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Patterns of Spontaneous Magnetoencephalographic Activity in Schizophrenic Patients

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Abstract

Magnetoencephalography (MEG) non-invasively measures the magnetic fields produced by the brain. Pertinent research articles from 1993 to 2009 that measured spontaneous, whole-head MEG activity in schizophrenic patients were reviewed. Data on localization of oscillatory activity and correlation of these findings with psychotic symptoms are summarized. While the variety of measures used by different research groups makes a quantitative meta-analysis difficult, it appears that MEG activity in patients may exhibit identifiable patterns, defined by topographic organization and frequency band. Specifically, 11 of the 12 studies showed increased theta (4–8 Hz) and delta (1–4 Hz) band oscillations in the temporal lobes of patients; of the 10 studies that examined the relationship between oscillatory activity and symptomatology, 8 found a positive correlation between temporal lobe theta activity and positive schizophrenic symptoms. Abnormally high frontal delta activity was not seen. These findings are analyzed in comparison to the EEG literature on schizophrenics, and possible confounds (e.g., medication effects) are discussed. In the future, MEG might be used to assist in diagnosis, or might be fruitfully used in conjunction with new neuroscience research approaches such as computational modeling, which may be able to link oscillatory activity and cellular-level pathology.

Keywords

magnetoencephalography; schizophrenia; resting state networks; oscillations; positive symptoms; antipsychotic agents

1. Introduction

A growing body of functional neuroimaging data has shown that the brain, in its baseline or resting state, is far from quiescent. In fact, resting state patterns of structured brain activity carry out important psychological functions (Gusnard and Raichle, 2001; De Luca et al., 2006; Mantini et al., 2007). These resting state networks (RSNs) are anatomically distributed brain areas that tend to co-activate simultaneously, often at very low frequencies (on the order of 0.1 Hz). One such network that has received a good deal of research interest

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has been termed the *default network* (Buckner and Vincent, 2007; Raichle and Snyder, 2007; Buckner et al., 2008). Core components of this network include areas of the frontal lobe (ventral medial prefrontal cortex and dorsal medial prefrontal cortex), parts of the temporal lobe (lateral temporal cortex and hippocampal formation), and other brain areas (posterior cingulate and inferior parietal lobule) (Buckner et al., 2008). While the functional role of the default network is a topic of ongoing research, it has been hypothesized that it “may reflect neural functions that consolidate the past, stabilize brain ensembles, and prepare us for the future” (Buckner and Vincent, 2007).

To better understand the functional significance of RSNs, some researchers have asked if they are characterized not only by a particular *topographic* configuration, but also by particular *temporal* patterns of electrophysiologic activity (Laufs et al., 2003; Mantini et al., 2007; Chen et al., 2008). For example, Mantini et al (2007) performed a simultaneous EEG-fMRI study and found that RSNs had specific signatures—that is, they were characterized by particular distributions of oscillatory activity in the delta, theta, alpha, beta, and gamma frequency bands. This neurophysiological approach to the study of RSNs makes sense given the significant and growing body of literature on the manner in which activity in particular frequency bands may subserve particular cognitive tasks, such as memory or perception. Analyzing oscillatory activity may help to bridge the gap between neurobiology and behavior, both in the functional and dysfunctional state, and a good deal of research work has generated hypotheses on the functional importance of each of the frequency bands; this is briefly reviewed below.

Delta activity (1–4 Hz) is normally seen during drowsiness and early slow-wave sleep. If present during wakefulness, it is generally associated with brain dysfunction, such as coma (Kandel et al., 2000). Focal delta waves may characterize localized brain pathology, such as cerebral infarcts, contusion, tumors, local infectious processes, or subdural hematomas (Niedermeyer and Lopes da Silva, 1993). *Theta* waves, usually defined as anywhere from 4–7 to 4–12 Hz, are often present during REM sleep (Jouvet, 1969). In laboratory animals, hippocampal theta waves reliably correlate with a number of behaviors, which have been variously described as “voluntary”, “preparatory”, “orienting”, or “exploratory” (Vanderwolf, 1969; Buzsaki, 2002). They are generally absent in the immobile animal. They are thought to be important in the memory encoding process, perhaps by coordinating the firing of cell assemblies, so that LTP (long term potentiation) and LTD (long term depression) can occur (Stanton and Sejnowski, 1989). LTP and LTD are forms of synaptic plasticity that are thought to be the cellular mechanisms of learning and memory acquisition. While much of this information is from rodent studies, it is felt that analogous processes may be at work in humans (Tesche and Karhu, 2000). Activity in the *alpha* range (around 8–13 Hz) in healthy adults is most pronounced over the parietal and occipital areas, and is typical of a state of relaxed wakefulness. *Beta* activity (13–30 Hz) is seen prominently in frontal lobes, as well as other brain areas during intense mental activity (Kandel et al., 2000). The *gamma* frequency band is defined variously as 30–50 Hz to 30–80 Hz, and it has been hypothesized that oscillation in this range is crucial in synchronizing neural assemblies in a process that is responsible for “binding” the various features of an object together within a given sensory modality or across different sensory modalities (Traub et al., 1996; Tallon-Baudry and Bertrand, 1999).

If resting state oscillations in various frequency domains and their topographical organization index aspects of normal cognitive functioning, one would expect to see abnormalities in these measures in schizophrenia and other mental illnesses (Green, 1999). Indeed, recent fMRI studies of schizophrenics have shown that the default network in this patient group tends to be overactive (Fehr et al., 2003; Harrison et al., 2007; Zhou et al., 2007). Of note, one group found that among patients, there existed a positive correlation

between positive symptoms of the illness (e.g., hallucinations and delusions) and increased activity in certain areas of the default network (Garritty et al., 2007). Also, greater *correlations* among the many anatomic components of the default network were seen in patient groups (Zhou et al., 2007). Neurophysiologic abnormalities have also been investigated: since its inception in the 1920's, EEG has been used in an attempt to diagnose schizophrenia and understand its pathophysiology (Torrey, 2002). Indeed, a number of reviews of this literature have been published (Buchsbaum and Haier, 1987; Sengoku and Takagi, 1998; Hughes and John, 1999). As revealed by these reviews, an abnormality commonly found in schizophrenic patients is increased delta activity in the frontal lobes (e.g., Morihisa et al., 1983; Morstyn et al., 1983; Morihisa and McAnulty, 1985). Another frequent finding is decreased alpha activity, though there is not convergence on its location—some reviewers have identified it as a fairly general phenomenon (e.g., Itil, 1977; Fenton et al., 1980; Koukkou, 1982), while others found this effect to be more pronounced in the occipital areas (e.g., Buchsbaum et al., 1982; Guenther and Breitling, 1985). Increased beta activity in various areas has also been seen in schizophrenic patients (e.g., Laurian et al., 1984; Kemali et al., 1986). Clearly, a number of abnormal findings have been reported in various frequency bands, but no absolute consensus on the findings has emerged.

