

Running head: Brain Functioning in Patients with a Bipolar Diagnosis

Brain Functioning in Patients with a Bipolar Diagnosis: Neurocognitive and Quantitative
EEG (qEEG) Correlates

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Acknowledgements

Table of Contents

Abstract

Summary of Tables

List of Figures

Table of Abbreviations

History

Epidemiology of Bipolar Disorder

Etiology

 Dysregulation Theory

 Chaotic Attractor Theory

 Kindling Theory

 Catecholamine Theory

 HPA Axis Theory

 Protein Signaling Theory

 Calcium Signaling Theory

 Neuro-anatomical Theories: Cellular Resiliency

 Neuro-anatomical Theories: Genetic & Family Theories

Diagnostic Criteria

 Bipolar I Disorder

 Single Manic Episode

 Most Recent Episode Hypomanic

 Most Recent Episode Manic

 Most Recent Episode Mixed

Most Recent Episode Depressed

Bipolar II Disorder

Neuropsychology and Behavioral Medicine

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Neuroimaging

Electroencephalography (EEG)

Quantitative Electroencephalography (qEEG)

Low Resolution Electromagnetic brain Tomography (LORETA)

Electroencephalography Research

Genetic Vulnerability

Hypothesis and Rationale

Methods

Participants

Measures

CANTAB

Intradimensional/Extradimensional Shift (ID/ED Shift)

Stockings of Cambridge (SOC)

Spatial Working Memory (SWM)

QEEG

Results

Patient 1

CANTAB

qEEG

Summary

Patient 2

CANTAB

qEEG

Summary

Patient 3

CANTAB

qEEG

Summary

Patient 4

CANTAB

qEEG

Summary

Discussion

Broadmann Areas

Cingulate Cortex

Frontal Lobe

Temporal Lobe

Occipital Lobe

Implications of Abnormal EEG

Conclusion

Clinical Implications

Limitations

Future Directions

References

Abstract

The localization of neurological impairments in bipolar disorder has been a subject of great interest in the literature (Clark, Iverson, & Goodwin, 2002; Clark, Kempton, Scarna, Grasby, & Goodwin, 2005; Powell & Miklowitz, 1994) and past research has demonstrated prefrontal lobe involvement in patients with mania (Clark, et al. 2005). This research study evaluated four veterans with a historical diagnosis of bipolar disorder. The experimental hypotheses proposes that individuals diagnosed with bipolar disorder will show neuropsychological deficits on executive functioning measures, as well as abnormal neuroimaging records. Brain functioning was assessed via the Cambridge Neuropsychological Test Automated Battery (CANTAB) and Quantitative Electroencephalography (qEEG) data. Results indicate that both of the above hypotheses were validated. Review of available neuropsychological and neuroimaging data revealed deficits on CANTAB measures of sustained attention, specifically the Intradimensional/Extradimensional (ID/ED) Shift, Stockings of Cambridge (SOC), and Spatial Working Memory (SWM). Additionally, qEEG records were found to be abnormal in all four cases with abnormalities located in Broadman Areas 6, 18, 21, 23, 24, and 31. qEEG was found to correlate with CANTAB results.

Summary of Tables:

| | |
|-----------|--|
| Table 1. | Neuropsychological Testing |
| Table 2. | CANTAB Research |
| Table 3. | Neuroimaging & Bipolar Disorder Research |
| Table 4. | EEG & Bipolar Disorder Research |
| Table 5. | Z-score Ranges by Qualitative Descriptor |
| Table 6. | ID/ED Shift Results for Patient 1 |
| Table 7. | SOC Results for Patient 1 |
| Table 8. | SWM Results for Patient 1 |
| Table 9. | ID/ED Shift Results for Patient 2 |
| Table 10. | SOC Results for Patient 2 |
| Table 11. | SWM Results for Patient 2 |
| Table 12. | ID/ED Shift Results for Patient 3 |
| Table 13. | SOC Results for Patient 3 |
| Table 14. | SWM Results for Patient 3 |
| Table 15. | ID/ED Shift Results for Patient 4 |
| Table 16. | SOC Results for Patient 4 |
| Table 17. | SWM Results for Patient 4 |
| Table 18. | Completion Times for All Measures |
| Table 19. | Mean Completion Times |
| Table 20. | ID/ED Shift Comparison |
| Table 21. | Mean Scores for ID/ED Shift Task |
| Table 22. | Comparison of SWM Scores |

- Table 23. Mean Scores for SWM
- Table 24. Comparison of SOC Scores
- Table 25. Mean Scores for SOC
- Table 26. Summary of individual's CANTAB & qEEG results

List of Figures:

- Figure 1. International 10-20 System of Electrode Placement
- Figure 2. Intradimensional/Extradimensional (ID/ED) Shift
- Figure 3. Stockings of Cambridge (SOC)
- Figure 4. Spatial Working Memory (SWM)
- Figure 5. International 10-20 System of Electrode Placement
- Figure 6. Z-scored FFT Absolute Power (Patient 1)
- Figure 7. Z-score of Absolute Power (Patient 1)
- Figure 8. 2Hz LORETA output (Patient 1)
- Figure 9. 5Hz LORETA output (Patient 1)
- Figure 10. 14Hz LORETA output (Patient 1)
- Figure 11. Z-scored FFT Absolute Power (Patient 2)
- Figure 12. Z-score of Absolute Power (Patient 2)
- Figure 13. 7Hz LORETA output (Patient 2)
- Figure 14. Z-scored FFT Absolute Power (Patient 3)
- Figure 15. Z-score of Absolute Power (Patient 3)
- Figure 16. 1Hz LORETA output (Patient 3)
- Figure 17. 2Hz LORETA output (Patient 3)
- Figure 18. 8Hz LORETA output (Patient 3)
- Figure 19. 14Hz LORETA output (Patient 3)
- Figure 20. Z-scored FFT Absolute Power (Patient 3)
- Figure 21. Z-score of Absolute Power (Patient 3)
- Figure 22. 4Hz LORETA output (Patient 3)

- Figure 23. 12Hz LORETA output (Patient 3)
- Figure 24a. Lateral Surface with Numbered Brodmann Areas
- Figures 24b. Medial Surface with Numbered Brodmann Areas
- Figure 25. Brodmann Areas 23, 24, and 31
- Figure 26. Brodmann Area 6
- Figure 27. Brodmann Area 21
- Figure 28. Brodmann Area 18

Table of Abbreviations

| | |
|-------------|--|
| AC | Anterior Cingulate |
| BPD | Bipolar Disorder |
| CANTAB | Cambridge Automated Neuropsychological Test Assessment Battery |
| CPT | Continuous Performance Test |
| CPT-DS | Continuous Performance Test- Digit Span |
| CT | Computed Tomography |
| CV | Coefficient of Variation |
| CVLT | California Verbal Learning Test |
| DLPFC | Dorsolateral Pre-Frontal Cortex |
| DSM-II | Diagnostic & Statistical Manual of Mental Disorders- 2 nd Edition |
| DSM-III-R | Diagnostic & Statistical Manual of Mental Disorders- 3 rd Edition, Revised |
| DSM-IV | Diagnostic & Statistical Manual of Mental Disorders- 4 th Edition |
| DSM-IV-TR | Diagnostic & Statistical Manual of Mental Disorders- 4 th Edition, Text Revision |
| EEG | Electroencephalography |
| EKG | Electrocardiogram |
| EMG | Electromyography |
| FFT | Fast Fourier Transform |
| GABA | Gamma-Aminobutyric Acid |
| fMRI | Functional Magnetic Resonance Imaging |
| ID/ED Shift | Intradimensional/Extradimensional Shift |
| LORETA | Low Resolution Electromagnetic brain Tomography |

| | |
|-------|--|
| MRF | Mesencephalic Reticular Formation |
| MRI | Magnetic Resonance Imaging |
| mV | Microvolts |
| NIMH | National Institute of Mental Health |
| NOS | Not Otherwise Specified |
| PET | Positron Emission Tomography |
| qEEG | Quantitative Electroencephalography |
| rCBF | Regional Cerebral Blood Flow |
| SOC | Stockings of Cambridge |
| SPECT | Single Photon Emission Computed Tomography |
| SWM | Spatial Working Memory |
| ToM | Test of Memory |
| uV2 | Absolute Power |
| WCST | Wisconsin Card Sorting Test |

History

Although the term bipolar disorder was not formally included in the *Diagnostic and Statistical Manual of Mental Disorders* until 1980, the disorder itself has been described in writings since antiquity. The second century Greek physician Aretaeus described the symptomatology of manic and melancholic states and noted a relation between the two (Arieti, 1974, as cited in Belmaker & van Praag). In 1851 Falret, inspired by the early writings of Aretaeus, wrote of the “circular and intermittent nature” (Belmaker & van Praag, p. 7) of this disorder. However, it was Kraepelin who termed the phrase ‘manic-depressive psychosis’ as a syndrome comprised of simple mania, periodic and circular insanities, and melancholia. The *DSM-II* (1968) included the terminology *manic-depressive illness* as “an acknowledgement of the potential significance of organic (as opposed to “functional”) factors in this form of depression” (Schuyler, 1974, p.23). Bipolar disorder has been recognized since its inclusion in the *DSM-III* (1980) and in subsequent revisions (*DSM-III-R* (1987); *DSM-IV* (1994); and *DSM-IV-TR* (2000)).

Epidemiology of Bipolar Disorder

Current statistics from the National Institute of Mental Health estimate that 5.7 million American adults have been diagnosed with bipolar disorder (NIMH, 2006). This number accounts for approximately 2.6 percent of the United States population over the age of 18 in a given year (NIMH, 2006). The ratio for prevalence of bipolar disorder is generally equal for men and women, although it is estimated that women experience rapid cycling three times more often than men (NIMH, 2006). Further, it is estimated

that one-third of children ages six to twelve years who are diagnosed with major depressive disorder will develop a bipolar disorder within a few years (NIMH, 2006).

Etiology

Causal factors have yet to be definitively identified in bipolar disorder. With the induction of Lithium as an efficacious treatment for the disease in the 1970's came an influx of research on causative factors as they pertain to diagnosis and treatment (Preston, O'Neal, & Talaga, 2004). The numerous theories are summarized below.

Dysregulation Theory

Rosenthal et al (1986, as cited in Preston, 2004) postulated that there are several homeostatic mechanisms responsible for the regulation of mood and that when a part of that system fails, mood disturbances such as mania or depression will result. Post, Weiss, and Chuang (1992) proposed a similar theory, whereby overactivity in a mechanism of mania or depression results in the behavioral and affective disturbances that are hallmarks of bipolar disorder (Preston, et al., 2004).

Chaotic Attractor Theory

Crutchfield et al (1986, as cited in Preston, 2004) proposed that a biochemical defect leads to a "dysregulation of neurotransmitter synthesis" (Preston et al. 2004, p. 93) that is a consistent, rather than fluctuating, deficiency. Further, the Chaotic Attraction Theory postulates that although the biochemical defect is consistent, the resulting mania or

depression is related to the environmental conditions present (Preston et al 2004) and therefore the deficit itself is not solely predictive of the development of bipolar disorder.

Kindling Theory

Proposed by Ballenger and Post (1980), the Kindling Theory theorized that psychiatric symptoms are caused by “cumulative subclinical changes in the limbic system” (Preston et al 2004, p. 93). These changes accumulate over time causing the neurons to become progressively more excitable until symptoms become clinically observable (Preston et al 2004). Although this theory is not considered sufficient in fully explaining the causative aspects of bipolar disorder, it is considered an important potential indicator of the progression of the illness over time, particularly the worsening of symptoms throughout the lifespan (Preston et al 2004).

Catecholamine Theory

Past research has implicated catecholamine in bipolar disorder (Goodwin & Jamison 1990; Schatzberg & Schildkraut 1995; Manji & Porter 1997; Manji 2001; as cited in Preston et al 2004), although not as a primary causative mechanism. The predominant theory relates to noradrenergic abnormalities, specifically norepinephrine (NE) and its metabolite MHPG. Moreover, MHPG has been found to be lower in individuals with bipolar disorder, higher in individuals with unipolar depression, and elevations in CSF concentrations of NE and MHPG are seen in patients with mania (Preston et al 2004). The role of serotonin remains unsubstantiated in the research to date (Preston et al 2004). Current research is focused on examining the role of reduced levels of serotonin,

serotonin transporter alterations, and the role of the dopaminergic system (Willner 1995, as cited in Preston et al 2004).

The HPA Axis Theory

Past research has implicated the overaction of the HPA Axis most convincingly in the mixed and depressive states of bipolar disorder (Goodwin & Jamison, 1990; Garlow, Musselman, & Nemeroff, 1999; as cited in Preston et al 2004).

Protein Signaling Network Theory

Preston et al (2004) identified two signaling pathways that have been implicated in bipolar disorder: the G protein pathway and protein kinase C (PKC) pathway. To date, more research is available to support the implication of the PKC pathway (Preston et al 2004), although research in this area is continuing to expand on the G protein pathways role in bipolar symptomatology. Research by Manji (2001, as cited in Preston et al 2004) indicates that the protein signaling pathways work to “integrate complex biochemical input and output and to regulate feedback mechanisms” (p. 94).

Calcium Signaling Theory

Research has implicated elevated intracellular calcium levels in individuals diagnosed with bipolar disorder (Preston et al 2004). However, the exact cause of the elevation has yet to be discovered. Preston et al (2004) identified the lack of clinical effectiveness in psychotropic medications that block calcium channels as complicating factor.

Neuro-anatomical Theories: Cellular Resiliency

Post-mortem and neuroimaging research has shown “decreases in CNS volume and cell numbers, neurons, and/or glia cells” (Preston et al 2004, p. 94) in patients with mood disorders. This data has been applied successfully to both bipolar and depressed individuals and research in this area will likely continue to expand (Soares & Mann 1997; Manji, Moore, Rajkowska & Chen 2000; as cited in Preston et al 2004). However, the most exciting aspect of this research is the identification of the existence of a cytoprotective proteins in the frontal lobes (Preston et al 2004). Research is currently focusing on identifying the mechanism by which mood stabilizers influence the production of these proteins for the effective treatment of psychiatric disorder, including bipolar disorder (Preston et al 2004).

Neuro-anatomical Theories: Genetic & Family Theories

Studies conducted on families, twins, and adopted individuals generally supports a genetic link to bipolar disorder (Preston et al 2004). Past research has indicated that monozygotic twins is 50 to 60 percent for heritability of bipolar disorder and first-degree relatives have a four to six times greater chance of developing the illness as compared to the general population (Preston et al 2004). Further, there is evidence of specific chromosomal involvement, particularly Chromosome 22, which is also implicated in schizophrenia and raises questions regarding the distinction of the two disorders (Nurnberger & Foroud 2000; Potash & DePaulo 2000; Kelsoe et al 2001, as cited in Preston et al 2004).

Diagnostic Criteria

Bipolar I Disorder

According to the *DSM-IV-TR* (2000), the diagnostic features of Bipolar I Disorder are characterized by one or more manic or mixed episodes, and the patient often has one or more depressive episode as well. These episodes cannot be caused by a Substance Induced Mood Disorder or Mood Disorder due to a General Medical Condition, or be better explained by Schizoaffective Disorder or superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS. Bipolar I Disorder is diagnosed as either signal episode or recurrent, with recurrent episodes defined as a shift in an episodes polarity or intervals of at least two months between episodes without mania. Bipolar I Disorder is coded according to whether it is a Single Manic Episode, Most Recent Episode Hypomanic, Most Recent Episode Manic, Most Recent Episode Mixed, or Most Recent Episode Depressed (*DSM-IV-TR*, 2000, p. 382).

Single Manic Episode

According to the *DSM-IV-TR* (2000), in order to meet criterion for Bipolar I Disorder, Single Manic Episodes, individuals must meet either Criterion A or B. Criterion A requires the presence of only one Manic Episode without past Major Depressive Episodes. Criterion B, the manic episode is not better explained by a diagnosis of Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. If full criterion are met for a Manic, Mixed, or Major Depressive Episode, the associated features an individual is currently experiencing are coded: 1) Mild, Moderate,

Severe Without Psychotic Features/Severe With Psychotic Features; 2) With Catatonic Features; or 3) With Postpartum Onset. If full criteria are not met for Manic, Mixed, or Major Depressive Episode, clinical status of the most recent episode are coded: 1) In Partial Remission, In Full Remission; 2) With Catatonic Features; or 3) With Postpartum Onset (*DSM-IV-TR*, 2000).

Most Recent Episode Hypomanic

According to the *DSM-IV-TR* (2000), the following criteria must be met to receive a diagnosis of Bipolar I Disorder, Most Recent Episode Hypomanic. Criterion A, the person is currently or most recently in a Hypomanic Episode. Criterion B, there be a history of at least one Manic Episode or Mixed Episode. Criterion C, mood symptoms cause significant impairment or distress in an individuals ability to function socially, occupationally, or in other important areas. Criterion D, mood episodes in Criteria A and B are not better explained by Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. Most Recent Episode Hypomanic is coded by: 1) Longitudinal Course Specifiers (With and Without Interepisode Recovery); 2) With Seasonal Pattern; and 3) With Rapid Cycling (*DSM-IV-TR*, 2000).

Most Recent Episode Manic

According to the *DSM-IV-TR* (2000), the following criteria must be met for a diagnosis of Bipolar I Disorder, Most Recent Episode Manic. Criterion A, individual currently or most recently experiencing a Manic Episode. Criterion B, individual has

previously experienced at least one Major Depressive, Manic, or Mixed Episode. Criterion C, mood episodes in Criteria A and B are not better explained by Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. If individual meets full criteria for a current Manic Episode, clinical features are specified as: 1) Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features; 2) With Catatonic Features; or 3) With Postpartum Onset. If criteria are not met for a current Manic Episode, clinical features are specified as: 1) In Partial Remission; 2) With Catatonic Features; or 3) With Postpartum Onset. Additional clinical specifications for diagnosis include: 1) Longitudinal Course Specifiers (With and Without Interepisode Recovery; 2) With Seasonal Pattern; and 3) With Rapid Cycling (*DSM-IV-TR*, 2000).

Most Recent Episode Mixed

According to the *DSM-IV-TR* (2000), diagnostic criteria for Bipolar I Disorder, Most Recent Episode Mixed are as follows. Criterion A, current or most recent episode is a Mixed Episode. Criterion B, individual has previously experienced at least one Major Depressive, Manic, or Mixed Episode. Criterion C, mood episodes in Criteria A and B are not better explained by Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. If the individual meets the criteria for a Mixed Episode, the clinical components are specified as follows: 1) Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features; 2) With Catatonic Features; or 3)

With Postpartum Onset. If full criteria are not met for a Mixed Episode, the clinical status is specified as: 1) In Partial Remission, In Full Remission; 2) With Catatonic Features; or 3) With Postpartum Onset. Additionally, the clinical status is coded as: 1) Longitudinal Course Specifiers (With and Without Interepisode Recovery); 2) With Seasonal Pattern; or 3) With Rapid Cycling (*DSM-IV-TR*, 2000).

Most Recent Episode Depressed

According to the *DSM-IV-TR* (2000), the following criteria must be met for a diagnosis of Bipolar I Disorder, Most Recent Episode Depressed. Criterion A, individual is currently or most recently in a Major Depressive Episode. Criterion B, individual has previously experienced at least one Manic or Mixed Episode. Criterion C, mood episodes in Criteria A and B are not better explained by Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. If the individual currently meets criteria for Major Depressive Episode, it is coded as: 1) Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features; 2) Chronic; 3) With Catatonic Features; 4) With Melancholic Features; 5) With Atypical Features; or 6) With Postpartum Onset. If full criteria are not met for a Major Depressive Episode, clinical status is coded as: 1) In Partial Remission, In Full Remission; 2) With Catatonic Features; 3) With Melancholic Features; 4) With Atypical Features; or 5) With Postpartum Onset. Additionally, the clinical status is coded as: 1) Longitudinal Course Specifiers (With and Without Interepisode Recovery); 2) With Seasonal Pattern; or 3) With Rapid Cycling (*DSM-IV-TR*, 2000).

Bipolar II Disorder

The diagnostic features of Bipolar II Disorder are clinically characterized as having one or more Major Depressive Episodes (Criterion A) with at least one Hypomanic Episode (Criterion B). As with the diagnosis of Bipolar I Disorder, the euthymic period associated with the first several days of remission following a Major Depressive Episode should not be confused with Hypomania. The presence of a Manic or Mixed Episode negates a diagnosis of Bipolar II Disorder (Criterion C). Episodes of Substance Induced Mood Disorder and Mood Disorder Due to a General Medical Condition are not associated with Bipolar II Disorder and should be ruled out. Additionally, the episode can not be better explained by Schizoaffective Disorder, and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified (Criterion D). Symptoms of Bipolar II Disorder must cause significant impairment or distress in areas of functioning (social, occupation, or other important functional areas) (Criterion E). It should be noted that this impairment in functioning is not always the result of the Hypomanic Episode, and may also be related to the Major Depressive Episode or from chronic patterns of unpredictability in mood or the fluctuation in performance in areas of interpersonal or occupational functioning. Insight is often impaired, with Bipolar II Disordered individuals viewing the Hypomanic Episodes as non-pathological, while others are troubled by the erratic, unpredictable behavior. As such, information from collateral sources is considered paramount in the diagnosis of this disorder (*DSM-IV-TR*, 2000).

