57, 60) and negative symptoms (61). Correlations with positive symptoms have also been shown (Table 1). These findings have been inconsistent, however, with observations of both

negative and positive correlations between gamma-band power and positive symptoms (see (48) for review).

Neurobiological Basis of Pathology: Hypotheses and Evidence

Several hypotheses have been proposed to explain gamma synchrony abnormalities in schizophrenia. In one model, hypofunction of NMDA receptor-mediated signaling on GABAergic interneurons leads to reduced calcium influx and decreased expression of GAD-67, resulting in decreased synthesis of GABA and a reduction in GABAergic signaling onto excitatory pyramidal neurons (48). The resulting loss of GABAergic tone may result in impaired generation of synchronous high frequency oscillations.

Lewis and colleagues have proposed an alternative model, in which genetic and/or environmental factors induce a reduction in the number of dendritic spines on pyramidal neurons (49). Excitation of these cells is thereby reduced and compensatory downregulation of GABAergic tone occurs to restore excitatory and inhibitory balance in the system. As a result, the dynamic range of excitation and inhibition is reduced, with insufficient inhibitory capacity available to change gamma-band power during times of need (i.e. challenging cognitive tasks). The primary contributors to the effect may be a loss of parvalbumin-expressing inhibitory basket cells, which project onto excitatory pyramidal cell bodies and primary dendrites, rhythmically inhibiting their activity and producing high-frequency, synchronized firing (62). This model may explain why the majority of schizophrenia-associated genetic polymorphisms are located on genes involved in glutamatergic signaling, whereas differences in GABAergic tone are reflected by changes in protein expression (49).

Studies with Novel and Existing Treatments

Although the etiology is not fully resolved, a common theme of gamma oscillatory dysfunction is a loss of inhibitory GABAergic tone in schizophrenia. To target the GABAergic system, clinical trials recently have examined the physiological and neurocognitive effects of the GABA-A receptor partial agonist MK-0777. Preliminary findings examining a small number of schizophrenia patients were encouraging as MK-0777 improved measures of cognition on the Repeatable Battery for the Assessment of Neuropsychological Status as well as suggested possible strengthening of frontal gamma power during a cognitive control task (63). However, a follow-up study using a larger sample size found no cognitive benefit in patients with MK-0777 as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (64). The follow-up study did not measure gamma activity, so relationships between drug effects, gamma activity, and cognitive function using the larger sample size are unclear. The study authors suggest that because MK-0777 has only 10-20% of the potency of a full GABA agonist, it is possible that compounds with higher potency would have increased efficacy. An important concern, however, is that high gamma power most frequently predicts positive symptoms in schizophrenia, despite showing the opposite relationship with cognitive and negative symptoms (Table 1). Indeed, a drug more potent than MK-077 may enhance gamma activity and improve cognition, but also worsen positive symptoms. At present, enhanced gamma after drug treatment should therefore not be considered evidence that a patient has “improved.” A minimum, future clinical studies that

examine effects of investigational compounds on gamma band activity should closely monitor symptoms to minimize any potentially deleterious effects.

Normalization of gamma-band activity also has been examined non-pharmacologically. Using repeated administration of transcranial magnetic stimulation (TMS), Farzan et al. (65) repressed “excessive” gamma power in the dorsolateral prefrontal cortex in patients during a working memory task, an effect associated with improved task performance. Using cognitive exercises (auditory processing/working memory “training”), Popov et al. observed increased time-locked, auditory stimulus-evoked gamma power as well as improved verbal memory in patients (66).

In summary, gamma-band abnormalities are an emerging biomarker in schizophrenia whose potential for use in drug development is just beginning to be explored. Although a clinical trial with the GABA-A partial agonist MK-0777 did not improve cognition in schizophrenia, future studies using drugs with higher potency at GABA receptors that also examine gamma-band activity merit consideration. Animal models may be useful in the development of these compounds. Indeed, an NMDAR-hypofunction rodent model of schizophrenia shows gamma-band abnormalities that are normalized by GABA_B receptor agonist baclofen (67). Additionally, mice expressing a catechol-O-methyltransferase gene variant associated with cognitive deficits in schizophrenia show gamma-band abnormalities that are reversed by nicotine (68).

Default Mode Network

Historically, fMRI studies often have examined neuronal activity during a task or stimulus-related condition compared to a “rest” or “baseline” condition during which the stimulus is not presented, the task is not performed, varies or is made easier along a dimension of interest. Early fMRI experiments largely ignored activity during the baseline state, as it was thought to be too variable between subjects. It is now understood, however, that individuals show remarkably similar spatial patterns of activity during rest. Furthermore, network analysis and connectivity techniques now have convincingly demonstrated that these spatial patterns of synchronous activity exist in the presence or absence of cognitive tasks, and likely represent an intrinsic functional characteristic of the human brain (69). The most-studied of these intrinsic networks is the default mode network. The network was originally shown to exhibit greater activity during rest periods and to “deactivate” during task periods. It was therefore hypothesized to represent a “default” mode of brain activity and was termed the default mode network (DMN) (70, 71).