Magnetoencephalography is a technology that measures the *magnetic* fields produced by intracranial currents. It was introduced in the early 1970's (Cohen, 1972) and, as described below, has been increasingly used to study brain function and dysfunction. The questions this paper aims to address are: What MEG abnormalities have been identified in schizophrenia in the resting state? Are they consistent with the EEG findings? What can this tell us about the underlying neuropathology of the illness? This technology and its relationship to EEG are described below.

2. Background

An in-depth description of magnetoencephalography and its theoretical basis is beyond the scope of this review. For such a treatment, the reader is referred to one of the many excellent papers on it, such as those by Hamalainen et al (1993) or Papanicolaou (1995). Given below is a brief introduction that will allow for an understanding of the study results reviewed here.

Within neurons, signals are carried electrically—that is, via the movement of ions. These moving charges generate an electrical field, which can be measured via EEG, and an orthogonal magnetic field, which can be measured by MEG. Thus, magnetoencephalography is closely related to electroencephalography. A localized source of neural activity can be represented as a *current dipole*, or when source analysis is performed an *equivalent current dipole* (ECD). A number of the research studies reviewed here (Sperling et al., 1999; Fehr et al., 2001; Sperling et al., 2002; Fehr et al., 2003; Wienbruch et al., 2003; Ropohl et al., 2004) use the term “dipole density” to denote the prevalence in a particular brain area of dipole activity oscillating in a given frequency range, which is the number of ECDs calculated per unit time. The dipole density results are typically normalized by the specific sampling rate of the dipole fit and by other non-focal sources (Sperling et al., 2002). The important point for this review is that this provides a quantitative estimate of the strength of focal oscillatory activity arising from a particular brain area (e.g., prefrontal, frontal, temporal, parietal, or occipital). A number of works—such as those by Vieth (1990) or Kober et al. (1992)—offer detailed explanations of dipole density techniques in the analysis of MEG data. Other methods of localizing spontaneous oscillatory activity provide a distributed current dipole solution, rather than a focal ECD, for the estimation of oscillatory activity (Jensen and Vanni, 2002; Lin et al., 2006).

Some have argued that MEG, as compared with EEG, is capable of providing more accurate localization of source activity in the brain. Researchers have estimated that MEG can localize neural activity to within a few millimeters under favorable circumstances; those who have attempted to address this question directly have estimated maximum localization errors of 3 mm using MEG (Yamamoto et al., 1988). One reason researchers cite for the possibly improved localization accuracy over EEG is that electrical potentials recorded at the scalp are strongly influenced by inhomogeneities in conductivity of the various tissues they must pass through. In contrast, magnetic fields are minimally distorted as they pass through various tissue layers. In particular, the volume currents influenced by the skull-scalp interface can effectively be ignored as contributions to the MEG-recorded magnetic field, but produce a spatial ‘blurring effect’ on the EEG (Hamalainen et al., 1993; Okada et al., 1999).

It should be noted that MEG and EEG have different sensitivities to brain electrical activity, which are complementary. MEG more readily detects superficial, as opposed to deep or distributed current sources (Goldenholz et al, 2009). Also, strictly *radially* oriented current sources (that is, those perpendicular to the surface of the skull) do not produce a magnetic field component that is visible to MEG at the surface of the scalp directly above it. Therefore MEG, in contrast to EEG, preferentially records activity in the cortical sulci, as opposed to the gyri (Hamalainen et al., 1993). Of course, current sources may be picked up, to varying degrees, by *several* MEG sensors; various techniques, as discussed above, are used to accurately localize current dipoles based on this information. Thus, the current consensus is that MEG and EEG are complementary in detecting neural activity, but that they provide qualitatively different pieces of information (Srinivasan et al., 2006).

The manner in which MEG is performed experimentally is illustrated in Figure 1. The subject sits with his/her head within a helmet shaped device containing the MEG sensors, or gradiometers, which is often housed in a larger cylindrical apparatus. There are various types of gradiometers: *planar* gradiometers measure activity in a focal area directly under the sensor, whereas *axial* gradiometers will detect activity some distance from the sensor (Hamalainen et al., 1993).

3. Review of the Current Literature

3.1. Included and Excluded Studies

Magnetoencephalography is increasingly used as a research tool to understand brain activity. A PubMed search on *magnetoencephalography* OR *magnetoencephalogram* produced 3,781 citations, dating from 1972. The majority of these (77%) were published in the last ten years. The subset of the above MEG studies containing the search term *schizophrenia* numbered 100. In the current review, we include all studies that performed whole-head MEG and quantified oscillatory activity across a number of frequency bands. As we were interested in spontaneous activity, we excluded studies that looked only at brain activity evoked by auditory or other sensory stimuli, as it was felt that these may be tapping qualitatively different brain processes. All of the studies reviewed, aside from two case studies, include a matched group of psychiatrically well controls. All told, there were 13 studies from five different research groups; the studies represented readings from a total of 205 patients and 208 controls. Some research groups re-use subjects in separate studies; to the extent that this is known quantitatively (because it is stated by the authors), this has been taken into account in this number. In some cases, more than one study was performed by a particular research group, and the extent of overlap between subject groups is not explicitly stated—therefore there is a possibility that some patients were counted multiple times. None of the studies reviewed used combination MEG + EEG readings.

For all papers, a summary of findings is presented, followed by a brief critique. Many studies examined both topographic localization of MEG oscillatory activity *and* correlation of these findings with psychotic symptoms. For the sake of clarity, these two aspects are discussed in separate sections below, and are presented in summary form in Tables 1a and 2, respectively. Two other questions that are important in assessing the MEG studies are (1) Did the researchers perform a source analysis? If so, what methodology did they use—equivalent current dipole, dipole density, or a distributed inverse solution? (2) What type of gradiometer (planar vs. axial) was used. This information, if presented by the authors, is discussed below and summarized in Table 1a. Demographic and clinical information on the patients included in these studies is presented in Table 1b.

Because EEG studies of schizophrenics have been reviewed elsewhere (Buchsbaum and Haier, 1987; Sengoku and Takagi, 1998; Hughes and John, 1999), they are not included in detailed manner below. However, in the Discussion section, both our MEG findings and the EEG literature on brain oscillations in schizophrenia are examined.

3.2. Studies Including Medicated and Unmedicated Patient Groups

(i) Canive et al (1996) performed MEGs, using planar gradiometers, on 11 schizophrenic patients at the end of a ten day medication-free washout period. Five of these patients were then placed on “novel” (presumably atypical) antipsychotics and re-tested by MEG after a period of 8 weeks. Three additional patients who were on this antipsychotic (and not previously in the medication-free group) were also evaluated by MEG. Four of 11, or 36%, of unmedicated patients showed an increase in delta and theta frequencies bitemporally, compared with controls, who showed little temporal lobe delta or theta oscillations to speak of. Three of these four showed normalization in these areas after treatment with medications. Additionally, the unmedicated schizophrenic patients, as a group, showed less total alpha power and lower peak alpha frequency than controls; this finding did not change significantly when the patients were medicated (their Figures 7 and 8, p. 748).

(ii) In a follow-up study, Canive et al. (1998) tested five schizophrenic patients with MEG, using planar gradiometer, after a ten day medication washout. They were then treated with the atypical antipsychotic aripiprazole and re-tested after 8 weeks. Three out of five of the unmedicated patients showed increased delta bitemporally, compared with controls; one of these showed increased theta in these areas. When medicated, the authors found normalization in these frequencies. As above, patients showed lower alpha peak frequencies and amplitudes, with no significant difference between medicated and unmedicated states.

