Cognitive Impairment In Primary Psychiatric Disorders:
Role In The Diagnosis Of Cognitive Disorders In Clinical Neurology

How does the presence of an ongoing primary psychiatric disorder with or without pharmacotherapy play a role in our aging population who present to the neurologist with symptoms of memory loss and cognitive decline?

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The specialties of neurology and psychiatry have had a long history of working together. In the early and mid-twentieth century, before and early after the formation of the American Academy of Neurology in 1948, many physicians were trained in neuropsychiatry. When I completed my neurology residency in 1972, many of my mentors and teachers both in residency and in early private practice had been heavily disciplined in both specialties.

Over the last 50 years these specialties have slowly drifted apart, partly because of increasingly different scientific knowledge and pharmacotherapy. But both specialties continue to remain in close contact because of the continued requirement of both training programs to spend clinical time in each field, and board certification is still granted by the American Board of Psychiatry and Neurology.

Psychiatry training in clinical neurology has traditionally focused on primary psychiatric disorders (bipolar, obsessive compulsive, schizophrenia, post-traumatic stress disorders, etc.), along with emotional symptoms such as depression, anxiety and psychotic symptoms (hallucinations and delusions). Cognitive deficits in primary psychiatric disorders have not been traditionally emphasized in neurology training and few, if any, articles on this topic have been written in primary neurology journals. The field of cognitive and behavioral neurology has mushroomed in the last 45 years and has become a subspecialty of its own with its own board certification.

As the human life span continues to lengthen, neurology will continue to see more and more people with changes in memory, cognitive decline, and increasing fear of developing Alzheimer’s disease. Many of these same people will have been previously diagnosed with a primary psychiatric disorder with continued symptoms and need for treatment and follow-up. How does the presence of an ongoing primary psychiatric disorder with or without pharmacotherapy play a role in our aging population who present to the neurologist with symptoms of memory loss and cognitive decline? This subject has intrigued me for a number of years and so I decided to look at it more closely.

Historically, the study of the human mind has been subdivided into two broad categories: The cognitive (how we know the world) and affective (how we feel about it). These two broad categories have been developed based on traditional brain lesion experiments in the past that suggested that the amygdala is very important in affective function and the lateral prefrontal cortex is important in cognitive function. In the last 25 years research has strongly suggested that “affective” and “cognitive” brain areas are highly interconnected. As a result, each of these categories can affect each other. For example, the amygdala makes very widespread connections with all but eight cortical areas and is one of the most highly connected regions of the brain and well situated to integrate and distribute information as well.
as the lateral prefrontal cortex. Cognitive status can color the processing of emotions, and mood changes can affect cognitive function.1 Luiz Pessoa in 20082 reviewed this topic extensively and strongly argued that the emotional and cognitive aspects of brain function should no longer be conceptualized as separate. Change in emotion has been universally recognized as the key factor in primary psychiatric disorders, where cognitive impairment, with an equally disabling effect on patients, has been relatively neglected. The cognitive deficits of primary psychiatric disorders are not just secondary to disturbed affect, because psychopharmacology does not usually improve cognitive impairment and in some cases, may worsen it.1,3 In this review, I will focus on a group of common primary psychiatric disorders: schizophrenia, bipolar disorder, obsessive compulsive disorder, post-traumatic stress disorder, and moderate to severe depression. This is not an exhaustive review and will predominantly focus on the cognitive abnormalities that are clinically recognized and will not focus on the cellular and cerebral circuits in these disorders. Table 1 summarizes the cognitive impairment in all these disorders, including some of the neurodegenerative disorders (Alzheimer’s and Parkinson’s).

