Specific Ways Brain SPECT Imaging Enhances Clinical Psychiatric Practice


Abstract — Our objective was to ascertain in a prospective case series how often brain single photon emission computed tomography (SPECT) neuroimaging adds relevant information for diagnosis and/or treatment beyond current standard assessment tools in complex psychiatric cases. Charts of 109 consecutively evaluated outpatients from four psychiatrics clinics that routinely utilize SPECT imaging for complex cases were analyzed in two stages. In stage one, psychiatrists reviewed detailed clinical histories, mental status exams, and the Structured Clinical Interview for DSM-IV, but not the results of SPECT studies, assigned a diagnosis based on DSM-IV criteria, and then developed a comprehensive treatment plan. In stage two, evaluators were given access to the SPECT studies for each patient. The addition of SPECT modified the diagnosis or treatment plan in 78.9% (n = 86; rated level 2 or 3 change) of cases. The most clinically significant changes were undetected brain trauma (22.9%), toxicity patterns (22.9%) and the need for a structural imaging study (9.2%). Specific functional abnormalities were seen as follows that potentially could impact treatment: temporal lobe dysfunction (66.1%) and prefrontal hypoperfusion (47.7%). SPECT has the potential to add clinically meaningful information to enhance patient care beyond current assessment tools in complex or treatment resistant cases.

Keywords — brain SPECT, enhance diagnosis, modify treatment, psychiatric care, treatment resistant

Psychiatry has been plagued since its inception with the dilemma of how to reliably diagnose and treat patients to optimize treatment outcome. Assessing the heterogeneity underlying each patient’s clinical presentation is difficult using standard diagnostic methods. Current best practice procedures rely primarily on (1) the skill of the psychiatric interviewer in obtaining all the relevant clinical information necessary to make criteria-based primary diagnoses and to accurately identify meaningful comorbidities; (2) the accuracy of the patient and his/her loved ones’ report of symptoms, life situation, and responsiveness to prior treatments; (3) the completeness of the psychiatric interview and the interviewer’s ability to obtain all the necessary clinical information; and (4) the accuracy of the reported symptoms and life situation.

Dr. Daniel G. Amen, M.D., had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No author reports a conflict of interest or financial disclosure.

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patient’s and his/her biological relatives’ medical history; and (4) the use of psychometric measures to validate the presence of specific symptoms and to quantify their severity.

Identifying additional procedures to properly diagnose patients, and thereby better tailor their treatment, is critical to advancing psychiatric practice. While the DSM-IV is the current gold standard for psychiatric diagnosis, its limitations are perhaps made most evident by the fact that treatment effectiveness rates, after its introduction, have shown little improvement from what they were in the 1970s despite forty years of randomized controlled trials (RCT) resulting in more than 130 FDA-approved medications used in treating various DSM-defined disorders. This troubling fact is highlighted in the 2006 *American Journal of Psychiatry* editorial by Dr. Raymond DePaulo, who in summarizing the results of the largest “effectiveness plus” studies ever conducted for bipolar disorder (Systematic Treatment Enhancement Program for Bipolar Disorder—STEP-BD/$28-million), major depression (Sequenced Treatment Alternatives to Relieve Depression—STAR*D/$35-million), and antipsychotics (Clinical Antipsychotic Trials in Intervention Effectiveness—CATIE/$70-million) stated, “the three studies taken together, however, underline the suggestion that modern pharmacological treatments may be no more beneficial than older ones, despite their added cost” (DePaulo 2006). More recently in 2009, Dr. Thomas Insel, NIMH’s director, made observations similar to Dr. DePaulo’s, noting that despite their added costs, in every NIMH-funded comparative effectiveness study the second-generation psychotropic drugs were found to be no better than the first-generation ones. He then went on to state, “The unfortunate reality is that current medications help too few people to get better and very few people to get well” (Insel 2009).