(iii) Reulbach et al (2007) examined MEG activity in two frequency ranges—2–6 Hz, intersecting the delta and theta frequency bands, and 12.5–30 Hz, the beta band—among schizophrenics with and without auditory hallucinations. Medications were withheld for the 3 days prior to measurement. Both hallucinating and non-hallucinating patient groups showed greater dipole density in the 2–6 Hz range in temporal lobes bilaterally, as compared with controls. Interestingly, hallucinating patients showed significantly greater beta activity than non-hallucinating patients; this was seen in the superior temporal gyrus bilaterally and in some cases in the dorsolateral prefrontal cortex as well.

One question raised by all of the above studies is that of the timing of medication effects. Specifically, the medication washout periods were ten (Canive et al., 1996; Canive et al., 1998) or three (Reulbach et al., 2007) days. There is a body of research indicating antipsychotics can have an immediate and dose-dependent effect on individual conductances, such as the Na⁺ (Ogata and Tatebayashi, 1989) or Ca⁺⁺ (Ogata and Narahashi, 1990) channels. Three to ten day washout periods certainly would preclude the possibility these kinds of acute neurophysiologic effects. However, any changes resulting

from, for example, changes in synaptic connectivity (Konradi and Heckers, 2001) occurring due to neurotransmitter induced changes in intracellular second messengers and gene transcription (Hyman and Nestler, 1996), and/or expression of receptor proteins (which have been suggested as mechanisms of neuroleptic action, though not proven) would probably still be present.

3.3. Studies Containing Entirely or Predominantly Medicated Patients

(iv) Sperling et al (1999) studied ten patients treated with haloperidol, ten patients treated with clozapine, and a group of twenty matched controls. They found that in the slow frequency range (2–6 Hz), both neuroleptic treatment groups showed dipoles localized predominantly in the temporo-parietal area (in contrast to central locations [i.e., near the central sulcus] in controls). The treatment groups differed from one another in that those treated with clozapine showed an increase in beta activity over the left hemisphere, particularly in the temporo-parietal area. Patients treated with haloperidol tended to show a generalized increase in alpha frequency activity.

(v) In a follow-up study, Sperling et al (2002) studied 30 schizophrenic patients treated with haloperidol and 30 controls. They categorized dipole activity as slow (2–6 Hz) or fast (12.5–30 Hz). They found that in both schizophrenics and controls, localization of dipole activity was similar: activity in both frequency ranges localized in the temporo-parietal area and central (apparently fronto-prefrontal) areas. Schizophrenics, however, showed overall greater dipole densities than controls, for both slow and fast activity. Medication effects were also analyzed. In the slow frequency range, there was greater dipole activity in the left hemisphere for patients with higher cumulative neuroleptic doses. In the high frequency range, the authors found no effect of medication on dipole localization, but an apparent propensity for it to increase dipole density generally.

(vi) In a subsequent study, reported in a letter to the editor, Sperling et al. (2003) studied 20 new schizophrenic patients and 20 controls. They found distributions of oscillatory activity in schizophrenic patients similar to that described in their 2002 study above.

(vii) Fehr et al. (2001) studied 27 medicated schizophrenic patients and one unmedicated patient. 19 subjects were on standard neuroleptics alone, four were on atypicals alone, and four received a combination. The mean daily antipsychotic dosage, in chlorpromazine equivalents, was 231.71 ± 167.38 mg. Using dipole density analysis, they found that schizophrenics showed increases in the delta frequency band, most pronounced in the left frontal area, and increases in temporal and occipital areas bilaterally. In the theta frequency band, schizophrenics showed increases in the left frontal and bilateral occipital areas. This group also used a source analysis technique on the MEG, the *minimum norm estimate* (MNE), which is sensitive to activity generated at multiple locations (Hamalainen and Ilmoniemi, 1994; Hauk et al., 1999; Fehr et al., 2001). Using this approach, it appeared that schizophrenics showed general increases in delta activity, and increases in theta activity in all areas except frontal and prefrontal lobes bilaterally (see their Figure 3, p. 113).

(viii) In a follow-up study, Fehr et al (2003) looked at the distribution of MEG slow wave (delta and theta) activity during three conditions—a mental arithmetic task, and an imagery task, and at rest—in a group of 30 schizophrenic patients and 17 controls. They found that patients showed more focal delta activity than controls, and that these increases tended to be greatest in the temporal and parietal areas. Delta was equally prominent in medicated and unmedicated schizophrenics. There was no interaction between dipole activity in this frequency band and condition. In the theta frequency range, schizophrenic patients again produced greater activity than controls; similarly, they were most pronounced in the temporal and parietal areas. The only condition effect seen was a higher density of theta

dipoles during the spatial imaging tasks; this was true for schizophrenics and controls. The authors' main conclusion is that there is a pattern of prominent temporal slowing in schizophrenics; this is independent of the mental task they are asked to perform.

(ix) Kissler et al (2000) conducted a study focusing on the gamma frequency band. They studied 15 patients, 13 of whom were on typical antipsychotics; none was treated with atypical antipsychotics. They found that in healthy subjects, a mental arithmetic task produced a left lateralized increase in gamma in frontal and fronto-temporal areas. Schizophrenics showed a different pattern of gamma activity: in the gamma1 range (which the authors define as 30–45 Hz) they showed no elevation with the task, and in the gamma2 (46–60 Hz) and gamma3 (61–71 Hz) ranges, they showed reversed lateralization, with increased activity over the right frontal and right fronto-temporal areas. Also, patients showed increased activity in the beta2 (21–29 Hz) range generally. The authors correlated gamma activity with medication dose in CPZ equivalents, and found no statistically significant relationship. A strength of this study is that it investigates a frequency range that has received relatively little attention in the MEG-schizophrenia literature. While the particular pattern of findings in the beta and gamma bands and sub-bands in schizophrenics is interesting, it is difficult to draw conclusions about its functional significance.

(x) Wienbruch et al (2003) performed a study to determine whether or not schizophrenics showed increased slow wave (delta or theta) activity, and whether or not the patterns observed differentiated these patients from those suffering from affective disorders. They examined 25 patients with schizophrenia, 18 psychiatrically well controls, and 27 patients with affective disorder; 17 schizophrenic patients were receiving antipsychotic medications, with 11 receiving typicals and six taking atypicals. The average daily dosage in chlorpromazine equivalents was 129.7 ± 162.4 mg. They found that compared with controls schizophrenic patients showed significantly greater dipole densities in the temporal and parietal areas. Patients with mood disorders showed significantly *lower* dipole densities in the delta and theta bands in the prefrontal and frontal areas, compared with controls and schizophrenics. In an effort to understand medication effects, the authors compared theta dipole densities between subsamples of 18 controls, 11 schizophrenic patients taking typical neuroleptics, and 11 depressed patients taking SSRIs. The schizophrenic group showed significantly higher theta activity in the left temporal area ($p < 0.05$) than the other two groups.

