Published in final edited form as:

Schizophr Res. 2008 February ; 99(1-3): 225–237.

The Status of Spectral EEG Abnormality as a Diagnostic Test for Schizophrenia

Nash N. Boutros, Cynthia Arfken, Silvana Galderisi, Joshua Warrick, Garrett Pratt, and William Iacono

Abstract

Objective—A literature review was conducted to ascertain whether or not EEG spectral abnormalities are consistent enough to warrant additional effort towards developing them into a clinical diagnostic test for schizophrenia.

Methods—Fifty three papers met criteria for inclusion into the review and 15 were included in a meta-analysis of the degree of significance of EEG deviations as compared to healthy controls. Studies were classified based on a 4-step approach based on guidelines for evaluating the clinical usefulness of a diagnostic test.

Results—Our review and meta-analysis revealed that most of the abnormalities are replicated in the expected directions with the most consistent results related to the increased preponderance of slow rhythms in schizophrenia patients. This effect remained consistent in un-medicated patients. Only a small number of studies provided data on the sensitivity and specificity of the findings in differentiating among the psychiatric disorders that frequently appear on the same differential diagnostic list as schizophrenia (step 3 studies). No multicenter studies using standardized assessment criteria were found (step 4 studies).

Conclusions—Additional Step 3 and Step 4 studies are needed to draw conclusions on the usefulness of EEG spectral abnormalities as a diagnostic test for schizophrenia

Keywords

Schizophrenia; EEG; Spectral analysis; alpha; beta; theta; delta; differential diagnosis

INTRODUCTION

Laboratory tests are an essential part of the practice of modern medicine. Laboratory tests can be used to confirm a diagnosis, provide supportive evidence for one diagnosis vs. another, or rule out a specific disorder. The last fifty years of biological research into the pathophysiology of psychiatric disorders have yielded a number of highly replicable abnormalities. These abnormalities have the potential for being developed into clinically useful diagnostic tests. While psychiatrists do use lab tests to rule out general medical conditions as causes for mental disorders, there is no tradition for using laboratory tests in differentiating among primary psychiatric disorders. As a field, psychiatry has lagged behind in developing lab tests according to well-defined epidemiological principles.

Corresponding Author: Nash Boutros, MD, Wayne State University, School of Medicine, UPC-Jefferson, 2751 E. Jefferson, Detroit, MI 48207. Tel: 313-577-6687, Fax: 313-577-5201, Email: nboutros@med.wayne.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Laboratory tests in psychiatry tend to either not be developed into diagnostic tools (e.g., P300 evoked response in schizophrenia) or to be disseminated before their validity is fully documented (e.g., Quantified EEG) (1). The premature release of such tests could lead to disappointment of the medical community and premature abandonment of the test. Moreover, when tests are used out of context they may hinder the diagnostic and treatment process and increase the cost of management unnecessarily (2). On the other hand, an APA task force published a report in 1991 indicating that quantified EEG (QEEG) is particularly useful in detecting slow wave abnormalities and concluded that clinical replications and sharing of normative and patient data bases are necessary for the advancement of this field. They further stated that standards for training and for use of the technology in psychiatry are urgently needed. In fact, the situation has not changed appreciably since then (3).

The development of ancillary diagnostic procedures is important to help the field move forward as diagnosis in psychiatry remains the major limiting step in biological research and treatment studies (4). In order to promote a standard approach we have recently proposed a four-step process for developing laboratory-based diagnostic tests for use in aiding the diagnostic process in psychiatry (5-7). The Four-Step approach proposed is based on the guidelines for deciding the clinical usefulness of diagnostic tests published by Sackett et al (8) and the more recently published criteria specified by the Standard for Reporting Diagnostic tests (STARD) (9,10).

For Step 1, a biological variable is observed to be deviant from healthy controls in a particular patient population. The demonstration of test-retest reliability of the finding using blinding procedures is an essential component of this early step. Replication of the finding by the same or collaborating groups is important but confirmation by independent groups is essential for this particular test to move into the next step of development.

Step 2 involves demonstrating the potential clinical usefulness of the specific finding. The two most important objectives at this step are demonstration of difference between the target patient population and appropriate comparison groups (these should be groups of patients with diagnoses that commonly appear on the differential diagnostic list of the target disorder). This is an important point as a biological abnormality may be common to two disorders that hardly ever appear on the same differential diagnostic list (e.g., schizophrenia and dementia in a young adult). While such finding would be of considerable scientific interest, it would not particularly decrease the diagnostic potential of the finding. On the other hand, an abnormality that is equally common to disorders that frequently need to be differentiated from one another (e.g., Bipolar Disorder and Schizophrenia) is not likely to be useful clinically. Abnormalities with significant differential prevalence among disorders to be differentiated are likely to be able to significantly contribute to the differential diagnostic process and should progress to Step 3. Estimation of the effect size of the finding could be a reasonable guide to which findings should be considered good candidates for Step 3 studies.

During Step 3 the performance characteristics of the test should be established. Specifically, the sensitivity, specificity, positive and negative predictive values of the biological marker should be examined. These data should allow the estimation of the added diagnostic value resulting from incorporating the test into the work-up of a particular patient. The choice of the "gold standard" or reference test is an essential component of this step. This is the standard against which the test being developed will be measured. The currently accepted gold standard in psychiatric diagnosis is the "Best Estimate Diagnosis" (11). Best Estimate Diagnosis is reached by agreement among a number of experts relying on multiple sources of information and with a standardized scale with demonstrated validity and reliability. At this step, the clinical characteristics of the patient group identified by the test are usually further delineated. Due to the heterogeneous nature of psychiatric disorders, it would be naïve to expect any one biological test to be able to identify all patients that are classified into a certain DSM-based category (e.g.,

schizophrenia). It is much more likely that a particular test will be able to identify one or more subgroups within these categories. Defining the clinical characteristics of the subgroup that is identifiable by a particular test would be very important for the test to be considered for clinical use. Factors such as effects of illness duration, severity, and the effects of medications should also be defined during step three. At this step, the test would be considered “promising” for development as a diagnostic test (12).

Step 4 defines the clinical application of the test and helps standardize the technique used in large and multicenter clinical trials. Multicenter trials should pave the road towards standardization of laboratory procedures used to conduct the test as well as providing data regarding cost effectiveness and impact on both short-term and long-term clinical outcomes. Studies in earlier steps depend on smaller samples of control subjects that are usually locally formed. On the other hand, Step 4 studies should begin to develop larger normative databases that can eventually be used to examine an individual’s data. Development of such databases can be challenging and will require collaboration among research groups concerned with the specific test being developed.

We have previously documented that the four-step approach can be useful in determining the stage of development of a biological finding into a clinically utilizable laboratory test (6). In that report, the reported increased theta activity in the resting EEGs of individuals with ADHD is a highly promising finding for development into a clinical test and that step 4 studies (large and multicenter studies) are still needed for the actual clinical dissemination of the test. The purpose of the current report is to examine, in a similar manner, the status of development of spectral EEG deviations as a diagnostic tool for schizophrenia. This is important because as early as 1965 Fink and Colleagues (13) provided evidence that spectral analysis of the resting EEG of schizophrenia patients could differ significantly from that of patients with depressive disorders. Subsequently, an extensive EEG in schizophrenia literature has accumulated (14, 15).