A key question is whether the limitations acknowledged by Drs. DePaulo, Insel and others (Angell 2011a, b) are related to the inadequacies of current treatments or to the limitations of the procedures used in diagnostic workups. Currently, diagnostic procedures are often unable to predict clinical responses to specific treatments and/or combinations of treatments, probably because they fail to capture the underlying heterogeneity of each patient’s illness. Each of the NIMH-funded comparative effectiveness studies from the Multimodal Treatment study (MTA Cooperative Group 2004, MTA Cooperative Group 1999) for attention deficit hyperactivity disorder (ADHD) as well as follow-up studies (Molina et al. 2009; Jensen et al. 2007) yielded disappointing results, far less robust than expected by the researchers conducting the studies. Furthermore, many of these studies found that the gains that were made during acute-phase treatment too often disappeared during follow-up due to either loss of efficacy of study treatments and/or patient dropout. Finally, despite the millions of dollars spent on these studies, in general they have provided little new guidance to clinicians treating the most common psychiatric disorders. Few, if any, of the findings of these studies have become universally accepted practice guidelines. Such meager results may be due to these studies’ (1) near universal failure to identify clinically-meaningful differences between compared treatments at the aggregate level, and more importantly, (2) their failure to identify any patient-level predictors of response to specific treatments.

Even more worrisome is the fact that such meager clinical results were obtained while using evidence-based treatments (EBTs) that had been found most promising in prior randomized controlled trials (RCTs), and that they used the current best practice standards in their diagnostic workups. The inevitable question is, what if the root cause for the disappointing outcomes that were repeatedly found in these “effectiveness plus” studies of exemplary and free care was the inability of these “best practice” diagnostic procedures to fully account for the heterogeneity of each patients’ illness, and to provide enough information to tailor treatment accordingly? In other words, what if these exemplary diagnostic workups were still missing key neuropathological findings?

It is our contention that a primary problem with obtaining adequate treatment results is substantially related to the field’s tenuous ability to adequately diagnose patients. While additional clinical measures may be useful, we have argued (Amen et al. 2011) that the use of an objective measure such as functional brain imaging could provide an important source of diagnostic information that can lead a clinician to better diagnosis, and ultimately, to more effective treatment planning. With this hypothesis in mind, the purpose of this study was to determine whether the addition of brain single photon emission computed tomography (SPECT) imaging to a comprehensive diagnostic workup significantly changed the diagnosis and/or treatment plan in four outpatient clinics that primarily treat complex/treatment-resistant psychiatric patients. The study was designed to build on the findings of Bloom and colleagues (1996) and Borghesani and colleagues (2010) who reported that SPECT imaging added significant value in the diagnostic workup and clinical management of neurologically-involved patients.

