Abstract
Apathy is a common neurobehavioral feature in a variety of neuropsychiatric disorders. Apathy is often interpreted as a sign of depression or as a nonspecific symptom of other medical conditions. However, recent research indicates that the essential meaning of apathy is lack of motivation. This article presents a framework for the classification and differential diagnosis of apathy and addresses issues related to the assessment and treatment of apathy in neuro psychiatric patients.

Introduction
To most clinicians, apathy is a vaguely defined symptom suggesting a lack of interest or emotion. Patients who present with these and related symptoms (e.g., lack of feeling or concern, indifference, flat affect and/or emotional unresponsiveness) are often described as being apathetic. In the clinical setting, apathy is commonly interpreted as a sign of depression or as a non-specific symptom of a variety of other medical disorders.

The prevalence of apathy in different neuropsychiatric populations and research data indicating that apathy may occur in the absence of other depressive symptoms have led to the development of a framework for classification and differential diagnosis of apathy. Additionally, criteria for diagnosing apathy as a clinical syndrome have been proposed.

Definition of Apathy
Defining apathy as a lack of emotion or interest leads to ambiguity because emotion and interests are related but clearly not the same. More recently, apathy has been defined as lack of motivation. Lack of motivation is operationalized as the "simultaneous decrease in the overt behavioral, emotional, and cognitive concomitants of goal-directed behaviors." The central role of goal-directed behavior in the definition identifies apathy with the domain of psychological functioning concerned with motivation.

The diagnosis of apathy requires a diminution in observable goal-directed behavior relative to a person's age and culture. Apathy under the above definition also requires evidence of a decrease in emotional reactivity. For example, patients with apathy will show diminished emotional distress in response to pleasant or unpleasant event. Finally, thought content must be considered. The diagnosis of apathy requires diminution of goal-related cognitions such as diminished goals for the future, diminished interest.

Syndrome of Apathy
The application of the above definition of apathy to clinical practice requires guidelines for distinguishing apathy as a symptom and syndrome. According to the American Psychiatric Association, a syndrome is a recurring and discriminable pattern of symptoms that has heuristic value for diagnosing and treating patients. Once the presence of apathy has been determined, therefore, the next question is whether to regard as a symptom of some other syndrome or as a syndrome itself.

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Table 1: Criteria for the syndrome of Apathy

A. Lack of motivation relative to the patient's previous level of functioning or the standards of his/her age and culture, as evidenced by all three of the following:

I. Diminished goal-directed behavior
   • Lack of productivity
   • Lack of effort
   • Lack of time spent in activities of interest
   • Lack of initiative or perseverance
   • Compliance/dependency on others to structure activity

II. Diminished goal-directed cognition
   • Lack of interests, lack of interest in learning new things, lack of interest in new experiences
   • Lack of concern about one's personal health or functional problems
   • Diminished importance or value attributed to such goal-related domains as socialization, recreation, productivity, initiative, perseverance, curiosity.

III. Diminished emotional concomitants of goal-directed behavior
   • Unchanging affect
   • Lack of emotional responsivity to positive and negative events
   • Euphoric or flat affect
   • Absence of excitement or emotional intensity

B. Lack of motivation is the dominant feature of the clinical presentation. If the lack of motivation is not the dominant feature, then apathy is a symptom of some other syndrome such as dementia, delirium, or depression.

Definition of Apathy

As a general rule, apathy is considered to be a symptom if the apathy is mild relative to other symptom. In such cases, the patient is described syndromally in terms of the other syndrome and apathy is considered a symptom of that syndrome. Examples include syndromes of intellectual impairment (ego dementia) and syndromes of impaired level of consciousness (eg, delirium).

