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# Emotional and Behavioral Symptoms in Neurodegenerative Disease: A Model for Studying the Neural Bases of Psychopathology

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## Keywords

neurodegeneration, psychopathology, emotion, neural circuits, Alzheimer's disease, frontotemporal dementia

## Abstract

Disruptions in emotional, cognitive, and social behavior are common in neurodegenerative disease and in many forms of psychopathology. Because neurodegenerative diseases have patterns of brain atrophy that are much clearer than those of psychiatric disorders, they may provide a window into the neural bases of common emotional and behavioral symptoms. We discuss five common symptoms that occur in both neurodegenerative disease and psychopathology (i.e., anxiety, dysphoric mood, apathy, disinhibition, and euphoric mood) and their associated neural circuitry. We focus on two neurodegenerative diseases (i.e., Alzheimer's disease and frontotemporal dementia) that are common and well characterized in terms of emotion, cognition, and social behavior and in patterns of associated atrophy. Neurodegenerative diseases provide a powerful model system for studying the neural correlates of psychopathological symptoms; this is supported by evidence indicating convergence with psychiatric syndromes (e.g., symptoms of disinhibition associated with dysfunction in orbitofrontal cortex in both frontotemporal dementia and bipolar disorder). We conclude that neurodegenerative diseases can play an important role in future approaches to the assessment, prevention, and treatment of mental illness.

## Contents

INTRODUCTION.....	582
NEUROLOGICAL PATIENTS VERSUS FUNCTIONAL IMAGING.....	583
NEURODEGENERATIVE DISEASE: AN OPPORTUNITY TO STUDY NEURAL CIRCUITS .....	584
NEURODEGENERATIVE DISEASE: FROM CONS TO PROS .....	585
USING PATIENTS WITH NEURODEGENERATIVE DISEASE TO STUDY THE NEURAL CIRCUITRY OF PSYCHOPATHOLOGY .....	586
NEURODEGENERATIVE DISEASES.....	587
Alzheimer's Disease.....	588
Frontotemporal Dementia .....	588
NEUROPATHOLOGY AND FIVE MAJOR SYMPTOMS OF PSYCHOPATHOLOGY.....	589
Anxiety .....	590
Dysphoric Mood .....	592
Apathy.....	593
Disinhibition.....	593
Euphoric Mood .....	595
DISCUSSION .....	596
Sharpening the Behavioral Phenotypes.....	597
Implications for Etiology, Diagnosis, and Treatment .....	599
CONCLUSION .....	600

## INTRODUCTION

The major premise of this review is that neuropathology provides a royal road for understanding psychopathology. Historically, neurological injuries have largely been seen as causing deficits in cognitive domains such as memory. Although certainly relevant to some forms of mental illness (e.g., amnesia in dissociative disorders), these kinds of deficits do not really capture the dramatic emotional and social changes that form the bedrock symptoms of psychopathology. Moreover, although prevailing diathesis-stress models of mental illness (Monroe & Simons 1991) surely could accommodate both biological and psychological vulnerabilities and exacerbations, mid-twentieth-century research on the etiology of severe psychopathologies put greatest emphasis on the importance of psychological factors rather than biological ones. During this period, the spotlight shone most brightly on psychological etiologies such as communication patterns (e.g., double bind communications and schizophrenia; Bateson et al. 1956), parental styles (e.g., refrigerator mothers and autism; Kanner 1943), and the familial emotional climate (e.g., expressed emotion and relapse; Brown 1959).