Presently, there are a number of brain SPECT imaging patterns that have been shown to be associated with different pathologies that are relevant to psychiatric practice and helpful in suggesting different treatments (Amen et al. 2011). For example, diffuse decreased perfusions (or “scalloping” pattern) is often found to be due to diffuse encephalopathy, as those caused by drug or alcohol abuse or by exposure to environmental toxins (Amen et al. 2011; Kucuk et al. 2000). Hypoperfusion in the prefrontal pole, combined with decreased anterior temporal pole perfusion or with focal decreases, is often indicative...
of traumatic brain injury (Kant et al. 1997). In cases of suspected dementia, SPECT is useful in differentiating between Alzheimer’s disease (AD), frontal lobe dementia (FLD), vascular dementia (VaD), Lewy body dementia (LBD), normal pressure hydrocephalus (NPH) and pseudodementia (PSD) (Ishii et al. 2009; Pinloot & Ebmeier 2007; Bonte et al. 2006; Yoshikawa et al. 2003a, b; Devous 2002; Jobst, Barnetson & Shepstone 1998; Starkstein et al. 1996; Hanyu, Abe et al. 1993; Jagust, Budinger & Reed 1987). SPECT perfusion imaging has been shown to be predictive of a progression to dementia in patients with mild cognitive impairment, as well as predictive of the type of dementia (Tranfaglia et al. 2009; Johnson et al. 2007; Ishiwata et al. 2006; Huang et al. 2002; Kogure et al. 2000; Wolfe et al. 1995). Many patients with OCD show increased activity, manifested by increased perfusion and metabolism, in the frontal cortex, anterior cingulate gyrus, caudate, putamen and thalamus (Van Laere et al. 2006; Carey et al. 2004; Diler, Kibar & Avci 2004; Saxena et al. 2002; Rauch et al. 2001; Lucey et al. 1995; Hoehn-Saric et al. 1991; Machlin et al. 1991). Symptom provocation by exposure to relevant phobic stimuli (e.g., skin contact with “contaminated” objects in the case of patients with OCD who have germ phobias) leads to increased activity in these same brain structures. During effective pharmacotherapy, perfusion and metabolism decreased toward normal in these structures (Carey et al. 2004; Diler, Kibar & Avci 2004; Saxena et al. 2002; Hoehn-Saric et al. 1991). The hyperfrontal pattern can also be associated with psychiatric disorders that share clinical features such as cognitive inflexibility and persistent negative thoughts. Such patterns are present in disorders such as posttraumatic stress disorder (PTSD), autism, and in some forms of anxiety and mood disorders (Hollander 1996). Hypofrontality, on the other hand, is often associated with behavioral problems, resulting from the exercise of poor judgment and from impulsivity. Its presence has been shown to predict a both a positive treatment response to stimulants (Amen, Hanks & Prunella 2008) as well as a negative response to serotonergic medication in depression (Brockmann et al. 2009). Many patients with ADHD show decreased perfusion (activity) of the prefrontal cortex and middle temporal gyrus in a baseline scan compared to controls, whether studied with SPECT (Kim et al. 2002; Spalletta et al. 2001; Amen & Carmichael 1997) or functional magnetic resonance imaging (fMRI) (Rubia et al. 2011, Rubia et al. 2005; Pliszka et al. 2006). A recent comprehensive review of the neuroimaging in ADHD assessed data from SPECT, PET and fMRI (Cherkasova & Hechtman 2009). The authors reached the conclusion that all modalities showed similar findings and emphasized the central role of the frontostriatal circuit in a large proportion of cases of ADHD. Temporal lobe abnormalities (hypo or hyperperfusion) are common in temporal lobe dysrhythmia or epilepsy (Thadani et al. 2004) and thus the clinical problems associated with such findings may be more likely to respond to anticonvulsant-based medications.

METHODS AND PROCEDURES

Subjects, Setting and Study Design

The charts of 109 consecutively evaluated outpatients were sequentially acquired from December 15th, 2010 through January 5th, 2011 from four psychiatric clinics that utilize SPECT neuroimaging for complex cases. The clinics are located in four geographically dispersed areas: Washington, DC area (Reston, VA), Pacific Northwest (Bellevue, WA), Northern California (Brisbane) and Southern California (Newport Beach). All patients in this study gave consent for their clinical information to be used anonymously in research conducted by Amen Clinics. The patient’s refusal to participate in the research had no impact on their care.

All clinical charts were divided into two files so that a two-stage analysis could be conducted. Included in the first chart was: (1) a detailed typewritten clinical history taken by a trained medical historian that included history of the present illness, current and past psychiatric treatments (including medications and supplements), medical, family, school, sleep, occupational, military, drug and legal history; (2) a detailed mental status exam; (3) results from a computerized version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al. 1997) and (4) Beck Depression Inventory (BDI; Beck et al. 1996). Clinical diagnoses and treatment recommendations were collected via two forms included in the medical record.

The second chart contained the results of two brain SPECT studies of the same patient, including the images and report of the SPECT findings. One SPECT study was performed at baseline; the other while doing a concentration task (Conner’s Continuous Performance Test II V.5 (CCPT; Conners 2004).

Five board-certified psychiatrists with expertise in evaluating SPECT neuroimaging in clinical practice then sequentially evaluated the charts assigned to them, with no other knowledge of the patients. All psychiatrists had been conducting diagnostic workups with SPECT imaging for a minimum of two years prior to this study and the average number of new evaluations using SPECT, except for the principal investigator (PI), was 649 (range 397 to 1259). The PI has been using SPECT neuroimaging in clinical practice for more than 20 years. To ensure consistency among the evaluators, each psychiatrist underwent two weeks of training and inter-rater agreement trials with the PI. Inter-rater reliability was not specifically tested in the cases included in this study.