The essential feature of the syndrome of apathy is diminished goal-directed behavior due to a lack of motivation. The extent to which apathy dominates the clinical picture determines the presence of a syndrome of apathy. In other words, apathy is considered a syndrome when lack of motivation is not attributable to such other syndromes as dementia, delirium, or depression. Deciding whether apathy is secondary to some others syndromes depends on the process of evaluating a patient's overall clinical state and judging which symptoms are most prominent. For example, if a patient with diminished interests is intensely dysphoric, a diagnosis of depression would be more likely. The criteria for diagnosing the syndrome of apathy are summarized in Table 1.

Patients may show the syndrome of apathy and another syndrome simultaneously, eg, in Parkinson's disease and Alzheimer disease. Patients with Parkinson's disease often present with both apathy and dementia, while patients with Alzheimer disease may exhibit apathy, dementia, and psychosis. In each case, the patients exhibit diminished motivation, but the symptoms meet criteria for some other syndrome, eg, dementia.

Assessment of Apathy

Recognition of apathy has important implications for clinical care because motivation is essential for adaptive behavior. Comprehensive medical assessment may be needed to evaluate many psychiatric, neurologic, and medical condition that can produce apathy. Taking a thorough psychosocial history is necessary to determine whether apathy has been present throughout childhood or adult life, whether it is a symptom of a personality disorder or whether it represents a change in personality. The level of motivation must be interpreted in the context of the individual's cultural background and personal experiences. Apathy is considered to be clinically significant when:

1. there is evidence of diminished motivation relative to the norms of one age and culture;
2. the lack of motivation is severe enough to interfere with psychosocial functioning. In evaluating motivation, it is to remember that apathy need not be pervasive or incapacitating. In fact, adaptive functioning requires selectivity of choices. Healthy individuals are, of necessity, relatively or selectively apathetic about some goal in comparison with others. Characterizing the individual's skill accomplishments, goals and aspirations,
emotional relationship, and social interactions will help distinguish apathy that is adaptive (having functional significance) and selective (making a carefully chosen response) from that which is defensive (meaning response that is protective but not necessarily functional) and pervasive (meaning always present.)

Apathy Evaluation Scale (AES) is the most widely used and extensively validated rating scale for measuring the presence and severity of apathy. This 18-item instrument is specifically designed to assess the elements of apathy's operational definition, namely a decrease in the behavioral, cognitive and emotional concomitants of goal-directed behavior. Self-informant, and clinician-rated versions of the AES have been developed. The validity of the AES has been confirmed in studies of patients with stroke and Parkinson's disease. Psychometric analyses have also demonstrated that the AES discriminates between apathy and depression symptoms. Some patients have shown significant apathy without elevation of depression scores, a pattern consistent with the proposed concept of the syndrome of apathy. Taken together, these and other research findings strongly confirm the discriminability of apathy and depression in neuropsychiatric populations.

A recent study determined that four items of the Hamilton Depression Rating Scale (HORS-17 items) may be used to estimate apathy. Apathy is assessed by deriving a subtotal score using the following HDRS items: (1) lack of interest; (2) psychomotor retardation; (3) lack of energy; and (4) lack of insight. The correlation between the AES and HDRS total scores in this study is significantly reduced when the four "apathy items" are excluded from the HDRS total score. This finding supports the notion that this HDRS subtotal score can serve as a measure of apathy when more specific instruments of apathy are not used.

**Differential diagnosis of Apathy Depression**

The essential difference between apathy and depression is that apathy is a syndrome of diminished motivation, whereas depression is defined by disturbances in mood. Differentiating the syndromes of apathy and depression is understandable, as both are associated with diminished motivation, often in depression and always in apathy. The most useful features for differentiating apathy and depression occur in the emotional and cognitive areas. Depression is, by definition, a dysphoric state, whereas patients with a syndrome of apathy do not report dysphoria. The emotional response of depressed patients also differs from that of patients with apathy. Whereas apathetic patients show attenuated emotional responses to both positive and negative rewards, depressed patients are biased to perceive and respond selectively to negative events. In the cognitive dimension, individuals with depression often report negative thoughts about the self, the present, and the future. In apathy, a lack of concern is present, with diminution in goals interests, and curiosity. Furthermore, in depressed patients who claim to lack interest, careful assessment generally reveals that their lack of interest actually reflects despair, hopelessness, and pessimism. Thus, the lack of interest of the depressed individual is due to diminished expectancy of achieving goals that, if anything, are now overvalued. In contrast, patients with apathy value their goals less than they used to and are therefore truly unconcerned.