Neuropsychology and Aspects of Bipolar Disorder

Neuropsychological test data has been used to elucidate the relationship between brain functioning and behavior in patients with a diagnosis of bipolar disorder. Bipolar disorder is characterized by recurrent episodes of depression and mania, interspersed with periods where there is a relative absence of symptoms mimicking recovery (Clark, Iverson, and Goodwin, 2002). Research on neuropsychological deficits associated with bipolar disorder indicate deficits across several measures including sustained attention, verbal learning and memory, psychomotor speed, and executive functioning. However, sustained attention is regarded as having a more significant association with bipolar disorder. Sustained attention may be assessed by using Continuous Performance Tasks (CPT), which are tests of vigilance lasting several minutes which assess the maintenance of focused attention (Clark, Kemptom, Scarna, Grasby & Goodwin, 2005, p.183). Impairments in sustained attention are regarded as a primary feature of both manic and depressive states (Clark et al., 2001; Clark et al., 2005) and research has shown that these deficits persist in euthymic states, which suggests the possibility of a genetic marker for the disorder.

Mania is undoubtedly the period in bipolar disorder associated with the most severe and debilitating impairments. Mania produces neuropsychological disturbances that resemble frontal lobe brain injury (Clark et al., 2001). Neuropsychological test results of those diagnosed with bipolar disorder show deficits in tests measuring attention and concentration. Fleck, Shear, and Strakowski (2004) examined the Continuous Performance Test (CPT) scores of 77 bipolar individuals. Overall, it was found that bipolar patients exhibited poorer performance on CPT tasks as compared to healthy

controls. Additionally, Fleck et al. (2004) found that manic patients exhibited decreased perceptual sensitivity, with the manic group performing faster on CPT tasks, with higher error rates. Results of Fleck et al.'s (2004) study is summarized in Table 1.

Neuropsychological research conducted on individuals who are in the manic phase of their illness have shown deficits that are phase specific. Increased error rates and reaction times have been reported to be the most reliable indicators of a manic episode (Liu et al. 2002; Nuechterlein et al. 1991, as cited in Fleck, et al. 2004). Research in this area using euthymic bipolar patients have found contrasting results, specifically attenuated error rates on tests measuring sustained attention with continuing deficits in reaction time (Wilder-Willis et al. 2001, as cited in Fleck, 2004). Clark, et al. (1999) studied individuals with bipolar disorder utilizing neuropsychological test measures and their findings were consistent with those summarized above (Table 1.).

A variable degree of neuropsychological impairment has been found across the different phases of bipolar disorder. However, much of the past research examining patients with bipolar disorder has focused on a single phase, rather than a comparative analysis of subjects in different phases of the illness. Kravariti, Frith, Murray and McGuire (2004) examined manic (n = 15), depressed (n = 15), remitted (n = 15) and healthy controls (n = 30) and compared the results of neuropsychological tests. Overall, Kravariti et al (2004) found that the patients currently in a manic state were significantly more impaired than the other subjects. Additionally, subjects in the depressed group appeared to have the greatest difficulty with set shifting. The results of this study are presented in greater detail in Table 1.

Research is beginning to shift focus to the euthymic phase. Research on the euthymic phase has revealed a greater preponderance of neurocognitive deficits than previously understood. Clark, Kemptom, Scarna, Grasby and Goodwin (2005) compared neuropsychological test results of 15 patients with bipolar disorder that were in the euthymic phase with 15 healthy controls. Research by Clark et al (2005) has indicated specific differences in the types of errors made during manic and euthymic states. On tasks of sustained attention, patients with a diagnosis of depression typically make errors of omission and patients with bipolar disorder, during the acute phase when impulsivity is a key feature of mania, make errors of commission (Olley, Malhi, Bachelor, Cahill, Mitchell & Berk, 2005).

When Kraepelin (1919, 1921) distinguished bipolar disorder from schizophrenia, he indicated that those afflicted with bipolar disorder tended to experience a period of remission while schizophrenics did not (Coffman, Bornstein, Olson, Schwarzkopf, & Nasrallah, 1990). Although this period of euthymia *mimics* recovery, it is not equal to a state of recovery and more recent research has shown that deficits do persist during these periods of relative health (Olley et al. 2005). Olley et al. (2005) examined neuropsychological test results for 15 patients with bipolar disorder currently in a euthymic phase and found that deficits were present independent of the state of illness. More specifically, research by Olley et al. (2005) revealed deficits on the STROOP inhibition task and overall reduced semantic fluency on the Controlled Oral Word Associate Test- FAS and category fluency (Table 1.).

The relationship between the course and severity of bipolar illness and related neurocognitive impairment has been explored minimally to date (Denicoff et al. 1998)

and the results of such research have been mixed. Neuchterlein et al. (1991, as cited in Denicoff et al. 1998) studied patients with bipolar disorder in the euthymic phase and found that deficits were not present during periods of relative resolution of symptoms. Van Gorp et al. (1998, as cited in Denicoff et al. 1998) studied individuals with bipolar disorder and found conflicting results. Specifically, patients with bipolar disorder were found to exhibit deficits which persisted into and during the euthymic phase of illness. Denicoff et al (1998) theorize that the differences in results are likely attributable to medication effects and small sample sizes.

Clinically, the euthymic period has been regarded as a period of relative health. The abovementioned research clearly points to neuropsychological disturbances that exist independent of state of illness. This indicates that deficits in sustained attention will be present in all phases of the bipolar illness, and the deficits will vary in terms of intensity depending on the current state the patient is in at the time of testing. Kraepelin (1919, 1920) distinguished bipolar disorder from schizophrenia on the basis of a period of relative health in bipolar patients. Research has begun to shed light on the euthymic period as not absent of symptomatology, but one where symptoms persist at a lesser degree.

Table 1. Neuropsychological Testing

| Author(s) | Number of Subjects | Procedure | Results |
|--------------------|--------------------|-------------------------------------|--|
| Clark, et al. 1999 | 60 | - CANTAB -Iowa Gambling -CVLT | - Impaired target detection - Reduced psychomotor speed - Impaired immediate recall on CVLT - Euthymic patients showed increased vigilance on measures of |

| | | | |
|-----------------------|----|---|---|
| | | | <p>sustained attention than controls</p> <ul style="list-style-type: none"> - Increased total errors on the ID/ED Shift |
| Fleck, et al. 2004 | 77 | - CPT-DS | <ul style="list-style-type: none"> - Manic patients exhibited perceptual sensitivity - Poorer performance on CPT measures for manic/euthymic patients compared to healthy controls - Manic patients exhibited more errors attributed to psychomotor acceleration, while euthymic patients were slower and more accurate |
| Clark, et al. 2004 | 30 | - RVIP | <ul style="list-style-type: none"> - Reduced target sensitivity and slower response latency in the bipolar disordered patients |
| Olley, et al. 2005 | 28 | <ul style="list-style-type: none"> - ToM - CANTAB - Stroop | <ul style="list-style-type: none"> - Reduced semantic fluency in bipolar individuals - Poorer performance on the Stroop inhibitory trial - Bipolar individuals exhibited more errors on the SOC task |
| Denicoff, et al. 1998 | 49 | <ul style="list-style-type: none"> - Stroop - CPT - Wisconsin Card Sorting Test - CVLT - Trails A & B - Purdue Grooved Pegboard | <ul style="list-style-type: none"> - Duration of illness correlated with poorer performance on attention/concentration tasks - Number of prior episodes/hospitalizations correlated with poorer performance on attention/concentration tasks, intelligence tests, and tests of memory and abstract reasoning - Older bipolar disordered individuals had fewer perseverative errors/conceptual level responses on WCST - Patients with higher education performed better on the WCST but |

| | | | |
|-----------------------|--|---|--|
| | | | performed poorer on the CVLT with more perseveration |
| Thompson, et al. 2006 | - 17 Euthymic Bipolar - 16 Control Subjects | - Sternburg Paradigm - Rey Auditory Verbal Learning Test | - Bipolar individuals were significantly ore impaired on verbal recognition memory - BPD patients made significantly more errors of omission and commission on working memory tasks |

Neuropsychological testing studies conducted on individuals diagnosed with bipolar disorder.

Cambridge Neuropsychological Test Automated Battery

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was designed to examine neuropsychological functions subserved by frontostriatal circuitry (Fray et al. 1997, as cited in Sweeney, et al. 2000) by utilizing tests measuring spatial working memory, complex problem solving, and attentional set shifting (Sweeney et al. 2000). The CANTAB tests are also sensitive to temporal lobe (via the Pattern Recognition and Delayed Match to Sample tests) and parietal lobe (via the Spatial Span test) functioning. This battery has several strengths, including “the separation of mnemonic and strategic components of working memory,” as well as a database of animal and human studies that have linked specific performance dysfunctions with focal brain lesions (Sweeny et al., 2000).

The CANTAB has been used in past studies of affective disorder, including depression and bipolar disorder. Past research has shown that depressed patients show impairments on delayed recognition memory, problem solving, spatial recognition memory, and attentional set shifting (Sweeny et al., 2000). Manic patients have been

found to exhibit deficits on the Pattern Recognition Memory, Delayed Matching to Sample test, and increased difficulty with problem solving (Sweeny et al., 2000).

The CANTAB appears to be sensitive to neurocognitive deficits during specific affective states. Murphy et al. (1999) found that subjects with bipolar disorder showed impairments on the Delayed Match to Sample, Stockings of Cambridge, Spatial Recognition, and Pattern Recognition Memory during the manic phase of illness. Sweeny et al. (2000) examined subjects with bipolar disorder during manic/mixed phase and depressed phase, and found that manic/mixed subjects were more impaired than depressed subjects. Similarly, Clark et al. (1999) examined euthymic subjects and found no significant impairment on the Stockings of Cambridge or Spatial Working Memory tasks. The results of these studies lend support to the theory that neurocognitive deficits are not stable, but rather the severity or presence of deficits are related to the affective state at the time of testing.

Sweeny et al. (2000) compared patients with a bipolar diagnosis with non-bipolar depressed patients and healthy controls with the goal of conceptualizing and specifying associated deficits in mood disordered patients across neuropsychological test measures. Results of this study showed deficits in executive functioning in patients with bipolar disorder, specifically in the frontostriatal, mesial temporal systems, and the posterior parietal lobe (Sweeny et al. 2000). In addition, the neuropsychological deficits associated with bipolar and non-bipolar patients were limited to only episodic memory, which “suggests a relatively restricted abnormality in mesial temporal lobe memory systems during episodes of depression” (Sweeny et al. 2000, p. 681). Summarization of Sweeny et al. (2000) data is found in Table 2.

Clark, Iverson, and Goodwin (2002) studied sustained attention in patients with bipolar disorder using the CANTAB. They reported that sustained attention, as measured by the intradimensional/extradimensional (ID/ED) shift, is impaired in patients with a bipolar diagnosis and is indicative of a potential vulnerability factor for psychosis (Table 2.). Similarly, Sweeney et al. (2000) found that the sustained attention measures of the CANTAB were impaired in bipolar patients. Additional deficits were found in executive functioning, episodic memory, and spatial span performance (Sweeney et al., 2000, p. 682). Finally, Sweeney et al. (2000) summarized the deficits associated with the CANTAB and found dysfunction in multiple cortical association areas. Research by Dickstein et al. (2003) revealed that bipolar disordered patients exhibited deficits on the CANTAB as compared to normal controls on the ID/ED Shift, pattern recognition memory, and spatial span (Table 2) which supports past research indicating executive functioning deficits in patients with bipolar disorder.

Table 2. CANTAB Research

| Author(s) | Number of Subjects | Procedure/Measures | Results |
|----------------------|--------------------|--------------------|---|
| Sweeney, et al. 2000 | - 144 | - CANTAB | <ul style="list-style-type: none"> - Mixed/manic bipolar disordered patients made significantly more excessive moves while solving problems compared to healthy controls on the SOC task - Mixed/manic patients showed significantly impaired performance on the SWM task - Mixed/manic patients were less consistent with strategy development than healthy controls on SWM |
| Clark, et al. 2002 | - 60 | - CANTAB | - Increased total errors on the ID/ED Shift |

| | | | |
|--|--|--|---|
| | | | - Increased errors at the EDS stage but not at stages requiring reversals |
|--|--|--|---|

CANTAB research conducted utilizing individuals diagnosed with bipolar disorder.

Neuroimaging

In 1936, Egas Monis published the results of frontal leukotomy performed on patients with schizophrenia and severe obsessive neurosis and provided the first irrefutable evidence of the contribution of the frontal lobes in the control of affect and emotion (Heilman & Satz, 1981). Perhaps one of the most famous cases of frontal lobe injury and subsequent increase in neuropsychological knowledge of frontal lobe functioning is that of Phineas Gage. Gage was injured in a railway accident when a dampening rod was accidentally shot through his skull, destroying his frontal lobes. The resulting personality changes provided indelible proof of the frontal lobes role in affective and emotional regulation.

The frontal lobe is considered to be the “executive control center of the human brain” (Powel, K. & Miklowitz, D., 1994). The frontal lobe is also considered to be a fundamental component in the regulation of the limbic system which appears to be of primary importance in bipolar disorder (Powel, K. & Miklowitz, D., 1994). As such, the frontal lobe governs the regulation of mood. Pathology in this region of the brain is associated with affective disturbances (Dolan, Poynton, Bridges, & Trimble, 1990, as cited in Powel & Miklowitz, 1994). Flors-Henry (1979, as cited in Powel & Miklowitz, 1994) reported that both “manic and depressive symptoms after frontal lobe head injuries, frontal lobe strokes, and focal frontal lesions led researchers to implicate the frontal lobe in personality and mood pathology” (p. 526). Sustained attention is typically described

as an executive function (Powel & Miklowitz, 1994), which is controlled by the frontal lobe.

Psychiatric research utilizing neuroimaging has implicated a vast number of brain regions as being related to specific symptomatology. Strakowski, Adler, Holland, Mills, and DelBello (2004) suggest that dysfunction in the medial orbitofrontal and ventrolateral prefrontal areas, as well as the reciprocal connections with the basal amygdala, anterior temporal regions, rostral insula, and subgenual and anterior cingulate, influence the symptoms of bipolar disorder (p. 1734). Strakowski et al. (2004) utilized fMRI to study patients with bipolar disorder and found activation differences between bipolar individuals and normal controls (Table 3). Further, the anterior cingulate is correlated with attention, emotion, and cognitive functioning (Blumberg et al 2000). Blumberg et al (2000) reported that the dorsal anterior cingulate is especially important in deficits related to bipolar disorder because of its association with “cognitive functions, such as the appropriate directing of attention, conflict monitoring, and response selection” (p. 1049). Blumberg et al. (2000) studied functional abnormalities in patients with a diagnosis of bipolar disorder using PET imaging and found differences in rCBF that are trait specific (Table 3).

The role of the limbic system in affective dysregulation is undeniable. Strakowski et al (2004) postulated that during a mood episode, “dysregulation of the anterior limbic network may inhibit cognitive brain regions, thereby producing both the affective and attentional impairments” (p. 1735) that are hallmarks of bipolar disorder. Further, Strakowski et al. (2004) indicated that even during the euthymic phase of bipolar disorder, individuals are still vulnerable to mood dysregulation as a result of hyperactive

limbic networks. Results of Strakowski et al. (2004) research supported their aforementioned hypotheses, which are highlighted in Table 3.

Past research examining functional brain images in patients with bipolar disorder appears to lend support to the theory of anterior limbic network involvement in bipolar disorder. Sassi et al (2004) reported decreased amygdala volumes on fMRI scans of patients with bipolar disorder versus healthy control subjects. Further, structural postmortem studies have been reported to be generally consistent in reporting decreases in cell density and size in the anterior cingulate (Sassi et al 2004, p. 472).

The role of the dorsolateral prefrontal cortex has been associated with the ability to hold and maintain attention while performing a specific task (Carter et al. 2000, as cited in Gruber et al. 2004). Therefore, the dorsolateral prefrontal cortex is of primary importance in research involving bipolar disorder due to the sustained attention component. Blumberg, Stern, Martinez, Ricketts, de Asis, White, Epstein, McBride, Eideberg, Kocsis, and Silbersweig (2000) indicated a hemispheric imbalance, with “right more than left, and ventral more than dorsal, frontal lesions are associated with mania” (p. 1047). Whalen et al (1998, as cited in Blumberg et al 2000) indicated that the ventral anterior cingulate is more connected to emotional stimuli, while the dorsal anterior cingulate is associated with cognitive functioning.

Research by Benson et al. (2000, as cited in Post, Speer, Hough, and Xing 2003) found deficits in reciprocal and/or inhibitory interactions between the cerebellum and the amygdala. In addition, this research highlighted the importance of the frontal-basal ganglia-thalamic loops (Alexander et al. 1990, as cited in Post et al. 2000), which suggests that the “loss of balanced positive and negative associativities of this area could

prove important to the behavioral and emotional imbalance and dyscontrol in bipolar disorder” (p. 87).

Studies utilizing Single Photon Emissions Computed Tomography (SPECT) on individuals with affective disturbances have shown abnormalities in cerebral blood flow, primarily in the prefrontal cortex (Benebarre et al. 2005). In individuals with mania, research has shown greater hypofrontality, as well as an increase in radio-ligand uptake in the temporal lobes (Benebarre et al. 2005). Additionally, Benebarre et al (2005) indicated right hemisphere v. left hemisphere asymmetry in individuals during the manic phase with “less perfusion in the right and basal temporal cortex than in the left and dorsal regions” (p. 229). Benebarre et al. (2005) research is summarized in Table 3.

Neuroimaging research points to cerebral involvement that extends beyond the frontal lobes. Gyulai et al. (1997) studied twelve individuals with a bipolar diagnosis (four unmedicated, eight medicated with lithium carbonate) and found asymmetry in the anterior portion of the temporal lobes in the depressive and manic phase, with symmetry in the euthymic phase. This is suggestive of a ‘temporal dysfunction’ that is state dependent in patients with a bipolar diagnosis (Gyulai et al., 1997).

There is no disputing the role of the frontal lobe in affective disturbances (Powel & Miklowitz, 1994; Dolar et al. 1990; Flors-Henry, 1979; Strakowki et al. 2004; Blumberg et al 2000; Sassi et al. 2004; and Carter et al. 2000). However, through the advent of modern functional imaging techniques, we know that the interconnectedness of the different regions of the brain means that functional deficits are not relegated to one specific area of the brain. Rather disturbances in one area can cause a cascading effect that also implicates other brain regions as being responsible for symptom production.

Imaging research on bipolar disorder has implicated not only the frontal lobes, but also the temporal lobe, parietal lobe, and cerebellum. However, the frontal lobes appear to be the metaphorical “ground zero” in affective disorders, thereby establishing this region as a primary location for disturbances that result in psychiatric and neuropsychological pathology.

Table 3. Neuroimaging Research

| Author(s) | Number of Subjects | Procedures/Measures | Results |
|--------------------------|--------------------|---------------------|---|
| Blumberg, et al. 2000 | - 11 | - PET | - Increased rCBF in manic patients in the bilateral dorsal AC and left head of the caudate |
| Gruber, et al. 2003 | - 21 | - fMRI | - Patients with bipolar disorder exhibited increased DLPFC activation |
| Strawkowski, et al. 2004 | - 20 | - fMRI | - Healthy subjects had greater activation in the fusiform gyrus and medial frontal cortex - Patients with bipolar disorder had greater activation in the limbic area (hypothalamus, parahippocampus/amygdala), paralimbic (insula), and prefrontal and visual association areas - A positive correlation was found between task performance and the right ventrolateral frontal regions |
| Althshuler, et al. 2005 | - 11 | - fMRI | - Blunted activation in the lateral orbitofrontal cortex in 4 unmedicated individuals with bipolar disorder |
| Lyoo, et al. 2003 | - 39 | - fMRI | - Individuals with bipolar disorder showed significant decreases in grey matter density in the left anterior cingulate gyrus and left medial frontal gyrus - Significant decreases in grey matter density in the right inferior frontal gyrus and right prefrontal gyrus - Greater grey matter density |

| | | | |
|----------------------|---------------------------|-------|---|
| | | | changes were seen in patients who had experienced more historical manic episodes |
| Aylward, et al. 1994 | - 30 BPD - 30 Controls | - MRI | - Male BPD individuals had significantly larger right and left caudate volumes than female BPD individuals or controls - 11 BPD subjects (34.4%) had hypertensities compared with 1 subject in the control group - Majority of hypertensities were located in the white matter, 2 BPD subjects had hypertensities in the grey matter - Most common location in the brain for hypertensities was in the frontal lobes and frontal/parietal junction - 3 BPD individuals had hypertensities in the occipital and temporal lobes |
| Ali, et al. 1999 | - 26 BPD | MRI | - Larger right hippocampal volumes were correlated with poorer performance on neuropsychological test measures |

Neuroimaging research conducted on individuals with a bipolar disorder diagnosis.