Each case was initially evaluated based on clinical information alone (first chart). Afterwards, the cases were re-evaluated by the same psychiatrist with the inclusion of the SPECT imaging data (chart 2). Additions and/or
changes to clinical management included: (1) ordering other studies (such as a CT or MRI); (2) addressing newly found medical morbidities (unexpected space occupying lesions, unexpected trauma patterns, unexpected toxicity patterns, unexpected signs of mild cognitive impairment or dementia, unexpected seizure activity, unexpected potential vascular problems); and (3) discovering other target for treatments beyond those defined by the presence of an Axis I, Axis II, Axis III diagnosis, such as hyperfrontality, hypofrontality, cerebellar hypoperfusion, limbic system hyperperfusion, temporal lobe abnormalities and others that were found through the use of SPECT scanning and had not been found or even suspected by the state-of-the-art diagnostic evaluation described above. The expert clinicians then classified the changes in the diagnosis and treatment recommendation which resulted from including the SPECT findings into the following level of change categories: (1) no change; (2) mild change—when it was concluded that clinicians would likely have come to the same conclusion through trial and error; (3) moderate change—when it was estimated that the new findings could make a significant clinical impact; and (4) highly significant change—when the new findings would completely change the course of treatment.

Clinical SPECT Report

Using slices from all three orientations (coronal, sagittal, and transaxial), 14 left and right regions of interest (ROIs) were visually inspected and rated by a clinician trained in neuroanatomy using the Mai Atlas of the Human Brain (Mai, Assheuer & Paxinos 1997); these included prefrontal poles, inferior orbits, lateral PFC, temporal poles, lateral temporal lobes, medial temporal lobes, parietal lobes, occipital lobes, cerebellum, anterior cingulate gyrus, anterior insular cortex, caudate, putamen, and thalamus. Raters had access to patients’ age, gender, medications, and general complaints.

rCBF for each area above was visually rated on a Step-20 scale using the following formula: activity above the top 95% was assigned a score of 4+; 91%-95% was scored 3+; 86%-90% was scored 2+; 81%-85% was scored 1+; 61%-80% was scored 0; 56%-60% was scored –1; 51%-55% was scored –2; 46%-50% was scored –3; and 41%-45% was scored –4. In addition to the ratings for each area, each scan was rendered in two 3-D images: a surface view, looking at the top 45% of brain activity, which allows physicians to quickly visualize significant cortical hypoperfusion; and an active view, where the most active 15% and 8% of the brain are rendered, allowing physicians to quickly visualize areas of hyperperfusion.

Statistical Analysis

All statistics were performed using IBM SPSS (PASW) version 18.

RESULTS

Subject Characteristics

Of the 109 consecutive patients, 49 were female and 60 were male with an age range of 18 to 87 years (mean age 38.42, S.D. = 16.95). The average number of diagnoses upon entering the study was 4.2 per patient. The most common diagnostic categories included: anxiety (99/109; 90.8%), mood disorders (76/109; 69.7%), substance abuse (70/109; 64.2%), ADHD (58/109; 53.2%), OCD (17/109; 15.5%), dementia of any type (11/109; 10.0%), schizophrenia (4/109; 3.6%), epilepsy (2/109; 1.8%), and head injury (39/109; 35.7%).

Impact of SPECT on Diagnoses and Treatment

Table 1 summarizes a sample of findings. Overall, in 52.3% of cases (n = 57), SPECT imaging changed the clinical diagnostic assessment in a highly substantial way (i.e., completely changed the course of treatment); 26.6% of cases (n = 29) were rated as a moderate change (new findings that could make a substantial clinical impact), while 11% (n = 12) had a mild change (would likely get to the same conclusion with trial and error) and 10.1% of cases (n = 11) had no change in the diagnosis and treatment plan with the addition of SPECT imaging.

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TABLE 1
Summary of Primary Findings

<table>
<thead>
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<th>SPECT Changed Clinical Diagnostic Assessment</th>
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<tbody>
<tr>
<td>Highly Significant (Completely Changed Course of Treatment)</td>
<td>52.3% (N = 57)</td>
<td></td>
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<tr>
<td>Moderate (New Findings Could Make Substantial Impact)</td>
<td>26.6% (N = 29)</td>
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<tr>
<td>Mild (Likely Get to Same Conclusion with Trial And Error)</td>
<td>11.0% (N = 12)</td>
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<tr>
<td>None</td>
<td>10.1% (N = 11)</td>
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New Diagnostic Questions/Unexpected Issues