The DMN includes the medial prefrontal cortex (mPFC)/ventral anterior cingulate cortex (vACC), the posterior cingulate cortex (PCC), the inferior parietal lobule (IPL), and the precuneus. The medial temporal lobe (including the hippocampus) and the temporal cortices constitute accessory hubs of the network (72). DMN activity is believed to reflect internally-directed thoughts, including memories, self-reflections, and future plans (73). Activation of the network is anticorrelated with task difficulty (74) and performance (75) and may represent the intrusion of task-nonspecific processing, particularly during boring tasks requiring little cognitive load (73). The DMN and other intrinsic networks are highly

relevant to brain function, as up to 80% of total brain metabolism is thought to arise from resting-state activity (76).

Abnormalities in Schizophrenia

One of the first reports of DMN dysfunction in schizophrenia was a 2007 report by Garrity et al. (77), which reported differences in the spatial and temporal organization of the DMN in patients, with overinclusion of medial temporal brain regions and underrepresentation of frontal areas. Furthermore, patients showed increased activity in the PCC, parahippocampal gyrus, and medial prefrontal areas, and decreased activity in the precuneus. PCC DMN overactivation also was associated with positive symptoms.

Multiple studies have since confirmed DMN alterations in schizophrenia. Many of these studies have used independent components analyses (ICA) techniques to identify the DMN as a functionally connected network, in which activity reflects the amplitude of intrinsic signal fluctuations. These studies have consistently observed increased DMN activity in schizophrenia, with activity being positively correlated with symptoms, particularly psychotic symptoms (Table 1). Studies also have used seed-based methods, in which the functional connectivity between DMN-related regions and other DMN and non-DMN regions is examined. An early report examining resting-state data found altered within- and between- DMN connectivity, with patients showing significantly greater within-DMN connectivity (78). Whitfield-Gabrieli and colleagues observed increased DMN connectivity in patients during both rest and task conditions. Connectivity during rest was negatively correlated with working memory performance and associated with positive and negative symptoms (79). Connectivity differences in schizophrenia may be region-specific: using a seed-based approach, increased connectivity was observed between the PCC and the mPFC/vACC, a difference that correlated with positive symptoms. DMN connectivity findings are not entirely consistent, however, as other studies have also reported decreased network connectivity in schizophrenia (e.g. (80) and (81), reviewed by (73)).

In addition to studies examining DMN intrinsic activity and connectivity, DMN differences in schizophrenia have been reported in the context of altered suppression or “deactivation” of the network during goal-directed tasks, including working memory (82), language (83), and attention (84). Additionally, relative to healthy controls, patients are unable to suppress the DMN as working memory processing demands increase (79, 82). DMN dysfunction also may be associated with structural abnormalities, as gray matter volume reductions have been observed in medial areas of the brain that overlap with the DMN (85).

Neurobiological Basis of Pathology: Hypotheses and Evidence

DMN overactivity in schizophrenia may be related to inhibitory dysfunction. The GABAergic agonist lorazepam has been shown to decrease activity in the mPFC (86). Additionally, GABAergic concentration in the ACC negatively correlates with neuronal response (87). Postmortem labeling with the GABA agonist muscimol has shown increased expression of GABA receptors in the PCC in schizophrenia (88). This increase was hypothesized to reflect compensatory upregulation in the wake of reduced activity of GABAergic interneurons (88, 89). Taken together, evidence for GABAergic dysfunction in

schizophrenia, coupled with suggestions of GABAergic modulation of DMN-related brain regions suggests a possible role of inhibitory dysfunction as a mechanism for altered DMN function in the illness.

The dopaminergic system may also play an important role in DMN dysfunction in schizophrenia. Using the dopamine receptor agonist apomorphine, enhanced deactivation of the mPFC during conditions of high cognitive load was observed in elderly patients (90). Using PET, Tomasi et al. (91) reported a negative correlation between dopamine transporter availability and DMN deactivation during an attention task, suggesting that dopamine release may reduce DMN activity. The most direct link between DMN function and dopaminergic function comes from the observation that conventional antipsychotic medications, which act via dopaminergic antagonism, show a dose-dependent correlation with DMN activity in schizophrenia patients (92).