Today, psychopathology research has clearly shifted toward a more biological, brain-centric focus. This transition arguably began with the introduction of pharmacological and biological treatments for severe mood disorders and psychosis (e.g., the introduction of chlorpromazine and electroconvulsive therapy into psychiatric practice in the 1940s and 1950s) and the accumulating evidence of the heritability of psychiatric syndromes arising from twin and family studies (e.g., Gottesman 1991). In more recent times, dramatic methodological advances in brain imaging opened the floodgates for a deluge of studies reporting that the brains of the mentally ill

are different in structure, function, resting activity, and connectivity from those of the mentally healthy. Contemporary biological models of mental illness often emphasize the importance of a “holy trinity” consisting of genes, molecules, and circuits. Most recently, the place of the brain at the top of this rarified hierarchy was underscored with the emergence of the Research Domain Criteria (RDoC; Insel et al. 2010) initiative at the National Institute of Mental Health (NIMH). In RDoC, psychopathology is not viewed in terms of traditional *Diagnostic and Statistical Manual of Mental Disorders* (DSM; Am. Psychiatr. Assoc. 1994) syndromes (e.g., schizophrenia, major depressive disorder) but rather in terms of dimensions of neurobiology and observable behavior (e.g., sustained responsiveness to reward; perception and understanding of self and others; Cuthbert & Insel 2013). For a “construct” (i.e., a behavior that spans a dimension of normal to abnormal functioning) to be included in RDoC, there must be a plausibly associated brain circuit. Genes and molecules still play an important role in RDoC, representing specifications of the constructs at different levels of analysis, but it is the existence of an associated brain circuit that is necessary for a behavior to be included.

Psychopathology research has clearly embraced imaging studies of patients with psychiatric disease. These studies take advantage of significant advances in scanner sensitivity; ways to study brain networks and assess their intrinsic connectivity; and methods for pipelining, processing, and analyzing imaging data. Against this backdrop, we present a somewhat contrarian position, namely that patients with neurodegenerative disease may provide an ideal model system for understanding the neural circuitry associated with key symptoms of mental illness. In addition to differences in the types of patients, the neurodegenerative disease approach differs in its greater use of structural relative to functional magnetic resonance imaging. Because neurodegenerative diseases can produce widespread damage in multiple brain regions in ways that differ among individual patients, structural imaging is critical for precisely characterizing areas that are injured and those that are spared. These differences notwithstanding, we believe studies of neurodegenerative disease can be extremely useful in understanding the neural circuitry that underlies some of the most important symptoms of mental illness.

## NEUROLOGICAL PATIENTS VERSUS FUNCTIONAL IMAGING

At their core, psychopathologies are manifest as dysfunctions in emotional, cognitive, and social functioning. Historically, studies of neurological patients have contributed immensely to fundamental discoveries in psychology related to the neural circuitry that underlies these processes. As previously noted (Levenson 2007, p. 158):

Studies of neurological patients have been critical to advancing our understanding of the human brain. In some instances, fundamental insights were gained and doors opened to entire new areas of inquiry based on findings from a single patient such as Phineas Gage and the frontal lobes (Harlow 1848) and Patient H.M. and the organization of memory (Scoville & Milner 1957). In other instances, findings from a small group of patients were seminal, such as epileptics treated with cerebral commissurotomy and hemispheric specialization (Gazzaniga & Sperry 1967). In addition to these spectacular advances, there has been a steady and continuing parade of findings derived from the deceptively simple strategy of identifying individuals with loss in particular brain areas of interest, determining how their abilities and functioning differ from the norm, and studying the ways that they change over time.

Ironically, despite this illustrious history, studies with neurological patients seem much less prevalent in contemporary clinical science than studies using functional imaging. However, it is important to recognize that functional imaging methodologies come with their own set of

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**Neurodegenerative disease:** a progressive neurological disease that targets specific distributed brain networks critical for cognitive, emotional, behavioral, and motor functioning

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**Emotions:**  
short-lived,  
psychological-  
physiological  
phenomena that are  
efficient modes of  
adaptation to changing  
environmental  
demands

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constraints and limits, including imposing an experimental environment in which participants must lie down in a cramped tube, stay still, and endure a cacophony of banging sounds. Fortunately for psychology, there are many cognitive processes that can be studied in this environment without great compromise (e.g., learning, memorizing, deciding, recognizing, calculating, choosing). But this is not an ideal environment for studying the kinds of complex emotional and social behaviors that are impacted by psychopathology; such full-blown emotional and social processes tend to involve action, movement, and other people, and are highly vulnerable to environmental distractions.