Choice of spectral EEG as the focus of this review was based on the fact that it is the simplest quantifiable EEG measure that has long been studied in schizophrenia. Given its long history of proven applicability in clinical neurology, it is of considerable interest to appraise the status of this literature for its potential as a diagnostic aid for schizophrenia. While the focus of the current review is not on the physiological mechanisms underlying EEG abnormalities in schizophrenia, an extensive literature addressing this aspect does exist. Most prominently, slowing of the EEG has been linked to an impaired subcortical synchronization system including the mesencephalic reticular formation, nucleus reticularis and the thalamus (16). Other EEG derived measures, such as event related potentials and evoked gamma oscillations, that may have similar utility, have been recently reviewed elsewhere (17).

METHODS

We began with a search for all papers that were cross referenced for EEG and psychosis. The search included Medline, PsychInfo, and Current Contents and yielded 215 citations. The search was then narrowed by including the terms “human” and “English Language”. With these two terms the number of citations decreased to 147. A second search strategy looking for cross references between EEG and schizophrenia was also utilized and proved more profitable with 820 citations and 652 citations with the “human” and “English Language” terms added. All Medline and most Current Contents citations were included among the PsychINFO citations.

The first level of screening was based on study titles. This step was mainly for the exclusion of irrelevant topics and methodologies. Papers not examining the clinical entity of

schizophrenia or using methodology other than quantified EEG (i.e., routine visual analysis of the EEG, evoked potentials, or polysomnography), were excluded.

Abstracts of the remaining citations were then reviewed to determine the papers that specifically examined the spectral analysis of the EEG in schizophrenia populations. Papers were excluded for the following reasons: using quantified EEG to examine laterality deviations, examining EEG coherence abnormalities, and lacking both one schizophrenia study group and one normal control group. The remaining studies (N=80) were then reviewed by two of the authors (NB and either JW or GP) to define the articles that specifically examined the presence or absence of the various EEG spectral abnormalities reported in schizophrenia during resting condition (either alone or among other conditions). This was an important inclusion criterion as the activating procedures varied widely among studies. Upon review of the full manuscripts, seventeen additional papers were excluded for lack of a healthy control group, six were excluded for not reporting spectral EEG data, and three had no resting condition. All papers meeting all criteria (N=53) were included in the review (Table 1).

The 53 included studies were reviewed for the criteria proposed by Sackett (8) as well as the Four-Step approach. The reader is referred to Table 1 in Boutros et al, 2005 for a Table listing the 8 Sackett criteria as well as their corresponding steps of the proposed Four-step approach (6). Studies were assigned to a step based on the goals of the study. Studies aiming at demonstrating differences between patients and healthy controls were considered Step 1 studies (these included all papers contributing to the meta-analysis). Studies incorporating appropriate patient control groups were considered Step 2 studies. Studies examining the performance characteristics of the test (and thus addressing its clinical utility) were classified as Step 3 studies. Finally, multi-center studies incorporating appropriate patient control groups are classified as Step 4 studies.

A meta-analysis of spectral EEG abnormality in schizophrenia was also conducted. The meta-analysis was limited to those studies comparing spectral power between one group of schizophrenia patients and one group of healthy control subjects, irrespective of topographic location, and testing the hypotheses that EEG abnormalities were in the expected directions. These expected directions were increased delta, increased theta, decreased alpha, and increased beta power. Unfortunately, the studies lacked sufficient information (i.e., means and standard deviations) to calculate magnitude of effect sizes. In cases where findings from the same samples were reported in different papers, duplicate reports were excluded.

The hypotheses were tested using one-sided p-values with statistical significance set at the 0.008 level to correct for multiple comparisons. For studies reporting “not significant”, the F-statistic (if reported) was used to determine the p-value. Otherwise, a sensitivity analysis was conducted by assigning a p-value of 1.0, 0.5 and 0.6 as well as excluding the study from the analysis. Analysis also considered the subgroup of unmedicated patients (n=7 studies) separately. The significance level was set at 0.025 for this later analysis. As stated by many, including Petitti (18), meta-analysis’ contribution is greatest when there are many studies examining an issue, each with few participants. As one of the major threats to meta-analysis is publication bias in which nonsignificant differences are not submitted or accepted for publication, combining 3 or fewer studies would be especially vulnerable to this bias. Hence, only those bandwidths with at least four published studies meeting criteria were included in the analysis.

The meta-analysis used the Stata statistical package version 9.0 (Stata Corp, Texas) with the METAP module (19). This module requires only the one-sided p-values to test the hypotheses.

In order to conduct a meta-analysis for studies comparing the differential prevalence of spectral EEG abnormalities between schizophrenia and other disorders (i.e., step 2 studies), a sufficient

number of studies with rather similar methodologies (i.e., group choices, inclusion exclusion criteria, recording and analysis methods), would be necessary. Based on the initial review of the literature, it was decided that the available literature cannot support a meta-analysis even for the most obvious differential diagnostic entities like major depression with psychotic features or bipolar disorder.

RESULTS

Table 1 shows the studies included and the step they qualified for. Of the 53 studies included in the review, 40 studies qualified as Step 1 studies, 10 as Step-2 and only three as Step 3 (14,15,20).

A total of 15 studies comparing one patient group with one healthy control group with sufficient summary information were included in the meta-analysis (starred papers in Table 1). The total sample size of participants included was 799 (for the patient group the range was 12 - 102 and for the healthy control group the range was 9 - 102). Table 2 lists the frequency ranges utilized by studies included in the meta-analysis. For **theta**, there were 13 studies included in the meta-analysis with 11 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant”, the estimated p-value was $1.05 * 10^{-9}$. For **delta**, there were 13 studies included in the meta-analysis with 10 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant”, the estimated p-value was $6.17 * 10^{-8}$. For **alpha**, there were 7 studies included in the meta-analysis with 4 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant”, the estimated p-value was 0.001. For **alpha 2**, there were 7 studies included in the meta-analysis with 5 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant” the estimated p-value was 0.0009. For **beta 1**, there were 6 studies included in the meta-analysis with 2 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant”, the estimated p-value was 0.02 or not significant. For **beta 2**, there were 8 studies included in the meta-analysis with 2 of them statistically significant. For the analysis assigning p-value of 0.5 to “not significant”, the estimated p-value was 0.006 or not significant. Finally, the meta-analysis was limited to studies including un-medicated patients. Given the small number of available studies, the meta-analysis was restricted to theta and delta activity. The nominal p-values were 0.000069 and 0.00027, respectively.

DISCUSSION

A number of major findings emerge from the analyses above. First, an overwhelming majority of published research on EEG spectral abnormalities in schizophrenia samples document the presence of such deviations. As strongly suggested by the work of Kemali et al (21) and Galderisi et al (22), these EEG deviations are unlikely to be medication induced, and this was borne out by the meta-analysis performed for all studies meeting criteria for inclusion as well as studies where only un-medicated patients were included. Our second important observation concerned the lack of evidence supporting a systematized effort toward translating the demonstrated EEG abnormalities to a clinically utilizable test. Among the ten identified Step 2 studies, an early study suggested that an EEG profile can be detected in schizophrenia patients but not in non-schizophrenia psychotic patients (23). A number of subsequent studies suggested that the noted increased slow wave is seen significantly more in schizophrenia populations (24-27). In a latter study, the investigators pointed out that the slow wave abnormality (mainly delta increase) is more or less localized to frontal lobe regions (28). A frontal localization of EEG abnormalities received support from a number of studies (24,29-38). A smaller number of studies found spectral EEG abnormalities to be localized to the more posterior regions of the brain (39-41). The work by John et al (29) strongly suggests that patients showing different patterns of topographical distribution of EEG deviations represent different biological subtypes

of the disorder. Other studies failed to support a differential prevalence of slow wave abnormality in schizophrenia population when compared to bipolar patients (42). When schizophrenia patients were compared to healthy controls, the classification power was high but when a depression group was added the classification power decreased (28). Nonetheless, they noted that schizophrenia patients who were classified correctly did demonstrate the increased delta activity in the frontal regions (28)

Sponheim and colleagues (41) suggested that the difference in slow wave prevalence may be more related to the season of birth rather than the diagnostic group. They reported that non-winter born schizophrenia and non-schizophrenia psychotic patients had similar increase in the preponderance of slow waves. Subsequently, the same group provided evidence that within the schizophrenia population, it is the group with more negative symptoms and larger ventricles that exhibit the increased slow wave abnormality (42). It should be noted that both studies recorded EEG activity only from central regions, and thus did not examine the added value from the topographical distribution of the abnormality.