- Toxicity | 22.9% (N = 25) |
- Brain Trauma | 22.9% (N = 25) |
- Seizure Pattern | 2.8% (N = 3) |
- Dementia Pattern | 6.4% (N = 7) |

Additional Targets of Treatment Seen on SPECT

- Temporal Lobe Dysfunction | 66.1% (N = 72) |
- Hyperfrontality | 14.7% (N = 16) |
- Hypofrontality | 47.7% (N = 52) |
- Cerebellar Hypoperfusion | 43.1% (N = 47) |

results added to Axis III diagnoses in 76.1% cases (n = 83), with temporal lobe dysfunction (66.1%, n = 72) being most common, and hypofrontality of the prefrontal cortex (47.7%, n = 52) present in nearly half of cases. Cerebellar dysfunction was identified in 43.1% of cases (n = 47), a pattern commonly observed with hypoperfusion of the frontal lobes due to the high interconnectivity of these neural networks (Glickstein 2006). Scallopings and diffuse decreased perfusion (toxicity) was observed in 22.9% of cases (n = 25), suggestive of a diffuse encephalopathic process from drugs, alcohol, environmental toxins or other diffuse neuropathology, such as infections or metabolic issues (e.g., hypothyroidism). A traumatic brain injury pattern (TBI) was present in 22.9% of cases (n = 25), while hyperfrontality, or increased perfusion of the prefrontal cortex, was observed in 14.7% of cases (n = 16).

One of the most clinically accepted uses of SPECT neuroimaging is in the evaluation of patients with suspected dementia, and in this cohort, a previously unknown suggestion of mild cognitive impairment or early dementia pattern was observed in 64.4% of cases (n = 7). Due to the findings from SPECT imaging, structural imaging (CT/MRI) was recommended in 9.2% of cases (n = 10). In four of these cases SPECT imaging had revealed suspected ventricular enlargement.

The addition of SPECT imaging yielded 67% of cases (n = 73) where at least one medication change was recommended. Of these, the suggestion was for additional medications in 93.2% of cases (68 of 73), while 31.5% (23/73) had recommendations for medications reduction. Antiepileptic medications were recommended in 61.6% of cases (45/73), consistent with the high incidence of temporal lobe abnormalities. Stimulant medications were recommended in 37% of cases (27/73). Alternatively, in 9.6% of the cases (7/73) a reduction in stimulant medications was suggested. Antidepressant changes were advocated in 30.1% of cases with bupropion recommended in 11% (8/73), a selective-serotonin reuptake inhibitor (SSRI) recommended in 9.6% (7/73) and a serotonin-norepinephrine reuptake inhibitor (SNRI) recommended in 9.6% (7/73). The latter finding correlates with the patients who showed hyperfrontality patterns on SPECT (14.7%, n = 16 out of 109), as this is likely to predict a positive treatment response to serotonergic medication in depression (Mayberg et al. 1997). Interestingly, these same antidepressant medications were recommended to be discontinued in 28.8% (21/73) of those cases where SPECT imaging suggested a medication change. Discontinuation of bupropion was recommended in 2.7% (2/73), of an SSRI in 16.4% (12/73), and SNRI in 9.6% (7/73). This reduction in the use of antidepressant medication can possibly be attributed to those patients with hypofrontality patterns who were depressed and taking SSRIs. As hypofrontality has been associated with a negative treatment response to serotonergic mediation in depression (Brockmann et al. 2009), such medications needed to be discontinued in a sizable number of such depressed patients with hypofrontal patterns revealed by SPECT imaging.

Patients who were rated as having “no change” (rating = 0) between their initial evaluation and the addition of SPECT imaging to their evaluation had no suggested medication change. Medication changes were evenly distributed among those who were rated as having a “mild change” (n = 6 no change; n = 6 medication change). Those who were rated as having a “moderate change” were three times as likely as others with this rating (compared to the entire cohort) to have a suggested change in their medication profile (n= 7 no change; n = 22 medication change). Those rated as “highly significant change” were four times as likely to have a suggested medication change (n = 12 no change; n = 45 medication change). The higher rating scale scores correlated with a higher incidence of a medication change (χ² = 28.6, P < 0.001). Figures 1 through 4 give illustrative case examples.