**BIPOLAR DISORDER**

Bipolar disorder was one time called manic depressive illness. It affects men and women equally. It begins usually between ages 15-25 and is more common in relatives of bipolar patients. The current classification is: bipolar type I: At least one manic or mixed episode; depression episode not required but often occurs. Type II: Less severe. It requires at least one depressive episode and one hypomanic episode or never any manic or mixed episode. Hypomania is a much milder version of mania. It does not cause the degree of functional impairment and does not require hospitalization. Cause is unclear but can be triggered by drug and alcohol abuse and lack of sleep. The prevalence of bipolar disorder is: 1.4 percent (age 18-44), 0.4 percent (45-64), 0.1 percent (>65). Decreased prevalence with age is due to spontaneous recovery, high suicide rate (20 percent), and medical comorbidities.3

Kurtz and Gerraty5 did a meta-analysis of the neuropsychological studies of patients with bipolar disorder consisting of 42 studies (1197 patients) in remission (euthymia); 13 studies (314 patients) in a manic/mixed state; and eight studies (96 patients) in a depressed phase. This large meta-analysis yielded a number of important findings: (See Table 1)

Euthymia individuals compared to normal controls showed mild impairment in visual spatial function and moderate impairment in executive function (attention, working (immediate) memory, verbal fluency, and multi-tasking). More severe impairment was noted in delayed verbal and visual memory.

In the manic state, individuals showed all the same cognitive impairment as in 1 but greater impairment in verbal learning.
In the depressed state, individuals showed the same features as in 1 but greater fluency deficits.

Bipolar patients in general with higher mean level of education showed less impairment in working memory and other features of executive dysfunction suggesting that education may have a protective benefit against these deficits.

Similar but attenuated cognitive deficits were found in first degree asymptomatic relatives, suggesting a genetic component to this disorder.

The use of pharmacotherapy in euthymia, manic, and depressive states versus controls were also studied to see if it caused in itself cognitive impairment. Euthymic patients on or off mood stabilizing drugs had none or minimal effects on cognitive performance. Patients studied during a first episode of illness before exposure to medications also show neuro-cognitive deficits that are similar or worse than in those chronically medicated.

The limitation of this and previous meta-analyses in some studies showed different definitions of euthymia and included patients with residual symptoms, while other studies showed no residual symptoms. The latter studies showed less cognitive deficits when compared to controls.

**OBSESSIVE COMPULSIVE DISORDER (OCD)**

OCD has a lifetime prevalence of one to three percent and is characterized by recurrent obsessions (thoughts or impulses concerned with themes of “germs” or fear of harming others) and compulsions (urges to perform repetitive behaviors or mental acts) to counteract these obsessions. It is one of the leading causes of functional disability with impaired quality of life. OCD has a strong genetic basis. Monozygotic twins concordance is 65-81 percent. Burdick, et. al. studied neuropsychological testing in 26 adults with OCD (moderate to severe severity) and 38 healthy controls appropriately matched for age and reviewed the literature. Thirty-five percent were women with mean age of 37. Seven subjects were medication free, six had SSRI monotherapy, and 13 had multiple medications (tricyclics: 5, atypical antipsychotics: 6, mood stabilizers: 3, and modafinil: 3). See Table 1.

The main findings in this study were:

The patients demonstrated overall a global deficit of one half standard deviation from the healthy volunteers. The patients had significant impairment in verbal and visual memory (immediate recall) and processing speed.

Other parameters, such as delayed visual and verbal memory, reasoning, language skills and problem solving, were normal and similar to the controls.

Of importance was that medication regardless of type did not affect cognitive status.

There was no relationship between neuro-cognitive deficits and either OCD symptom severity or depression.

It is currently very difficult to determine a direction of causality between brain structure, cognition, and a clinical diagnosis of OCD. Longitudinal follow-up studies are needed.

**SCHIZOPHRENIA**

Schizophrenia is a chronic severe mental disorder with frequent features of delusions, hallucinations, bizarre behavior, inappropriate affect, and it occurs in about one percent of the world population. In the past, cognitive dysfunction was felt to be minimal and attributed to the symptoms and/or medication. In the last 25 years, deficits in neuropsychological testing have been well documented. They have been described at first presentation, prior to first episode of the disease, in unaffected relatives, and during the course of the disease. Verbal learning and memory are one of the most impaired cognitive abnormalities. Others showed greater impairment in executive dysfunction.