**Delirium**

Apathy is a common symptom of delirium. Persons with delirium who are sedate, drowsy, or hypoactive are likely to be characterized as apathetic. Presumably, the mechanism of apathy in these cases is suppression of the reticular activating system by the metabolic effects of medical conditions, or the effects of gross brain disease on the neural connections or blood supply of this system or structures mediating attention.

**Dementia**

Dementing diseases, particularly those involving the frontal lobes and basal ganglia, often cause apathy. Alzheimer disease may
produce apathy, but does not necessarily do so in the earliest stages of the disease. It may cause apathy by impairing the cognitive basis of motivation (via deterioration of frontal lobes and association areas): by disrupting the right parietotemporal circuits involved in perceiving emotional significance of information; or by impairing the subcortical mechanisms necessary for normal mood and drive.

**Abulia**
Individually with abulia associated with mesial frontal (ie. anterior cingulate) damage show diminished will or motivation. Abulia is associated with damage to the anterior cingulate gyrus, which is part of the mesial frontal system in the brain. In clinical practice, abulia generally refers to patients who are fully awake but otherwise severely impaired in their ability to communicate and to initiate and self-regulate purposeful behavior. Apathy and abulia have been viewed as part of a continuum of motivational impairment, with abulia representing the more severely impaired patients. Consistent with this, the gross brain lesions that cause abulia may cause apathy when they are smaller and less completely destructive, or evaluated during the recovery stage.

**Akinesia**
Akinesia is primarily a disorder of movement, not motivation. However, the two syndromes are not necessarily unassociated. A mildly akinetic patient can be severely apathetic, and a severely akinetic patient can be highly motivated. Akinetic patients show diminution or loss of the initiation of speech and actions. Basal ganglia disease and use of neuroleptic medications, the most prominent causes of akinesia, also cause apathy.

**Aprosodia**
Aprosodia is a disorder of emotion in which patients show impaired ability to perceive, interpret, or express emotion. Aprosodias are generally attributed to disease of the right hemisphere. Flat affect and inappropriate cheerfulness can occur in both apathy and aprosodia. Therefore, apathy and aprosodia may be difficult to distinguish from each other on the basis of emotional responsivity.

**Neural substrates of apathy**
The neural mechanisms of apathy in neuropsychiatric disorders have been described in a review by Mega and Cummings. Clinical research suggests that dopaminergic activity mediates diminished motivation in a number of conditions, such as subcortical diseases, frontal lobe syndromes, negative symptoms of schizophrenia, and post psychotic depression. Thus, increasing dopaminergic activity is the primary strategy or the pharmacologic treatment of patients with apathy. Apathy, however, should not be viewed simply as a problem of dopaminergic hypoactivity.

**Dopamine systems**
Apathy has been associated with hypofunctionality of the frontal cortex. The mesocortical dopaminergic system arises in the ventral tegmental area of the mesencephalon and innervates the cerebral cortex, particularly the frontal cortex. Increased mesocortical dopaminergic function associated with dopamine agonist or stimulant therapy is presumed to be an important source of clinical improvement in patients whose apathy is primarily associated with frontal rather than subcortical dysfunction.