Even if it were possible to induce powerful emotions in the scanner, the attendant muscular activity in the body and face and vocalizations would produce huge signal artifacts. As a result, a great deal of emotional and social research conducted in the scanner falls into the realms of social and emotional cognition where the focus is on how we think about and make judgments about social and emotional processes rather than the actual processes as they unfold in real time. An example in the realm of emotion may be illustrative. Most scanner studies of fear are more likely to assess brain activity when people are recognizing fear (e.g., in a photograph) rather than when they are actually experiencing fear. Or if they are experiencing fear, it is likely to be of the mildest and most nonmotoric form. Similar constraints exist when studying social behaviors, with scanner studies more likely to involve assessing brain activity when individuals make social judgments rather than when they engage in actual social interactions (although some simple, nonactive social behaviors such as hand holding have been successfully brought into the scanner; Coan et al. 2006). These constraints in studying social and emotional behaviors become all the more critical when applied to the study of psychopathology. Although problems with emotional and social cognition are important in some psychopathologies (e.g., distorted views of self and others in narcissistic personality disorder and in schizophrenia; deficits in recognizing emotions in others in antisocial personality disorder and autism), dysfunctions in these domains often involve high levels of activation and high levels of interpersonal complexity.

In studies of patients with brain damage, the scanner can play an important but very different role: obtaining a “snapshot” that documents the morphology of the injury. Behaviors are not constrained by the need to be assessed in the scanner. Instead, the behaviors of interest can be observed under controlled conditions in the laboratory (Levenson 2007) or clinic or in more naturalistic conditions in the patient’s world, including at home and at work. Importantly, given the impact that mental illness has on social functioning, patient behavior can be observed in a full range of social contexts including actual interactions with friends, family, and coworkers. As previously noted (Levenson 2007, pp. 158–59):

The great power and advantage of patient studies is that the behavioral, cognitive, and emotional “dependent measures” need not be constrained. Patient studies allow use of the entire armamentarium of methods and techniques available for studying the full range of basic behavioral and social processes under both controlled and naturalistic conditions.

## **NEURODEGENERATIVE DISEASE: AN OPPORTUNITY TO STUDY NEURAL CIRCUITS**

Brain lesions can result from a number of processes including trauma, inflammation, tumor, stroke, and neurodegenerative disease. With H.M. and the cerebral commissurotomy patients mentioned previously, the lesions were produced surgically (to control epilepsy) and thus could be specified quite precisely. As a result, they provided a remarkable opportunity to examine the behavioral deficits that accompanied injury to particular brain regions (e.g., hippocampus and medial temporal lobe structures in H.M.; corpus callosum in the cerebral commissurotomy patients). Studying the

function of particular brain structures and relating them to psychopathology remains an active area of inquiry (e.g., the specialization of the fusiform gyrus for face recognition and its role in autism; Kanwisher et al. 1997, Weigelt et al. 2012). Increasingly, however, the focus in contemporary neuroscience has turned to consideration of how multiple structures participate in more distributed circuits. This influence can be clearly seen in RDoC, with its explicit emphasis on neural circuits.

When Phineas Gage had his unfortunate encounter with the errant tamping iron, he suffered quite extensive damage throughout his left frontal lobe (Harlow 1848). Debate about the exact anatomy of this injury (Damasio et al. 1994, Ratiu et al. 2004) and the nature of the associated behavioral change continues to this day (Macmillan 2000). The uncertainty around the injury to Gage's brain and the associated changes in behavior underscore the importance of having precise ways to characterize both the anatomy of brain injuries and the associated behavioral changes.