Only three studies qualified as Step 3 investigations. Starting with the landmark Shagass paper (14), the EEGs of schizophrenia patients were compared to those of patients with affective disorders, personality disorders and healthy controls. They reported a sensitivity of 50% and specificity of 90% when schizophrenia patients were compared to patients with major depression. Subsequently, 78% sensitivity and 85% specificity were reported comparing largely similar groups (20). Most recently, investigators could not confirm a significant differentiating power with reliance on EEG alone (15). These investigators suggested that batteries of tests may be necessary to improve the power of differentiation among patient groups. Most interestingly, they reported that nailfold plexus visibility was the most differentiating variable between schizophrenia and affective disorder patients (15).

No Step 4 studies were found. This could reflect the fact that such studies would be too expensive particularly in the current funding environment. Alternately, the absence of Step 4 studies could reflect a sense of prematurity of such study at this time. Given the large number of Step 1 and Step 2 studies and the relatively consistent findings among the studies, we propose that either additional Step 3 or Step 4 studies are appropriate at this time.

The next major finding is the relative consistency across reports indicating an increased preponderance of slower rhythms. While a number of studies failed to support the increased slow waves, decreased alpha, increased beta pattern, a majority of studies were supportive of this profile. A small number of studies found deviations in directions opposite to that proposed by the more common pattern. This most likely is a reflection of the heterogeneity of the disorder. Indeed, in view of the recognized heterogeneity, it is surprising that a reasonably consistent pattern emerges. The landmark study by John and colleagues (29) showed that five clusters of EEG variables can be identified among large groups of chronic schizophrenia patients. When only drug naïve patients are included only three clusters can be found. None of these clusters correlated significantly with clinical variables. The above findings are indeed amazing in light of the marked variations in the techniques used to collect EEG data. For example, four of the studies included in the meta-analysis reported relative (i.e., the percentage of the entire power of the EEG signal in each of the frequency ranges; marked studies in Table 2). The majority of studies however reported the absolute power in each of the examined frequency ranges (μV^2). Table 2 provides a summary of the recording and analyzing techniques used in the studies included in the meta-analysis. It becomes readily apparent that there are no two studies that utilized identical techniques. While this strongly suggests that the identified abnormalities may be resistant to the effects of technique, there is no doubt that such variation (e.g., spectral frequency ranges utilized, eyes-open vs. eyes-closed, reporting absolute vs. relative power) decreases the effective accumulation of data in order to move more

expeditiously towards clinical applicability. It should be noted however that in general investigators in this field paid attention to the issue of artifact contamination, particularly eye-movement resulting in increased slow wave activity in the frontal regions. The degree to which this caution was exercised varied among reports and the technique used to exclude or remove artifacts varied from simple visual inspection to complicated procedures like high-resolution fragmentary decomposition (43). One study specifically looked at the effect of careful removal of eye artifact on the distribution of delta activity (44). They found that after removal of eye movement artifact, the frontal preponderance disappeared but the overall increased delta activity in schizophrenia patients remained, further highlighting the importance of standardizing this procedure in future studies.

It is strongly justified, based on available literature, to conclude that the delta excess (and to a lesser extent the theta excess), is a strong and bona fide biological marker of schizophrenia. With proper development, it carries a significant promise for being translated into a clinically useful test.

Heterogeneity of schizophrenia is multifactorial. Besides the varied possible essential pathophysiologies, heterogeneity can be secondary to subject-related factors like age, race and gender or illness-related factors like effects of medications (including acute effects or time between dosing and recording and chronic long-term effects including comparison between patients who developed tardive symptoms and those with comparable exposure who did not), chronicity (including effects of institutionalization), drug abuse and other co-morbid conditions. Recording technique related factors like eyes open and eyes closed, the employment of a cognitive task during recording, or the number and locations of electrodes used can also contribute to variation across studies. All the above factors are potential moderators of the biological abnormality under examination. It is thus not entirely surprising that some studies deviated from the modal pattern. Multiple studies, many more than were available for this meta-analysis, specifically addressing one or more of these moderators, would be needed to characterize the influence of any particular variable. We found only single studies addressing some of these factors, as discussed below.

A number of studies included two schizophrenia groups and a healthy control group. In most of these studies, the three groups differed significantly on some spectral EEG parameters. For example, treatment responsive patients tended to have more fast activity and a lesser increase in slow activity as compared to treatment non-responsive patients (45). Other studies found differences between paranoid and hebephrenic patients (32), medicated and un-medicated patients (46), and patients with and without enlargement of lateral ventricles (37). Moreover, a lack of standardized methodology, including reporting the means and standard deviations, characterizes the literature. In attempting to assess the effect sizes of the different EEG spectral findings, this became a major obstacle and caused the calculation of the effect size to be abandoned. Many of the above mentioned moderators can be examined as part of Step 2 or Step 3 studies either by including different groups or co-varying for the specific factor (like age, gender, medication dosage, years since diagnosis, etc.).

While most studies did not perform repeat testing to examine test-retest reliability of their EEG findings, the test-retest reliability of the quantified EEG signal has been reasonably well established (47-48). It is of interest that in some studies the correlation coefficient is higher in schizophrenia patients $r=0.94$ than healthy controls with $r=0.70$ (49). Work by Lund and colleagues documented that test-retest reliability of $r=.9$ can be obtained in both schizophrenia and healthy control subjects when eight artifact-free eight-second epochs of data are used (50). In addition, EEG spectral characteristics are highly heritable (16,38,43,51-54). These findings suggest that while EEG is state dependent (varies with state of wakefulness and relaxation); each person has the equivalent of an EEG set-point, a natural spontaneous rhythm

that the individual shows under similar recording circumstances over time. The concept of a set point suggests that repeated testing with averaging across test sessions would help eliminate measurement error, thus maximizing the chances of detecting illness-related changes. It was also noted that longer recording time will be needed in patients to obtain the required artifact-free data. Modest reliability was also demonstrated when subjects were tested nine months apart (54).

In order to build on an already voluminous literature, it would be prudent to recommend procedures used by majority of studies for future studies that are aspiring to the goal of translating the EEG findings in schizophrenia to clinical diagnostic tests. We feel that at a minimum, EEG data should be reported from frontal, temporal, central, parietal and occipital electrodes bilaterally. Studies should include a “resting state” with eyes closed condition. The “resting state” needs to be clearly defined. By definition the resting state is the absence of specific mental activity. Instructions could be limited to “lie still and stay awake”; eyes closed in a light and sound attenuated room. In spite of the fact that it is impossible to make precise assumptions concerning subjects’ mental states, neuroanatomical activity patterns have been associated with resting wakefulness, which then seems to define a different functional state with respect to both sleep and any task involving perception or motor activities (55-57).