The mesolimbic dopaminergic system, which also emerges from the ventral tegmental area, innervates the nucleus accumbens, amygdala, hippocampus, ventral pallidum and other forebrain structures. These and other interconnected structures (eg, the medial dorsal nucleus of the thalamus, the prefrontal cortex, and the pedunculopontine region of the brainstem) comprise a highly integrated series of circuits that represent the motivational state of the organism. This network translates motivation into action. Output of this motivation circuitry depends substantially on the pedunculopontine region and its connection to the basal ganglia and reticulospinal system. The benefit of dopamine agonist therapy in cases of subcortical disorders are believed to result from an increase in mesolimbic dopaminergic activity.
Frontal-Subcortical circuits

Three syndromes produced by frontal lobe damage are associated with apathy. Each frontal region is part of a specific cortical-subcortical circuit involving the thalamus, basal ganglia and forebrain. Damage affecting the anterior cingulate/mesiofrontal region produces a clinical syndrome of apathy. Dorsolateral prefrontal dysfunction is associated with impairment in the executive cognition necessary for planning and monitoring goal-directed behavior. Patients with damage to the lateral orbitofrontal cortex present with charges in personality marked by irritability, angry outbursts, or disinhibited sexual behavior. In these patients, however, there is often an underlying background of abulia and apathy that pervades the clinical picture. These frontal regions are connected to specific regions of caudate nucleus, nucleus accumbens, globus pallidus, and medical dorsal nucleus of the thalamus. Injury to any component of these three circuits produces the behavioral, emotional, and/or cognitive symptoms of that circuit.

Clinical causes of apathy

Clinically significant apathy can be due to primary neurologic processes and medical conditions that alter the neural systems subserving motivation. Table-2 lists clinical conditions associated with apathy.

Alzheimer disease

Apathy is a pervasive neurobehavioral disturbance in Alzheimer disease. The prevalence and severity of the syndrome of apathy increases with the progression of Alzheimer disease, with prevalence reports varying from 29% to 88%. Functional imaging studies suggest that the syndrome of apathy in this patient group is related to the severity of prefrontal and anterior temporal dysfunction.

Frontal lobe dysfunction

Neurologic diseases of any etiology affecting the frontal lobes produce changes in cognition and behavior in which motivational loss is often sufficiently prominent to be characterized as a syndrome of apathy. Multiple sclerosis, Pick's disease, other non-Alzheimer frontal dementias, frontal tumors, stroke, and hydrocephalus are examples of pathologic processes that may produce frontal lobe syndromes.

Basal ganglia disease

The syndrome of apathy has been associated with damage to the ventral striatum and globus pallidus. Systematic investigations of basal ganglia disease have focused primarily on Parkinson's disease, Huntington's disease, Progressive supranuclear palsy, and human immunodeficiency virus HIV) infection. In these and other subcortical diseases, loss of motivation often occurs in association with symptoms of mood disturbance and cognitive loss. HIV infection can lead to significant neuronal cell loss in the basal ganglia. Clinical studies indicate that apathy may reach syndromal proportions in the latter stages of disease progression. A recent study examined the relationship between apathy, depression and neurocognitive functioning during the asymptomatic stage of HIV infection. The study results showed that psychomotor slowing was associated with an increase in apathy but not depression in this cohort. These findings support the notion that apathy symptoms may be one of the earliest clinical manifestations of central of nervous system involvement in HIV-infected patients.

Diencephalic and amygdala damage

Dysfunction of the diencephalon and amygdala may also produce the syndrome of apathy. The best known of the conditions affecting these areas of the brain is Korsakoff's syndrome. Tumor, stroke, and trauma injuring the diencephalon may also produce a syndrome of apathy. The role of the amygdala in motivation is reflected by the Kluver-Bucy syndrome, which is, in part, characterized by blunted affect and apathy.

Hemispheric stroke

Apathy is a frequent finding among patients with acute stroke lesions and may coexist with other emotional and cognitive poststroke disturbances. Apathy is more common after focal right hemispheric stroke. In one
investigation, a reaction of indifference occurred in approximately 25% of patients with right hemispheric stroke. In another study a syndrome of apathy was detected in 23% of patients with right hemispheric stroke and 11% of patients with left hemispheric stroke. A notable finding was that these patients presented with elevated apathy scores but did not show elevated HRDS depression scores.