(xi) Reeve et al. (1993) presented a case study of a woman with a 20-year history of psychotic symptoms. MEG analysis carried out using a 37 channel biomagnetometer revealed slow wave (defined by the authors as 1–6 Hz) clusters bilaterally in the temporal and parietal areas. The study, which was presented in the form of an abstract, did not state the patient's medication status.

3.4. Correlations Between MEG Activity and Symptomatology

Most of the MEG studies above also correlated localized oscillatory activity with the clinical manifestations of schizophrenia. These findings are summarized in Table 2, and reviewed briefly below.

Canive et al (1996) measured psychopathology with the Positive and Negative Symptom Scale (PANSS). Of the *unmedicated* patients, the four who exhibited bitemporal increases in delta and theta showed a trend toward higher PANSS scores, compared with the other seven. The medicated patients, as a group, showed lower PANSS scores compared to the unmedicated patients (and, as mentioned above, did not exhibit bitemporal delta and theta abnormalities).

In a subsequent study, Canive et al. (1998) found that three out of the five unmedicated schizophrenics showed increased delta activity; two of these showed marked elevations on the PANNS. After treatment with aripiprazole the patients, as a group, did not show slow wave abnormalities, and their PANSS scores were significantly lower than seen in the unmedicated condition.

Sperling et al (2002) measured psychopathology using both the BPRS and the PANSS. They found a significant positive correlation between 2–6 Hz oscillatory activity in the temporo-parietal areas bilaterally and the items of the PANNS measuring positive symptoms (P1-P7). For beta activity (12.5–30 Hz), no correlations with psychopathology were seen. In their subsequent study of 2003 (Sperling et al., 2003), they found a positive correlation between beta activity in the left temporo-parietal area and one item of the PANSS-P (P2, which indexes formal thought disorder). They also found a positive correlation between beta activity here and one item of the PANSS-N (N4, which indexes social passivity and apathy).

Fehr et al (2001) measured symptomatology using the BPRS, the Scale for Assessment of Negative Symptoms (SANS), and the PANSS. They found a significant correlation between delta and theta activity in the frontal, prefrontal, and to some extent parietal areas and positive symptoms, as measured by the PANSS-P. A similar relationship was seen for the right temporal area. In their following study (Fehr et al., 2003), this group found a significant correlation between delta activity in the temporal areas bilaterally and negative symptoms, as measured by the PANSS-N.

Wienbruch et al (2003) found that there was a positive correlation between left temporal lobe delta activity and hallucinations and paranoia scores (combined) on the PANSS-P.

Ishii et al. (2000) present a case study in which they perform MEG, using axial gradiometers, on a patient who is experiencing auditory hallucinations (AH). They observed bursts of theta activity (defined as 4–8 Hz) in the left superior temporal cortex during AH; no significant activity was seen in other frequency bands. Measurements were made when the patient was drug naïve.

Ropohl et al. (2004) published an MEG case study of a patient treated with clozaril and suffering from chronic AH. During periods of hallucinations, he showed increased beta band (defined as 12.5–30 Hz) activity in the left auditory (superior temporal) cortex. This beta activity was not present in 13 non-psychiatric controls.

In two cases (Sperling et al., 1999; Reulbach et al., 2007), only patients with prominent positive symptoms and no negative symptoms to speak of were included in the study, and showed robust delta/theta activity in the temporal lobes¹. While quantitative regressions between symptom profile and oscillatory activity were not performed, these studies suggest a correlation between positive symptoms and slow wave temporal lobe activity, and were included as such in Table 2.

4. Discussion

A large number of research studies employing a variety of methodologies have shed light on the neurobiological lesions underlying schizophrenia. What is not clear is the functional

¹Specifically, the inclusion criteria for these studies was that patients carry the diagnosis of F20.0, under the ICD-10 system. This is defined as a symptom constellation “dominated by relatively stable, often paranoid delusions, usually accompanied by hallucinations, particularly of the auditory variety, and perceptual disturbances. Disturbances of affect, volition and speech, and catatonic symptoms, are either absent or relatively in conspicuous” (WHO. *The ICD-10 classification of mental and behavioral disorders : clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: W.H.O., 1992.)

manner in which these abnormalities result in the clinical manifestations of the illness. Brain region-specific oscillatory patterns may help to clarify this question: they provide neurocognitive information at an intermediate level of complexity, between the single neuron and an entire brain area. Moreover, our understanding of activity in the various frequency bands—theta, beta, gamma, etc.—and their possible functional (cognitive) interpretation has increased in the past several years. Therefore magnetoencephalography, in conjunction with functional and structural imaging, holds the possibility of elucidating the pathophysiology and etiology of schizophrenia in a fundamental way.

Because the number of MEG studies of schizophrenics is, as of yet, small, and because of methodological differences and dissimilar patient populations, it would be difficult to perform a full meta-analysis on these studies at this point. However, a statistical analysis in the form of the sign test was applied (Guttman et al., 1982); p-values, when indicating statistical significance ($p < 0.05$), are presented with the major findings below.

4.1. Summary of Major Findings

1. 11 of the 12 studies showed a tendency for increased slow wave activity in the temporal lobes bilaterally in schizophrenic patients ($p = 0.01$). This was exhibited in the delta band only in two studies (Canive et al., 1998; Fehr et al., 2001), the theta band only in one study (Ishii et al., 2000), and in both delta and theta bands in eight studies² (Reeve et al., 1993; Canive et al., 1996; Sperling et al., 1999; Sperling et al., 2002; Fehr et al., 2003; Sperling et al., 2003; Wienbruch et al., 2003; Reulbach et al., 2007). This was seen in medicated and unmedicated patient groups, as discussed in greater detail below.
2. Of the ten studies that looked at the relationship between brain oscillatory activity and symptomatology, eight found a correlation between temporal lobe slow wave activity and positive symptoms ($p = 0.05$). One showed this for the delta band only (Wienbruch et al., 2003), two showed for the theta band only (Canive et al., 1998; Ishii et al., 2000), and five showed it for both delta and theta (Canive et al., 1996; Sperling et al., 1999; Fehr et al., 2001; Sperling et al., 2002; Reulbach et al., 2007).
3. Excluding those studies in which patients were medicated with typical antipsychotics such as haldol (Sperling et al., 2002; Sperling et al., 2003), only one out of ten studies showed increased frontal delta activity in patients ($p = 0.01$). This is in contrast to the older EEG literature, which has shown increased frontal delta activity in schizophrenic patient groups.
4. Of the six studies that included the beta band, four showed increases in this frequency in various brain areas (left temporal, temporo-parietal bilaterally, frontal-prefrontal bilaterally) (Sperling et al., 1999; Sperling et al., 2002; Sperling et al., 2003; Ropohl et al., 2004). The brain areas in which beta increases were present were not common across studies.
5. Alpha effects tended to be weak, and not highly consistent, in terms of direction or localization, across studies.