Electroencephalography (EEG)

Electroencephalography (EEG) was used in animal studies in the 19th century, although human EEG studies were pioneered by the work of Austrian psychiatrist, Hans Berger, in 1929. EEG is a neuroimaging procedure whereby cortical activity is measured via electrodes placed on the scalp. Fisch and Spehlmann (1999) define EEG as “the difference in voltage between two different recording locations plotted over time” (p. 4). Typically, one or both ears are used as a reference point. EEG waves are measured using microvolts (mV) and must be amplified by a factor of 1,000,000 to be displayed on a computer screen or write-out.

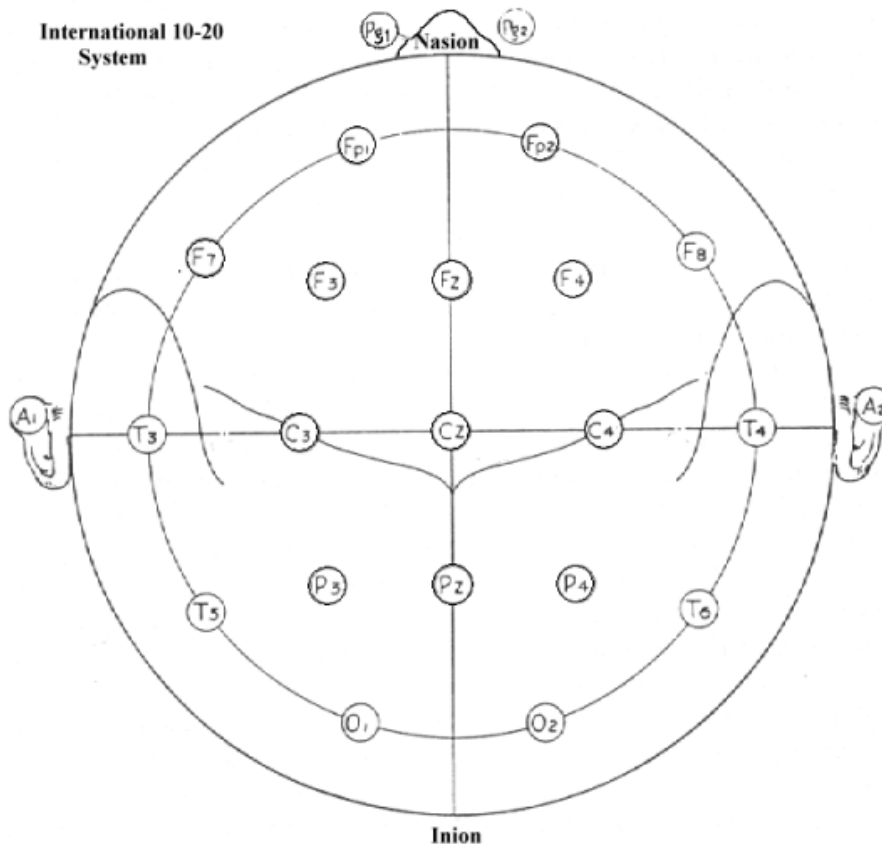
Electrodes measure the summations of post-synaptic activity, not pre-synaptic axonal activity, and they consist of both inhibitory and excitatory potentials. More specifically, an action potential generates the release of neurotransmitters into the synapse of the pre-synaptic axon. This released neurotransmitter travels across the synaptic cleft to bind to the post-synaptic dendrite. It is this flow of ions in and out of the extracellular space that results in measurable EEG discharges. What is measured is the result of changes in thousands of neurotransmitters located in the brain beneath the scalp. Therefore, there are many potential generating sites of electrical activity measured by one electrode. The most measurable discharge is located proximal to the scalp, and deeper structures are typically not able to be measured via scalp electrodes.

Frequency is defined as the time it takes a wavelength to repeat its cycle per second. The different amplitudes of brain waves are called alpha waves, beta waves, theta waves, and delta waves. Alpha and beta waves are typically found in a normal, waking state. Alpha waves are defined as being between 8Hz to 13Hz and beta waves are defined as being between 14Hz and faster. Theta and delta waves are typically seen during sleep. In a normal waking adult, delta and theta waves are considered abnormal and likely representative of a pathological process. Theta waves are defined as being between 4Hz and 7Hz and delta waves are between 1Hz and 3Hz.

Electrode placement is determined by the International 10-20 system which was developed to ensure uniform placement of recording electrodes. Landmark protrusions on the skull are used to create a virtual map of lines which cross the skull and intersect at intervals of 10 or 20% their total length (Fisch & Spehlmann, 1999). Electrodes are affixed to the skull via a conductive paste at these intersections. Measurements for

electrode placement depend on three skull landmarks: the inion (bony protrusion at the back of skull), the nasion (bridge of nose inferior to the forehead), and preauricular point (depression of bone proximal to the ear canal) (Figure 1).

Figure 1. International 10-20 System of Electrode Placement



Location of electrode placement in accordance with the International 10-20 System.
Public domain imaged retrieved from:
<http://neurocog.psy.tufts.edu/images/10-20system.gif>

Standard placement of electrodes calls for 21 recording electrodes and 1 grounding electrode. All recording electrodes are associated with a letter and subscript. The letter provides an abbreviation of the underlying region of cortex: Fp (prefrontal), F (frontal), C (central), P (parietal), O (occipital), and A (auricular). The associated

subscript is either z (midline sagittal) or a number (lateral placement). Numbers will increase in value as the distance increases from the anterior posterior midline of the head (Fisch & Spehlmann, 1999). Odd numbers indicate placement on the left and even numbers indicate placement on the right.

Although the mechanisms that drive EEG pacing have yet to be definitively identified, research suggests that “anatomically complex homeostatic systems regulate the EEG power spectrum” (Hughes & John, 1998, p.191). This regulation is postulated to be maintained by neuronal processes in the brainstem, thalamus, and other cortical processes involving large networks of neurons. In a healthy adult, the EEG power spectrum is considered to be generally stable due to this homeostatic regulation (Hughes & John, 1998).

Most abnormal EEG patterns are termed “paroxysmal” because they typically occur in bursts lasting no more than a few seconds. Between these paroxysmal discharges, normal EEG records will be seen. Gross (1981) noted five distinct abnormal EEG patterns: “(1) high-voltage fast waves, (2) slow waves during waking state, (3) spikes, which are sharp bursts of electricity, (4) spike-wave complexes, which consist of a spike followed by a slow wave, and (5) disorganized or dysynchronized patterns” (p.40). These abnormalities can occur focally, as in a specific area of the brain, or globally. If a spike points upward on the EEG record, it is defined as having negative polarity and as originating from the cortex. If the spike is pointed downward, the polarity of the spike is said to be positive and the activity originates from the deeper structures of the brain.

Implications of Abnormal EEG

An abnormal EEG is defined as “a) epileptiform activity, b) slow waves, c) amplitude abnormalities, or d) certain patterns resembling normal activity but deviating from it in frequency, reactivity, distribution, or other features” (Fisch & Spehlmann, 1999, p. 237).

Localized slow waves are associated with structural damage relegated to subcortical white matter or the thalamus or to localized disorders of cerebral blood flow and/or metabolism (Fisch & Spehlmann, 1999). Similarly, reductions in amplitude are influenced by superficial lesions or to matter located between the cortex and the electrode (Fisch & Spehlmann, 1999). Localized slow waves are defined as being below 8Hz and appearing at one or a few electrodes. Fisch and Spehlmann (1999) indicate that “continuous, irregular, delta activity (i.e. polymorphic delta) results primarily from lesions affecting cerebral white matter” (p. 356). Irregular delta activity that is either localized or lateralized can be caused by ipsilateral lesions located in the thalamus or midbrain recicular formation (Fisch & Spehlmann, 1999).

Focal slow waves have been reported in research across a broad spectrum of psychiatric disorders (Fisch & Spehlmann, 1999). However, Fisch and Spehlmann (1999) caution that “this occurrence is so rare and without clear relation to specific diseases that focal slow waves cannot be accepted as a manifestation of psychiatric disease and a local cerebral lesion must be excluded by other examinations (p. 361).

Abnormal EEG's infrequently occur in people without evidence of cerebral dysfunction and low amplitude is observed in 5% to 15% of normal adults over the age of 20. Further, low voltage is more common with increasing age due to changes in cortical

structure that result in greater distance between the cortex and electrode. Further, genetic factors can contribute to low amplitude, as well as a prior history of substance abuse.

In contrast, high amplitude may be due to the short distance between the cortex and the electrode or to a skull defect (Fisch & Spehlmann, 1999). Fisch and Spehlmann (1999) indicated that “other causes of high amplitude in normal activity in adults are unknown” (p. 412).

Fisch and Spehlmann (1999) reported that an EEG may still appear normal if the lesions in the brain are small, chronic, or located in the deeper structures. Due to the fact that abnormalities in EEG output can be caused by multiple diseases, which can in turn influence more than one abnormal electrophysiological pattern, an EEG alone can not be used to diagnose, but rather to provide additional evidence for diagnosis (Fisch & Spehlmann, 1999).

Quantitative Electroencephalography

Quantitative Electroencephalography (qEEG) involves computerized analysis of a vast amount of data accumulated during an EEG recording session. This affords the clinician the opportunity to graphically examine the EEG record, either through topographical mapping or spectral analysis. Through this procedure, specific features of interest in the EEG record are converted to a numerical value. In order to quantify the record, the EEG signal must be converted from time domain (amplitude v. time) to frequency domain (amplitude v. frequency). Fisch and Spehlmann (1999) caution that when the record is transformed to frequency domain, the original morphology will no longer be able to be viewed. However, they provide three reasons why this

transformation is advantageous: “1) a great deal of data can be summarized by a few descriptors; 2) selected features in the signal can be examined quantitatively; and 3) the relationships between signals can be revealed more precisely than by visual inspection” (p. 124). As variables such as heart rate (EKG) and muscle movement (EMG) can influence the EEG records, these extraneous variables must be removed prior to qEEG analysis.

A mathematical computation referred to as the Fast Fourier Transform (FFT) is used to convert the record from time domain to frequency domain. FFT is a spectral analysis procedure developed by a French mathematician named Joseph Fourier. Fourier postulated that “any signal can be described as a combination of sine and cosine waves of various phases, frequencies, and amplitudes” (Fisch & Spehlmann, 1999, p. 125). Fast Fourier Transformation (FFT) is used to provide a power spectrum, which refers to the averaged power at each frequency. Amplitude spectrum is identified by taking the square root of the power spectrum.

After the power spectrum and amplitude spectrum have been calculated, specific spectral features of the EEG can be examined. These features are absolute band amplitude, relative band amplitude, spectral edge frequency, mean peak frequency, and absolute peak frequency. According to Fisch and Spehlmann (1999) “the absolute band value corresponds to the area under the curve of the spectrum between two frequencies that define the bandwidth,” while the “relative band value refers to one absolute band value divided by another” (p.126). The spectral edge frequency is defined as “the frequency below which a pre-selected percentage of the total frequency range absolute band lies” (Fisch & Spehlmann, 1999, p. 126). Finally, the absolute peak frequency

“refers to the peak value in a selected band of the frequency spectrum” (Fisch & Spehlmann, 1999, p. 126). These values can be statistically analyzed or topographically represented according to electrode placement.

According to Congedos and Lubar (2003) these features may include “univariate and multivariate measures of absolute power, relative power and mean frequency for each electrode location in addition to coherence, phase and asymmetry for each electrode pair” (p.3). Extracted quantitative features are referred to as descriptors. These descriptors are compared to a normative database of normal controls, and a statistical measure of deviance from population norms is derived.

The four frequency bands (alpha, beta, delta, and theta) were discussed in depth above. The results are then presented in either absolute power in each band, relative power in each band, coherence, or symmetry. These are defined, according to Hughes and John (1998) as: total uV² (absolute power); percentage of total power in each channel (relative power); a measure of synchronization between activity in two channels (coherence); and the ration of power in each band between a symmetrical pair of electrodes (symmetry) (p.191).

One disadvantage to qEEG is the limited ability to localize cortical activity. Each electrode measures activity coming from several distinct areas of the brain. The further the signal is from the electrode, the weaker the signal produced and vice versa. Therefore, in order to gain a clear understanding of localization, as well as to elucidate the amount each site contributes to the localization, the data must be filtered through a program called LORETA, discussed below.

Low Resolution Electromagnetic brain Tomography (LORETA)

Low resolution electromagnetic brain tomography (LORETA) (Pascual-Marqui, Michel & Lehmann, 1994) is a functional imaging technique whereby neuroanatomical and electrophysiological data are combined to produce a 3-dimensional map of cortical activity (Pascual-Marqui, Esslen, Kochi & Lehmann, 2002). This cortical output is superimposed on a standardized normative image of the brain for ease of localization. According to Hughes and John (1998) localization via LORETA was found to “correspond well to the actual position of the abnormalities” (p. 199).

LORETA (Pascual-Marqui, 1995, 1999, 2000; Pascual-Marqui, Michel & Lehmann, 1994; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002a, 2002b, as cited in Cannon, Lubar, Thornton, Wilson, & Congedo, 2004), is regarded as the “most accepted inverse solution procedure” (Congedo, 2003, as cited in Cannon et al., 2004), and has been extensively utilized in electrophysiological studies (Bosch-Baynard et al., 2001; Isotani et al., 2001; Pizzagalli et al., 2002; Lehmann et al., 2001; Pascual-Marqui et al., 1999, as cited in Cannon et al., 2004). Pascual-Marqui et al. (1994, as cited in Cannon et al., 2004) report the “inverse problem of neurophysiology suggests that electroencephalogram/magnetoencephalogram (EEG/MEG) measurements do not provide enough information for ascertaining the neuronal activity distribution in the volume the brain occupies” (p. 7). LORETA uses a dense grid of electrodes placed over the scalp to measure the distribution of electrical neuronal activity in three dimensional space (Cannon et al., 2004). LORETA takes the electric potential variations measured by EEG and estimates current density that results in a “quantifiable potential divergence or the source of the electric field on the scalp (EEG), for which it is feasible to co-register

the resolution to a brain atlas and map electrical activity in the cortical structures”
(Cannon et al. 2004, p. 7).

Electroencephalography Research

In 1984, Flor-Henry and Koles conducted a qEEG study comparing patients diagnosed with unipolar and bipolar depression and found that in the eyes open condition, patients with mania showed “significant reductions in right temporal power” (p. 261). In terms of coefficient of variation (CV), Flor-Henry and Koles (1984) found that patients with mania had higher CV in the right parietal and left hemisphere (temporal/parietal) compared to patients with unipolar depression (p. 263). Additionally, patients diagnosed with bipolar disorder showed less power overall in the right temporal lobe, which supports the results of functional imaging studies (discussed above) that found decreased perfusion in the right temporal lobe.

Cook, Shukla, and Hoff (1986) studied abnormalities in EEG results in patients diagnosed with bipolar disorder. This research found varying abnormalities including generalized slowing, left temporal-parietal slowing, left occipital slowing, left temporal spike waves, left temporal slow waves, right parietal slow waves, bilateral frontal-temporal spike slow waves and right central sharp waves (Table 4). More contemporary research utilizing qEEG has found abnormalities in the right hemisphere (Abrams and Taylor, 1979, as cited in Small et al. 1999), small sharp spikes (Small et al. 1975, as cited in Small et al. 1999), and brief periods of deep sleep occurring during EEG and behavioral wakefulness termed ‘microsleep’ (Van Sweden, 1986). Research by Lieber and Newbury (1988) found patients diagnosed with bipolar disorder had an increased

probability of abnormal decreases in frontal lobe alpha activity compared to unipolar depressed patients (Table 4).

According to Hughes and John (1999), past research has shown that an intricate homeostatic systems comprised of the brainstem, thalamic, and cortical processes, combined with neuronal activity, mediate the EEG power spectrum (Hughes & John, 1999). Alpha rhythms (7.5 to 12.5 Hz) are postulated to be the result of efferent projections of pacemaker neurons located throughout the thalamus. When gamma-aminobutyric acid (GABA) is released by the nucleus reticularis, the cell membrane hyperpolarizes slowing alpha to the lower theta range of 3.5 to 7.5 Hz. It is theorized that oscillator neurons located in the deeper cortical areas and in the thalamus results in slow delta activity (1.5 to 3.5 Hz) (Hughes & John, 1999). Further, Hughes and John (1999) indicate that beta (12.5 to 20 Hz) is related to corticocortical and thalamocortical transactions (p. 192).

Hughes and John (1999) noted that when the mesencephalic reticular formation (MRF) is activated the nucleus reticularis is inhibited via serotonergic and cholinergic mediation (p. 192). This, in turn, causes the nucleus reticularis to release the inhibited thalamic cells (Hughes & John, 1999). As such, the “dominate activity of the EEG power spectrum becomes more rapid, with the return of alpha activity and the higher frequency beta activity, and the flow of information through the thalamus to the cortex is facilitated” (Hughes & John, 1999, p. 192).

The nucleus reticularis can be activated by the cortex via glutamatergic pathways which works to “suppress the arrival of information to the cortical level and, by striatal projections, dopamine can inhibit the MRF” (Hughes and John, 1999, p. 192). When the

MRF is inhibited, it allows for inhibition of the thalamic neurons, as well as blocking the flow of sensory information through the thalamus to the cortex (Hughes & John, 1999, p. 192).

Past research utilizing QEEG has found high reliability in examining patients diagnosed with bipolar disorder (Arruda et al. 1996; Burgess & Gruzelier, 1993; Corsi-Cabera, Solis-Ortiz, & Guevara, 1997; Fein, Galin, Yingling, Johnstone & Nelson, 1984; Gasser, Bacher, & Steinberg, 1985; Hamilton-Bruce, Boundry, & Purdie, 1991; Harmony et al., 1993; John et al., 1983; John, Prichep, & Easton, 1987; Kaye, John, Ahn, & Prichep, 1981; Kondacs & Szabo, 1999; Lund, Sponheim, Iacono & Clementz, 1995; Oken & Morehead, 1991; Van Dis, Corner, Dapper, Hanewald, & Kok, 1979, as cited in Hammond, Walker, Hoffman, Lubar, Trudeau, Gurnee, & Horvat, 2004) which is equivalent or superior to common clinical tests including MRI and CAT scans (Swets, 1988, as cited in Hammond et al., 2004).

Table 4. EEG & Bipolar Disorder Research

| Author(s) | Number of Subjects | Procedures/Measures | Results |
|---------------------------------|--------------------|---------------------|---|
| Flors-Henry, et al. 1984 | - 191 | - qEEG | <ul style="list-style-type: none"> - Eyes open condition: significant decreases in right temporal lobe power in manic subjects compared to depressed subjects - Left parietal power was decreased in manic subjects - Right temporal power was decreased in manic subjects - Eyes closed condition: reduction of left temporal alpha in mania compared to depression - Reduction of right intra-hemispheric |

| | | | |
|---------------------------|--------------|---------------|---|
| | | | parieto-temporal coherence in psychosis - Left hemisphere activation in mania |
| Small, et al. 1998 | - 202 | - qEEG | - Manic subjects exhibited slowing and sharp activity - Significant association between family history of affective disorder and abnormal qEEG |

EEG research studying subjects diagnosed with bipolar disorder.

Genetic Vulnerability

Bipolar disorder has a high rate of heritability, with family members having a ten to twenty percent greater chance of developing a bipolar diagnosis over the general population (Craddock & Jones, 1999, as cited in Clark et al. 2005). Additionally, evidence pointing to cognitive deficits that persist despite relative absence of symptoms during the euthymic phase of illness is suggestive of a trait deficit which could be used to diagnosis or identify individuals at risk for bipolar disorder (Quraishi & Frangou, 2002). Benabarre et al (2004) reported finding deficits in selective and sustained attention in 75% of bipolar patients, which supports the theory that abnormalities in sustained attention may be a possible benchmark for bipolar disorder. Past research on possible genetic markers for bipolar disorder generally emphasize the role of the frontal lobe, subcortical structures, striatum, and the limbic system (Benabarre, et al 2004). Hays (1976, as cited in Small et al. 1999) suggested that individuals with familial loading for bipolar illness show abnormalities on EEG located primarily in the frontal lobes.

The persistence of deficits during euthymic periods consistently points to an underlying structural pathology in bipolar disorder. Research by Ongur and Price (2000, as cited in Strkowski, Adler, Holland, Mills & DelBello, 2004) found evidence that the

“medial orbitofrontal and ventrolateral prefrontal areas receive processed sensory information through extensive reciprocal connections with basal amygdala, anterior temporal regions, rostral insula, and subgenual and anterior cingulate” (p. 1734).

Additional studies have found involvement in the anterior limbic network (Blumberg et al. 2003; Ketter et al. 2001; Phillips et al. 2003; Strakowski, 2002; Strakowski et al. 2002, as cited in Strakowski et al. 2004).