Based on the above review we recommend a minimum of 1 minute recording, provided that at least 25 artifact-free 2 sec epochs be available. Data reduction also needs standardization. Different investigators used different frequency ranges for the standard alpha, beta, theta, delta classification. This is an additional source of difficulty in interpreting the literature. Agreement on these ranges is an essential step towards standardization of EEG diagnostic studies. We propose the following frequency ranges for future studies: delta (0.5 to 3.5); theta1 (4-5.5 Hz), theta2 (6-7.5), alpha1 (8-10), and alpha2 (10.5-12.5). There is no unanimous consensus on the limits of beta bands. Kubicki et al. (58), used the following ranges: beta1 (12-18 Hz), beta2 (18-21 Hz), beta3 (21-30 Hz). Galderisi et al. (22) proposed the following ranges: beta1 (12.7-15 Hz), beta2 (15.2-26 Hz), and beta3 (26.2-35 Hz). Most recently, Laufs et al. (59), utilized the following ranges: beta1 (13-16 Hz), beta2 (17-23 Hz), and beta3 (24-30 Hz). The Galderisi recommended bands cover the widest frequency range and are recommended here. Standardization of artifact removal techniques, particularly eye movement, would also be desirable. Finally, statistical analysis should provide means and standard deviations as well as p-values.

In conclusion, the EEG profile of schizophrenia emerges as a strong candidate for development into a diagnostic test. Resting EEG has several advantages over other methods for intermediate phenotype investigations of psychiatric patients: it is easily assessed, it can be performed in almost any psychiatric setting, and is well tolerated by almost all patients (60). Even with the serious challenge of heterogeneity consistent effects were found, further supporting the need to systematically carry the research findings forward in a translational effort geared specifically towards developing a clinical laboratory-based diagnostic procedure for schizophrenia. Studies characterizing the performance characteristics of the test (sensitivity, specificity, positive and negative predictive values) are still necessary. Studies designed to address Step 3 questions in a multi-center design can also be useful in propelling the translation of this highly promising finding to a clinically useful test. As can be readily seen from Table 2, EEG studies can be particularly problematic when replications are necessary due to the large number of recording variables. Data analysis as well can be problematic for replication studies. Studies vary greatly in the data reduction methodology and statistics applied. In view of the progressive increase in the number of electrodes used to record the EEG from the standard 21 to 64, 128, or even 256, the development of methodology that would allow data from these studies to be amenable to subsequent reviews and meta-analyses is essential.

Could the adoption of the 4-step approach function more as a hindrance than a facilitator for translating promising biological findings to clinically useful tests? The answer to this can only be learned through experience. A number of major yard sticks necessary for this approach to be effective are yet to be developed. For example the number of independent replications necessary to consider a finding promising enough to move to Step 2 studies and the effect sizes that would predict the eventual success of a finding as a diagnostic test need to be ascertained. As mentioned above, only single studies addressed within-schizophrenia subgroups (and were suitable for the meta-analysis). This important issue will need to be addressed when sufficient studies become available as to allow cluster or multidimensional scaling analyses to be performed.

It should be noted that while scientific inquiry is usually hypothesis-driven with innovativeness being at its core, developing diagnostic tests (or for that matter pharmaceutical agents) would be data-driven with standardization at its core. It is thus essential that standards for studies attempting to develop a biological finding into a diagnostic test be developed and adopted by the scientific community. At a minimum, studies aspiring to contribute to the development of a diagnostic test should adhere to the publication requirements proposed by the STARD initiative (9).

From the current effort as well as our previous study (6) and available literature, we conclude that in view of the extreme heterogeneity problem existing in almost all psychiatric disorders, translating promising biological findings into clinically useful laboratory tests is a difficult proposition. In the absence of reasonably accepted guidelines for proceeding with such effort, the likelihood of success is minimal. Studies using standardized methodology and developed with the intent of translating a biological finding into a clinical laboratory test are essential for the eventual introduction of objective laboratory tests into the every day diagnosis and management of psychiatric disorders.

Acknowledgments

This work was supported in part by Grant 1 R01 MH58784 from the National Institute of Mental Health and by the Joe Young funds of the Department of Psychiatry and Behavioral Neurosciences at Wayne State University.

REFERENCES

1. Nuwer MR. Uses and abuses of brain mapping. *Arch Neurol* 1989;46(10):1134–6. [PubMed: 2803075]
2. Steffens, DC.; Krishnan, KRR. Laboratory testing and neuroimaging, in *Advancing DSM: Dilemmas in Psychiatric Diagnosis*. Philips, KA.; First, MB.; Pincus, HA., editors. American Psychiatric Press; Washington, DC: 2003. p. 264
3. Quantitative electroencephalography: a report on the present state of computerized EEG techniques. American Psychiatric Association Task Force on Quantitative Electrophysiological Assessment. *Am J Psychiatry* 1991;148(7):961–4. [PubMed: 2053652]
4. van Praag HM. Over the mainstream: diagnostic requirements for biological psychiatric research. *Psychiatry Res* 1997;72(3):201–12. [PubMed: 9406910]
5. Boutros NN, Struve F. Electrophysiological assessment of neuropsychiatric disorders. *Semin Clin Neuropsychiatry* 2002;7(1):30–41. [PubMed: 11782889]
6. Boutros N, Fraenkel L, Feingold A. A four-step approach for developing diagnostic tests in psychiatry: EEG in ADHD as a test case. *J Neuropsychiatry Clin Neurosci* 2005;17(4):455–64. [PubMed: 16387983]
7. Boutros N, Arfken C. A four-step approach to developing diagnostic testing in psychiatry. *Clin EEG and Neuroscience* 2007;38(2):62–65.
8. Sackett, D.; Haynes, R.; Guyatt, G.; Tugwell, P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. Lippincott Williams and Wilkins; Philadelphia: 1991.