Impact of SPECT in a Substance Abuse Cohort

Furthermore, we investigated the differences between those who were clinically diagnosed as substance abusers (n = 33; 7 female, 26 male) within our patient population versus those who were not (n = 76) and found no significant level of change between the two groups with regards to adding a SPECT scan to the diagnostic workup. The diagnostic categorization of this cohort revealed the majority of subjects abused alcohol (n = 21) or cannabis...
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FIGURE 1
Unexpected Toxicity (color figure available online)

Healthy Brain SPECT
Full, even, symmetrical perfusion.
Threshold set at 55%ile.

Patient A
Overall decreased perfusion

A, a 62-year-old female, was provisionally diagnosed with major depressive disorder, generalized anxiety disorder, and a panic disorder. Her SPECT results revealed an unexpected diffuse encephalopathic pattern. The addition of SPECT resulted in a new diagnostic categorization to major depression due to a medical condition with a need for a more in-depth work up to better understand and treat other potential causes of the pattern.

(n = 15) followed by cocaine (n = 5), nicotine (n = 3), amphetamines (n = 1) and hallucinogens (n = 1). Overall, in 51.5% of these cases (n = 17), SPECT imaging changed the clinical diagnostic assessment in a highly substantial way; 30.3% of cases (n = 10) were rated as a moderate change, while 12.1% (n = 4) had a mild change and 6.1% of cases (n = 2) had no change in the diagnosis and treatment plan with the addition of SPECT imaging. As in the whole cohort, SPECT results added to Axis III diagnoses in 75.8% cases (n = 25), with temporal lobe abnormalities (63.6%, n = 21), brain trauma (27.3%, n = 9) and toxicity (18.2%, n = 6) being present but unrecognized. These findings are noteworthy because when they are left untreated they can contribute to continued or accelerated substance abuse. We did find that the substance abuse cohort had a mean of 6.0 (± 1.84) diagnoses per patient versus 3.37 (± 2.0) for the whole group, which was highly significant at p < 0.001. Taken together, these data suggest that SPECT provides the same level of change as compared to the original cohort, but the increased number of diagnoses per patient makes a compelling case for the need for the clinical guidance SPECT can contribute to this population.

DISCUSSION

The aim of this study was to quantify the value of adding rest and concentration SPECT neuroimaging to the diagnostic workup in clinics, which evaluates a high percentage of treatment-resistant, complex psychiatric cases. Prospective analysis of 109 consecutive patients who presented with an average of 4.2 Axis I diagnoses showed that the addition of SPECT scans led to moderate or highly substantial changes of diagnoses and/or treatment in 78.9% of the cases. Two findings of particular clinical importance were that SPECT imaging detected high levels of previously unrecognized brain trauma (22.9%) and overall decreased perfusion (22.9%), consistent with a previously unknown diffuse encephalopathic process from drugs, alcohol, an environmental toxin or from insufficiently addressed medical problems. These findings support and corroborate the clinical wisdom of the following quote from Harold Bursztajn, M.D., cofounder of the Psychiatry and Law Program at Harvard, who said “SPECT scans do not give you the answer, they teach you to ask better questions” (Bursztajn 2002). SPECT scan results can give clues on how to investigate the clinical problems of patients suffering from complex and/or treatment resistant psychiatric disorders. For example, when a brain injury or diffuse encephalopathic pattern is seen but had not been identified by clinical history, it directs the clinician to conduct a more focused inquiry about past brain injuries, to investigate if drugs or alcohol are an issue, and to ascertain whether environmental toxins, or other potential medical conditions, may be present but unrecognized. The line of
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FIGURE 2
Unexpected Brain Trauma (color figure available online)

Patient B

B, a 48-year-old male, was diagnosed with panic disorder and severe insomnia of five months duration, made worse by benzodiazepines and sleep medication. The month before symptoms began, he had a “minor” fall from a mountain bike where he hit his head but had no loss of consciousness. SPECT scan revealed clear decreases in left prefrontal and temporal lobe region (arrows), consistent with prior brain trauma. This led to further questions and ultimately to brain trauma rehabilitation strategies, such as neurofeedback and hyperbaric oxygen therapy.

Inquiry and potential further work up can add valuable information.