According to research by Strakowski et al. (2004), there are indications that a dysregulation of the anterior limbic network “may inhibit cognitive brain regions, thereby producing the affective and attention impairments of bipolar disorder” (p.1735). In euthymic patients, there is a *relative* absence of symptoms, although dysregulation of emotional brain networks (i.e. the anterior limbic system) is still present to a lesser degree than during a manic phase. As such, this suggests that patients diagnosed with bipolar disorder are at invariably at risk for mood and cognitive disturbances. Strakowski et al. (2004) suggest that this persistent vulnerability can be identified through neuroimaging and tasks of sustained attention. This also highlights the importance of sustained attention as a potential endophenotype correlating neuropsychological tests measuring sustained attention and neuroimaging techniques may be able to identify individuals at risk for bipolar disorder.

Prodromal research has focused on identifying patterns of deficits that can be employed for early identification and treatment of psychiatric disorders. Deficits in sustained attention have been found to be present during the euthymic (i.e. healthy) period. This suggests that deficits in sustained attention may be used to identify an individual who is at risk for developing the disorder, but has not yet had their first

episode. In other words, a sustained attention deficit may be a dormant feature in those at risk due to a family history of bipolar disorder. Therefore, screening for deficits in sustained attention in those identified as having the potential for developing the disorder could aid in early diagnosis and treatment.

Hypothesis and Rationale

Patients who are diagnosed with bipolar disorder demonstrate a variety of neurocognitive and neuroimaging disturbances. QEEG studies on patients with bipolar disorder have indicated small, sharp spikes and paroxysmal events focused in the frontal and/or anterior temporal lobes, specifically in the right hemispheres, as well as decreased alpha activity and increased beta activity in the frontal and/or anterior temporal lobes. Data from each electrode is measured based on absolute power, which refers to the sum total of all the amplitudes of all frequencies, and by relative power in each band, which is the percentage of total power (Hughes and John, 1999). Neuropsychological measures of sustained attention have been identified in the research as a possible “neuropsychological blueprint” for bipolar disorder. This current research proposes to examine the existence of common patterns of deficits across individuals with a historical diagnosis of bipolar disorder by utilizing neuropsychological test data and QEEG. It is hypothesized that:

1. Individuals with a historical bipolar diagnosis will show impairments on the executive functioning tasks of the Cambridge Automated Neuropsychological Test Battery (CANTAB)

Intradimensional/Extradimensional Shift (ID/ED Shift), Stockings of Cambridge, and Spatial Working Memory

2. Patients with bipolar disorder will show abnormal qEEG activity.
3. Results of the two modalities will correlate.

Methods

Participants

This study utilized an archival data set of four male veterans from the Biological Markers study conducted at the Edward J. Hines Veterans Administration Hospital. The Biological Markers study was approved by the institutional review board at Edward J. Hines Veteran's Administration Hospital in Hines, Illinois. Data was collected within the Clinical Neuroscience Laboratory. Four volunteers with a historical diagnosis of bipolar disorder consented to and participated in research data collection which was then analyzed in this study. Subjects had been determined, prior to the collection of data, to meet criteria determined by the Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition (DSM-IV: 1) for bipolar disorder. Volunteers were referred for qEEG evaluations under the direction of Dr. Lukasz Konopka in the Clinical Neuroscience Section Imaging Laboratory. Participants also completed the Cambridge Automated Neuropsychological Test Battery (CANTAB; CeNeS Ltc, Cambridge, UK).

Selection of neuroimaging data/medication information from patient chart review:

Patient 1- 0179: No data available. No medications reported per chart. No toxicology results reported.

Patient 2- 0350: SPECT- Small perfusion deficit in left occipital region. MRI- Small pineal cyst (appears benign). No medications reported. No toxicology results to review. No medications reported per chart review. No toxicology results.

Patient 3- 0375: CT w/o contrast- low density regions in gyri recti of frontal lobes and possibly right temporal tip; no hydrocephalus/hemorrhage, no midline shift, no subdural hematoma; no recent infarct/herniation noted. No medications reported per chart review. No toxicology reports.

Patient 4- 0379: MRI- mild diffuse cortical atrophy; slight asymmetrical dilation of left lateral ventricle; no evidence of mass lesion; mild mucosal thickening of sphenoid/ethmoid sinuses. History of seizure disorder reported. No medications reported per chart review. No toxicology results reported.

Measures

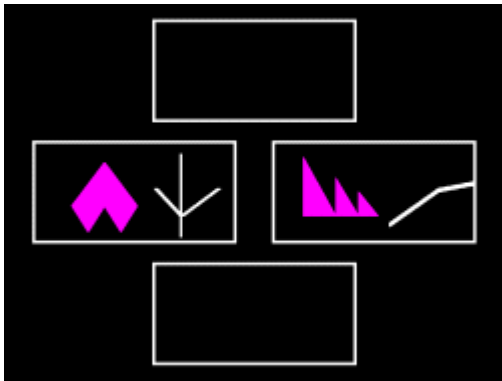
Cambridge Automated Neuropsychological Test Battery (CANTAB)

The Cambridge Automated Neuropsychological Test Battery (CANTAB; CeNeS Ltd, Cambridge, UK) is a computer administered test of neuropsychological functioning. The CANTAB has high test-retest reliability and was normed on over 2000 individuals ranging in age from 40 to 90 spanning four IQ groups. The CANTAB consists of 19 tests of cognition measuring spatial working memory, problem-solving, attention shifting, and rapid visual information processing. Participants use a touch screen format to respond to questions, which is effective in virtually eliminating experimental bias effects and helps to control for threats to internal validity. The CANTAB is used to measure cognitive skills in a wide range of disorders, including but not limited to: dementia,

neurodegenerative disorders, schizophrenia and related disorders, neural damage, and affective disorders. For the purpose of the present study, only tests which assessed frontal lobe dysfunction and executive functioning were included. Past research has noted that the CANTAB has a “significant focus on neuropsychological functions subserved by frontostriatal circuitry (Frey et al. 1997, as cited in Sweeney et al. 2000). A neuroanatomical link has been supported by imaging studies (Cambridge Cognition, 2003). It was predicted that impairments on measures of sustained attention via the CANTAB will correlate with abnormal qEEG results. This research will focus on the following tests:

Intradimensional/Extradimensional (ID/ED) Shift (Figure 2)

Figure 2. Intradimensional/Extradimensional (ID/ED) Shift



Example of ID/ED Shift screen. Retrieved on December 19, 2007 from:
<http://www.cantabeclipse.co.uk/science/cantab-tests-all.asp>

This test is a measure of executive functioning and assesses set shifting, reversal, and rule acquisition. This particular test is described in the literature as having been

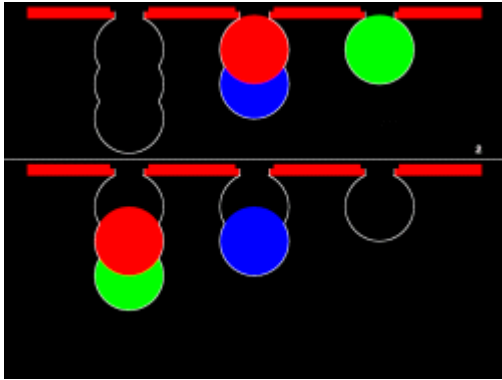
designed to test the sum components of the Wisconsin Card Sorting Test (WCST) (Cambridge Cognition, 2003). The ID/ED Shift task features visual discrimination and attentional set formation, as well as maintenance, shifting, and flexibility of attention (Cambridge Cognition, 2003). Administration time is dependent on the level of impairment and is generally around seven minutes. The ID/ED Shift task uses two dimensions: color-filled shapes and white lines. When a simple stimuli is presented, only one of these dimensions is shown. A complex stimuli consists of both, typically with white lines presented over a color filled shape. The subject is presented via computer screen with two color filled shapes, and must choose the correct shape by touching it on the screen. The subject learns by receiving feedback which is correct, and following six correct responses the rules are changed and the subject must use feedback to alter their response set. Failure to reach the six consecutive congruent correct criterion results in termination of the test. There are eighteen total outcome measures for this test, including assessing errors and numbers of trials and stages completed. Scores that are more than 1 standard deviation from the mean will be considered abnormal. The ID/ED Shift task is scored according to the following criteria:

- 1) ID/ED Pre-ED Errors: Number of errors occurring prior to the start of the extradimensional shift. An error is defined as failure to select the correct stimulus according to the rule
- 2) ID/ED EDS Errors: Errors made during the ED portion of the test.
- 3) ID/ED Total Errors: Total errors made, which is a measure of the individuals efficiency in completing the test.

- 4) ID/ED Completed Stage Errors: Total errors at the end of a stage.
- 5) ID/ED errors (block 1): Total errors on Block 1. This is a measure of perceptual dimensions and errors represent impairment in simple discrimination learning.
- 6) ID/ED errors (block 2): Total errors on Block 2. This is a measure of reversal learning and is sensitive to frontal lobe dysfunction.
- 7) ID/ED errors (block 3): Total errors on Block 3. During Block 3 two dimensions are present at the same time but are not congruent with each other (i.e. are separate).
- 8) ID/ED errors (block 4): Total errors on Block 4. During Block 4 two dimensions are present but one is superimposed on the other.
- 9) ID/ED errors (block 5): Total errors on Block 5. Errors on Block 5, when taken together with errors on Blocks 2, 7, & 9, are indicative of reversal learning and frontal lobe dysfunction.
- 10) ID/ED errors (block 6): Total errors on Block 6. Block 6 errors, when examined with extradimensional errors and errors on Block 8, indicate attentional flexibility.
- 11) ID/ED errors (block 7): Total errors on Block 7. Block 7 errors are a good measure of reversal learning and frontal lobe dysfunction.
- 12) ID/ED errors (block 8): Total errors on Block 8. This is the number of errors occurring prior to the successful completion of ED Shift.
- 13) ID/ED errors (block 9): Total Errors on Block 9. Errors at this stage are a measure of reversal learning and are sensitive to frontal lobe dysfunction.

Stockings of Cambridge (SOC) (Figure 3)

Figure 3. Stockings of Cambridge (SOC)



Example of Stockings of Cambridge test screen. Retrieved on December 19, 2007 from: <http://www.cantabeclipse.co.uk/science/cantab-tests-all.asp>

This task assesses spatial planning ability and measures frontal lobe functioning. It takes approximately ten minutes depending on subjects level of impairment. The SOC was designed to be comparable to the Tower of London. During this task, subjects are shown two displays with three colored balls per display. The displays are presented in a 3-D format which causes the balls to appear they are being suspended in stockings from a beam. Verbal instructions are presented to the subject. The balls in the lower display are manipulated via touch screen by the subject with the goal of matching them to the top display. Planning ability is measured according to the time taken to complete the task and the number of moves the subject takes. There are thirteen outcome measures for this task, specifically the number of problems solved with minimal moves, mean number of

moves for n-move problems, mean initial thinking time for n-move problems and mean subsequent thinking time for n-move problems (CANTAB, 2006).

The SOC will be scored by mean initial thinking time, mean subsequent thinking time, and problems solved with the fewest number of moves. Individuals with scores that differ from the norms by more than 1 standard deviation will be considered abnormal.

The thirteen outcome measures will be grouped as follows:

- 1) Problems solved in minimum moves.
- 2) Mean moves for 2, 3, 4, 5-move problems.
- 3) Initial thinking time for 2, 3, 4, 5-move problems,
- 4) Subsequent thinking time for 2, 3, 4, 5-move problems.

Scoring criteria is as follows:

Problems Solved in Minimum Moves

1) SOC Problems solved in minimum number of moves: Considered a fundamental measure which records the number of moves a subject makes before successfully completing the test. In the clinical mode, this is scored out of 12 potential moves, as the 8 practice moves are not included in the scoring.

Mean Moves for n-move Problems

- 2) SOC Mean Moves (2 Moves): In the clinical mode, this is calculated for 2-move problems.
- 3) SOC Mean Moves (3 Moves): In the clinical mode, this is calculated for 3-move problems.

4) SOC Mean Moves (4 Moves): In the clinical mode, this is calculated for 4-move problems.

5) SOC Mean Moves (5 Moves): In the clinical mode, this is calculated for 5-move problems.

Mean Initial Thinking Time for n-move Problems

1) SOC Mean Initial Thinking Time (2 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

2) SOC Mean Initial Thinking Time (3 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

3) SOC Mean Initial Thinking Time (4 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

4) SOC Mean Initial Thinking Time (5 Move): If the subject moves slowly on the follow condition, this may receive a score of 0. There is potential for measuring improvements in performance if the initial and subsequent thinking times are examined at the highest level of difficulty. This decreases the potential for ceiling effects.

Mean Subsequent Thinking Time for n-move Problems

1) SOC Mean Subsequent Thinking Time (2 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

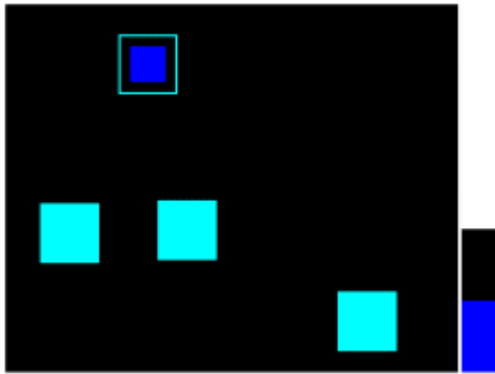
2) SOC Mean Subsequent Thinking Time (3 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

3) SOC Mean Subsequent Thinking Time (4 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

4) SOC Mean Subsequent Thinking Time (5 Moves): If the subject moves slowly on the follow condition, this may receive a score of 0.

Spatial Working Memory (SWM) (Figure 4)

Figure 4. Spatial Working Memory



Example of Spatial Working Memory test screen. Retrieved on December 19, 2007 from: <http://www.cantabeclipse.co.uk/science/cantab-tests-all.asp>

This task assesses a subject's ability to retain spatial information and manipulate these items in working memory. SWM measures executive and frontal lobe dysfunction. Administration time is generally eight minutes. At the beginning of the test, subjects are shown several colored boxes. Subjects move the boxes via touch screen to fill the empty column on the right side of the screen. The number of boxes increases as the subject completes trials, and the color and position of the boxes are changed to discourage the use stereotyped search strategies.

The SWM is scored for between errors, number of times the individual identifies an incorrect stimulus, and strategy, or number of times the individual begins a search by selecting the same box. Abnormality will be defined as a score that deviates from the

norm by more than 1 standard deviation. The fourteen outcome measures will be divided into Errors (between, within, double, and total) and Strategy and are scored as follows:

- 1) SWM Between Errors: number of times subject returns to a box where a token has already been identified. This measure is only calculated on trials with four or more tokens.
- 2) SWM Between errors (in boxes): In the clinical mode, potential values for $n = 4, 6,$ or 8. Possible outcome measures for aforementioned values of n are as follows:
 - a) SWM Between Errors (4 Boxes): recorded errors for 4-box problems only.
 - b) SWM Between Errors (6 Boxes): recorded errors for 6-box problems only.
 - c) SWM Between Errors (8 Boxes): recorded errors for 8-box problems only.
- 3) SWM Within Errors: recorded number of times subject visits empty box. Calculated for trials with four or more tokens only.
- 4) SWM Within Errors (in boxes): In clinical mode, potential values for $n = 4, 6,$ or 8. Possible outcome measures for aforementioned values of n are as follows:
 - a) SWM Within Errors (4 Boxes): recorded errors for 4-box problems only.
 - b) SWM Within Errors (6 Boxes): recorded errors for 6-box problems only.
 - c) SWM Within Errors (8 Boxes): recorded errors fro 8-box problems only.
- 5) SWM Double Errors: Occurs when a subject commits an errors categorized as a between and a within error. This measure is only calculated on trials with four or more tokens.
- 6) SWM Double Errors (in boxes): In clinical mode, potential values for $n = 4, 6,$ or 8. Possible outcome measures for aforementioned values of n are as follows:

- a) SWM Double Errors (4 Boxes): Categorized as both a within and between error on 4-box problems.
- b) SWM Double Errors (6 Boxes): Categorized as both a within and between error on 6-box problems.
- c) SWM Double Errors (8 Boxes): Categorized as both a within and between error on 8-box problems.
- 7) SWM Total Errors: Categorized as the number of times a subject selects a box that is certain to not contain a blue token and therefore should not have been selected by the subject.

The following chart illustrates the clinical ranges and qualitative descriptors used to describe CANTAB data:

Table 5. Z-Score ranges by qualitative descriptor

| Z-Score | Qualitative Descriptor |
|----------------|-------------------------------|
| >+2 | Very Superior |
| +1.34 to +1.99 | Superior |
| +.67 to +1.33 | High Average |
| -.66 to +.66 | Average |
| -1.33 to -.67 | Low Average |
| -1.67 to -1.34 | Mild Impairment |
| -2 to -1.68 | Mild to Moderate Impairment |
| -2.52 to -2.01 | Moderate Impairment |
| -3 to -2.53 | Moderate to Severe Impairment |

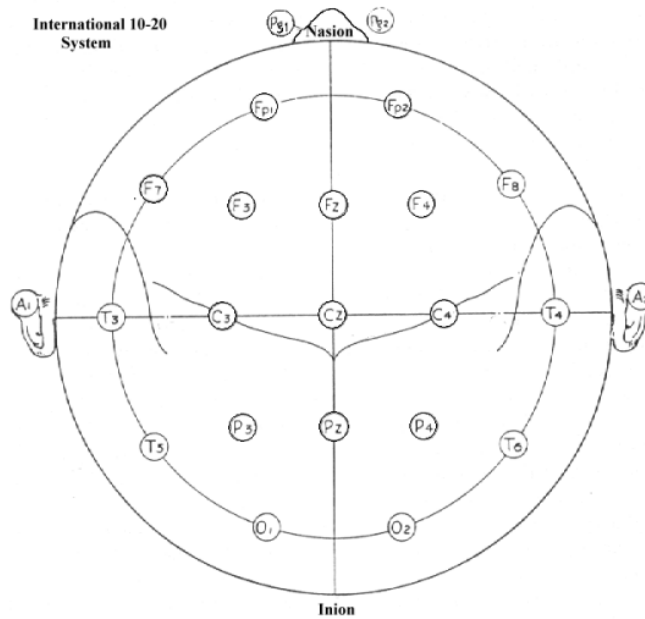
| | |
|----------------|----------------------------------|
| -3.49 to -3.01 | Severe Impairment |
| -4 to -3.5 | Severe to Very Severe Impairment |
| -4.5 to -4.01 | Profound Impairment |

Z-score ranges and associated qualitative descriptors used to describe CANTAB results.

Quantitative Electroencephalogram (QEEG)

Quantitative Electroencephalography (qEEG) is a brain imaging technique that yields information about the structural abnormalities. QEEG recordings were obtained during waking, photic stimulation, hyperventilation, and sleep while patients sat in a reclining chair in a sound-proof booth. Standard placement of 25 electrodes (A1, A2, FZ, FP1, FP2, F3, F4, F7, F8, CZ, C3, C4, T3, T4, T5, T6, Tp7, Tp8, PZ, P3, P4, OZ, O1, O2, & 12) is based on the 10/20 International System of Electrode Placement (Figure 5).

Figure 5. Electrode placement based on the international 10/20 system.



Location of electrode placement in accordance with the International 10-20 System.
Public domain imaged retrieved from:
<http://neurocog.psy.tufts.edu/images/10-20system.gif>

Electrode impedance was set at $<5\text{k}\Omega$. Data was acquired with a sampling rate of 50 Hz and filter settings set at 0.1 Hz and 70 Hz. Quantitative analysis of EEG background and foreground activity was conducted using Neuroguide 1.8.1 EEG software and Z scores and Z transformed brain maps were generated. For analysis, manual selection of epochs without artifacts was conducted. Epochs were compared to the NeuroGuide normative database for evaluation of normality. Z scores more two or more standard deviations from the mean are considered statistically significant. Additionally, the Key Institutes LORETA system (Pascual-Marqui, Michel & Lehmann, 1994) was used to determine areas that include deviant sources of electrical activity.

Results

Individual Patient CANTAB Results

Patient #1- 0179

*CANTAB Results*Intradimensional/Extradimensional Shift (ID/ED)

Patient 1 completed the ID/ED task with a time of 14:09. The results of the stages are presented in Table 6.

Table 6. ID/ED Shift Results for Patient 1.

| Block | Score | Z-Score | Qualitative Description |
|--------------|--------------|----------------|--------------------------------|
| 1 | 1 | 0.31 | Average |
| 2 | 1 | 0.34 | Average |
| 3 | 2 | 0.23 | Average |
| 4 | 0 | 0.54 | Average |
| 5 | 2 | -0.08 | Average |
| 6 | 1 | 0.3 | Average |
| 7 | 1 | 0.24 | Average |
| 8 | 22 | -1.68 | Mild to Moderate Impairment |

Results for Blocks 1 through 8 for patient 1.