9. Bruns DE. The STARD initiative and the reporting of studies of diagnostic accuracy. *Clin Chem* 2003;49(1):19–20. [PubMed: 12507955]
10. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Standards for Reporting of Diagnostic Accuracy. Clin Chem* 2003;49(1):1–6. [PubMed: 12507953]
11. Kosten TA, Rounsaville BJ. Sensitivity of psychiatric diagnosis based on the best estimate procedure. *Am J Psychiatry* 1992;149(9):1225–7. [PubMed: 1503136]
12. Boutros N, Zouridakis G, Rustin T, Peabody C, Warner D. The P50 component of the auditory evoked potential and subtypes of schizophrenia. *Psychiatry Res* 1993;47(3):243–54. [PubMed: 8372162]
13. Fink M, Itil T, Clyde D. The classification of psychoses by quantitative EEG measures. *Recent Adv Biol Psychiatry* 1965;8:305–12. [PubMed: 5895848]
14. Shagass C, Roemer RA, Straumanis JJ, Josiassen RC. Psychiatric diagnostic discriminations with combinations of quantitative EEG variables. *Br J Psychiatry* 1984;144:581–92. [PubMed: 6743925]
15. Sponheim SR, Iacono WG, Thuras PD, Nugent SM, Beiser M. Sensitivity and specificity of select biological indices in characterizing psychotic patients and their relatives. *Schizophr Res* 2003;63(12):27–38. [PubMed: 12892855]
16. Kirino E. Correlation between P300 and EEG rhythm in schizophrenia. *Clin EEG Neurosci* 2004;35(3):137–146. [PubMed: 15259620]
17. Van der Stelt O, Belger A. Application of Electroencephalography to the Study of Cognitive and Brain Functions in Schizophrenia. *Schiz Bull* 2007;33(4):955–970.
18. Petitti, D. Meta-analysis, decision analysis and cost-effectiveness analysis. Oxford University Press; NY: 1994.
19. Tobias, A. sbe28: Meta-analysis of *p*-values. In: Newton, HJ., editor. *Stata Technical Bulletin Reprints*. 9. Stata Corporation; College Station, TX: 1999. p. 138-140.
20. Gerez M, Tello A. Selected quantitative EEG (QEEG) and event-related potential (ERP) variables as discriminators for positive and negative schizophrenia. *Biol Psychiatry* 1995;38(1):34–49. [PubMed: 7548470]
21. Kemali D, Galderisi S, Maj M, Mucci A, Di Gregorio M, Bucci P. Computerized EEG topography findings in schizophrenic patients before and after haloperidol treatment. *Int J Psychophysiol* 1992;13(3):283–90. [PubMed: 1459885]
22. Galderisi S, Mucci A, Mignone ML, Maj M, Kemali D. CEEG mapping in drug-free schizophrenics. Differences from healthy subjects and changes induced by haloperidol treatment. *Schizophr Res* 1991;6(1):15–23. [PubMed: 1786232]
23. Etevenon P, Pidoux B, Rioux P, Peron-Magnan P, Verdeaux G, Deniker P. Intra- and interhemispheric EEG differences quantified by spectral analysis. Comparative study of two groups of schizophrenics and a control group. *Acta Psychiatr Scand* 1979;60(1):57–68. [PubMed: 474178]
24. Schellenberg R, Knorr W, Schindler M, Kropf S, Beyer H. EEG-power spectral components of schizoaffective disorders. *Schizophr Res* 1990;3(56):357–9. [PubMed: 2282342]
25. Merrin EL, Floyd TC. Average reference EEG lateralization in schizophrenic patients. *J Neuropsychiatry Clin Neurosci* 1991;3(3):307–14. [PubMed: 1687964]
26. Mientus S, Gallinat J, Wuebben Y, Pascual-Marqui RD, Mulert C, Frick K, Dorn H, Herrmann WM, Winterer G. Cortical hypoactivation during resting EEG in schizophrenics but not in depressives and schizotypal subjects as revealed by low resolution electromagnetic tomography (LORETA). *Psychiatry Res* 2002;116(12):95–111. [PubMed: 12426037]
27. Wuebben Y, Winterer G. Hypofrontality -- a risk-marker related to schizophrenia? *Schizophr Res* 2001;48(23):207–17. [PubMed: 11295374]
28. Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, Herrmann WM. Frontal dysfunction in schizophrenia--a new electrophysiological classifier for research and clinical applications. *Eur Arch Psychiatry Clin Neurosci* 2000;250(4):207–14. [PubMed: 11009074]
29. John ER, Prichep LS, Alper KR, Mas FG, Cancro R, Easton P, Sverdllov L. Quantitative electrophysiological characteristics and subtyping of schizophrenia. *Biol Psychiatry* 1994;36(12):801–26. [PubMed: 7893845]

30. Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res* 2001;50(12):41–53. [PubMed: 11378313]
31. Wada Y, Takizawa Y, Kitazawa S, Jiang ZY, Yamaguchi N. Quantitative EEG analysis at rest and during photic stimulation in drug-naïve patients with first-episode paranoid schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 1994;244(5):247–51. [PubMed: 7893770]
32. Kahn EM, Weiner RD, Coppola R, Kudler HS, Schultz K. Spectral and topographic analysis of EEG in schizophrenic patients. *Biol Psychiatry* 1993;33(4):284–90. [PubMed: 8471683]
33. Gattaz WF, Mayer S, Ziegler P, Platz M, Gasser T. Hypofrontality on topographic EEG in schizophrenia. Correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci* 1992;241(6):328–32. [PubMed: 1504108]
34. Saletu B, Kufferle B, Anderer P, Grunberger J, Steinberger K. EEG-brain mapping in schizophrenics with predominantly positive and negative symptoms. Comparative studies with remoxipride/haloperidol. *Eur Neuropsychopharmacol* 1990;1(1):27–36. [PubMed: 1983779]
35. Mukundan CR. Computed EEG in schizophrenics. *Biol Psychiatry* 1986;21(12):1225–8. [PubMed: 3756268]
36. Serafetinides EA. EEG lateral asymmetries in psychiatric disorders. *Biol Psychol* 1984;19(34):237–46. [PubMed: 6151857]
37. Takeuchi K, Takigawa M, Fukuzako H, Hokazono Y, Hirakawa K, Fukuzako T, Ueyama K, Fujimoto T, Matsumoto K. Correlation of third ventricular enlargement and EEG slow wave activity in schizophrenic patients. *Psychiatry Res* 1995;55(1):1–11. [PubMed: 8047626]
38. Omori M, Koshino Y, Murata T, Murata I, Nishio M, Sakamoto K, Horie T, Isaki K. Quantitative EEG in never-treated schizophrenic patients. *Biol Psychiatry* 1995;38(5):305–9. [PubMed: 7495924]
39. Miyauchi T, Tanaka K, Hagimoto H, Miura T, Kishimoto H, Matsushita M. Computerized EEG in schizophrenic patients. *Biol Psychiatry* 1990;28(6):488–94. [PubMed: 2223918]
40. Clementz BA, Sponheim SR, Iacono WG, Beiser M. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. *Psychophysiology* 1994;31(5):486–94. [PubMed: 7972603]
41. Sponheim SR, Iacono WG, Clementz BA, Beiser M. Season of birth and electroencephalogram power abnormalities in schizophrenia. *Biol Psychiatry* 1997;41(10):1020–7. [PubMed: 9129782]
42. Sponheim SR, Clementz BA, Iacono WG, Beiser M. Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. *Biol Psychiatry* 2000;48(11):1088–97. [PubMed: 11094142]
43. Harris A, Melkonian D, Williams L, Gordon E. Dynamic spectral analysis findings in first episode and chronic schizophrenia. *Int J Neurosci* 2006;116(3):223–46. [PubMed: 16484051]
44. Karson CN, Coppola R, Morihisa JM, Weinberger DR. Computed electroencephalographic activity mapping in schizophrenia. The resting state reconsidered. *Arch Gen Psychiatry* 744(6):514–7.198
45. Czobor P, Volavka J. Level of haloperidol in plasma is related to electroencephalographic findings in patients who improve. *Psychiatry Res* 1992;42(2):129–44. [PubMed: 1631250]
46. Morihisa JM, Duffy FH, Wyatt RJ. Brain electrical activity mapping (BEAM) in schizophrenic patients. *Arch Gen Psychiatry* 1983;40(7):719–28. [PubMed: 6860073]
47. Lifshitz K, Lee KL, Susswein S. Long-term replicability of EEG spectra and auditory evoked potentials in schizophrenic and normal subjects. *Neuropsychobiology* 1987;18(4):205–11. [PubMed: 2900484]
48. McGuire K, Katsanis J, Iacono W, McGue M. Genetic influences on the spontaneous EEG: An examination of 15-year-old and 17-year-old twins. *Developmental Neuropsychology* 1998;14:7–18.
49. Goldstein L, Sugerman AA, Stolberg H, Murphree HB, Pfeiffer CC. Electrocerebral activity in schizophrenics and non-psychotic subjects: quantitative EEG amplitude analysis. *Electroencephalogr Clin Neurophysiol* 1965;19(4):350–61. [PubMed: 4158067]
50. Lund TR, Sponheim SR, Iacono WG, Clementz BA. Internal consistency reliability of resting EEG power spectra in schizophrenic and normal subjects. *Psychophysiology* 1995;32(1):66–71. [PubMed: 7878171]
51. Lykken DT, Tellegen A, Iacono WG. EEG spectra in twins: Evidence for a neglected mechanism of genetic determination. *Physiological Psychology* 1982;10:60–65.