Working memory, which requires the maintenance and manipulation of information and recall, has been shown impaired in many meta-analytic studies comparing schizophrenic patients from controls. A higher level failure of executive processes in regulating control of attention represents one explanation of these findings. Vigilance (the ability to sustain ones attention over a period of time) and processing speed are often abnormal. This has a major effect on encoding and retrieval of information. Motivation, self awareness, planning, abstract reasoning, fluency and word generation, visual perception, and constructional skills have been found to be moderately impaired.

Cannon, et. al. have shown that unaffected relatives of schizophrenics have milder forms of deficits. Egan studied 193 unaffected siblings of schizophrenics versus controls. They found the former had disturbances in executive dysfunction and verbal memory. The impairments were distinct and represented independent markers of risk for the development of the illness. A National Institute of Mental Health consensus meeting identified five areas of cognitive deficits in schizophrenia: attention, verbal declarative memory, working memory, face recognition memory, and emotional processing.

Most of the previous cited studies have mainly evaluated young and middle-aged adults with schizophrenia and controls. Other studies conducted among elderly patients have shown global and specific cognitive deficits suggesting that cognitive impairment remains present throughout lifetime. These authors studied a meta-analysis on the nature and course of cognitive function in late-life schizophrenia. They identified 23 articles comparing late life schizophrenia and healthy controls and 19 articles on cognitive changes during longitudinal follow-up (six years or more). They defined late-life schizophrenia as: schizophrenia or related disorder...
(schizoaffective) in an individual greater than 50 years of age. They defined very late onset as similar but onset at age 60 or greater. The summary of their findings are found in Table 1. Prevalence of schizophrenia in older adults is one percent, same as in young adults.

The number of individuals with late-life schizophrenia will increase as the population continues to grow older.

Neuropsychological assessment in late-life schizophrenia versus controls showed specific deficits in executive function, visual spatial constructional abilities, verbal fluency, psychomotor speed with less deficits in working and delayed memory and attention.

In the longitudinal course of cognition in late-life schizophrenia, global cognition is stable through age 65. Thereafter is a cognitive decline at an incremental rate as age increases, unlike Alzheimer’s disease, which progresses across different age groups. Over a six-year follow-up period the MMSE drop was one point per year as opposed to Alzheimer’s, which is two to three points per year. The reason for cognitive decline in late-life schizophrenia is not clear.

A number of studies evaluated chronically institutionalized individuals. They were found to be more cognitively impaired than community dwelling individuals. Many of these individuals were found to be early-onset schizophrenia (schizophrenia beginning before age forty).

Overall, no difference in cognitive profile between early-onset and late-onset of schizophrenia. Similar conclusions were reached by other authors.3

**DOES ANY TREATMENT HELP COGNITIVE IMPAIRMENT IN SCHizophrenIA?**

A meta-analysis of cognitive remediation in schizophrenia was done in 2007 by McGurk, et al.14 Data from 26 studies (1,151 subjects) were included. Mean age of patients was 36 (range 16-47). They were 69 percent men, and 60 percent were inpatients. The mean duration of therapy was 13 weeks (1-100 hours). There was evidence of mild improvement in cognition an average of eight months later. The number of hours of cognitive training did not correlate with global improvement, but verbal learning and memory did better with longer training. Cognitive remediation in improving emotional symptoms was not very successful. This goes along with other studies showing that cognitive impairment is independent of other schizophrenic symptoms.15 Psychiatric rehabilitation improved psychosocial function, which improved patient chances in obtaining competitive jobs and improved interpersonal relationships.

**POST TRAUMATIC STRESS DISORDER (PTSD)**

PTSD is an anxiety disorder that occurs in response to an overwhelming terrifying, often life-threatening event. The hallmark characteristics are numbing/avoiding reminders of the traumatic event, intrusive re-experiencing of the trauma, and hyperarousal. Symptoms include irritability, sleep disturbance, exaggerated startle, and involuntary recollection of the trauma, such as intrusive thoughts, nightmares, and vivid memories (flashbacks).