Patient 1 performed in the Average range on ID/ED Errors (Blocks 1-7). On ID/ED Errors (Block 8), Patient 1 made 22 errors and his performance fell in the Mild to Moderate Impairment range ($z = -1.68$).

Taken together, errors on Blocks 2, 5, 7 and 9 are considered accurate measures of reversal learning and are considered sensitive to neurocognitive deficits shown in frontal lobe dysfunction. Patient 1 earned Average scores on Block 2 ($z = 0.34$), Block 5 ($z = -0.08$), and Block 7 (0.24). Block 9 was not attempted as the patient discontinued on Block 8. On these measures, Patient 1 exhibited adequate reversal learning skills.

ID/ED Errors (Block 6) and ID/ED errors (Block 8) are considered good measures of attentional flexibility. Patient 1 performed in the Average range on Block 6 ($z = 0.30$) and in the Mild to Moderate Impairment range on Block 8 ($z = -1.68$). This pattern of scores is indicative of difficulty with attentional flexibility characterized by a generally good ability to shift focus intradimensionally but not extradimensionally. More specifically, the ID/ED Errors (Block 6) is an “intradimensional shift” stage and the ID/ED Errors (Block 8) is an extradimensional shift stage. ID/ED Errors (Block 6) and ID/ED Errors (Block 8) are considered key stages within this task (Cambridge Cognition, 2003).

Stockings of Cambridge (SOC)

Patient 1 completed the SOC task with a time of 14:19. Results of this task are presented in Table 8.

Table 8. SOC Results for Patient 1.

| | Score | Z-Score | Qualitative Description |
|-------------------------------|--------------|----------------|--------------------------------|
| Mean Initial Thinking Time (5 | 5424 | 0.54 | Average |

| | | | |
|---|-----|-------|--------------|
| Moves) | | | |
| Mean Subsequent Thinking Time (5 Moves) | 578 | 0.82 | High Average |
| Problems Solved in Minimum Moves | 8 | -0.23 | Average |

Results for patient 1.

Patient 1's overall performance on the SOC task fell in the Average to High Average range. On the Mean Initial Thinking Time (5 Moves) measure, Patient 1 performed in the Average range ($z = 0.54$), indicating that he thoughtfully planned his responses before executing them. Patient 1's score on the Mean Subsequent Thinking Time (5 Moves) measure is in the High Average range ($z = 0.82$), which indicates that he completed the problem quickly following his initial thinking time.

The Problems Solved in Minimum Moves measure is considered fundamental for the SOC task. Patient 1's performance was Average ($z = -0.23$), indicating that he solved tests problems in minimal moves. His performance on this task was characterized by accuracy in planning of responses.

Spatial Working Memory (SWM)

Patient 1 completed the SWM task with a time of 14:19. The results of this task are presented in Table 7.

Table 7. SWM Results for Patient 1.

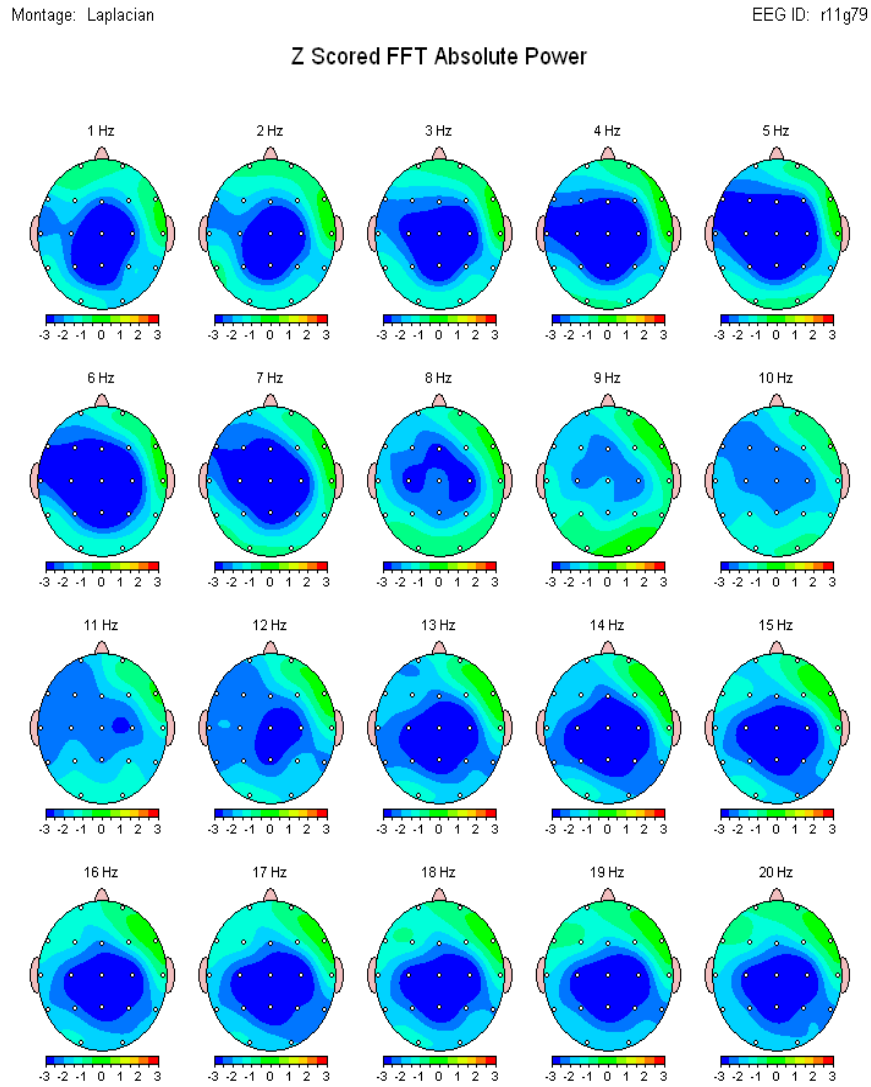
| | Score | Z-Score | Qualitative Description |
|----------------|--------------|----------------|--------------------------------|
| Between Errors | 24 | 0.31 | Average |
| Strategy | 45 | -1.95 | Mild to Moderate Impairment |

Between Errors and Strategy results for patient 1.

On the SWM Between Errors measure, Patient 1 performed in the Average range ($z = 0.31$). In terms of SWM Strategy, Patient 1's performance fell in the Mild to Moderate Impairment range ($z = -1.95$). This indicates that Patient 1 was inefficient at developing a successful strategy.

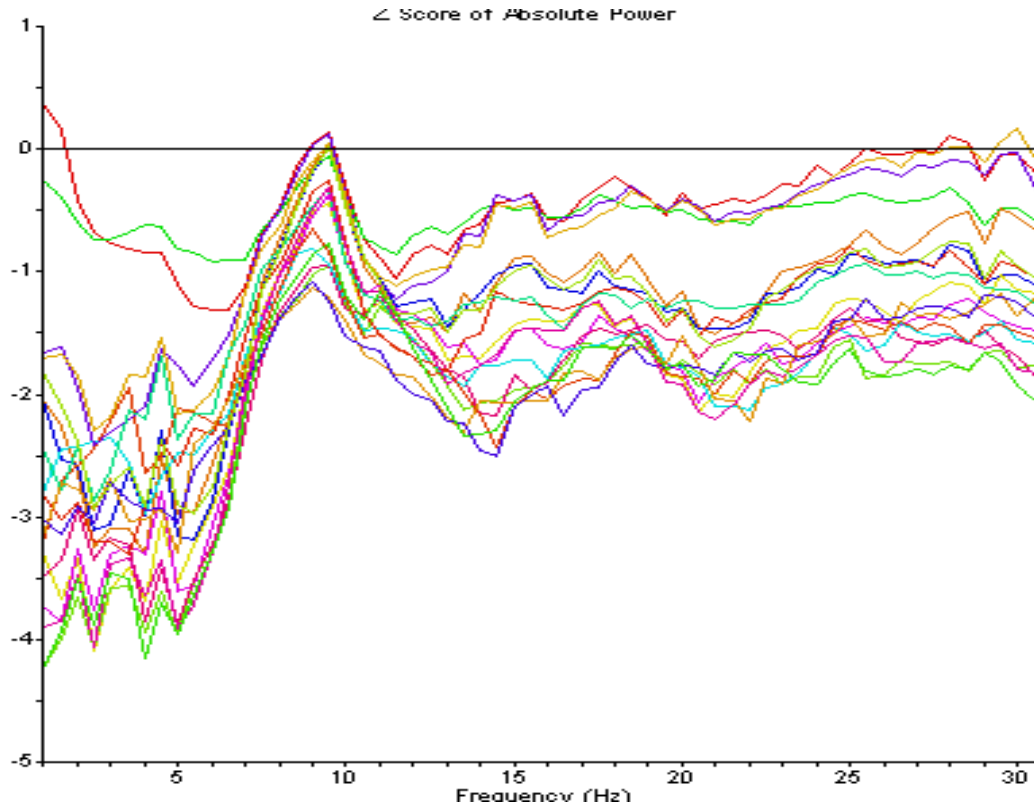
Quantitative EEG (qEEG) Results

Figure 6. Z-Scored FFT Absolute Power (Patient 1)



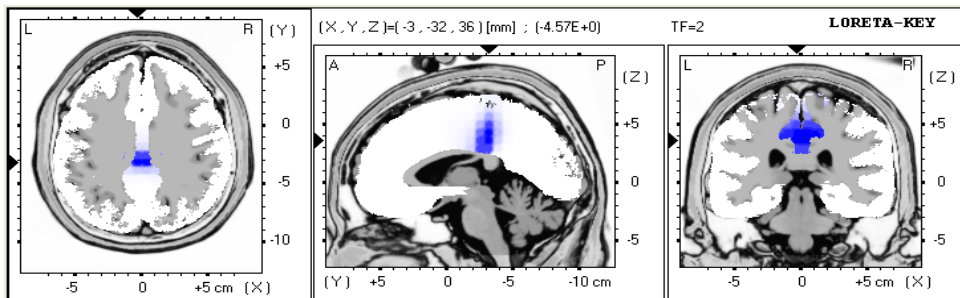
Results of patient 1's EEG in Z-scored FFT Absolute Power. Chart shown in Laplacian montage.

Figure 7. Z-Score of Absolute Power (Patient 1)

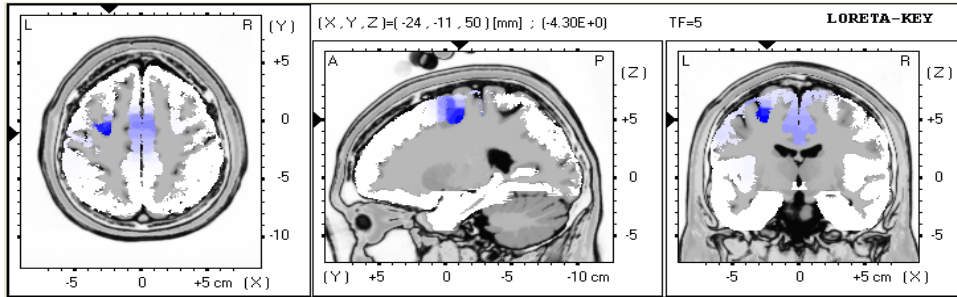


Graphical representation of patient 1's EEG record.

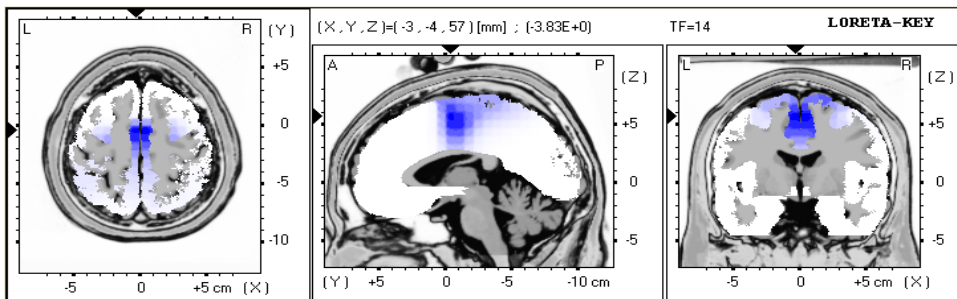
Figure 8. 2Hz LORETA output (Patient 1)



This figure shows a statistically significant deficit in delta at 2Hz. Talairach coordinates (x,y,z = -3, -32, 36) correspond with Brodmann Area 31. Blue represents areas of decreased activity as compared to the normative database.

Figure 9. 5Hz LORETA output (Patient 1)

This figure shows statistically significant deficit in theta at 5Hz. Talairach coordinates (x,y,z = -24, -11, 50) correspond with Brodmann Area 6. Blue represents areas of decreased activity as compared to the normative database.

Figure 10. 14 Hz LORETA output (Patient 1)

This figure shows statistically significant deficit in beta at 14Hz. Talairach coordinates (x,y,z = -3, -4, 57) correspond with Brodmann Area 6. Blue represents areas of decreased activity as compared to the normative database.

Patient 1's qEEG record was abnormal. Deficits were noted most prominently at 2Hz (Delta; SD = -4.57), 5Hz (Theta; SD = -4.30), and 14Hz (Beta; SD = -3.83) (see Figures 8, 9, & 10, respectively). Talairach coordinates at 2Hz corresponded to deficits in activity in the left cerebrum, limbic lobe, cingulate gyrus and gray matter, as well as more specifically with Brodmann Area 31 (Dorsal Posterior Cingulate Cortex). Talairach coordinates at 5Hz reflected deficits in activity in the left cerebrum, frontal lobe, precentral gyrus, and gray matter and 14 Hz reflected deficits in activity in the left

cerebrum, frontal lobe, medial frontal gyrus, and gray matter. Both 5Hz and 14Hz coordinated with Broadmann Area 6 (Premotor Cortex).

Patient 1 Summary

Neuropsychological deficits were present on the ID/ED Shift and SWM tasks of the CANTAB. Deficits in qEEG activity were noted at 2Hz (Delta), 5Hz (Theta), and 14Hz (Beta). These deficits coordinated with Broadmann Areas 31 and 6. Broadmann Area 31 has been associated with decision-making and Broadmann Area 6 with simple and complex motor control.

Patient #2- 0350

CANTAB Results

Intradimensional/Extradimensional Shift (ID/ED)

Patient 2 failed the ID/ED task with a time of 11:02. He completed 7 stages ($z = -5.08$; Profound Impairment) and made 30 errors ($z = -2.31$; Moderate Impairment).

Patient 2's performance on the ID/ED task was characterized by inefficiency in test competition, difficulty with set shifting, and failure to attend to rules. Results of the stages are presented in Table 9.

Table 9. ID/ED Shift Results for Patient 2.

| Block | Score | Z-Score | Qualitative Description |
|--------------|--------------|----------------|--------------------------------|
| 1 | 0 | N/A | N/A |
| 2 | 1 | 0.45 | Average |

| | | | |
|---|----|------|--------------------------------|
| 3 | 0 | 0.92 | High Average |
| 4 | 0 | 1.82 | Superior |
| 5 | 1 | 0.46 | Average |
| 6 | 0 | 1.42 | Superior |
| 7 | 1 | 0.46 | Average |
| 8 | 27 | -2.6 | Mild to Moderate Impairment |

Results for Blocks 1 through 8 for patient 2.

Patient 2's performance on ID/ED Errors (Block 1-7) was characterized by Average to Superior performance. However, his performance on ID/ED Errors (Block 8) was in the Moderate to Severe Impairment range ($z = -2.6$).

Taken together, errors on Blocks 2, 5, 7 and 9 are considered accurate measures of reversal learning and are considered sensitive to neurocognitive deficits shown in frontal lobe dysfunction. Patient 2 earned Average scores on Block 2 ($z = 0.45$), Block 5 ($z = 0.46$), and Block 7 (0.46). Block 9 was not attempted as the patient discontinued on Block 8. On these measures, Patient 2 exhibited adequate reversal learning skills.

ID/ED Errors (Block 6) and ID/ED errors (Block 8) are considered good measures of attentional flexibility. Patient 2 performed in the Superior range on Block 6 ($z = 1.42$) and in the Mild to Moderate Impairment range on Block 8 ($z = -2.6$). This pattern of scores is indicative of difficulty with attentional flexibility characterized by a generally good ability to shift focus intradimensionally but not extradimensionally. More specifically, the ID/ED Errors (Block 6) is an "intradimensional shift" stage and the ID/ED Errors (Block 8) is an extradimensional shift stage. ID/ED Errors (Block 6) and

ID/ED Errors(Block 8) are considered key stages within this task (Cambridge Cognition, 2003).

Stockings of Cambridge (SOC)

Patient 2 completed the SOC task with a time of 11 minutes, 41 seconds. Results of this task are presented in Table 10.

Table 10. SOC Results for Patient 2.

| | Score | Z-Score | Qualitative Descriptor |
|---|--------------|----------------|-------------------------------|
| Mean Initial Thinking Time (5 Moves) | 5484 | 1.12 | High Average |
| Mean Subsequent Thinking Time (5 Moves) | 8490 | -6.49 | Profound Impairment |
| Problems Solved in Minimum Moves | 7 | -1.44 | Mild Impairment |

Results for patient 2.

Patient 2's overall performance on the SOC task fell in the Profound Impairment to High Average range. On the Mean Initial Thinking Time (5 Moves) measure, Patient 2 performed in the High Average range ($z = 1.12$), indicating that he thoughtfully planned his responses before executing them. On the Mean Subsequent Thinking Time (5 Moves) measure, Patient 2 performed in the Profound Impairment range ($z = -6.49$), which

indicates that he completed was unable to quickly complete the problem once establishing a plan.

The Problems Solved in Minimum Moves measure is considered fundamental for the SOC task. Patient 2's performance was in the Mild Impairment range ($z = -1.44$), indicating that he had difficulty with solving the problems in a lesser number of moves.

Spatial Working Memory (SWM)

Patient 2 completed the SWM task with a time of 11:25. Results are presented in Table 11.

Table 11. SWM Results for Patient 2.

| | Score | Z-Score | Qualitative Descriptor |
|----------------|--------------|----------------|-------------------------------|
| Between Errors | 69 | -2.53 | Moderate Impairment |
| Strategy | 54 | -4.51 | Profound Impairment |

Results for patient 2.

On the SWM Between Errors measure, Patient 2's performance was in the Moderate Impairment range ($z = -2.53$). In terms of SWM Strategy, Patient 2 performed in the Profound Impairment range ($z = -4.51$). Patient 2's overall performance on the SWM task was characterized by extreme difficulty with developing an effective strategy and learning from consequences.