52. van Beijsterveldt CE, van Baal GC. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. *Biol Psychol* 2002;61(12):111–38. [PubMed: 12385672]
53. Moore JH. Computational analysis of gene-gene interactions using multifactor dimensionality reduction. *Expert Review of Molecular Diagnostics* 2004;4(6):795–803. [PubMed: 15525222]
54. Clementz BA, Sponheim SR, Iacono WG, Beiser M. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. *Psychophysiology* 1994;31(5):486–94. [PubMed: 7972603]
55. Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houde O, Crivello F, Joliot M, Petit L, Tzourio-Mazoyer N. Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull* 2001;54(3):287–98. [PubMed: 11287133]
56. Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. *J Sleep Res* 2000;9(3):207–31. [PubMed: 11012860]
57. Shulman GL, Corbetta M, Buckner RL, Raichle ME, Fiez JA, Miezin FM, Petersen SE. Top-down modulation of early sensory cortex. *Cereb Cortex* 1997;7(3):193–206. [PubMed: 9143441]
58. Kubicki S, Herrmann WM, Fichte K, Freund G. Reflections on the topics: EEG frequency bands and regulation of vigilance. *Pharmakopsychiatr Neuropsychopharmakol* 1979;12(2):237–45. [PubMed: 223177]
59. Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, Kleinschmidt A. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci U S A* 2003;100(19):11053–8. [PubMed: 12958209]
60. Winterer G, Egan MF, Radler T, Hyde T, Coppola R, Weinberger DR. An association between reduced interhemispheric EEG coherence in the temporal lobe and genetic risk for schizophrenia. *Schizophr Res* 2001;49(12):129–43. [PubMed: 11343872]
61. Ramos J, Cerdan LF, Guevara MA, Amezcua C, Sanz A. Abnormal EEG patterns in treatment-resistant schizophrenic patients. *Int J Neurosci* 2001;109(12):47–59. [PubMed: 11699340]
62. Koukkou M, Lehmann D, Federspiel A, Merlo MC. EEG reactivity and EEG activity in never-treated acute schizophrenics, measured with spectral parameters and dimensional complexity. *J Neural Transm Gen Sect* 1995;99(13):89–102. [PubMed: 8579811]
63. Sponheim SR, Clementz BA, Iacono WG, Beiser M. Resting EEG in first-episode and chronic schizophrenia. *Psychophysiology* 1994;31(1):37–43. [PubMed: 8146253]
64. Koles ZJ, Lind JC, Flor-Henry P. Spatial patterns in the background EEG underlying mental disease in man. *Electroencephalogr Clin Neurophysiol* 1994;91(5):319–28. [PubMed: 7525228]
65. Locatelli M, De Angeli A, Leone E, Grassi B, Scarone S. Factor analysis and computerized EEG: preliminary data on schizophrenic patients. *Int J Neurosci* 1993;72(34):265–70. [PubMed: 8138381]
66. Schellenberg R, Schwarz A. EEG- and EP-mapping--possible indicators for disturbed information processing in schizophrenia? *Prog Neuropsychopharmacol Biol Psychiatry* 1993;17(4):595–607. [PubMed: 8103234]
67. Elbert T, Lutzenberger W, Rockstroh B, Berg P, Cohen R. Physical aspects of the EEG in schizophrenics. *Biol Psychiatry* 1992;32(7):595–606. [PubMed: 1450286]
68. Omori M, Koshino Y, Murata T, Murata I, Horie T, Isaki K. Quantitative EEG of elderly schizophrenic patients. *Jpn J Psychiatry Neurol* 1992;46(3):681–92. [PubMed: 1362590]
69. Gasser T, Ziegler P, Gattaz WF. The deleterious effect of ocular artefacts on the quantitative EEG, and a remedy. *Eur Arch Psychiatry Clin Neurosci* 1992;241(6):352–6. [PubMed: 1504112]
70. Gambini O, Colombo C, Macciardi F, Locatelli M, Calabrese G, Sacchetti E, Scarone S. EEG power spectrum profile and structural CNS characteristics in schizophrenia. *Biol Psychiatry* 1990;27(12):1331–4. [PubMed: 2364121]
71. Westphal KP, Groezinger B, Diekmann V, Scherb W, Rees J, Leibing U, Kornhuber HH. Comparison of untreated and treated schizophrenic patients, normals, and neuroleptic-treated normals: “hypofrontality” and different EEG spectra before and during voluntary movement. *Psychiatry Res* 1989;29(3):395–8. [PubMed: 2608800]
72. Williamson PC, Kaye H. EEG mapping applications in psychiatric disorders. *Can J Psychiatry* 1989;34(7):680–6. [PubMed: 2680048]
73. Karson CN, Coppola R, Daniel DG, Weinberger DR. Computerized EEG in schizophrenia. *Schizophr Bull* 1988;14(2):193–7. [PubMed: 3201177]

74. Williamson P, Mamelak M. Frontal spectral EEG findings in acutely ill schizophrenics. *Biol Psychiatry* 1987;22:1021–1024. [PubMed: 3607126]
75. Muller HF, Achim A, Laur A, Buchbinder A. Topography and possible physiological significance of EEG amplitude variability in psychosis. *Acta Psychiatr Scand* 1986;73(6):665–75. [PubMed: 3751669]
76. Morihisa JM, McAnulty GB. Structure and function: brain electrical activity mapping and computed tomography in schizophrenia. *Biol Psychiatry* 1985;20(1):3–19. [PubMed: 3965037]
77. Iacono WG. Bilateral electrodermal habituation-dishabituation and resting EEG in remitted schizophrenics. *J Nerv Ment Dis* 1982;170(2):91–101. [PubMed: 7057175]
78. Stevens JR, Livermore A. Telemetered EEG in schizophrenia: spectral analysis during abnormal behaviour episodes. *J Neurol Neurosurg Psychiatry* 1982;45(5):385–95. [PubMed: 7086451]
79. Fenton GW, Fenwick PB, Dollimore J, Dunn TL, Hirsch SR. EEG spectral analysis in schizophrenia. *Br J Psychiatry* 1980;136:445–55. [PubMed: 7388249]
80. Kemali D, Vacca L, Marciano F, Celani T, Nolfi G, Iorio G. Computerized EEG in schizophrenics. *Neuropsychobiology* 1980;6(5):260–7. [PubMed: 6997773]
81. Tarrier N, Cooke EC, Lader MH. The EEG's of chronic schizophrenic patients in hospital and in the community. *Electroencephalogr Clin Neurophysiol* 1978;44(5):669–73. [PubMed: 77771]
82. Giannitrapani D, Kayton L. Schizophrenia and EEG spectral analysis. *Electroencephalogr Clin Neurophysiol* 1974;36(4):377–86. [PubMed: 4140064]
83. Itil TM, Saitu B, Davis S, Allen M. Stability studies in schizophrenics and normals using computer-analyzed EEG. *Biol Psychiatry* 1974;8(3):321–35. [PubMed: 4605141]