In his 2005 keynote address to the American Psychiatric Association (APA), Insel (2005) said:

The DSM-IV has 100% reliability and 0% validity . . . We need to develop biomarkers, including brain imaging, to develop the validity of these disorders . . . Trial-and-error diagnosis will move to an era where we understand the underlying biology of mental disorders . . . We are going to have to use neuroimaging to begin to identify the systems pathology . . . to develop treatments that go after the core pathology, understood by imaging.

The same year Insel made similar observations in writing:

Patterns of regional brain activity associated with normal and pathological mental experience can be visualized . . . and ultimately, biomarkers for mental disorders may not be proteins or neurotransmitters but may emerge from neuroimaging (functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT), etc. Logically, if these are disorders of brain systems, then the visualization of abnormal patterns of brain activity should detect the pathology of these illnesses (Insel & Quirion 2005).

In 2009, the NIMH unveiled a new initiative, known as Research Domain Criteria (RDoC; Insel 2010) to

. . . develop new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures . . . Increasing evidence suggests that abnormality in one dimension, such as impulsivity, frequently occurs in multiple diagnoses of mental disorders . . . It will shift the way we do research and think about mental disorders.

It has become increasingly unlikely that DSM diagnoses represent distinct neurophysiological entities. They will likely prove to represent groups of neurophysiological processes. Individual symptoms likely represent abnormal neurophysiological processes that span across diagnoses (e.g., impulsivity is a key component of the diagnosis of Impulse Control Disorder NOS, ADHD, bipolar mania, and certain personality disorders; but is also seen following frontal lobe injury, as in mild TBI, and in Frontal Temporal Dementia). So, it only follows that functional neuroimaging will fail to reveal a singular neurophysiological process corresponding in a one-to-one fashion with a DSM diagnosis. Such correspondences do not exist. There is substantial evidence that there are multiple neurophysiological cases and imaging findings associated with conditions such as depression (Savitz & Drevets 2009), bipolar disorder (Pan et al. 2009), and ADHD (Cherkasova & Hechtman 2009). As this study suggests, SPECT imaging helps to provide clinical guidance in the management of individual patients by adding critical new information to better assess the heterogeneity underlying his or her particular clinical presentation. Given the disappointing findings in the various NIMH-funded “effectiveness plus” trials and, in particular, their failure to identify patient-level predictors of response to specific treatments despite their large Ns, one must wonder what undiagnosed neuropathology contributed to each individual patient’s failure to respond to best practices treatment. The current study indicates that SPECT neuroimaging might have been helpful in uncovering and in providing guidance for their treatment.

In the authors’ opinion, SPECT neuroimaging, as well as any other neuroimaging or laboratory tool, should never be used in isolation, but always as an integrated part of a thorough clinical evaluation. In this context, the addition of SPECT imaging is capable of revealing potential new targets for treatment, as evidenced by the increased number of Axis III diagnoses found in 76.1% (n = 83) of our cases, although this finding may cause some to reconsider current diagnostic nomenclature. We also found abnormal
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FIGURE 3
Spect Helps Direct Medication Choice (color figure available online)

C’s surface SPECT scan
Note deficit in cerebellum and occipital region

C’s active SPECT scan
Red and white show most active areas of brain, usually seen in cerebellum with HMPAO.
Note marked hyperfrontality (increased perfusion in the anterior cingulate and lateral prefrontal cortices).

C, a 19-year-old female diagnosed with cerebral palsy and Asperger’s syndrome, was evaluated for inattention, anxiety and social detachment after another student at school died suddenly. Her SPECT scan showed damage to her cerebellum and occipital lobes consistent with past oxygen deprivation and findings common in cerebral palsy and an autistic spectrum disorder. It also showed marked increased hyperfrontality, a pattern that suggests a positive response to a serotonergic intervention.

Even though there are reported common brain SPECT imaging patterns for many different psychiatric diagnostic categories, such as OCD and ADHD, our extensive experience tells us that the findings are variable in individual patients, which is the reason why it is essential to know the individual imaging patterns in treatment resistant or complex cases to better personalize treatment.