PTSD individuals also complain about difficulty concentrating and memory impairment in everyday life. These individuals have experienced enhanced memories for threatening disorder-related material but are impaired in the encoding and retrieval of neutral event information. Memory impairment for verbal material, sustained attention, and working memory have been shown in Gulf War veterans with this disorder.17 Many of these individuals had attention deficit disorder and delayed walking and talking in childhood. Many also had lower intelligence measured before the trauma experience (war), which predicted severity of the PTSD decades later. There was no evidence that PTSD lowers IQ scores, but higher IQs may be protective. PTSD individuals have been shown to have difficulties generating specific and detailed autobiographical memory in response to an emotion-related word, such as happy, frustrated, or sad, compared to the normal population.

Gilbertson, et. al18 showed that smaller Hippocampi are very likely to constitute a vulnerability factor for developing PTSD among those exposed to trauma. In monozygotic twin pairs, hippocampal volume was measured. In 17 twin pairs, one twin developed combat-related PTSD and healthy twin was normal with no PTSD or trauma exposure. In another 23 twin pairs, one saw combat but did not have PTSD, the other saw no combat and did not have PTSD. The twins with PTSD with or without trauma had smaller hippocampal volume. The latter might reflect a genetic vulnerability for developing PTSD among trauma-exposed individuals. Lindauer et al19 found significantly smaller hippocampi volumes, higher cortisol levels, and memory impairment in police officers with PTSD, suggesting that memory impairment in this disorder is related to functional and morphological changes in brain structures implicated in episodic memory including the frontal, hippocampal, and amygdala structures. Prolonged stress during a trauma experience may cause neurodegeneration of pyramidal cells in hippocampi, secondary to release of corticosteroids and encephalins, which in turn suppresses long-term potentiation (LTP). During high levels of emotional arousal, the amygdala, which holds the core of the trauma experience, inhibits the hippocampi which in turn impairs episodic memory formation for peritraumatic events.

**MAJOR DEPRESSION**

It is well known that major depression may interfere with...
ability to focus and think, make decisions, formulate ideas, and reason and remember. Thoughts of worthlessness, suicidal persecution to point of delusions are common. Most research points to the fact that memory impairment is due to a disturbance in attention, lack of motivation, and poor cognitive initiative, rather than problems with memory storage. In addition, information processing, writing, drawing, and speech all slow down. Executive function has been shown to be impaired, though not as severe as in schizophrenia, it includes verbal fluency, organized searching, and abstract reasoning. In most cases, if a mistake is made in a simple task, this heightens their sense of failure.

In the elderly, memory loss is usually the chief complaint. Common executive dysfunction complaints such as planning, sequencing, organizing and processing speed are often impaired. Herrmann, et. al found that early onset of depression showed mainly impaired episodic memory as opposed to late onset. Some studies have shown in young adulthood that those with major depression and memory impairment disappears after clinical remission, but executive function and verbal learning impairment still persists. An increase of prosocial behavior may be present, but individuals may not enjoy these social interactions due to persistent inability to experience pleasure or positive emotions. The severity of depression correlated with cognitive performance scores. Major depression and anxiety showed very significant impairment in verbal episodic memory. Minor depression did not affect memory.