Table 1**Studies Included and Step they qualified for**

Study	Step	Sample	Findings	Comments
Harris & Melkonian, 2006* (43)	1	40 (12F) first episode, 40 (14F) CS, 40 (14F) HC.	CS had significantly higher delta, theta power.	Only central locations examined.
Kirino, 2004* (16)	1	25 (9F), UM, 25 (9F).	Increased delta and slow theta.	Increased slow activity maximal in Central and Parietal while increased B2 in frontal regions.
Sponheim et al, 2003 (15)	3	136 CS (20F), 71 AD (18F) (with psychotic symptoms), 123 (59F) HC.	Only nailfold plexus visibility differentiated affective from schizophrenia patients.	Suggests that battery of tests may be necessary.
Mientus et al, 2002 (26)	2	19 (9F) CS/ UM, 19 (9F) schizotypal, 30 (10F) depressed/um, 20 (10F) HC.	Increased delta in CS.	LORETA showed decreased slow and fast activity in the anterior cingulate in both depressive and schizotypal subjects.
Ramos et al, 2001 (61)	1	10 CS (tx resistant, 10 CS tx responsive, 10 HC	Responsive patients showed higher alpha and less delta and resistant patients showed higher fast beta.	Different EEG patterns of tx unresponsive patients
Winterer et al, 2001 (60)	1	105CS (24F), 58 (28F) HC.	Increase slow wave. No alpha or beta differences.	
Knott et al, 2001* (30)	1	17 (1F) treatment resistant CS, 17 (1F) HC.	Increased total power and power in theta and delta bands.	Delta increase is maximal in frontal and temporal regions while theta increase is generalized.
Wuebben & Winterer, 2001 (27)	2	39 (19F), CS/UM, 21 (10F) schizotypal, 68 Depressed, 254 (115F) HC.	Increase delta frontally only in CS.	Large sample size documenting differential prevalence of EEG abnormality in CS.
Winterer et al, 2000 (28)	2	32 CS, 60 AD, 49 HC	The inclusion of a depression group significantly decreased the classification power.	Schizophrenia patients classified correctly had increased frontal delta.
Sponheim et al, 2000 (42)	2	112 (20F) schizophrenia (54 first episode), 78 (21F) AD, 107 (48F) HC.	Schizophrenia patients exhibiting the pattern of increased slow and decreased alpha had more negative symptoms and larger ventricles.	The presence of these abnormalities in other patient groups did not correlate with clinical symptoms.
Sponheim et al, 1997 (41)	2	28 (4F) winter born CS, 81 (16F) non-winter born CS, 18 (7F) winter born, 58 (19) non-winter born non-schizophrenia psychosis, 31 (15F) winter born, 66 (30F) non winter born HC	Non-winter born CS and non schizophrenia psychotic patients had increased low frequency and decreased alpha power. Winter born CS and nonschizophrenia psychotic patients had no power abnormalities.	This paper strongly documents heterogeneity within schizophrenia groups.
Omori et al, 1995 (38)	1	20 (4F) CS never medicated, 20 (4F) HC.	Increased fast theta and slow alpha, and decreased fast alpha	EEG frequency at O1 correlated negatively with positive symptoms.
Koukkou et al, 1995 (62)	1	22 CS (UM, 8F), Control groups: remitted schizophrenics, neurotic, and HC.	Increased slow wave frontally and decreased alpha generally.	
Gerez & Tello, 1995 (20)	3	17 (5F) CS (pos), 17 (4F) CS (neg), 12 (7F) AD, 12 (6F) HC.	78% sensitivity and 85% specificity for classifying subjects.	Used a discriminant for schizophrenia.
Takeuchi et al, 1995* (37)	1	28 (14F) CS, 22 (11F) HC.	Increased delta, theta, and beta and decreased alpha.	Delta and theta increase maximal in posterior regions. Alpha 2 decrease is generalized.
Sponheim et al, 1994* (63)	1	44 first episode schizophrenia (11F), 58 (6F) CS, 102 (30F) HC.	Increased delta and theta and decreased alpha.	Differences between the groups in EEG bands were not dependent on electrode location.
Wada et al, 1994* (31)	1	14 (7F) CS (paranoid), never medicated, 20(10F) HC.	Increased delta and decreased fast alpha activity.	Delta increase maximal in frontal region and alpha-2 decrease seen in all brain regions.
Koles et al, 1994 (64)	2	31 (11F) CS, 22 (13F) manic, 33 (17F) depressed, 113 (56F) HC.	Spatial patterns are most differentiating with CS showing left-sided hyperactivity, depression showing right-sided hyperactivity, and bipolars bilateral hyperactivity.	

Study	Step	Sample	Findings	Comments
Clementz et al, 1994 (40)	2	50 (11F) CS, 31 (12) Bipolar, 113 (45F) HC.	Both schizophrenia and bipolar subjects showed increased delta and theta and decreased alpha.	EEG spectra did not differentiate the two groups of patients.
John et al, 1994 (29)	1	94 CS (9F), 25 (all men), 15 (2F) never medicated, 162 HC (84F)	UM and medicated groups looked largely similar: frontal theta excess, posterior alpha deficit, a very significant posterior beta deficit. Excess frontal delta was seen in UM patients only.	Drug naïve patients had excess total power with increased alpha, beta and theta. No delta abnormality.
Kahn et al, 1993* (32)	1	13 CS, 9 HC	Increase delta and alpha frequency in frontal region.	Alpha finding in contrast to most other studies.
Locatelli et al, 1993 (65)	1	23 CS (7F), 50 HC (26F).	Increased delta and theta and decreased alpha.	
Schellenberg & Schwarz, 1993 (66)	1	8 CS, 24 HC	Decreased alpha power occipitally.	
Elbert et al, 1992* (67)	1	12 (4F) CS, 12 (5F) HC.	Increased slow activity.	Only examined central regions.
Omori et al, 1992 (68)	1	20 CS (10F), 20 HC (10F). All subjects above age 60.	Increased delta and theta and decreased alpha.	Patients were CS and not late onset schizophrenia.
Gattaz et al, 1992* (33)	1	17 (5F) paranoid CS, UM, 15 (7F) HC.	Higher power in delta, fast alpha and beta bands.	Deviation most marked in left frontal sites.
Gasser et al, 1992 (69)	1	17 CS, 15 HC	Increased theta and delta.	Slow wave increase more prominent after correction for eye movement.
Kemali et al, 1992 (21)	1	20 CS (UM) and HC.	A generalized increase in delta and fast beta (15-35Hz).	
Galderisi et al, 1991 (22)	1	20 CS (7F) UM, 21 HC (8F).	Widespread increase of delta, theta, and beta amplitudes.	Chronic neuroleptics seem to normalize the abnormalities.
Merrin & Floyd, 1991 (25)	2	14 (all male) CS, UM, 9 (all male) AD, 13 (all male) HC.	Increased delta, and slow and fast beta.	
Saletu et al, 1990 (34)	1	48, UM CS, matched HC.	Decrease alpha I, increased B. Neg symptoms patients had bitemporal and frontal increased slow wave activity not seen in + sx patients.	
Schellenberg et al, 1990 (24)	2	17 CS, 20 AD, 20 SA, 23 HC.	Increased delta in right frontal region when compared to SA. Increased theta diffusely as compared to AD. Decreased alpha.	
Miyauchi et al, 1990* (39)	1	30 (9F) CS, UM, 30 (9F) HC	Increased delta and theta, Also increased slow beta and decreased fast alpha.	Abnormalities maximal in posterior regions.
Gambini et al, 1990 (70)	1	13 (3F) CS with LVE, 29 (6F) without LVE, 14 (5F) HC.	Only patients without LVE showed decrease of fast alpha.	No evidence of delta increase with LVE.
Westphal et al, 1989 (71)	1	31 CS, 13 UM CS, matched HC to each CS group.	Unmedicated did not differ from controls. Significantly increased theta power diffusely seen in medicated patients.	Study suggests increased slow activity may be drug induced.
Williamson & Kave, 1989 (72)	1	12 (2F) CS, 12 (4F) HC.	Increased beta, no theta or delta differences.	
Karson et al, 1988* (73)	1	19 (3F) CS, UM, 21(6F) HC.	Increased delta. Increased fast activity mainly on left side. Some patients had reduced alpha.	Increased delta mainly in the right hemisphere. Patients with reduced alpha had larger ventricular size.
Lifshitz et al, 1987 (47)	1	4 CS, 5 HC. Repeated testing on and off medications.	When medicated there was an increase in alpha, and less consistently decrease in delta and increase in beta.	Psychopathology tended to be inversely related to alpha power.
Williamson and Mamelak, 1987 (74)	1	12 CS (2F), 12 HC.	No significant differences in slow activity (frontal or otherwise) between CS and HC.	Faster frequencies frontally and temporally during acute exacerbation.
Mukundan, 1986* (35)	1	29 (14F) never medicated, CS, 26 (11F) HC.	Increased delta, and slow and fast beta activity. Theta and slow alpha activities were reduced.	Delta and beta-3 increase only in frontal regions. Increased beta-2 only in right frontal and decreased theta seen in temporal areas.
Muller et al, 1986 (75)	1	10 CS (5F), 10 HC.	CS more theta greatest in frontal regions.	
Morihisa & McAnulty, 1985 (76)	1	11 CS (UM), 14 CS, (medicated), HC (??).	CS (both groups) had increased delta frontally.	
Serafetinides, 1984* (36)	1	15 (all male) CS, UM, 15 (all male) HC.	Increased theta, delta and beta.	EEG measured in a frontal-temporal and a