## NEURODEGENERATIVE DISEASE: FROM CONS TO PROS

Neurodegenerative diseases [e.g., Alzheimer's disease (AD), Parkinson's disease, and frontotemporal dementia (FTD)] present challenges for studying brain-behavior relationships when compared to studies of focal lesions. Historically, neurodegenerative diseases have been seen as presenting problems in (a) anatomy (the damage is diffuse, far-flung, and sometimes seemingly random), (b) stability (the damage is progressive and constantly expanding), and (c) measurement (the damage is difficult to characterize precisely in living patients, often requiring autopsy to specify the underlying neuropathology). Moreover, neurodegenerative diseases have been thought to affect cognitive processes primarily (e.g., memory, visuospatial abilities, language, executive control, computation) and thus do not capture the emotional and social processes that are so important in psychopathology. As is often the case, there are elements of truth in each of these arguments. However, increasingly the tide seems to be turning in the other direction, with neurodegenerative diseases emerging as highly promising model systems for studying brain-behavior relationships in general and for studying the neural circuitry associated with psychopathology in particular. The causes of these changes are instructive.

In terms of anatomy, increasingly it appears that neurodegenerative diseases are not diffuse and random but rather target and spread along neural networks that are structurally connected and have functional significance (Buckner et al. 2005, Seeley et al. 2009). Put in simple terms, major neural networks in normal brains serve as highways along which neurodegeneration progresses. For example, AD targets the default mode network (medial temporal, posterior cingulate/precuneus, lateral temporoparietal) involved in episodic memory (i.e., memory for specific events and experiences), whereas behavioral variant FTD targets a very different network (anterior insula, temporal pole, pregenual anterior cingulate cortex, ventral striatum, hypothalamus, periaqueductal gray, amygdala) linked to emotional salience processing (Seeley et al. 2009). This affinity for networks means that neurodegenerative diseases can provide an ideal model for understanding the functions these networks serve in normal brains and for documenting the behavioral changes associated with network damage.

In terms of stability, patients with focal lesions are often studied long after the brain injury occurred. As a result, compensatory mechanisms (in both brain and behavior) may have developed that obscure the original relationships between brain injuries and behavioral deficits. With neurodegenerative diseases, behavioral changes can be studied quite close to the time of injury. One particularly promising and still largely untapped approach is to use repeated assessments and longitudinal data analyses to link changes in brain circuits with changes in behavior. This kind of approach can help control for the confounding effects of premorbid individual differences in the circuits and behaviors of interest.

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### Alzheimer's disease (AD):

a neurodegenerative disease characterized by neurodegeneration in the medial temporal and parietal lobes that typically causes prominent deficits in episodic memory and may also affect visuospatial processing, language, and executive functioning

### Frontotemporal dementia (FTD):

a neurodegenerative disease characterized by neurodegeneration in the frontal and anterior temporal lobes that causes pronounced deficits in emotion, social behavior, and empathy

### Neurodegeneration:

progressive deterioration of the structure and function of neurons

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**Dementia:** a decline in cognition or behavior that impacts daily functioning

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In terms of measurement, remarkable advances have been made in ways to characterize the location and extent of brain injury in living patients with neurodegenerative diseases. These include (a) measuring the extent and location of volume loss using voxel-based morphometry (Ashburner & Friston 2000) and semiautomated methods such as FreeSurfer (Dale et al. 1999), (b) assessing the integrity of white matter tracts using diffusion tensor imaging (Basser et al. 1994), and (c) assessing the accumulation of particular neurotoxic substances using marking compounds and positron-emission tomography (e.g., Pittsburgh compound B to detect beta-amyloid accumulation; Klunk et al. 2004).

The high prevalence rates of neurodegenerative diseases constitute an enormous public health problem. For example, estimates are that there are over 5 million Americans currently living with AD. Sizeable patient populations also create remarkable opportunities to study brain-behavior relationships using much larger samples than has been the case in typical studies of patients with focal lesions. These large samples beget significant scientific benefits including greater statistical power, the ability to aggregate anatomically similar cases to increase signal-to-noise ratios, improved control for premorbid behavioral differences, the availability of replication samples, and the ability to study exemplars of particular degeneration patterns of interest.