The same authors studied the effects of anxiety and depression on cognition in later life in 3,017 elderly citizens in the Netherlands. The study found that mild anxiety symptoms seemed to be beneficial for memory, whereas severe anxiety negatively influenced cognitive performance. Anxiety interferes with cognitive performance by preempting some of the processing and storage resources of the working memory system. Mild anxiety can have an arousing function, but more severe anxiety overwhelms the information processing abilities. In the same study, the authors found a linear association with depression and cognitive performance. Airaksinen et. al examined verbal episodic memory in different subgroups of depression including major depression, dysthymia, mixed anxiety-depression disorder, and minor depression. Overall the entire group showed significant verbal episodic memory impairment. When, however, each subtype was specifically analysed, major depression and mixed anxiety-depression subtypes exhibited the worst verbal episodic memory impairment, whereas dysthymic individuals and those with minor depression showed intact performance. Ekrem Dere et. al, in their review of cognitive impairment in major depression, suggest that verbal episodic memory impairments are related to pathological changes in perception, emotional processing, cognitive evaluation, autonomic and behavioral response to both emotionally non-competent or competent stimuli. The authors stated, “[s]ince emotional activation is a prerequisite for episodic memory formation, humans with major depression would show intact episodic memory performance for aversive events, but might be specifically impaired in remembering episodes with positive or rewarding content. This is also evident in the autobiographical memory test, which asks the individual to produce a detailed autobiographical episodic memory in response to a cue word such as ‘party.’ The depressed individuals respond with a generic or global summary rather than reporting a specific episode in the past.” Weniger et. al found that individuals with major depression exhibit an enlargement of the amygdala and reduction in hippocampal size that could be used to predict the severity of memory impairment.

**STUDY LIMITATIONS ON COGNITIVE IMPAIRMENT AND TREATMENT IN PRIMARY PSYCHIATRIC DISORDERS**

Most of the studies cited in this review focused predominantly on neuropsychological testing with little or no direct evaluation of detailed simple or complex activities of daily living. From the clinical standpoint, this is very important and in reviewing many of these articles, one doesn’t get a real sense of how the cognitive impairment impairs everyday life. In neurodegenerative and other causes of cognitive impairment, the main focus has been to find a medication or medical food product that will arrest, slow down, or improve cognitive function. This strategy is relatively new in primary psychiatric disorders and is being aggressively pursued, though it is more limited because of lack of animal models in these disorders and often no visual pathology such as is seen in Alzheimer’s disease. Recruiting pro-cognitive mechanisms that are independent of pathology or aetiology and spared is being pursued in primary psychiatric disorders. For example, cognitive deficits in schizophrenia are being studied. There is preliminary evidence that antagonists of 5-HT6 or histamine H3 receptors may improve cognitive deficits even though there is no evidence for hyperactivation of these receptors.

**HOW IS THE COGNITIVE INFORMATION IN PRIMARY PSYCHIATRIC DISORDERS RELEVANT FOR CLINICAL NEUROLOGISTS?**

The majority of clinical neurologists see patients with complaints of memory loss or other areas of cognitive impairment on a daily basis. Many of these individuals will range from 55 to 85 years of age. A number of these patients will have a history of a primary psychiatric disorder with past or ongoing use of psychiatric medications. Others will have ongoing...
symptoms of a primary psychiatric disorder with or without use of psychiatric medications. Based on the information from this topic, the following are suggested guidelines:

Be sure to include a detailed history of any past or present primary psychiatric disorder. If the individual comes alone and has cognitive complaints, be sure to contact, with permission, a family member or friend who can confirm cognitive impairment and a past or present psychiatric disorder. Try to determine who made this diagnosis and prescribed treatment. Many patients who receive a primary psychiatric diagnosis will often remain on pharmacologic treatment but do not follow up with a behavioral or health provider and get their medications filled by their family physician. Behavioral health providers include psychologists, neuropsychologists, psychiatrists, psychiatric nurse practitioners/physician assistants, and social workers.

Request medical records from the known behavioral health provider(s) by having the individual sign a release of medical records form. Because of HIPAA laws, non-psychiatric health care providers (family, internal medicine and geriatricians) cannot release psychiatric medical records to other physicians. You must get them from the behavioral health care provider.

The standard office neuro-cognitive evaluation for these individuals should not change. This should include a detailed neurological and medical history, office cognitive test and neurological examination. Simple and more complex activities of daily living assessment forms should be completed by the accompanied caregiver or friend in the waiting room while the patient is being thoroughly examined. This will give very important information about the patient’s capabilities and eliminate arguments that frequently occur when questions about activities of daily living are addressed to the caregiver with the patient in the same room. If there is no person accompanying the patient, or if the person present does not have much information, be sure to ask the patient who you can contact to get more details and contact them later that day or the following day.