4.2. Implications

4.2.1. Abnormal temporal lobe slow wave activity may be important in the pathogenesis of positive symptoms in schizophrenia—The pattern of findings that emerges from this review is striking because it is consistent with a large body of literature, of various methodologies, that has implicated temporal lobe structures in the neuropathology

²This includes studies that grouped δ and θ into a single broad frequency range (e.g., Reeve et al [1993], who define δ - θ as 1–6 Hz), as well as studies that separate these two frequencies (e.g., Fehr et al [2003]); in the later case, in all instances both δ and θ were increased.

of schizophrenia. A line of research dating back to Kraepelin argues that temporal lobe abnormalities may underlie positive symptomatology, whereas the frontal lobe may be the seat of negative symptoms, and this has been supported by a number of studies (Barta et al., 1990; McCarley et al., 1993; Flaum et al., 1995; Shenton et al., 2001).

The increase in slow wave temporal lobe activity seen among schizophrenic patients in the studies reviewed and its correlation with positive symptomatology have striking parallels in the neurological literature on temporal lobe epilepsy (TLE). There is an extensive history of research documenting a schizophrenia-like syndrome in patients with TLE (Hill, 1953). Slater and Beard (1963) studied a case series of patients with TLE and psychotic symptoms—the vast majority manifested the positive psychotic symptoms of delusions (98%) and hallucinations (71%); interestingly, these patients tended not to exhibit negative symptoms. This has been confirmed in a considerable subsequent literature. Perez et al (1985) showed a clinical relationship between the so-called Schneiderian first rank symptoms³ of schizophrenia (Kaplan and Sadock, 1995) and TLE; as above, these patients had relatively well preserved affect and did not have notable negative symptoms. There is also clinical data supporting a relationship between temporal lobe epilepsy and paranoid symptomatology (Trimble, 1983). Of note, studies that have quantified ictal oscillatory frequencies in patients with TLE have found activity in the delta and theta bands—again, consistent with the MEG studies reviewed. For example, Foldvary et al (2001) found that the majority of seizures of temporal origin (69%) showed rhythmic theta activity; in contrast, extra-temporal seizures showed theta activity only 5% of the time. Similar results were found by Zaveri et al (2001), who studied patients with TLE using depth electrodes and saw that all patients showed spectral peaks in the delta band, and 64% also showed peaks in the theta band.

The similarities identified above point to temporal lobe as the neural substrate for many of the positive symptoms of schizophrenia. Moreover, they suggest a way that this might be mediated *functionally*—via aberrantly increased slow wave activity. Precisely how this leads to the clinical phenotype is not entirely clear, but some speculative mechanistic hypotheses can be made. It has been argued that hippocampal theta frequency oscillations are central to the memory encoding process (e.g., Lisman and Idiart, 1995; Tesche and Karhu, 2000). If schizophrenic hippocampus is characterized by aberrant or excessive activity in this frequency range, it would not be surprising if they systematically encoded odd or erroneous percepts or cognitions, leading to frank psychotic symptoms. Furthermore, a number of researchers feel that schizophrenia can be understood as a *disconnection* syndrome (Friston, 1998). According to this body of research, deficiencies of neural wiring—resulting from, for example, overactive pruning or disordered synaptic development—underlie the clinical symptoms of schizophrenia. Researchers have offered arguments for the manner in which this kind of aberrantly connected neural tissue could provide the substrate for hallucinatory and delusional experiences (McGlashan and Hoffman, 2000; Hoffman and McGlashan, 2003). It has been argued that delta oscillations are characteristic of diseased neural tissue generally (Fehr et al., 2003), including, perhaps, the kind of poorly connected neural tissue likely to exist in hippocampal temporal lobe structures in schizophrenia.

4.2.2 Medication effects should be taken into account in the analysis of MEG oscillatory activity—One potential confound in the MEG studies reviewed involves medication effects. As shown in Table 1a, many of the studies were done in patient groups that were receiving antipsychotics. As in post-mortem or neuroimaging studies of schizophrenia, the following question arises: are the observed effects due to the illness process, or due to the medications used to treat it? Fehr et al. (2001, 2003) addresses this by

³The Schneiderian first rank symptoms are audible thoughts, voices heard arguing or discussing or both, voices commenting on one's behavior, experience of somatic influences, thought withdraw, thought insertion, thought broadcasting, and delusional perceptions.

examining whether or not there is a relationship between medication dosage and oscillatory activity in any frequency range or location. In their first study, they found that among patients, as antipsychotic dose in chlorpromazine equivalents increased, there was increased theta band activity in the right temporal and right frontal areas. In their second, they showed similarly that patients with higher daily antipsychotic dosages showed more pronounced temporal theta activity.

However, an issue with the above studies is the manner in which the researchers converted atypical medication doses into chlorpromazine (CPZ) equivalents. Regarding the first study, according to American Psychiatric Association guidelines, A CPZ dose of 100 mg is equivalent to a clozapine dose of approximately 50 mg (A.P.A., 1997). Thus, a CPZ equivalent of 2 would probably be more accurate than the 0.9 given by the authors. This 0.9 CPZ equivalent is used for the atypical medication risperidone also. However, according to recent research studies (A.P.A., 1997; Woods, 2003; Labbate et al., 2010), a risperidone dose of 1–2 mg is equivalent to a CPZ dose of 100 mg, producing a CPZ equivalent of 50–100, markedly different from the 0.9 assumed in this paper. As 8/28 (29%) of the patients were on these medications, this introduces a potentially significant source of error—specifically, it is possible that a number of patients having modest delta-theta oscillatory activity have relatively high, rather than low, medication dosages. In the following paper, they used 0.9 and 8 for the clozapine and risperidone dose equivalents, respectively. This still understates the risperidone conversion by a factor of 6–12. As 8/21, or 38%, of the medicated patients were on these atypical antipsychotics a bias similar to that mentioned above, though less severe, could have been introduced. Of note, Canive et al (1996, 1998), who analyzed patient groups on and off antipsychotic medications, did not find greater temporal delta-theta in the treated groups.

Even if there is a positive correlation between neuroleptic dosage and theta activity, as some of the EEG studies have shown (Galderisi et al., 1990; Czobor and Volavka, 1993; Wetzel et al., 1995; Joutsiniemi et al., 2001; Knott et al., 2001; Cerdan et al., 2005), it does not necessarily mean that the former is causative. It is possible that the relationship represents an epiphenomenon: those with more severe psychotic symptoms receive higher neuroleptic dosages, but it is possible that these symptoms themselves are causally related to the oscillatory activity.

The implications of the above are threefold. First, it suggests that it would be useful to enroll first-break, relatively drug naïve patients in future MEG studies of schizophrenia, to the extent possible. Serial MEGs could then be performed to help ascertain the effects of psychotropic medications. Second, additional analysis of existing data—for example, explicitly calculating the correlation between medication dosage and extent and nature of psychotic symptoms—may help to clarify this question. Finally, even if future MEG studies do prove some causative relationship between neuroleptic dosage and temporal lobe theta activity, this is a potentially significant finding, perhaps giving insight into the mechanism of action of these drugs.

4.2.3 MEG studies did not reveal prominent frontal delta activity in

schizophrenic patients—Historically, a number of EEG studies of schizophrenic patients have found increased frontal lobe delta band activity (Buchsbaum and Haier, 1987; Sengoku and Takagi, 1998; Hughes and John, 1999). However, this was not a notable finding of the MEG studies reviewed here (see Table 1a). What accounts for this difference? Three possible explanations are detailed below.