Depression
Apathy is well recognized as a symptom of depression. It has been reported frequently in adolescent depression, and is often a salient feature of late-life depressive disorders. A substantial percentage of cases of subsyndromal depression in the elderly may actually be apathy cases, because the features generally attributed to depression may actually reflect a syndrome of apathy. Accurately diagnosing such subsyndromal "depressions" as apathetic states has important implications for assessment and treatment. In all age groups, identifying apathy as an accompaniment of depression can improve outcome by making recovery of motivation a critical goal of antidepressant treatment and, by implication, a criterion for evaluating adequacy of treatment.

Psychotic disorders
Apathy is well known in chronic schizophrenia. The clinical Improvement of negative symptoms (motivational impairment) in schizophrenia is critical in that unmotivated patients have adverse social and functional prognoses. Post psychotic depression is usually believed to be a depressive syndrome that follows remission from acute schizophrenia or other psychotic disorders. Multiple studies of postpsychotic depression suggest, however, that it often present as a syndrome of apathy rather than dysphoria.

Current medications
Drugs disrupting the dopaminergic systems of the brain share the ability to produce apathy. The most familiar form of drug-induced apathy is associated with neuroleptics. Commonly, such apathy occurs as part of neuroleptic-induced akinesia. Selective serotonin reuptake inhibitors (SSRIs) may also produce varying degrees of a syndrome of apathy. Some patients experience a disabling or distressing loss of motivation, while others show an attenuation of emotional responsivity that may actually contribute to the reduction in dyphoria in that is part of the antidepressant benefit.

Other medical conditions
Apathy is commonly viewed as a nonspecific symptom of various medical conditions. It may be a prominent symptom in hypoaroused cases of delirium. Patients with chronic fatigue syndrome and Lyme disease will present with a syndrome of apathy, although the prominence of anergia and fatigability in these patients is distinctive. In addition, a syndrome of apathy has been described in some elderly patients with hyperthyroidism. It also result from pseudohypoparathyroidism, presumable as a result of associated central dopaminergic abnormalities.

Table 2: Conditions associated with the syndrome of apathy

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Alzheimer disease</td>
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<td>Frontal lobe dysfunction</td>
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<tr>
<td>Conditions affecting the frontal-subcortical circuit involving the anterior cingulate gyrus and associated globus pallidus, nucleus accumbens, and medial dorsal nucleus of the thalamus</td>
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<tr>
<td>Parkinson's Disease</td>
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<td>Huntington's disease</td>
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<tr>
<td>progressive supranuclear palsy, HIV infection, etc.</td>
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<tr>
<td>Diencephalic and amygdala damage</td>
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<tr>
<td>Kluver-Buch syndrome, Korsakoff's syndrome, tumor, stroke, etc.</td>
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<tr>
<td>Right hemisphere damage</td>
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<tr>
<td>Stroke, tumors and other conditions involving the inferior parietal lobule and its connections to the frontal lobe</td>
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<tr>
<td>Other neurologic disorders</td>
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<tr>
<td>Conditions affecting any of the above neural structures</td>
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<tr>
<td>Partially treated depression</td>
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<tr>
<td>Schizophrenia</td>
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<td>Deficit syndrome (enduring negative symptoms)</td>
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<tr>
<td>Drug-induced conditions</td>
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<tr>
<td>Neuroleptics, selective serotonin reuptake inhibitors, chronic marijuana use, amphetamine or cocaine withdrawal</td>
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Treatment approaches - Medication history
In all patients with apathy, it is important to consider the presence of neuroleptic drugs or SSRIs' either of which may include or exacerbate symptoms of loss of motivation. The SSRIs presumably produce apathy because of serotonergic modulation of the brainstem dopaminergic systems. In patients with apathy receiving neuroleptics or SSRIs, dose reduction or drug discontinuation is often an essential first step in management. Other psychoactive agents, such as benzodiazepines and anticholinergic drugs, may impair motivation indirectly because of their effects on attention and memory. Pharmacologic interventions for the treatment of negative symptoms associated with schizophrenia are under investigation. Atypical anti-psychotic medication may be particularly useful in schizophrenia and other patient groups with prominent negative symptoms.