When reviewing the patient’s office evaluation information and there is a history—current or past—of a primary psychiatric disorder, be sure to include this important information when deciding the severity and causes of cognitive impairment. Your opinion may change after you receive the pertinent medical records.

If neuropsychological testing is indicated, be sure to discuss pertinent psychiatric history with the referring neuropsychologist and let him know you are aware of cognitive impairments in different primary psychiatric diagnosis. They will usually make a great effort to obtain all pertinent history when they interview many different family members. If previous neuropsychological tests were done and especially if ordered by a psychiatrist, a copy of this will be very helpful. As mentioned above, HIPAA laws will only allow you to receive neuropsychological test results from the neuropsychologist directly, with the patient’s permission.

If the basic lab work and MRI or CAT scan of the brain is normal, non-specific, or has diffuse white matter “vascular” lesions, and the diagnosis is dementia in a background of a primary psychiatric disorder that is known to impair cognition, and you are considering a degenerative or stroke dementia (Alzheimer’s, lewybody, stroke or frontal temporal) further special testing such as a FDG PET scan and/or spinal fluid analysis for the degenerative dementias should be seriously considered. Amyloid PET Scan imaging may help play a role in these diagnostic conditions. This test however is not covered by insurance, is very expensive and currently is more valuable as a diagnostic procedure if no or minimal amyloid is present (likely eliminates Alzheimer as a diagnosis).

There is no current evidence that primary psychiatric disorders discussed in this topic increase the risk for future degenerative dementias.

Hippocampal atrophy on MRI of the brain has also been reported in post traumatic stress disorder and major depression (see the sections) and needs to be taken into account if Alzheimer’s disease (usually has hippocampal atrophy) is being considered in those individuals.

Does the patient have mild cognitive impairment (amnestic or non-amnestic, single or multiple domain) of unknown cause that normally has a 60 percent risk of developing into a neurodegenerative or vascular dementia, or 40 percent risk of no change over a five to six year period? Are some of the cognitive changes in the MCI individuals related to the history of, or ongoing primary psychiatric disorder? These individuals will need to be followed very closely for any future cognitive decline and may require specific tests PET (FDG/amyloid and/or CSF) to help rule out earlier neurodegenerative disorders. Follow-up or initial consultation with a behavioral health care provider may be necessary. An incorrect diagnosis can lead to a negative emotional (family and patient) and therapeutic (medication) consequences.

CONCLUSIONS
This paper has emphasized (infrequently discussed) cognitive impairments that occur in a number of common primary psychiatric disorders. This is important for the clinical neurologist who will continue to see more cognitive impaired individuals as the population continues to age. Many of these individuals will have a history and ongoing treatment for many of these disorders at all age groups including the elderly. When evaluating anyone for cognitive decline, but especially those over 65, who have a primary psychiatric disorder discussed in this review, careful atten-
tion must be given to the past psychiatric medical records, any previous neuropsychological testing, and consideration of more specific tests (PET FDG/amyloid and/or CSF) if degenerative or vascular dementias are being considered. A wrong diagnosis can have negative emotional and therapeutic consequences. There is no evidence that the primary psychiatric disorders reviewed lead to the development of neurodegenerative dementias.

Although historically psychiatry has focused on the motivational and emotional symptoms of psychiatric disorders, cognitive impairment has been shown to be just as prominent, persistent, and disabling. We should no longer consider that emotional and cognitive abnormalities in brain disorders, especially primary psychiatric disorders, be treated as entirely separate entities. Putting together information on functional structural brain networks, linking molecular and neural events, and studying novel drug concepts hopefully will lead to improved cognitive performance in patients with primary psychiatric disorders.

5. Depp et al. Bipolar Disorder in Older Adults: A Critical Review. Bipolar Disorder; (6); (5); 343-367 2004.