Most schizophrenic subjects in EEG and, as mentioned above, MEG studies are medicated. Because the nature of these medications has changed over time (Shen, 1999), the bias they

introduce in studies of oscillatory activity may have changed also. Initially used antipsychotics—the so-called typical neuroleptics—have D2 receptor blockade as their putative mechanism of action. They include medications such as chlorpromazine (introduced 1954), haloperidol (1958), and molindone (1975). The so-called atypical antipsychotics employ a different, though not entirely understood, mechanism of action and have agonisms and antagonisms at multiple receptor sites (Rosenbaum et al., 2005). These medications include risperidone (1994), olanzapine (1996), and quetiapine (1997), among others. Because it was felt that the atypical antipsychotics had generally more favorable side effect profiles, these drugs have seen increasing use as first-line agents for schizophrenia since their introduction.

There is a substantial literature examining antipsychotics' effects on EEG frequency distribution. Studies looking at chlorpromazine (Small et al., 1987), haloperidol (Saletu et al., 1990; Begic et al., 2000; Yamada et al., 2004), and the typical antipsychotics chlorprothixine (Saletu et al., 1987) and remoxipride (Saletu et al., 1990) have shown that these agents increase delta band activity in frontal lobes. There fewer studies looking at the atypical antipsychotics, but, in contrast to the typicals, they are seen to have minimal effect on frontal delta activity (Czobor and Volavka, 1993; Wetzel et al., 1995; Hubl et al., 2001; Cerdan et al., 2005). This is significant because many of the EEG studies in question were carried out in the period *pre-dating* atypical antipsychotics—when the frontal delta enhancing effects of the typicals would be seen. In contrast, the MEG studies reviewed were performed since 1993 (and the few patient groups treated with the typical antipsychotic haloperidol [see Table 1a] did show increased frontal delta).

Another reason that the EEG literature may show increased frontal delta activity is that it might contain blink or eye movement artifacts. Studies that have looked at this phenomenon in non-psychiatric subject groups have found that removing the effects of eye blink, horizontal eye movement, or vertical eye movement markedly decreases frontal delta activity (Torello, 1989). Indeed, it has been shown that the measured effect of ocular artifact in the frontal region can be larger than the underlying brain activity that the EEG is intended to record (Gasser et al., 1992). In schizophrenic patient groups this effect is magnified as these patients tend to show more eye movements and blinking than controls (Stevens, 1978; Karson, 1983; Matsue et al., 1986). Karson et al (1987) examined this question directly in an EEG study of schizophrenic patients. By monitoring horizontal eye movements via electrodes placed at the outer canthus of each eye, and monitoring blinks and vertical eye movements by examination of leads directly above the eyes, they were able to eliminate from analysis those epochs containing ocular motion contamination. Doing this, they found some generalized increased delta among schizophrenic patients; no tendency for greater frontal delta activity was seen. Of note, in 10 of the 13 MEG studies reviewed here, eye movement correction was included in the study design (in the remaining three studies—a case report, an abstract, and a letter—it is not mentioned).

One final possible explanation relates to differences between the two recording technologies. EEG is thought to be more sensitive to measuring distributed sources of brain activity than MEG (Goldenholz et al., 2008). Also, EEG is more apt to pick up deeper sources (Leijten, 2003; Goldenholz et al., 2008). Thus, it might not be safe to conclude that this 'frontal' delta is actually in the frontal lobe, as suggested by the EEG literature, unless some type of source analysis was performed.

4.2.4. It may be useful for future MEG studies to examine a broader range of frequencies—Almost all of the studies reviewed in this paper looked only at lower frequency (delta and theta) oscillations. However, those MEG studies that did examine faster frequencies (Kissler et al., 2000) found abnormalities in the gamma range also.

Importantly, some other studies have pointed to gamma frequency oscillations in understanding particular schizophrenic symptomatology: a case report (Baldweg et al., 1998) has been presented in which a schizophrenic patient experiencing hallucinations shows high degrees of EEG gamma activity. This is not surprising, given the hypothesized role of gamma activity in binding sensory stimuli into coherent percepts. Consistent with this functional interpretation is an MEG study (Llinas and Ribary, 1993) on non-psychiatric subjects, in which they found greater 40 Hz (gamma) activity in sleeping subjects during dreaming. One interpretation of these studies is that the gamma oscillations observed originated in auditory cortex (in the superior temporal lobe) or other sensory cortex, whereas the increased theta that has been seen among schizophrenics originates in hippocampus. There are also a number of studies that indicate that schizophrenics at baseline may show a decreased ability to support gamma band oscillations. For example, Kwon et al (1999) exposed schizophrenic patients to auditory click trains at 20, 30, and 40 Hz and simultaneously measured brain oscillatory activity. They found that schizophrenic patients had a unique inability to attune to 40 Hz (gamma) input. Clearly, the exact nature of the gamma dysfunction in schizophrenics is not clear, and there may be state, rather than strictly trait effects. It is likely, in any event, that additional MEG studies of the gamma frequencies could be very useful.

4.3. Conclusions and Future Directions

Schizophrenia is a highly heterogeneous disorder, one that may be more accurately described as a group of partially overlapping syndromes as opposed to one unified disease. Indeed, current classification schemes for the illness (A.P.A., 1994) are based on co-occurring clusters of clinical symptoms, rather than pathophysiologic considerations. This heterogeneity could in part explain some of the differences seen in the studies reviewed. MEG can provide information on function that imaging modalities like CT and MRI cannot, and may provide more precise localization than EEG. Further research with larger patient groups may reveal that subtypes of schizophrenia are characterized by particular configurations of brain oscillatory activity, and specific patterns may arise that could assist in the diagnosis of the illness. Moreover, it may be useful if future studies included correlations with patient demographic variables, such as age or length of illness.

This points to the possible importance of oscillatory activity as an “endophenotype”, of sorts, in understanding the etiology of schizophrenia. A number of experimental studies have revealed pathology at the cellular and synaptic level in the brains of schizophrenic patients, often in the areas shown to exhibit abnormal MEG activity. For example researchers have shown decreased densities of GABAergic interneurons (Zhang and Reynolds, 2002) or GABA synapses (Benes and Berretta, 2001) in schizophrenic hippocampi using post mortem studies. One difficulty with these kinds of studies is that it is often difficult to interpret their findings in terms that are clinically meaningful. The analysis of oscillatory activity of brain regions, which reflects the *emergent* behaviors of large numbers of neurons working together, is an approach that may be useful in making the link between neurobiology and behavior. It is possible that these cellular-level deficiencies contribute to the changes in frequency spectra of oscillatory activity in particular brain areas of schizophrenic patients. If such connections could be made, this could be useful in two ways. First, if a particular cellular or neurochemical abnormality changes oscillatory activity in a schizophrenogenic way, it would argue that this is important in the etiology of the disease. Second, such abnormalities could serve as targets for pharmacotherapeutic interventions for the illness.