Psychiatric Assessment
Apathy is commonly, but not always, seen in major depression. Formal ratings of apathy and depression may help clarify the extent to which motivational loss accounts for a patient's functional deficits. It is important to keep in mind that apathy symptoms along may account for significant elevation of depression rating scores. Apathy in the setting of depression is generally best treated by selecting the most effective antidepressant regimen for the patient's mood disorder. If apathy is particularly prominent, several modifications of treatment may be considered. In the case is otherwise uncomplicated stimulating antidepressants, those with dopamine uptake blocking selectivity may be preferable. Sertraline, in comparison, with other SSRIs, has relative strong dopaminergic uptake blocking activity. Bupropion also has some selectivity for dopaminergic reuptake mechanisms. Following a proper antidepressant treatment trial, some depressed patients show resouring of vegetative symptoms of depression, but continue to show symptoms of a syndrome of apathy (such as a lack of interest, anergy, diminished emotional reactivity, and diminished initiative). In these patients, treatments with methy phenidate or an amphetamine should be considered. If an SSRI was used initially, dose reduction is sometimes sufficient to provide optimal outcome. When apathy is prominent in the context of depression, the patients should also be evaluated carefully for the presence of coexisting frontal-subcortical diseases. It is not uncommon for such patients to be mistakenly diagnosed as depressed and treated for depression without benefit. Looking at such patients in retrospect, it is often clear that depression-specific symptoms (eg, depressed mood, guilt, suicidal ideation) are absent or minimal.

Neurologic assessment
In neurologic disease, apathy may be the dominant component of the clinical picture or it may occur in association with other symptom clusters (such as dementia or depression). In either case, its presence should be carefully discriminated. Subtle extrapyramidal findings are often important clues to conditions affecting basal ganglia and related frontal-subcortical circuits. An apathetic patient with an underlying neurologic disorder commonly requires separate treatment for apathy. Increasing dopaminergic function by reducing the neuroleptic dosage, switching to an atypical antipsychotic, or adding a dopamine agonist is often indicated for apathy.

Neuropsychological assessment
Apathy has been associated with executive dysfunction. An assessment of the patient's cognitive capacity will identify the extent to which executive function and other cognitive impairment account for difficulties in planning, initiating, and executing daily activities. Individuals without evidence of more widespread dementia symptoms (eg, impairments in language, visuospatial function, memory) tolerate drug therapy better. One therapeutic approach is treat such patients with stimulant drugs (eg, methylphenidate). Indirect dopamine agonists (eg, bromocriptine) also may be tried in this setting, although these are generally reserved with at least some evidence of extrapyramidal symptoms or diencephalic disease. Caregivers
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should be counseled to communicate with patients in a way that adapts to the specific pattern of executive impairment. For example, lack of initiative may be compensated for by structure and cueing. Complex or multiple-step activities may be accomplished by simplifying the task or providing instructions matched to the patient's sequencing limitations. Recognizing that the behavior is stimulus bound can be used advantageously by maintaining patients in their homes and by including familiar items in their new environment.

Conclusion

Apathy occurs as a symptom or syndrome in a variety of neuropsychiatric and medical conditions. Appropriate assessment, diagnosis and treatment of apathy may greatly improve patient quality of life. Treatment protocols are needed to examine systematically the effects of dopaminergic drugs (agonist drugs or SSRIs) on apathy in neuropsychiatric disorders. Identifying the indications and risk factors for treating apathy in neurologic disease will likely depend on the benefits of pharmacotherapy to clinical populations believed to be untreatable until recently. The advent of brain-imaging procedures, particularly functional imaging has opened many corridors for exploring the neurobiologic correlates of apathy.

References