The present study does not stand in isolation, but reinforces and extends previous studies. In 1996, Bloom and colleagues (1996) evaluated 94 consecutive patients referred for SPECT neuroimaging. These patients were assigned to one of nine groups based on the clinical indication for SPECT. All of the SPECT evaluations were conducted with knowledge of the patient’s clinical history. Two weeks after scans, a standardized interview was conducted with both the interpreting nuclear physician and the referring physician to determine if the addition of SPECT imaging had significantly altered patient management by changing either the planned surgical or medication therapy. The key findings of Bloom and colleagues were that SPECT neuroimaging: (1) significantly altered treatment in 47% of all referred patients; (2) altered treatment in three of six (50%) head trauma patients; and (3) altered treatment in 11 of the 18 (61%) dementia patients who were
D’s surface SPECT scan

D, a 51-year-old female, presented with anxiety, stress, disorganization, marital problems and a past history of bulimia. She experienced a whiplash injury at age 15 but did not hit her head. Without the scans, the psychiatrist rater in the study gave her the diagnoses of Generalized Anxiety Disorder, AD/HD inattentive type, and bulimia (in remission). Her SPECT scan showed severe prefrontal, temporal and parietal lobe areas of hypoperfusion, suggesting a more severe past brain injury, some form of toxicity and a vulnerability for early dementia. A more thorough medical work up was necessary to understand the cause of the overall decreased perfusion, and then a rehabilitation program to enhance overall perfusion to her brain.

referred for SPECT to differentiate Alzheimer’s disease from depression.

Fourteen years later, Borghesani and colleagues (2010) published a study evaluating 193 consecutively referred patients to a memory disorders clinic in which the DSM-IV diagnosis was determined for each patient during their initial visit using research criteria. All 193 patients then underwent SPECT neuroimaging, with almost 80% also having an MRI. The neuroimaging interpreters had access to both the SPECT and MRI reports (when available), thereby combining the additive value MRI and SPECT together versus assessing their utility alone. Patients’ images were classified as either appearing normal, evidencing cardiovascular disease, indicating one or more specific neurodegenerative diseases, or appearing abnormal yet not diagnostic-specific. This study’s key findings were that neuroimaging: (1) confirmed, clarified, or contradicted the initial diagnosis in more than 80% of referred patients, whereas less than 20% had abnormal yet not diagnosis-specific imaging patterns; (2) suggested multiple dementia etiologies in 21% of patients whose DSM-IV diagnosis attributed it to a single process; and (3) only suggested a single etiology in 46% of the of the complex cases.

The present study is aligned to Borghesani and colleagues’ (2010) conclusion that:

Neuroimaging was useful even if it only confirmed a suspected diagnosis. “Seeing” the disease process increased diagnostic confidence and the clinician’s ability to explain cognitive symptoms to patients and families. Visual images seem to have special resonance for patients and families, grounding clinical symptoms in observable brain changes.

Another benefit of using brain SPECT imaging is that the patient’s and family’s guilt, shame and stigma are significantly reduced as they see their illness as having a medical, rather than a moral origin with concurrent improvements in treatment compliance.

There are certain limitations to the current study. The psychiatrists involved were experienced with using brain SPECT imaging in their diagnosis and work up of patients. Thus, psychiatrists not familiar with this approach would require training in order to better understand how SPECT imaging can be useful in a clinical setting. Inter-rater reliability was not directly assessed on the subjects in this study. Another limitation to this study is that no patient outcomes were available, which would be necessary to determine if the reported changes yielded higher levels of treatment success. This issue is being investigated in a separate outcome study. It will be important to demonstrate that not only do the SPECT scans alter diagnosis and treatment, but that such changes lead to meaningful symptomatic and functional improvements in the patients.

CONCLUSION

Taken together, in the context of a thorough clinical workup, these findings illustrate how brain SPECT imaging can offer specific information to help guide the diagnosis and treatment of complex psychiatric cases. In our study, the use of SPECT neuroimaging modified the diagnostic thinking and led clinicians to make different, specific treatment recommendations in a high percentage of cases. While there is much work to be done to facilitate the widespread use of SPECT neuroimaging and other functional neuroimaging studies in the day-to-day clinical practice of psychiatry, it is important to have a sense of urgency so that we do not miss important information that can offer significant help in the healing process of patients.
REFERENCES