A research methodology that may be very helpful in making these kinds of connections is neurocomputational modeling. A number of neurocomputational models exhibiting oscillatory activity correlating closely with that observed *in vivo* have been described

(Wilson and Bower, 1992; Traub et al., 1999; Siekmeier, 2009). Some of these have highlighted the importance of particular cell types (e.g., inhibitory interneurons) in rhythmogenesis (Whittington et al., 2000; Vierling-Claassen et al., 2008). In the future, by constructing models of brain regions that are thought to be dysfunctional in schizophrenia and lesioning such models by including deficiencies in cell wiring that have been found in neuroanatomic studies of schizophrenic brain tissue and observing resulting oscillatory behaviors, researchers can conduct virtual or “in silico” experiments that may elucidate the underlying etiology of the illness.

Finally, future studies with MEG might benefit from the addition of simultaneous EEG recording. Recent studies have indicated that MEG has the greatest signal contribution from focal sources (less than 1 cm or so), but EEG gets significant signal contributions from larger, distributed neural currents (de Munck et al., 1992; Goldenholz et al., 2008). Thus, future studies might be advised to record both MEG and EEG simultaneously to maximized the spectral power from a variety of sources. It is also advisable to perform source analysis, such as a dipole density analysis, or using a source estimation technique that can produce distributed source estimates (Jensen and Vanni, 2002; Lin et al., 2006; Srinivasan et al., 2006).

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Figure 1.
MEG recording apparatus. (Source: <http://www.medgadget.com/archives/2005/>.)

Table 1

Table 1a. Summary of MEG studies of schizophrenics. All effects are relative to non-psychotic controls. In cases where p values are not indicated, they were not presented by authors. Abbreviations: SL source localization method (ECD equivalent current dipole, DD dipole density, MNE minimum norm estimate, SAM synthetic aperture magnetometry, O other), cntrl control, p-f prefrontal, front frontal, temp temporal, par parietal, occ occipital, α alpha, β beta, γ gamma, δ delta, θ theta, δ delta, θ theta, Hz Hertz, freq frequency, scz schizophrenic, AH auditory hallucinations.

Study	# of ctrls	# of pts	L hemisphere				R hemisphere				Freqs examined [Hz]	SL	Comments
			p-f	front	temp	par	occ	p-f	front	temp	par	occ	
Reeve et al (1993)	0												Abstract. Medication status not reported- assumed pt medicated, given chronicity of illness.
medicated		1			$\uparrow\delta/\theta$	$\uparrow\delta/\theta$				$\uparrow\delta/\theta$			ECD
Canive et al (1996)	10	11											4/11 pts (36%) vs 0% of controls showed $\uparrow$ slow waves: for 2, source was temp & par lobes; for 2, source was auditory area of superior temp plane. Pts showed lower a peak freq ($p < 0.01$) & lower total a power ($p < 0.005$) in occipital areas.
unmedicated ($\times 10$ d)		8			$\uparrow\delta, \uparrow\theta$		$\downarrow\alpha$ $\downarrow\alpha$	$\uparrow\delta, \uparrow\theta$				$\downarrow\alpha$ $\downarrow\alpha$	ECD
medicated ("novel antipsychotic")													
Canive et al (1998)	10	5			$\uparrow\delta$		$\downarrow\alpha^{**}$			$\uparrow\delta$		$\downarrow\alpha^{**}$	ECD
unmedicated ($\times 10$ d)													60% of pts vs 0% of controls showed $\uparrow\delta$; one of these also showed $\uparrow\theta$. The a abnormality seen
medicated		5					$\downarrow\alpha^{**}$					$\downarrow\alpha^{**}$	

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Study	# of ctrls	# of pts	L hemisphere					R hemisphere					Freqs ex- amined [Hz]	SL	Comments
			p-f	front	temp	par	occ	p-f	front	temp	par	occ			
															was an unusually low peak frequency & amplitude.
Sperling et al (1999) medicated (clozartil)	20	10	$\downarrow \delta/\theta$		$\uparrow \delta/\theta, \uparrow \beta^*$								δ/θ (2–6), α (7.5–12), β (12.5–30)	DD	For δ/θ , temp-par localization predominated in 80% of sez group, central location predominated in 90% of controls. “Central” location is taken to be in the front-temp region.
		10	$\uparrow \alpha^{\dagger}$		$\uparrow \delta/\theta, \uparrow \alpha^{\dagger}$								$\uparrow \alpha^{\dagger}$		
Ishii et al (2000) unmedicated	0	1											δ (0.5–4), θ (4–8), α (8–13), β (13–25), γ (25–60)	SAM	When MEG was subsequently performed & pt was medicated, no $\uparrow$ in θ was seen.
Kissler et al (2000) 13 medicated + 2 unmedicated	15	15	$\downarrow \gamma 1^{**}$	$\downarrow \gamma 1^{**}$	$\downarrow \gamma 1^{**}$								α (8–12), $\beta 1$ (13–20), $\beta 2$ (21–29), $\gamma 1$ (30–45), $\gamma 2$ (46–60),	O	$\gamma 1$ & $\gamma 2$ effects were seen during mental arithmetic task; $\gamma 3$ effects were generalized. Overall, pts tended to show more activity in $\beta 2$ than controls ($p = 0.08$, not

Table 1a. Summary of MEG studies of schizophrenics. All effects are relative to non-psychotic controls. In cases where p values are not indicated, they were not presented by authors. Abbreviations: SL source localization method (ECD equivalent current dipole, DD dipole density, MNE minimum norm estimate, SAM synthetic aperture magnetometry, O other), cntrl control, p-f prefrontal, front frontal, temp temporal, par parietal, occ occipital, α alpha, β beta, γ gamma, δ delta, θ theta, Hz Hertz, freq frequency, scz schizophrenic, AH auditory hallucinations.

Study	# of ctrls	# of pts	L hemisphere				R hemisphere				Freqs examined [Hz]	SL	Comments
			p-f	front	temp	par	occ	p-f	temp	par	occ		
Fehr et al (2001)	20	26 medicated + 1 unmedicated									$\gamma 3$ (61–71)		shown). No rel'n seen between med dose & $\gamma 1$, $\gamma 2$, or $\gamma 3$.
													The authors found generally good agreement between the dipole density & minimum norm estimate methods of localizing oscillations; only dipole density results are included here.
Sperling et al (2002)	30	medicated (haldol)									δ (1.5–4), θ (4–8)	DD, MNE	
Fehr et al (2003)	17	21 medicated + 9											Temporal δ was equally prominent in med-icated vs unmedicated pts. For temporal θ , there was no group difference; however pts with higher med dosage

Table 1a. Summary of MEG studies of schizophrenia. All effects are relative to non-psychotic controls. In cases where p values are not indicated, they were not presented by authors. Abbreviations: SL