Studies with Novel and Existing Treatments

To date, the effect of pharmacological agents on DMN function is not well established. Sambataro et al. (93) found that olanzapine increased connectivity of the mPFC with the remainder of the DMN. Paradoxically, increased connectivity after treatment was also associated with improved working memory (93), in contrast to previous work suggesting that hyperconnectivity of the DMN correlated with *poor* working memory in schizophrenia (79). Although the reason for this discrepancy is unclear, one contributing factor could be that the two studies analyzed the DMN using different methods: the earlier work used seed-based connectivity, whereas the olanzapine study used group ICA. Our group found that the $\alpha 7$ nicotinic receptor partial agonist DMXB-A reduced default network activity in the PCC, IPL, and medial frontal gyrus, and increased activity in the precuneus (46). These effects were interpreted as a putative “normalization” of the schizophrenia-control group differences observed by Garrity et al (77). A pharmacogenomic effect also was observed, such that reduced activity in the PCC was associated with a polymorphism in *CHRNA7*, the $\alpha 7$ nicotinic receptor gene (46).

DMN abnormalities have been observed in first-episode psychosis (94, 95), suggesting that differences may be present in early stages of the illness. These observations, together with early studies of drug effects on the network, highlight the possibility that DMN normalization may be useful as an early stage biomarker. One study, however, has suggested that antipsychotic drugs that primarily block dopamine receptors are associated with increased DMN activity (92). Although data from this study were acquired during a motor task, and as such may show an amplified effect of dopamine-sensitive striatal pathways, it raises the possibility that dopamine receptor blockade (i.e. using antipsychotics) may contribute to DMN dysfunction in schizophrenia. This study suggests that additional research to determine the relationship between current antipsychotic treatments and DMN function is urgently needed. This finding also suggests an intriguing alternative possibility, however, that current treatments actually exacerbate dysfunctional DMN activity in patients. A failure to improve the function of such an important intrinsic feature of brain function could explain why current treatments do not fully resolve schizophrenia symptoms. If true, focus on novel pharmacologic methods to target the DMN may be an especially rich avenue

for future therapeutic development. Animal models may soon be used to accelerate this process. Using fMRI, evidence for a DMN has recently been demonstrated in rats (96). Future studies could therefore be performed to determine if this network is altered by pharmacologic treatment in rodent models of schizophrenia.

Future Directions

The purpose of this review was to highlight and evaluate three potential neuroimaging biomarkers for schizophrenia that confer distinct advantages to researchers because they can be examined in the “resting state.” For the potential of these biomarkers to be fully realized, however, their clinical relevance needs to be more fully evaluated. Specifically, as suggested by the CNTRICs committee, important criteria for biomarkers include sensitivity to group differences (i.e. patient vs. control), test-retest reliability, and sensitivity to treatment (6). Sensitivity to group differences may be examined using “classifier” algorithms, as demonstrated in a recent study by Du et al. that observed 90% specificity for DMN abnormalities in schizophrenia (97). Test-retest reliability is another measure that has yet to be thoroughly examined for any of these biomarkers in schizophrenia, although a recent study observed high reliability for DMN function in healthy subjects (98). Finally, to more fully evaluate the sensitivity of these biomarkers to treatment, studies should examine how they are affected by and predict the effects of novel, typical, and atypical antipsychotic treatments. As demonstrated in this review, surprisingly few studies have examined the effects of drugs on any measure of resting-state activity in schizophrenia, highlighting the need for future research.

In the future, to more fully evaluate potential resting state biomarkers, a recommended research agenda is to acquire resting-state data in studies that examine both patients and comparison subjects on multiple occasions, in order to establish group sensitivity and test-retest reliability. Also, resting-state data should be acquired in clinical proof-of-concept studies that use neuroimaging to examine the treatment effects, so that sensitivity to treatment can be evaluated. Because resting data is relatively straight-forward to collect (e.g. a 10 minute fMRI scan with no task) it can be readily added to any fMRI or EEG session. As suggested by Carter and Barch (2007), the initial utility of these biomarkers would be to demonstrate proof-of-concept in early (Phase I or II) clinical trials (99), although the translational applicability of the measures would allow researchers to examine preclinical efficacy as well. If hippocampal hyperactivity, gamma-band deficits and default network abnormalities ultimately prove to be sensitive and reliable measures, these biomarkers would be a useful means to improve the development of treatment strategies for schizophrenia.

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Table 1

Summary of clinical correlates for the three candidate biomarkers examined in this review. For studies that report correlates with gamma band power/synchrony from more than one electrode source, or studies that report correlates with DMN activity/connectivity at more than one brain region, only the strongest effects are reported.