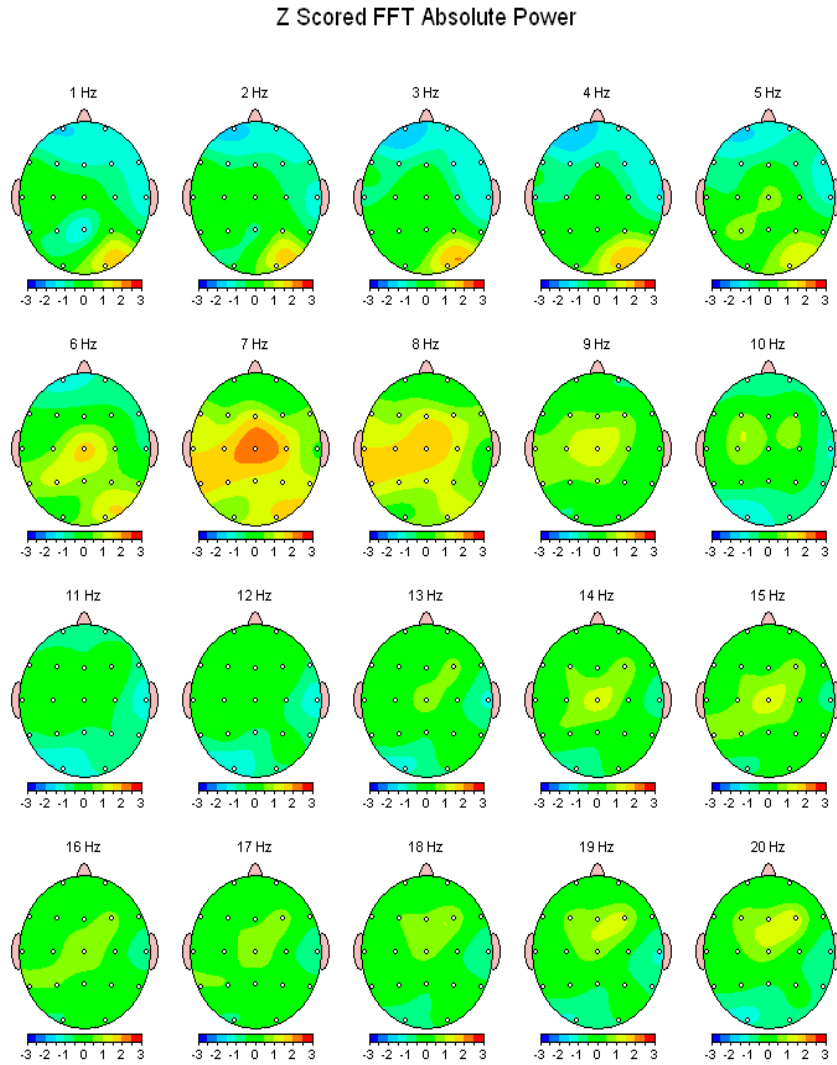
Quantitative EEG (qEEG) Result

S

Figure 11. Z-scored FFT Absolute Power (Patient 2)

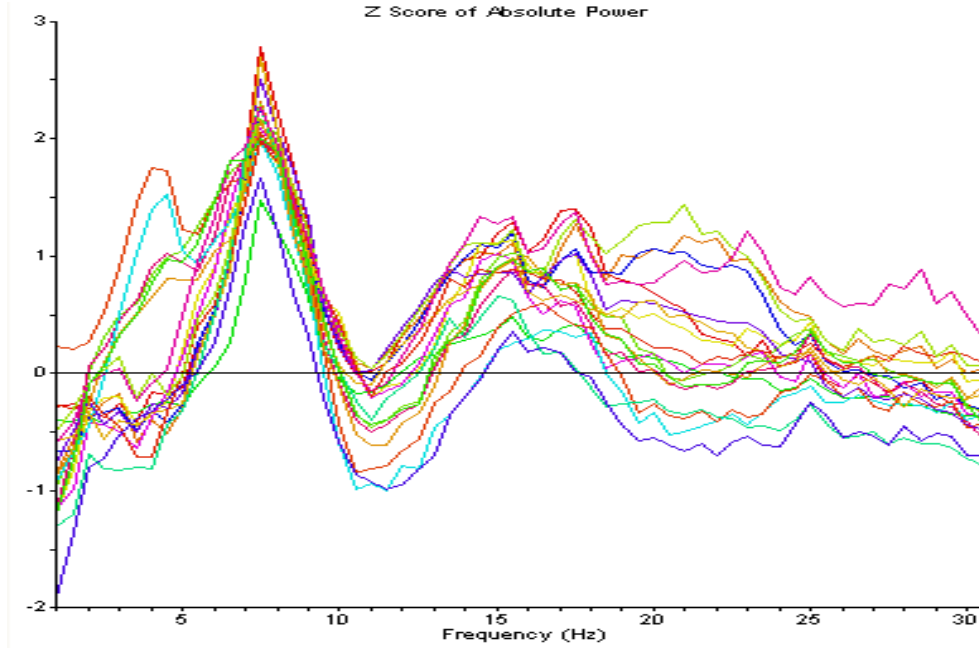
Montage: Laplacian

EEG ID: r1g50



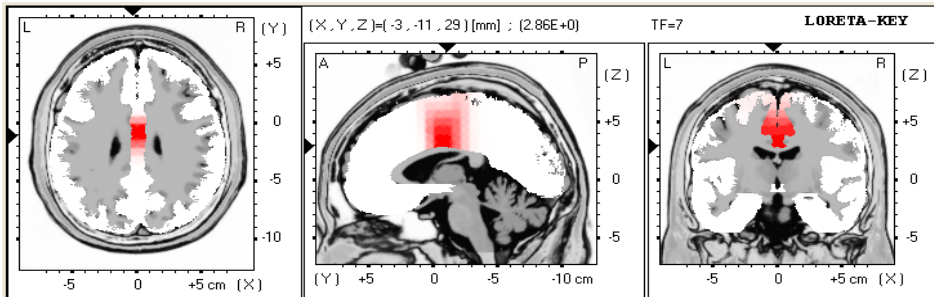
Results of patient 2's EEG in Z-scored FFT Absolute power. Chart shown in Laplacian montage.

Figure 12. Z-score of Absolute Power (Patient 2)



Graphical representation of patient 2’s EEG record.

Figure 13. 7Hz LORETA output (Patient 2)



This figure shows statistically significant excess in theta at 7Hz. Talairach coordinates (x,y,z = -3, -11, 29) correspond with Brodmann Area 23. Red represents areas of excessive activity as compared to the normative database.

Patient 2 exhibited an abnormal EEG record. Excesses were noted at 7Hz (theta; SD = 2.86) and reflected excessive activity in the left cerebrum, limbic lobe, cingulate gyrus,

and gray matter (Figure 13). Talairach coordinates corresponded with Broadmann's Area 23 (Ventral Posterior Cingulate Cortex).

Patient 2 Summary

Neuropsychological deficits were noted on the ID/ED Shift, SWM, and SOC tasks of the CANTAB. Excessive qEEG activity was noted at 7Hz (Theta). This coordinates with Broadmann Area 23. Broadmann Area 23 is associated with decision-making.

Patient #3- 0375

CANTAB Results

Intradimensional/Extradimensional Shift (ID/ED)

Patient 3 completed the ID/ED task in 9 minutes and 1 second. He completed 9 stages ($z = 0.36$; Average) and made 59 total errors ($z = -4.66$; Profound Impairment).

Results of the individual stages are presented in Table 12.

Table 12. ID/ED Shift Results for Patient 3.

| Block | Score | Z-Score | Qualitative Descriptor |
|--------------|--------------|----------------|-------------------------------|
| 1 | 12 | -37.66 | Profound |
| 2 | 1 | 0.52 | Average |
| 3 | 2 | -0.6 | Average |
| 4 | 6 | N/A | N/A |
| 5 | 15 | -10.33 | Profound |
| 6 | 11 | -12.78 | Profound |
| 7 | 8 | -10.63 | Profound |
| 8 | 3 | 0.41 | Average |
| 9 | 1 | 0.46 | Average |

Results of Blocks 1 through 9 for patient 3.

Patient 3's performance on ID/ED Errors (Block 1-7) was characterized by Profoundly Impaired to Average range performance.

Taken together, errors on Blocks 2, 5, 7 and 9 are considered accurate measures of reversal learning and are considered sensitive to neurocognitive deficits shown in frontal lobe dysfunction. Patient 2's performance was in the Average range on Block 2 ($z = 0.52$), Profoundly Impaired range on Block 5 ($z = -10.33$), and in the Profoundly Impaired range on Block 7 (-10.63), and in the Average range on Block 9 ($z = 0.46$). This pattern of scores is characterized by inconsistent performance on reversal learning measures.

ID/ED Errors (Block 6) and ID/ED errors (Block 8) are considered good measures of attentional flexibility. Patient 2 performed in the Profoundly Impaired range on Block 6 ($z = -12.78$) and in the Average range on Block 8 ($z = 0.41$). This pattern of scores is indicative of some difficulty with attentional flexibility characterized by a generally good ability to shift focus extradimensionally but not intradimensionally. More specifically, the ID/ED Errors (Block 6) is an "intradimensional shift" stage and the ID/ED Errors (Block 8) is an extradimensional shift stage. ID/ED Errors (Block 6) and ID/ED Errors (Block 8) are considered key stages within this task (Cambridge Cognition, 2003).

Stockings of Cambridge (SOC)

Patient 3 completed the SOC task in 9 minutes and 26 seconds. Results are presented in Table 13.

Table 13. SOC Results for Patient 3.

| | Score | Z-Score | Qualitative Descriptor |
|---|--------------|----------------|-------------------------------|
| Mean Initial Thinking Time (5 Moves) | 3784 | 1.13 | High Average |
| Mean Subsequent Thinking Time (5 Moves) | 2217 | -0.72 | Mild Impairment |
| Problems Solved in Minimum Moves | 8 | -0.33 | Average |

Results for patient 3.

Patient 3's overall performance on the SOC task fell in the Mildly Impaired to High Average range. On the Mean Initial Thinking Time (5 Moves) measure, Patient 3 performed in the High Average range ($z = 1.13$), indicating that he thoughtfully planned his responses before executing them. On the Mean Subsequent Thinking Time (5 Moves) measure, Patient 3 performed in the Mild Impairment range ($z = -0.72$), which indicates that he completed was unable to quickly complete the problem once establishing a plan.

The Problems Solved in Minimum Moves measure is considered fundamental for the SOC task. Patient 3's performance was in the Average range ($z = -0.33$), indicating no overt difficulty with solving the problems in minimal moves.

Spatial Working Memory (SWM)

Patient 3 completed the SWM task in 9 minutes and 16 seconds. Results are presented in Table 14.

Table 14. SWM Results for Patient 3.

| | Score | Z-Score | Qualitative Descriptor |
|----------------|--------------|----------------|-------------------------------|
| Between Errors | 16 | 0.42 | Average |
| Strategy | 42 | -1.78 | Mild to Moderate Impairment |

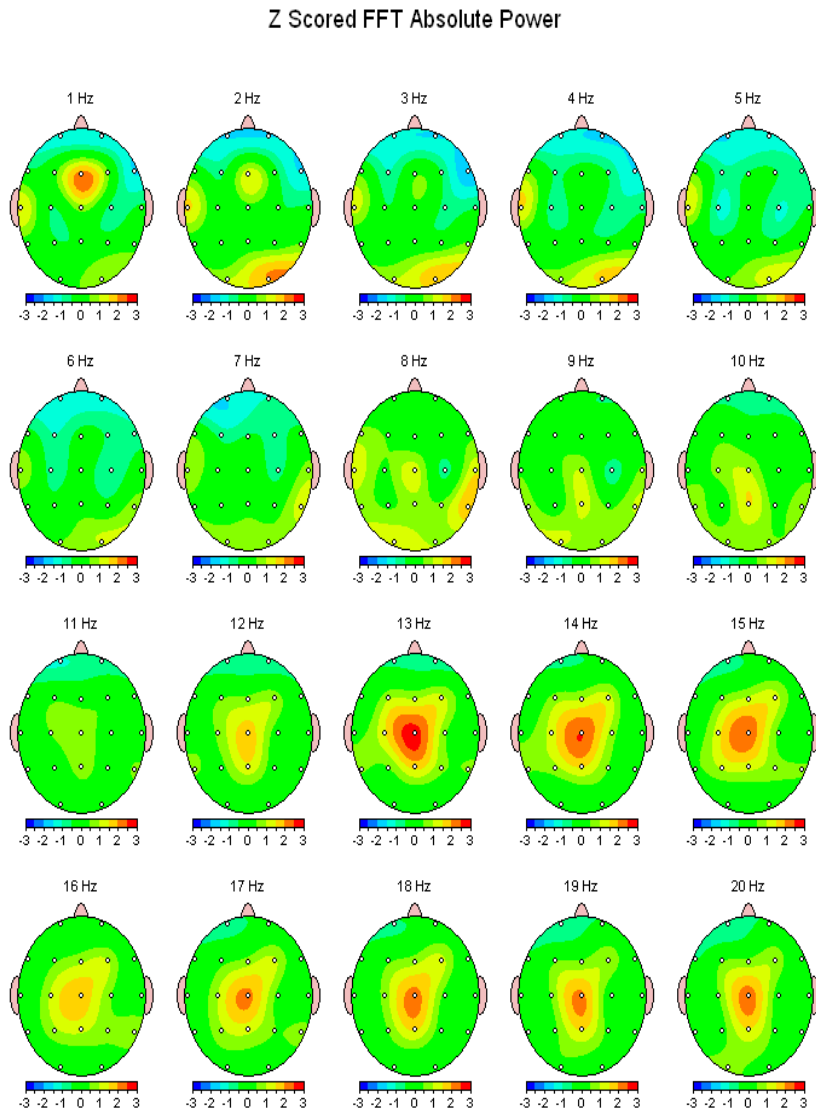
Results for patient 3.

On the SWM Between Errors measure, Patient 3's performance was in the Average range ($z = 0.42$). In terms of SWM Strategy, Patient 3 performed in the Mild to Moderate Impairment range ($z = -1.78$). Patient 3's overall performance on the SWM task was characterized by difficulty with developing an effective and efficient strategy.

*Quantitative EEG (qEEG) Results***Figure 14. Z-scored FFT Absolute Power (Patient 3)**

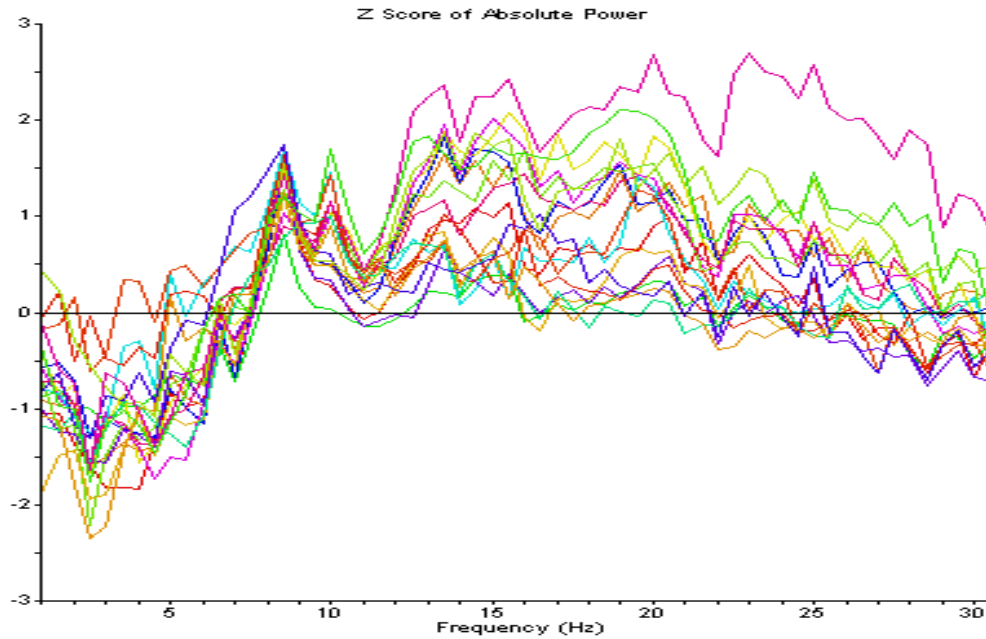
Montage: Laplacian

EEG ID: r1c75



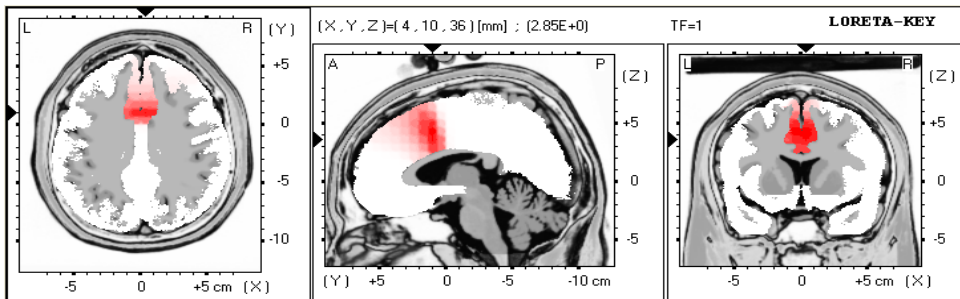
Results of patient 3's EEG in Z-scored FFT Absolute Power. Chart shown in Laplacian montage.

Figure 15. Z-score of Absolute Power (Patient 3)

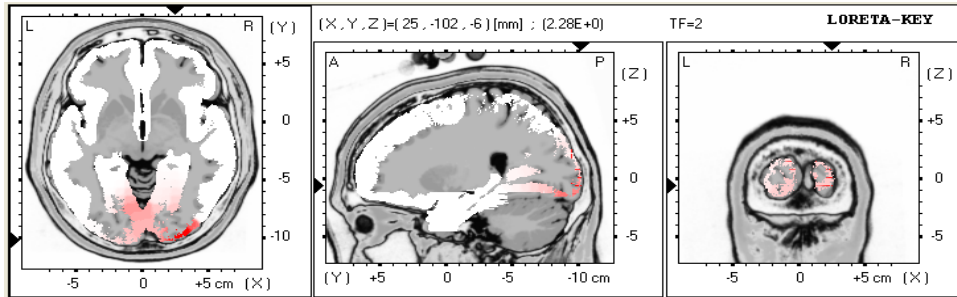


Graphical representation of patient 3's EEG record.

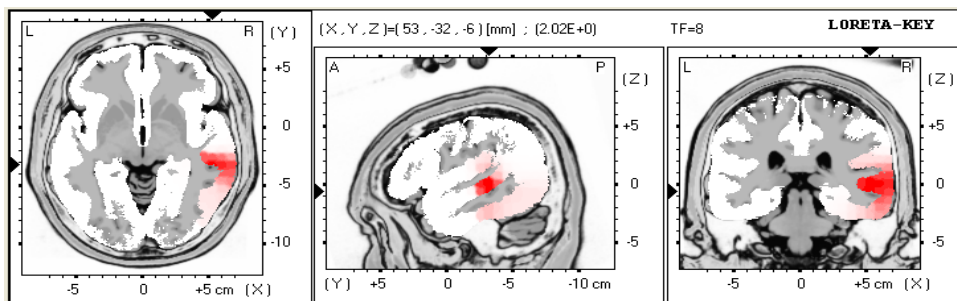
Figure 16. 1Hz LORETA output



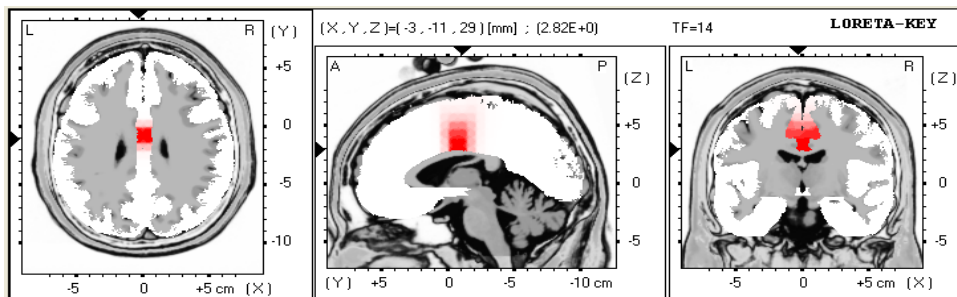
This figure shows statistically significant excess in delta at 1Hz. Talairach coordinates (x,y,z = 4, 10, 36) correspond with Brodmann Area 24. Red represents areas of excessive activity as compared to the normative database.

Figure 17. 2 Hz LORETA output (Patient 3)

This figure shows statistically significant excess in delta at 2Hz. Talairach coordinates (x,y,z = 25, -102, -6) correspond with Brodmann Area 18. Red represents areas of excessive activity as compared to the normative database.

Figure 18. 8Hz LORETA output (Patient 3)

This figure shows statistically significant excess in alpha at 8Hz. Talairach coordinates (x,y,z = 53, -32, -6) correspond with Brodmann Area 21. Red represents areas of excessive activity as compared to the normative database.

Figure 19. 14Hz LORETA output (Patient 3)

This figure shows statistically significant excess in beta at 14Hz. Talairach coordinates (x,y,z = -3, -11, 29) correspond with Brodmann Area 23. Red represents areas of excessive activity as compared to the normative database.

Patient 3 exhibited an abnormal EEG record. Excesses were noted most prominently at 1Hz (Delta; SD = 2.85), 2Hz (Delta; SD = 2.28), 8Hz (Alpha; SD = 2.02), and 14 Hz (Beta; SD = 2.82) (see Figures 16, 17, 18, & 19, respectively). Activity at 1Hz reflected activity in the right cerebrum, limbic lobe, and cingulate gyrus. Activity at 2Hz reflected activity in the right cerebrum, occipital lobe, lingual gyrus, and gray matter. Activity at 8Hz reflected activity in the right cerebrum, temporal lobe, middle temporal gyrus, and gray matter. Activity at 14Hz reflected activity in the left cerebrum, limbic lobe, cingulate gyrus, and gray matter. Talairach coordinates corresponded at 1Hz with Brodmann's Area 24 (Ventral Anterior Cingulate Cortex); 2Hz with Brodmann's Area 18 (Secondary Visual Cortex); 8Hz with Brodmann's Area 21 (Middle Temporal Gyrus); and 14Hz with Brodmann's Area 23 (Ventral Posterior Cingulate Cortex).

Patient 3 Summary

Neuropsychological deficits were seen on the ID/ED Shift, SWM, and SOC tasks of the CANTAB. Excessive qEEG activity was noted at 1Hz (Delta), 2Hz (Delta), Alpha (8Hz), and Beta (14Hz). This coordinates with Brodmann Areas 18, 21, 23, and 24. Brodmann Area 18 is correlated with attentional modulation; Brodmann Area 21 is associated with contemplation of distance, facial recognition, and word meaning; and Brodmann Areas 23 and 24 are associated with decision-making.

Patient #4- 0379

CANTAB Results

Intradimensional/Extradimensional Shift (ID/ED)

Patient 4 completed the ID/ED task in 8 minutes and 48 minutes. He completed 9 stages ($z = 0.18$; Average) and made a total of 18 errors ($z = 0.62$; Average). Results of the individual stages are presented in Table 15.