Study	# of ctrls	# of pts	L hemisphere					R hemisphere					Freqs ex- amined [Hz]	SL	Comments
			p-f	front	temp	par	occ	p-f	front	temp	par	occ			
unmedicated															
Sperling et al (2003)	20												δ/θ (2–6), β (12.5–30)	DD	Letter. For δ/θ and β frequency ranges, temp-par localization predominated for 89% of schizophrenic pts.
medicated (haldol)		20	$\uparrow\delta/\theta^*, \uparrow\beta^*$			$\uparrow\delta, \theta^*, \uparrow\beta^*$					$\uparrow\delta, \theta^*, \uparrow\beta^*$				
Weinbruch et al (2003)	18												δ (1.5–4), θ (4–8)	DD	No difference in distribution of δ & θ activity between medicated and unmedicated scz pts.
scz pts, medicated & unmedicated		29			$\uparrow\delta^*, \uparrow\theta^*$	$\uparrow\delta, \uparrow\theta$						$\uparrow\delta^*$			
affective d/o pts,		27	$\downarrow\delta^{**}, \downarrow\theta^{**}$	$\downarrow\delta^{**}$			$\downarrow\delta^{**}, \downarrow\theta^{**}$								
Ropohl et al (2004)	13												δ/θ (2–6), β (12.5–30)	DD	$\uparrow\beta$ was seen during periods of AH.
medicated		1			$\uparrow\beta$										
Reulbach et al (2007)	8												δ/θ (2–6), β (12.5–30)	DD	Hallucinating pts showed greater β activity in temporal lobes bilaterally compared w/ non-hallucinating pts (p < 0.001).
unmedicated ($\times 3$ d)		16			$\uparrow\delta, \theta^{**}$						$\uparrow\delta, \theta^{**}$				

Table 1b. Demographic and clinical information of patients in reviewed studies. Abbreviations: dx diagnosis; LOA length of illness; DSM IV/III-R Diagnostic and Statistical Manual of the American Psychiatric Association, Version 4/3-Revised; ICD International Statistical Classification of Diseases and Related Health Problems, Version 10. See text for additional details regarding diagnostic categories.

Study	# of pts	Male/female	Avg age (SD) [yrs]	Avg LOA (SD) [yrs]	Inclusion criteria & clinical characteristics
Reeve et al (1993)	1	0/1	41.0 (N/A)	20.0 (N/A)	Pt suffered from unremitting psychosis.
Canive et al (1996)	14 [*]	14/0	44.1 (7.7)	19.9 (6.5)	DSM III-R dx of schizophrenia; total PANSS score >60 and <120.
Canive et al (1998)	5 [*]	5/0	44.8 (--)	-- (--)	DSM IV dx of schizophrenia; total BPRS score > 36.
Sperling et al (1999)	20	20/0	29.8 (5.75)	6.8 (2.4)	ICD-10 dx of paranoid schizophrenia (F20.0).
Ishii et al (2000)	1	1/0	28.0 (N/A)	1.0 (N/A)	DSM IV dx of schizophrenia (paranoid type).
Kissler et al (2000)	15	11/4	30.2 (9.4)	-- (--)	DSM IV dx of schizophrenia (type not specified).
Fehr et al (2001)	28	22/6	30.9 (9.6)	0.6 (0.02-2.1) ^{**}	DSM IV dx of schizophrenia (paranoid or disorganized).
Sperling et al (2002)	40	23/17	36.0 (3.8)	6.6 (2.4)	ICD-10 dx of paranoid schizophrenia (F20.0).
Fehr et al (2003)	30	18/12	31.6 (8.9)	1.8 (--)	Majority of pts (22) had ICD-10 dx of paranoid schizophrenia (F20.0); remainder had other subtypes (disorganized, schizophreniform, undifferentiated, or schizoaffective).
Sperling et al (2003)	20	10/10	37.5 (3.4)	-- (--)	ICD-10 dx of paranoid (F20.0) or residual (F20.5) schizophrenia; newly diagnosed.
Weinbruch et al (2003)	29	17/12	31.6 (8.9)	-- (--)	DSM IV dx of schizophrenia (18 paranoid type, 11 disorganized type).
Ropohl et al (2004)	1	1/0	33.0 (N/A)	20.0 (N/A)	ICD-10 dx of paranoid schizophrenia (F20.0).
Reulbach et al (2007)	16	9/7	33.0 (2.8)	6.4 (2.4)	ICD-10 dx of paranoid schizophrenia (F20.0).

^{*} Significant at p < 0.05.

^{**} Significant at p < 0.01.

[†] Trend only (not significant at p < 0.05).

[‡] Numerical ranges were not specified.

^{*} Some patients were subjects in both medicated and unmedicated arms of the study; therefore, the total number of patients listed may differ from that of Table 1a.

^{**} SD not given; LOA range presented here

Table 2

Summary of relationships between MEG findings and psychotic symptoms. In all cases, there was a positive correlation between increased activity in the brain region/frequency band indicated and the symptoms shown. If authors quantify statistical significance, it is presented in Comments. Abbreviations: hem hemisphere, bilat bilateral, t-p temporo-parietal, pos positive, neg negative, PANSS Positive and Negative Syndrome Scale, BPRS Brief Psychotic Rating Scale, SANS Scale of Negative Symptoms, sxs symptoms. Other abbreviations are given in Table 1 caption.

Study	Hemisphere	Brain Region	Frequency	Symptoms	Instruments Used	Comments
Cantive et al (1996)	bilat	temp	δ, θ	pos & neg	PANSS	4/11 unmedicated patients showed MEG abnormalities—PANSS scores were elevated in these patients.
Cantive et al (1998)	bilat	temp	θ	pos & neg	PANSS, BPRS	3/5 unmedicated patients showed $\uparrow\theta$; 2 of these showed markedly higher PANSS scores.
Sperling et al (1999)	bilat	t-p	δ/θ^*	pos	PANSS, BPRS	Study included only pts w/ prominent pos sxs & no signif neg sxs. Formal regression not performed. See text for details.
Ishii et al (2000)	left	temp	θ	pos	AH (self report)	θ wave bursts were present during AH in unmedicated state; absent otherwise.
Fehr et al (2001)	bilat right	front, p-f temp	δ, θ δ, θ	pos pos	BPRS, SANS, PANSS	PANSS-P used for pos symptoms.
Sperling et al (2002)	bilat	t-p	δ/θ	pos	BPRS, PANSS	Significant correlation between dipole densities and PANSS P1-P7 (pos symptoms); $p < 0.002$.
Fehr et al (2003)	bilat	temp	δ	neg	PANSS-N	PANSS-N used for neg symptoms; $p < 0.05$.
Sperling et al (2003)	left left	t-p t-p	β β	pos neg	PANSS	Rel'n were found for P2 (indexes formal thought disorder; $p=0.023$) and N4 (indexes social passivity & apathy; $p = 0.016$).
Weinbruch et al (2003)	left	temp	δ	pos	PANSS-P	Rel'n was found for hallucination and paranoia subscores of the PANSS-P; $p<0.02$.
Ropohl et al (2004)	left	temp	β	pos	AH (self report)	
Reulbach et al (2007)	bilat	temp	δ, θ, β	pos	PANSS, AH (self report)	Study included only pts w/ prominent pos sxs & no signif neg sxs. Formal regression not performed. See text for details.

*This was the only effect seen in all patient groups; other effects in other frequency bands and brain areas were observed, but they varied with medication treatment (i.e., clozaril vs. haldol).