Author	Pub Year	Technique/Paradigm	Symptom Correlates	Pt Sample Size(s)	Effect Size(s) (Cohen's d)
Resting Hippocampal Activity					
Liddle et al. (100)	1992	PET/rCBF	+ correlation with reality distortion	30	1.04
Friston et al. (101)	1992	PET/rCBF	+ correlation with overall psychopathology	30	1.58
Elmeier et al. (102)	1993	SPECT/rCBF	+ correlation with disorganization, - correlation with reality distortion	20	0.69, 0.85
Gur et al. (103)	1995	PET/FDG	+ correlations with hallucinations and poor premorbid adjustment (laterality)	42	0.65, 0.87
Kawasaki et al. (104)	1996	SPECT/rCBF	- correlation with thought disorder	38	1.07
Molina et al. (16)	2005	PET/FDG	+ correlation with PANSS positive	11	1.20
Lahiti et al. (14)	2006	PET/rCBF	- correlations with BPRS total (1 st cohort), hallucinations/delusions (combined score, 1 st cohort), BPRS total (2 nd cohort)	32 (1 st cohort), 23 (2 nd cohort)	1.35, 1.19, 1.54
Schobel et al. (17)	2009	fMRI/rCBV	+ correlations with PANSS positive and PANSS negative	18	1.25, 1.54
Malaspina et al. (18)	2009	SPECT/rCBF	+ correlation with positive symptoms	not avail.	not avail.
Lahiti et al. (43)	2009	PET/rCBF	more activity in PR after haloperidol (week 6) or olanzapine (week 1) treatment	5 GR [*] , 7 PR [*] ; 4 GR ^{***} , 7 PR ^{***}	2.27 [*] , 2.82 ^{***}
Gamma Band Power/Phase Locking					
Haig et al. (105)	2000	EEG/Auditory Oddball	- correlation with PANSS Total	35	0.80
Gordon et al. (106)	2001	EEG/Auditory Oddball	+ correlation with reality distortion, -correlation with psychomotor poverty, -correlation with disorganization	35	1.32, 1.07, 0.98
Lee et al. (107)	2003	EEG/Auditory Oddball	+ correlation with reality distortion, + correlation with disorganization, - correlation with psychomotor poverty	38	0.70, 1.00, 1.00
Spencer et al. (108)	2004	EEG/Visual Closure	+ correlations with disorganization, hallucinations, delusions, PANSS negative	20	1.42, 1.35, 1.71, 1.39
Cho et al. (109)	2006	EEG/Cognitive Control	- correlation with disorganization	15	1.01
Uhlhaas et al. (110)	2006	EEG/Visual Closure	+ correlation with delusions, + correlation with hallucinations, - correlation with PANSS negative	19	1.19, 1.32, 1.35

Author	Pub Year	Technique/Paradigm	Symptom Correlates	Pt Sample Size(s)	Effect Size(s) (Cohen's d)
Hirano et al. (111)	2008	MEG/ASSR	- correlation with hallucinations	20	1.19
Spencer et al. (112)	2008	EEG/ASSR	+ correlation with PANSS positive	15	2.08
Spencer et al. (113)	2009	EEG/ASSR	+ correlation with hallucinations	18	1.28
Hamm et al. (61)	2011	MEG/ASSR	- correlation with SANS Total	17	1.12
Default Mode Network Activity/Connectivity					
Garrity et al. (77)	2007	fMRI/ICA	activity: + correlation with PANSS positive	20	2.71
Whitfield-Gabrieli et al. (79)	2009	fMRI/CONN	activity: + correlation with SANS and SAPS connectivity: + correlation with SAPS	13	1.85, 2.34, 3.71
Rotarska-Jagiela et al. (114)	2010	fMRI/ICA	activity: + correlation with PANSS positive connectivity: - correlations with hallucinations and delusions	16	1.91, 2.58, 1.42
Camchong et al. (115)	2011	fMRI/ICA	connectivity: + correlation with SAPS, SANS	29	0.97, 0.97
Tregellas et al. (116)	2011	fMRI/ICA	activity: + correlation with BPRS total, (drug effect)	16	1.39
Meda et al. (117)	2012	fMRI/ICA	connectivity: + correlation with PANSS positive, PANSS general	70	0.80, 0.93
Lutterveld et al. (118)	2013	fMRI/CONN	more connectivity in people with hallucinations (general population)	29	1.81

* Haldol,

** Zyprexa.

Poor responders (PRs) showed no improvement of symptoms after antipsychotic treatment, good responders (GRs) showed significant improvement.

Abbreviations: Pt – Patient, PET – Positron Emission Tomography, rCBF – resting cerebral blood flow, rCBV – resting cerebral blood volume, FDG – fluorodeoxyglucose, AP – antipsychotic, GR – good responder, PR – poor responder, BPRS – Brief Psychiatric Rating Scale, PANSS – Positive and Negative Syndrome Scale, EEG – electroencephalography, MEG – magnetoencephalography, ASSR – auditory steady state response, SANS – Scale for the Assessment of Negative Symptoms, fMRI – functional magnetic resonance imaging, ICA – independent components analysis, CONN – functional connectivity analysis, DMXB-A – 3-(2,4-dimethoxybenzylidene)-anabaseine, SAPS – Scale for the Assessment of Positive Symptom