Table 15. ID/ED Shift Results for Patient 4.

| Block | Score | Z-Score | Qualitative Descriptor |
|--------------|--------------|----------------|-------------------------------|
| 1 | 0 | N/A | N/A |
| 2 | 1 | 0.45 | Average |
| 3 | 4 | -0.37 | Average |
| 4 | 0 | 1.82 | Superior |
| 5 | 1 | 0.46 | Average |
| 6 | 1 | 0.71 | High Average |
| 7 | 1 | 0.46 | Average |
| 8 | 8 | -0.24 | Average |
| 9 | 2 | -0.96 | Low Average |

Results of Blocks 1 through 9 for patient 4.

Patient 4's performance on ID/ED Errors (Block 1-7) was characterized by Low Average to Superior range performance.

Taken together, errors on Blocks 2, 5, 7 and 9 are considered accurate measures of reversal learning and are considered sensitive to neurocognitive deficits shown in frontal lobe dysfunction. Patient 4's performance was in the Average range on Block 2 (z

= 0.45), Block 5 ($z = 0.46$), and Block 7 ($z = 0.46$), and in the Low Average range on Block 9 ($z = -0.96$).

ID/ED Errors (Block 6) and ID/ED errors (Block 8) are considered good measures of attentional flexibility. Patient 4 performed in the High Average range on Block 6 ($z = 0.71$) and in the Average range on Block 8 ($z = -0.24$). This pattern of scores is indicative of generally good attentional flexibility. More specifically, the ID/ED Errors (Block 6) is an “intradimensional shift” stage and the ID/ED Errors (Block 8) is an extradimensional shift stage. ID/ED Errors (Block 6) and ID/ED Errors (Block 8) are considered key stages within this task (Cambridge Cognition, 2003).

Stockings of Cambridge (SOC)

Patient 4 completed the SOC task in 9 minutes and 7 seconds. Results are presented in Table 16.

Table 16. SOC Results for Patient 4.

| | Score | Z-Score | Qualitative Description |
|---|--------------|----------------|--------------------------------|
| Mean Initial Thinking Time (5 Moves) | 5669 | 1.1 | High Average |
| Mean Subsequent Thinking Time (5 Moves) | 2639 | -1.37 | Mild Impairment |
| Problems Solved in Minimum Moves | 9 | -0.39 | Average |

Results for patient 4.

Patient 4's overall performance on the SOC task fell in the Mildly Impaired to High Average range. On the Mean Initial Thinking Time (5 Moves) measure, Patient 4 performed in the High Average range ($z = 1.10$), indicating that he thoughtfully planned his responses before executing them. On the Mean Subsequent Thinking Time (5 Moves) measure, Patient 4 performed in the Mild Impairment range ($z = -1.37$), which indicates that he was unable to quickly complete the problem once establishing a plan.

The Problems Solved in Minimum Moves measure is considered fundamental for the SOC task. Patient 4's performance was in the Average range ($z = -0.39$), indicating no overt difficulty with solving the problems in minimal moves.

Spatial Working Memory (SWM)

Patient 4 completed the SWM task in 8 minutes and 56 seconds. Results are presented in Table 17.

Table 17. SWM Results for Patient 4.

| | Score | Z-Score | Qualitative Descriptor |
|----------------|--------------|----------------|-------------------------------|
| Between Errors | 38 | -0.87 | Low Average |
| Strategy | 47 | -3.22 | Severe Impairment |

Results for patient 4.

On the SWM Between Errors measure, Patient 4's performance was in the Low Average range ($z = -0.87$). In terms of SWM Strategy, Patient 4 performed in the Severely

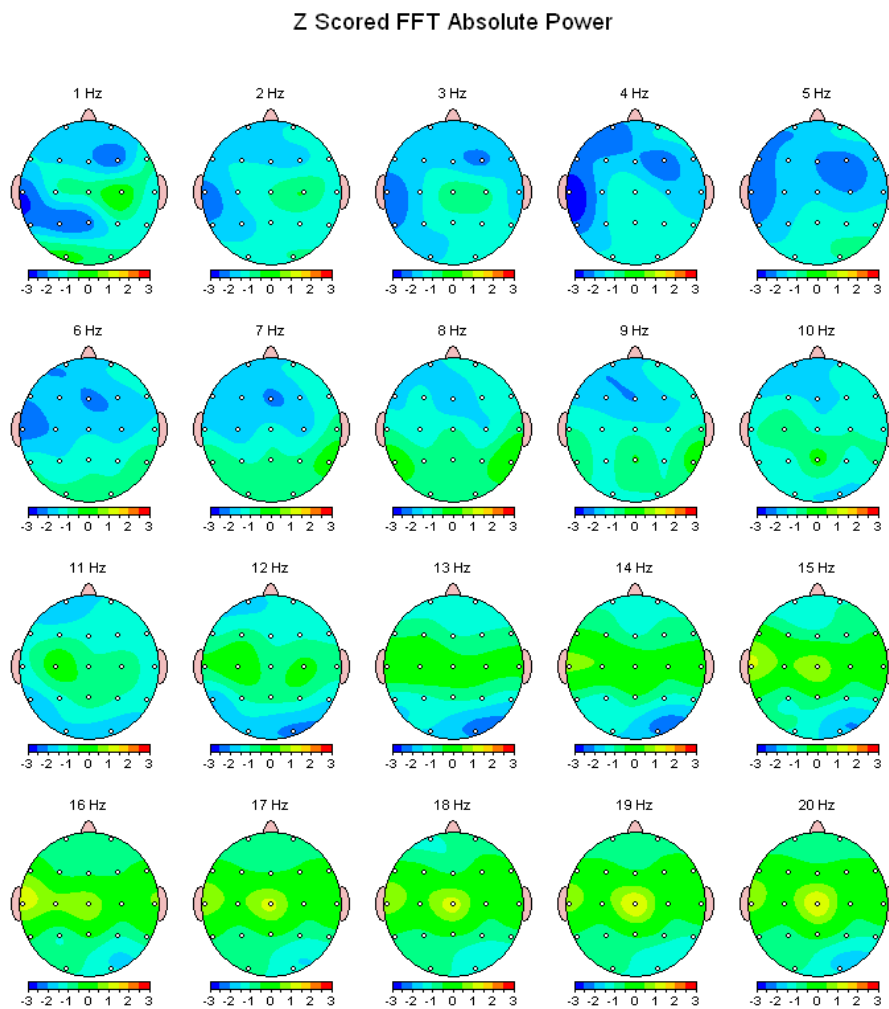
Impaired range ($z = -3.22$). Patient 4's overall performance on the SWM task was characterized by difficulty with developing an effective and efficient strategy.

Quantitative EEG (qEEG) Results

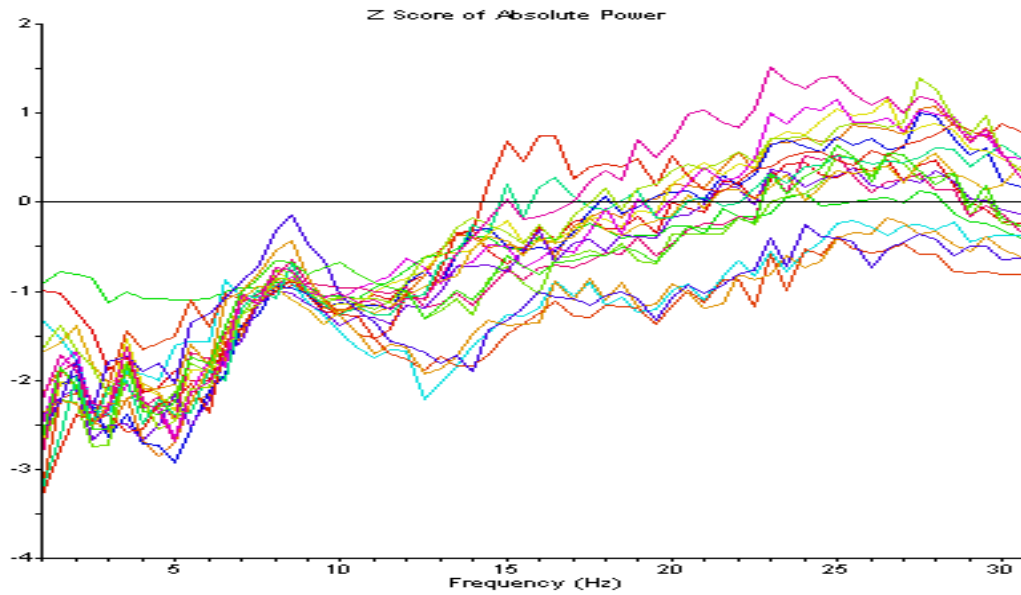
Figure 20. Z-scored FFT Absolute Power (Patient 4)

Montage: Laplacian

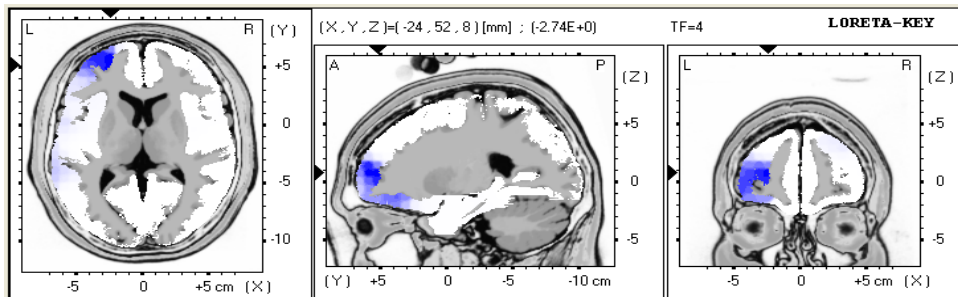
EEG ID: r2c-3-79



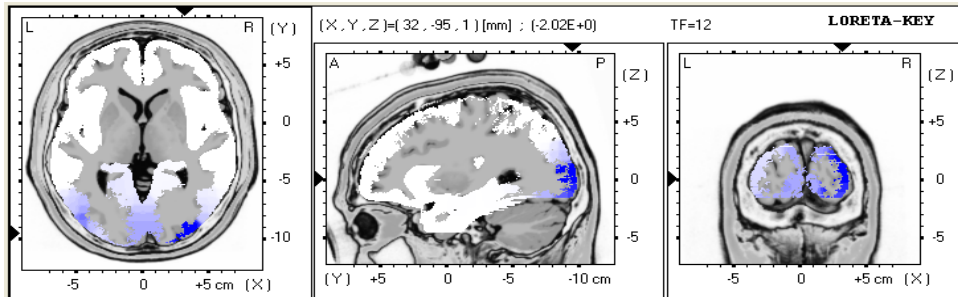
Results of patient 4's EEG in Z-scored FFT Absolute Power. Chart shown in Laplacian montage.

Figure 21. Z-score of Absolute Power (Patient 4)

Graphical representation of patient 4's EEG record.

Figure 22. 4Hz LORETA output

This figure shows statistically significant deficit in theta at 4Hz. Talairach coordinates $(x,y,z = -24, 52, 8)$ corresponded with Brodmann Area 18. Blue represents areas of decreased activity as compared to the normative database.

Figure 23. 12 Hz LORETA output

This figure shows statistically significant deficit in alpha at 12Hz. Talairach coordinates (x,y,z = 32, -95, 1) corresponded with Brodmann Area 18. Blue represents areas of decreased activity as compared to the normative database.

Patient 4's qEEG record was abnormal. Deficits were seen at 4 Hz (theta; SD = -2.74) and at 12 Hz (alpha; SD = -2.02) (see Figure 22 & 23, respectively). Activity at 4Hz was shown in the left cerebrum, frontal lobe, superior frontal gyrus, and gray matter. At 12Hz, activity was shown in the right cerebrum, occipital lobe, middle occipital gyrus, and gray matter. Talairach coordinates corresponded at 4Hz and 12Hz with Brodmann's Area 18 (Secondary Visual Cortex).

Patient 4 Summary

Neuropsychological deficits were seen on the SWM and SOC tasks of the CANTAB. Deficits in qEEG activity were noted at 4Hz (Theta) and 12 Hz (Alpha). This coordinates with Brodmann Area 18. Brodmann Area 18 is associated with attentional modulation.

*Summary of CANTAB Results**Group Comparison**Completion Time***Table 18. Completion Time for All Measures**

| Patient # | ID/ED | SWM | SOC |
|------------------|--------------------|--------------------|--------------------|
| 01-79 | 14 minutes, 09 sec | 14 minutes, 19 sec | 14 minutes, 19 sec |
| 03-50 | 11 minutes, 02 sec | 11 minutes, 25 sec | 11 minutes, 41 sec |
| 03-75 | 9 minutes, 01 sec | 9 minutes, 16 sec | 9 minutes, 26 sec |
| 03-79 | 8 minutes, 48 sec | 8 minutes, 56 sec | 9 minutes, 07 sec |

Comparison of individuals completion times across all CANTAB measures examined.

Individual patient times were uniform across measures. An analysis of the mean times across each neuropsychological test is presented below.

*Mean Completion Times***Table 19. Mean Completion Times**

| | ID/ED | SWM | SOC |
|-----------|--------------------|--------------------|--------------------|
| Mean Time | 10 minutes, 45 sec | 10 minutes, 59 sec | 11 minutes, 09 sec |

Mean completion times for all four individuals.

Completion times varied across the four patients. Mean time for completion for the IED task was 10 minutes and 45 seconds. On the IED, patient completion times ranged from 8 minutes and 48 seconds to 14 minutes and 9 seconds. On the SWM task, mean completion time was 10 minutes and 59 seconds. The patient's scores ranged from 8

minutes and 56 seconds to 14 minutes and 19 seconds. On the SOC, mean time for completion of the task was 11 minutes and 9 seconds. Completion times ranged from 9 minutes and 7 seconds to 14 minutes and 19 seconds.

Intradimensional/Extradimensional Shift (IED)

Table 20. ID/ED Shift Comparison

| Block | Patient 1 (01-79) | Patient 2 (03-50) | Patient 3 (03-75) | Patient 4 (03-79) |
|--------------|----------------------------------|---------------------------------|------------------------------|------------------------------|
| 1 | 0.31 (Avg) | N/A | -37.66 (Profound) | N/A |
| 2 | 0.34 (Avg) | 0.45 (Avg) | 0.52 (Avg) | 0.45 (Avg) |
| 3 | 0.23 (Avg) | 0.92 (H. Avg) | -0.6 (Avg) | -0.37 (Avg) |
| 4 | 0.54 (Avg) | 1.82 (Superior) | N/A | 1.82 (Superior) |
| 5 | -0.08 (Avg) | 0.46 (Avg) | -10.33 (Profound) | 0.46 (Avg) |
| 6 | 0.3 (Avg) | 1.42 (Superior) | -12.78 (Profound) | 0.71 (H. Avg) |
| 7 | 0.24 (Avg) | 0.46 (Avg) | -10.63 (Profound) | 0.46 (Avg) |
| 8 | -1.68 (Mild to Moderate Imp.) | -2.6 (Mild to Moderate Imp.) | 0.41 (Avg) | -0.24 (Avg) |
| 9 | (Timed Out) | (Timed Out) | 0.46 (Avg) | -0.96 (L. Avg) |

Group comparison of scores on the ID/ED shift broken down by Block.

Patient 1 performed in the Average range on Block 1 through Block 7. His performance was in the Mild to Moderate Impairment range on Block 8 ($Z = -1.68$). He exceeded the time limit on Block 9. Patient 2 performed in the Average to Superior range on Block 2

through Block 7. Patient 2's performance was in the Mild to Moderate Impairment range on Block 8 ($Z = -2.6$) and he exceeded the time limit on Block 9. Patient 3 exhibited Profoundly Impaired performance on Block 1. His performance was variable across the remaining measures, ranging from Profoundly Impaired to Average. Patient 4 was able to complete the task successfully with scores that ranged from Low Average to Superior.

Table 21. Mean Scores for ID/ED Shift Task

| Block | Mean Score | Qualitative Description |
|--------------|-------------------|--------------------------------|
| 1 | N/A | N/A |
| 2 | 0.44 | Average |
| 3 | 0.53 | Average |
| 4 | N/A | N/A |
| 5 | -2.37 | Moderate Impairment |
| 6 | -2.59 | Moderate-Severe Impairment |
| 7 | -2.37 | Moderate Impairment |
| 8 | -1.03 | Low Average |
| 9 | N/A | N/A |

Mean scores by block.

Mean scores for the IED task indicated more severe impairments on Block 5 ($Z = -2.37$), Block 6 ($Z = -2.59$), and Block 7 ($Z = -2.37$).

Spatial Working Memory (SWM)

Table 22. Comparison of SWM Scores

| | Patient 1 01-79 | Patient 2 03-50 | Patient 3 03-75 | Patient 4 03-79 |
|----------------|----------------------------------|-----------------------------|----------------------------------|----------------------------|
| Between Errors | 0.31 (Avg) | -2.53 (Moderate Imp.) | 0.42 (Avg) | -0.87 (L. Avg) |
| Strategy | -1.95 (Mild to Moderate Imp.) | -4.51 (Profound) | -1.78 (Mild to Moderate Imp.) | -3.22 (Profound) |

Comparison of individual scores.

Performance on the Between Errors component ranged from Moderately Impaired to Average range performance. Patient Strategy scores were in the impaired range. Scores ranged from Mildly to Moderately Impaired to Profound Impairment on the Strategy measure, indicating all patients exhibited difficulty with the development and implementation of a successful strategy.

Table 23. Mean Scores for SWM

| | Mean Score | Qualitative Description |
|----------------|-------------------|------------------------------------|
| Between Errors | -0.67 | Low Average |
| Strategy | -2.87 | Moderate-Severe Impairment |

Mean scores.

The mean score for Between Errors was in the Low Average range. The patients collectively demonstrated difficulty with the development of a successful strategy, as measured by the Moderately to Severely Impaired Strategy measure.

Stockings of Cambridge (SOC)

Table 24. Comparison of SOC Scores

| | Patient 1 (01-79) | Patient 2 (03-50) | Patient 3 (03-75) | Patient 4 (03.79) |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| Mean Initial Thinking Time (5 Moves) | 0.54 (Avg) | 1.12 (H. Avg) | 1.13 (H. Avg) | 1.1 (H. Avg) |
| Mean Subsequent Thinking Time (5 Moves) | 0.82 (H. Avg) | -6.49 (Profound) | -0.72 (Mild Imp.) | -1.37 (Mild Imp.) |
| Problems Solved in Minimum Moves | -0.23 (Avg) | -1.44 (Mild Imp.) | -0.33 (Avg) | -0.39 (Avg) |

Comparison of individual scores.

Patient scores ranged from Average to High Average on the Mean Initial Thinking Time (5 Moves) condition. Mean Subsequent Thinking Time (5 Moves) ranged from Profound Impairment to High Average performance, indicating variable performance across the four patients. The Problems Solved in Minimum Moves condition ranged from Mild Impairment to Average performance.

Table 25. Mean Scores for SOC

| | Mean Time | Qualitative Description |
|---|------------------|--------------------------------|
| Mean Initial Thinking Time (5 Moves) | 0.97 | High Average |
| Mean Subsequent Thinking Time (5 Moves) | -1.94 | Mild to Moderate Impairment |
| Problems Solved in Minimum Moves | -0.6 | Average |

Mean scores.

Mild to Moderate Impairments were noted on the Mean Subsequent Thinking Time (5 Moves) with a mean Z-score of -1.94. Mean Initial Thinking Time (5 Moves) was in the High Average range. This pattern of scores indicates High Average initial thinking abilities followed by slowed performance in the subsequent moves condition. The Problems Solved in Minimum Moves condition was in the Average range.

Discussion

An Overview

The purpose of this research was to examine neuropsychological and neuroimaging records of individuals with a historical diagnosis of bipolar disorder to determine their propensity for exhibiting abnormalities. Neurocognitive data via the CANTAB and qEEG data was analyzed and compared to quantify and qualify abnormalities. The CANTAB was selected amid other neuropsychological testing

measures because of its sensitivity in assessing neuropsychological functions subserved by frontostriatal circuitry (Fray et al. 1997, as cited in Sweeney et al. 2000). QEEG data was filtered through LORETA which facilitates the production of specific topographical representations of electrophysiological activity. This in turn made the specific localization of brain dysfunction a clinical reality.