Study	Step	Sample	Findings	Comments
				central-occipital derivations only. Most abnormalities seen in the frontal-temporal derivation.
Shagass et al, 1984 (14)	3	98 CS (47F), 52 AD (19F), 25 PD (4F), 94 (46F) HC.	Sensitivity of 54 and specificity of 89 when compared to non-patients and sensitivity of 50 and specificity of 90 when compared with major depression.	Used RDC criteria for diagnosis.
Morihisa et al, 1983 (46)	1	11 drug free (4F) and 14 medicated (3F) CS and 11 (3F) HC.	Both CS groups had elevated delta greatest in frontal regions and increased beta in postcentral region.	
Iacono, 1982* (77)	1	24 (13F) CS, 22 (15F) HC.	Increased delta and decreased alpha.	Only examined central regions.
Stevens & Livermore, 1982 (78)	1	18 CS, UM, 9 HC.	Increased delta and decreased alpha.	EEGs recorded while patients are mobile using telemetry.
Fenton et al, 1980 (79)	1	26 acute CS (13, UM, 13F), 30 CS living in the community, 22 CS institutionalized/UM, 39 HC (25F).	Acute patients had less alpha power in temporal regions, Chronic outpatients showed less alpha and beta while chronic inpatients had in addition increased slow wave activity.	Study suggests that slow wave increase may be a mark of severity.
Kemali et al, 1980 (80)	1	20 (6F) CS, UM, 19 (6F) HC	Decreased alpha occipitally.	Theta higher in non-paranoid as compared to paranoid patients.
Etevenon et al, 1979 (23)	2	6 (disorganized CS), 5 (paranoid), 7 (non-schizophrenic psychotic patients) 12 HC.	Disorganized had high alpha and paranoid low alpha. Non-schizophrenic psychotic patients did not cluster.	
Tarrier et al, 1978* (81)	1	18 CS (in community), 10 CS (chronic hospitalized/ UM, 18 HC.	Inpatients had higher energy in delta and beta ranges, CS combined had more theta than controls.	Only examined central regions.
Giannitrapani & Kayton, 1974 (82)	1	10 CS, 10 HC	Increased slow and fast waves and decreased alpha activity frontally.	
Itil et al, 1974 (83)	1	29 CS (15F), UM, 46 HC (15F).	Increased slow and fast activity and decreased alpha and lower amplitude variability.	High reliability of EEG measures in test retest.

UM=unmedicated (absence of UM designation means patients were medicated), AD=affective disorders, CS=chronic schizophrenia, HC= healthy controls.

* Indicates papers used in meta-analysis.

Table 2
Variations in EEG recording techniques among studies included in the meta-analysis

Study	#	Filter Hz	Ref	Frequency ranges (Hz) reported.						β	$\beta-1$	$\beta-2$	$\beta-3$
				Del	Th	α	$\alpha-1$	$\alpha-2$	β				
Harris & Melkonian (43)	19	0-50	LE	1-3	4-7	8-13	8-9	10-13	1				
Kirino (16) [†]	12	.5-120	LE	2-3.8	4-7.8		8-8.8	9-12.8			13-19.8	20-20.8	
Knott ^{**} (30)	21	.05-70	LE	1.5-3.5	3.5-7.5	7.5-12.5			12.5-25				
Takeuchi et al. (37)	16	1-60	LE	2-3.5	4-7.5		8-9	10-12.5			13-19.5	20-29.5	
Sponheim et al. (63) [†]	3	1-35	LE	1-3	3-1.8	8.1-13					13-1-20	20.1-25	25.1-30
Wada et al. (31)	16	.3-60	LE	2-3.8	4-7.8		8-8.8	9-12.8			13-19.8	20-29.8	
Kahn et al. (32)	19	1-70	LE	2.2-5	5.2-8	8.2-13					13.2-18	18.2-30	
Elbert et al. (67)	3	.5-15	Linked mastoids	1-7		8-12							
Mivauchi et al. (39) [†]	16	2-30	LE	2-3.8	4-7.8		8-8.8	9-12.8			13-19.8	20-29.8	
Karson et al. (73)	20	1-70	LE	4-3.9	4.3-7.8		8.2-12.9				13.5-19.9	20.3-27.3	
Mukundan (35)	16	1-70	Bipolar	2-4	4-8	8-13.2					13.2-20	20-30	30-48
Serafetinides (36)	8	NR	Bipolar	2Hz bins between 1-30 Hz (i.e., 15 ranges).									
Iacono (77) [†]	2	.1-20	LE	.1-2.9	3-7.9	8-12.9							
Tarrier et al. (81)	2	.8-250	To Cz	2-4-4	4-7.5	7.5-13.5			13.5-26				

Del=delta, Th=theta, α =alpha, β =beta.

=Number of scalp recording electrodes. All included studies had an eyes-closed condition. With the noted exceptions, all studies utilized sound attenuated and dimly lit rooms while subjects were quietly seated. LE= Linked ears, NR = not reported.

* Divided the theta range to theta-1 (4-5.8) and theta-2 (6-7.8) Hz.

** used overlapping ranges so for example a value of 3.5Hz can be classified in two frequency ranges.

[†] Studies reporting relative spectral powers.