As expected, all four patients previously diagnosed with bipolar disorder showed impairments on neuropsychological measures as well as EEG abnormalities. Both deficits and excesses in cortical activity were noted in the EEG records analyzed. Results of LORETA indicated that abnormalities were localized in the cingulate cortex, temporal lobe, frontal lobe, and occipital lobe. Further, impairments on CANTAB measures were found to correlate with the localized area of qEEG abnormalities. Individual patient results are summarized in Table 26:

Table 26. Summary of individual's CANTAB & qEEG results.

| Patient | ID/ED Shift | SWM | SOC | qEEG |
|---------|---|--|--|---|
| 1 | 1. Mild-Moderate Impairment (Block 8) | 1. Mild-Moderate Impairment (Strategy) | No Impairments | Deficits in: 1. Delta (2Hz) 2. Theta (5Hz) 3. Beta (14Hz) Deficits associated with Broadmann Areas 6 & 31 |
| 2 | 1. Mild-Moderate Impairment (Block 8) | 1. Moderate Impairment (Between Errors) 2. Profound Impairment (Strategy) | 1. Profound Impairment (Subsequent Thinking Time) 2. Profound Impairment (Problems Solved in Minimum Moves) | Excess in: 1. Theta (7Hz) Excess associated with Broadmann Area 23 |
| 3 | 1. Profound Impairment (Block 1) 2. Profound | 1. Mild-Moderate Impairment (Strategy) | 1. Mild Impairment (Subsequent Thinking Time) | Excesses in: 1. Delta (1Hz/2Hz) 2. Alpha (8Hz) 3. Beta (14Hz) |

| | | | | |
|---|--|---------------------------------|---|---|
| | Impairment (Block 5) 3. Profound Impairment (Block 6) 4. Profound Impairment (Block 7) | | | Excesses associated with Broadmann Areas 18, 21, 23, & 24 |
| 4 | No Impairments | 1. Severe Impairment (Strategy) | 1. Severe Impairment (Subsequent Thinking Time) | Deficits in: 1. Theta (4Hz) 2. Alpha (14Hz) Deficits associated with Broadmann Area 18 |

CANTAB & qEEG findings for the present study.

It is of note that the EEG records of the four individuals examined for this study include both deficits and excesses in electrical activity as compared to the normative database. When discussing this phenomenon, it is beneficial to review the theorized origins of the EEG power spectrum, summarized below.

According to Hughes and John (1999), past research has shown that an intricate homeostatic system comprised of the brainstem, thalamic, and cortical processes, combined with neuronal activity, mediates the EEG power spectrum (Hughes & John, 1999). Alpha rhythms (7.5 to 12.5 Hz) are postulated to be the result of efferent projections of pacemaker neurons located throughout the thalamus. When gamma-aminobutyric acid (GABA) is released by the nucleus reticularis, the cell membrane hyperpolarizes slowing alpha to the lower theta range of 3.5 to 7.5 Hz. It is theorized that oscillator neurons located in the deeper cortical areas and in the thalamus results in slow delta activity (1.5 to 3.5 Hz) (Hughes & John, 1999). Further, Hughes and John (1999) indicate that beta (12.5 to 20 Hz) is related to corticocortical and thalamocortical transactions (p. 192).

Hughes and John (1999) outlined a model which suggests that “deficiencies or excesses of any of the neurotransmitters should produce marked departure from the homeostatically regulated normative EEG spectrum” (p.192). Further, this is theorized to contribute to the pathophysiology of psychiatric conditions. Finally, Hughes and John (1999) noted that EEG is sensitive to abnormal patterns of cortical activity present in psychiatric disorders (p.192). The results of the present study indicate deficits and excesses across the power spectrum. When viewed in light of Hughes and John (1999), the results of this study are suggestive of dysfunction in the thalamus, corticocortical, thalamocortical regions, GABA, and lastly, the oscillator neurons of the deep cortical structures. In other words, abnormalities in these areas are theorized to drive the symptomatology of bipolar disorder. Further, it appears that it is not the existence of excesses or deficits in activity that is of primary importance in bipolar disorder, but rather the presence of any deviant electrical activity in relation to the outward expression of symptoms.

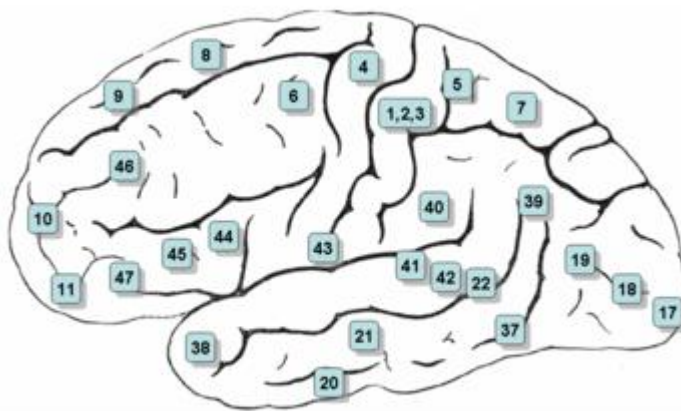
The relationship between the two normative databases utilized in this study is worth examining. When norms are collected for neuropsychological testing measures, the data collected represents the “active brain.” In other words, the CANTAB norms are an example of the dynamic brain, as individuals were actively completing the CANTAB subtests during the collection of normative data. Conversely, the Neuroguide normative data used for the purposes of this study was collected on the “idling brain,” as individuals were inactive or resting during the collection of EEG normative data. This lends support for the strength of the relationship found in the present study and suggests that a greater

relationship could be detected if brain activity was measured simultaneously with neuropsychological testing (e.g. both on the active brain).

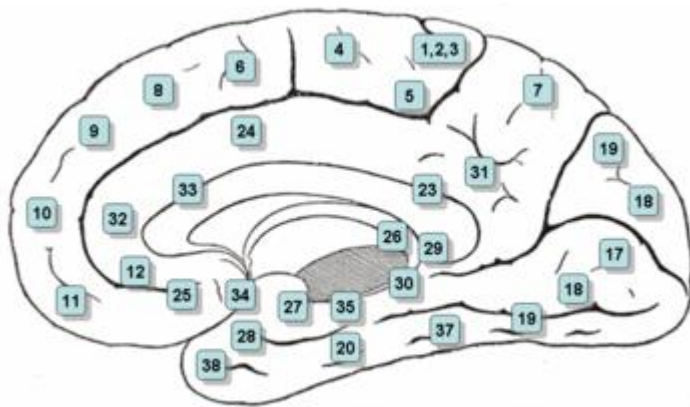
Broadmann Areas

Broadmann Areas 6, 18, 21, 23, 24, and 31 demonstrated clinical significance. Broadmann area 6 is located in the Premotor Cortex (frontal lobe). Broadmann Area 18 is located in the Secondary Visual Cortex (occipital lobe). Broadmann Area 21 is located in the Medial Temporal Gyrus (temporal lobe). And Broadman Areas 23, 24, and 31 are located in the Cingulate Cortex. Maps containing lateral and medial views of numbered Broadamann Areas are presented below (Figures 24a & 24b).

Figure 24a: Lateral Surface with numbered Broadmann Areas



Public domain image retrieved on April 16, 2008 from:
http://en.wikipedia.org/wiki/Brodmann_area

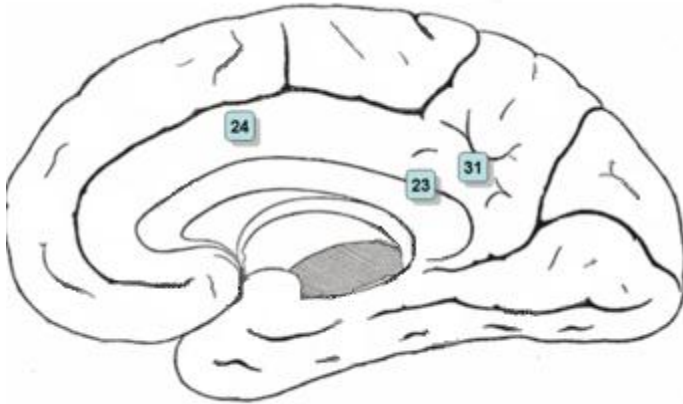
Figure 24b: Medial Surface with numbered Brodmann Areas

Public domain image retrieved on April 16, 2008 from:
http://en.wikipedia.org/wiki/Brodman_area

Cingulate Cortex

The limbic lobe contains three structures, the hippocampus, septum, and cingulate gyrus, which are responsible for emotion (Kolb & Whishaw, 2003). The cingulate cortex has been implicated in the mediation of behavior (Siegel & Chabora, 1971, as cited in Bennett, 1977). Further, Liotti and Mayberg (2001, as cited in Lambert & Kinsley, 2005) highlighted the importance of the anterior cingulate cortex in attentional processing. Research has suggested that decreased activity in the dorsal anterior cingulate is related to depression (Lambert & Kinsley, 2005). Brodmann Areas 23, 24, and 31 are located within the cingulate cortex (Figure 4) and are associated with both autonomic functioning (regulation of heart rate/blood pressure) and rational cognitive functions (anticipation of rewards, decision-making, empathy, and emotion).

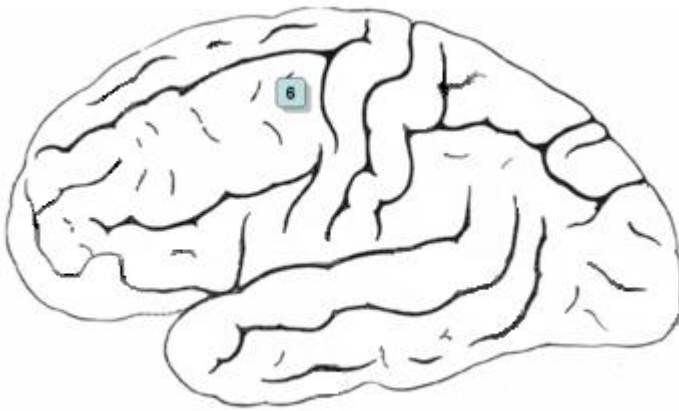
Figure 25. Brodmann Areas 23, 24, and 31



Original public domain image retrieved on April 16, 2008 from: http://en.wikipedia.org/wiki/Brodman_area. Image was edited to highlight Brodmann Areas 23, 24, and 31, specifically.

Frontal Lobe

The frontal lobes have been implicated in many functions, including emotion and behavior, social and motor skills, abstract thinking, reasoning, planning, judgement, and memory (Stoler & Hill, 1998). Damage to the frontal lobes causes a wide variety of symptomatology, including changes in personality, decreased judgement, planning and/or insight, increased disinhibition, and difficulty with set-shifting and strategy development (Cotman & McGaugh, 1980). The reciprocal connections from the prefrontal lobes to the limbic system which attributes to the frontal lobes function of integrating sensory information with emotional information (Cotman & McGaugh, 1980). Brodmann Area 6 is located within the frontal lobe (Figure 5) and is associated with simple and complex motor functioning.

Figure 26. Brodmann Area 6

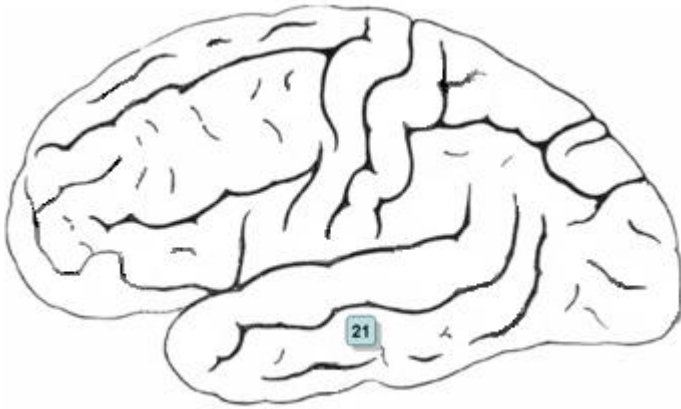
Original public domain image retrieved on April 16, 2008 from: http://en.wikipedia.org/wiki/Brodman_area. Image was edited to highlight Brodmann Area 6, specifically.

Temporal Lobe

The temporal lobe is closely associated with the functions controlled by the frontal lobes and in the healthy brain, it maintains an active role in higher level functioning (Cotman & McGaugh, 1980). The temporal lobe contains the primary auditory cortex, secondary auditory and visual cortex, limbic cortex, and the amygdala and hippocampus (Kolb & Whishaw, 2003). Kolb and Whishaw (2003) identify three basic sensory functions relegated by the temporal lobe: 1) processing of auditory input; 2) visual object recognition; and 3) long term storage of sensory input (p. 372-374).

Broadmann Area 21 is located within the temporal lobe (Figure 6) and is associated with various cognitive functions, including assessing distance, facial recognition, and recognition of word meaning.

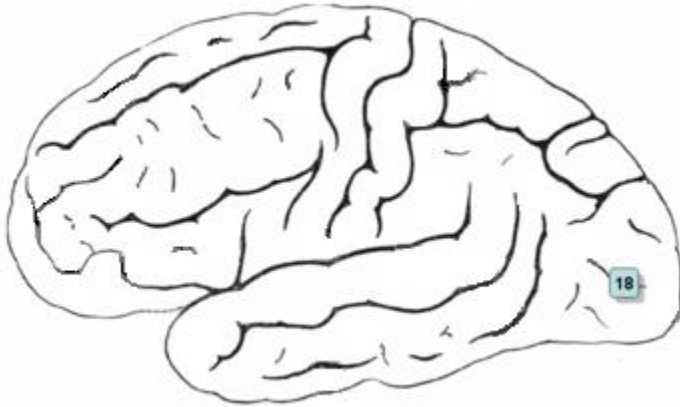
Figure 27. Brodmann Area 21



Original public domain image retrieved on April 16, 2008 from: http://en.wikipedia.org/wiki/Brodmann_area. Image was edited to highlight Brodmann Area 21, specifically.

Occipital Lobe

The role of the occipital lobe is related to integration of visual information, as well as the recognition of objects (Stoler & Hill, 1998). Further, this area of the brain is responsible for processing and understanding of spatial relationships and movement (Bard & Bard, 2002). However, contemporary research has identified that visual processing extends beyond the occipital lobe to the temporal lobe (object recognition) and the parietal lobe (visual movement) (Kolb & Whishaw, 2003). Brodmann Area 18 is located within the occipital lobe (see Figure 7). Brodmann Area 18 was originally thought to be relegated solely to control of visual processing. However, research has shown that Brodmann Area 18 is associated with attentional modulation.

Figure 28 : Brodmann Area 18

Original public domain image retrieved on April 16, 2008 from: http://en.wikipedia.org/wiki/Brodman_area. Image was edited to highlight Brodmann Areas 18, specifically.

Clinical Implications of Present Study

Although there have been many studies conducted using neuropsychological and EEG data separately, this study is unique in that it was the first of its kind to combine CANTAB and EEG results to examine bipolar disorder. The success of the present study in exploration of the various neurocognitive deficits associated with bipolar disorder suggests that future research combining these two techniques would be advantageous in the continuing investigation of the sequelae associated with psychiatric disorders.

The results of this study were concordant with past literature examining the CANTAB and EEG in bipolar disorder separately. The present study postulated that individuals diagnosed with bipolar disorder would exhibit impairments on measures of sustained attention, abnormalities on EEG, and that these two modalities would show a positive correlation. The proposed hypotheses were supported and were found to be

consistent with past CANTAB research (Clark et al. 2002; Sweeney et al. 2000) and EEG studies (Flors-Henry, et al. 1984; Small, et al. 1998).

Clark et al (2002) reported deficits in sustained attention, verbal learning/memory, psychomotor speed, and executive functioning as occurring in individuals with bipolar disorder. However, Clark et al (2002) reported that sustained attention has the most significance in relation to bipolar disorder due to the persistence of deficits across the different phases of the illness. It was for this reason that only sustained attention measures from the CANTAB were selected for inclusion in this study. Because this was an archival data study and a behavioral measure was not available to determine specific phase of illness at the time of data collection, sustained attention was ideal because of its persistence across each phase of the illness. As neuropsychological impairments on measures of sustained attention were found in all patients surveyed, our research is consistent with Clark et al (2002).

The Stockings of Cambridge, and Spatial Working Memory subtests were selected based on the following research. Murphy et al (1999) utilized the CANTAB when examining patients with bipolar disorder and found that individuals in the manic phase were impaired on the Delayed to Match, Stockings of Cambridge, Spatial Recongition, and Pattern Recongition Memory subtests. Clark et al (1999) studied individuals in the euthymic phase of bipolar disorder and found deficits on the Stockings of Cambridge and Spatial Working Memory subtests of the CANTAB. And finally, Clark et al (2005) identified the Intradimensional/Extradimensional Shift subtest as persisting through all phases of bipolar disorder. All three subtests examined for the

present study were found, via literature review, to have excellent sensitivity when testing individuals with bipolar disorder.

Research utilizing EEG and qEEG in reference to individuals diagnosed with bipolar disorder has implicated many different pathophysiological abnormalities. For example, Flor-Henry and Koles (1984) found that manic patients studied in the eyes open condition exhibited reductions in right temporal power. In a similar study, Cook et al (1986) found that bipolar disorder is associated with multiple EEG abnormalities, including: generalized slowing, left temporal-parietal slowing, left occipital slowing, left temporal spike waves, left temporal slow waves, right parietal slow waves, bilateral frontal temporal spike slow waves, and right central sharp waves. Finally, Lieber and Newbury (1988) found that individuals with bipolar exhibited an increased probability of abnormal decreases in frontal lobe alpha as compared to unipolar depression. The results of the present study showed both deficits and excesses spanning the EEG power spectrum with localization noted in the frontal, temporal, and occipital lobes, as well as in the cingulate cortex.

Analysis of the data revealed overlap between impairments on measures of sustained attention and the associated functionality of the localized areas of abnormality of qEEG. The impairments in decision-making (via Broadmann Areas 23, 24, & 31) and attention modulation (via Broadmann Area 18) have a direct, logical connection to the impairments noted on the sustained attention measures. The connection of Broadmann Area 6, which is related to simple and complex motor functioning, to the CANTAB is somewhat more abstract. It is believed that the best explanation for this is the result of the touch screen format of the CANTAB, as well as the fine and gross motor control

necessary for task completion. Brodmann Area 21, associated with assessing distance, recognizing faces, and word meaning, is somewhat difficult to interpret as it was only found in one patient surveyed. However, the results of this study do support a behavioral connection between neurological and neuropsychological modalities that is directly applicable to clinical practice.

Research Implications

Prodromal research is moving toward understanding psychiatric disorders from a neuropsychological and psychobiological perspective through the identification of structural pathology, as it relates to functional ability, and neurotransmitter involvement. This research lends support for continued exploration of neuropsychological and neuroimaging correlates in bipolar disorder. Deficits in sustained attention and abnormal EEG records were found in all patients examined. The use of LORETA in the qEEG analysis allowed for a more specific description of the constellation of neural areas involved in the bipolar spectrum.

The present research suggests that the use of imaging can be an important clinical tool when combined with neuropsychological testing in the differential diagnosis of psychiatric disorders. This research also underscores and elucidates an area of importance for further studies. Research has focused on the identification of biological profiles of psychiatric disorders that can aid in determination of diagnoses, early identification of psychiatric syndromes, and evaluation of medication efficacy. Due in part to its relatively low cost compared to other functional imaging techniques, EEG is an ideal imaging technique to use for such purposes. Moreover, Hughes and John (1999)

cited that the relative simplicity and compact equipment make accommodation by a hospital or clinic quite practical (p. 191).

Conclusions

The role of the frontal lobe in the spectrum of affective disorders remains relatively undisputed in prodromal literature. Clinically, bipolar disorder manifests as periods of highs (mania) and lows (depression) intermixed with periods of relative health (euthymia) (Clark et al. 2002). Historically, the euthymic period was regarded a 'return to health,' and it was assumed that symptoms and deficits disappeared entirely during this period. However, it has been determined that deficits persist during all phases of the disorder, which points consistently to the existence of an underlying structural and neurobiochemical pathology. The most persistent neuropsychological dysfunction in bipolar disorder is the existence of deficits in sustained attention (Clark et al. 2001; Clark et al. 2005) and it has been found to persist through all phases of the illness. For example, Benbarre et al (2004) found sustained attention deficits in 75% of individuals in a sample of 43 diagnosed with bipolar disorder. Therefore, the potential use of sustained attention as a genetic marker for the disorder and for differential diagnosis appears promising.

Limitations

In light of the present findings, several factors must be considered when conceptualizing the results. First, this study was conducted using a very small subset of individuals (N = 4) and therefore generalizability must be interpreted cautiously. The

individuals examined for the purpose of this study were veterans. As factors such as combat history, past drug use/abuse, PTSD/comorbid psychiatric diagnoses, could potentially contribute to dysfunctional neuropsychological and/or imaging results, this must be considered when examining the data. Although a review of available records was conducted, there was no mention of current medications or urine toxicology results in the patient's charts.

Future Directions

Prodromal research is an area of exciting possibilities in psychological research. Bipolar disorder has a high rate of heritability, and it is reported that family members have a ten to twenty percent greater chance of developing the disorder than the general population (Craddock & Jones, 1999, as cited in Clark et al. 2005). Research has focused on newer findings that deficits persist in the euthymic phase, which was previously regarded as a period of health absent of symptomatology. This points to an underlying structural pathology for the disorder. Hays (1976, as cited in Small et al. 1999) suggested that individuals with a family history of bipolar disorder may show deficits on EEG.

Past research on bipolar disorder has focused on specific phases of the illness. Future research utilizing a longitudinal approach that evaluates over the different stages of the illness would give a more comprehensive picture of the course of bipolar disorder and would allow for comparison of neuropsychological deficits across stages. Incorporating an additional functional neuroimaging measure, such as SPECT data, and coregistering these images for continuity would allow for a more thorough examination

of the relationship between electrical activity, the underlying cortical structural deficits, and functional brain/behavior relationships.

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