### **USING PATIENTS WITH NEURODEGENERATIVE DISEASE TO STUDY THE NEURAL CIRCUITRY OF PSYCHOPATHOLOGY**

Neurodegenerative diseases that target brain circuits involved in social and emotional processes create symptoms that mimic those seen in psychiatric disorders. This mimicry can be so close that the diagnostic efforts of even highly experienced clinicians are confounded (including psychiatrists, neurologists, family physicians, and clinical psychologists). Many of the patients that we see in our research who will go on to receive autopsy-confirmed diagnoses of FTD were given psychiatric diagnoses (e.g., mood and psychotic disorders; Woolley et al. 2007, 2011) before being correctly diagnosed with dementia. Moreover, many received psychotropic medications (e.g., antidepressants, mood stabilizers, and antipsychotics) for their emotional symptoms before a neurodegenerative disease was considered. As neurodegenerative diseases with prominent behavioral symptoms (such as FTD) become more familiar outside of university and medical research centers, diagnosticians are more likely to consider neurodegenerative diseases in their differential diagnoses. Nonetheless, similarities in presenting behavioral symptoms between neurodegenerative and psychiatric diseases can make differential diagnosis quite difficult.

The argument for using neurological diseases to shed light on the likely neural circuitry underlying psychiatric symptoms is based in large part on the similarity of the behavioral phenotypes. Thus, if a group of neurological patients with known brain atrophy (e.g., patients with FTD with damage to the circuit involving the anterior cingulate cortex and temporal pole documented on structural images via voxel-based morphometry) present with symptoms (e.g., blunted affect) that are essentially identical to those seen in psychiatric patients (e.g., those with schizophrenia or autism), then the same circuitry is a prime candidate for being involved in producing the symptoms in the psychiatric patients.

Clearly, this proof by analogy requires several significant assumptions and is not without controversy. Importantly, it is premised on an assumed one-to-one relationship between particular well-defined behavioral symptoms and particular neural circuits. The alternative hypothesis, that particular symptoms are associated with different underlying neural circuits in neurological and psychiatric patients, is certainly possible but seems unlikely and unparsimonious. Moreover, a small number of studies of psychiatric patients using sensitive assessments of brain structure and function to link symptoms with underlying neural structures show striking overlap with the links



derived from the study of patients with neurodegenerative disease (e.g., see section on disinhibition below).

We believe that in the new RDoC era, the use of patients with neurodegenerative disease can assume a place of prominence among the various approaches for identifying neural circuitry (e.g., animal models, functional imaging studies with patients and patient analogs, transcranial magnetic stimulation, and patients with focal lesions). Each approach has its strengths, weaknesses, and inherent biases; thus, there is great value in seeking areas of convergence in brain-behavior links established using different methods and different patient populations.

## NEURODEGENERATIVE DISEASES

Neurodegenerative diseases typically have an onset in mid to late life and are characterized by insidious onset and gradual decline. In the early stages of progression, each neurodegenerative disease is characterized by degeneration of a specific large-scale brain network that is associated with the clinical manifestations of the disease in terms of motor, cognitive, behavioral, and emotional symptoms (Seeley et al. 2009). As the diseases progress, the pathological process can become more diffuse and spread in patterns constrained by network-based organization (Zhou et al. 2012). Although postmortem pathological studies are the gold standard for determining diagnosis and disease etiology, clinical evaluations that include neurological, neuropsychological, and neuroimaging studies can distinguish between these diseases during life with increasing reliability (Miller 2009).

In this review, we focus on AD and FTD, two neurodegenerative diseases that target different neural networks (Zhou et al. 2010) and present with different socioemotional phenotypes (for a review, see Teng et al. 2009). Both of these diseases present major public health problems. AD is the most common form of dementia, with prevalence rates of about 11% among individuals age 65 or older and at least 32% among individuals age 85 and older (Thies & Bleiler 2013). FTD is much less prevalent than AD among individuals over the age of 65, but it is at least as common (Ratnavalli et al. 2002) or even more prevalent (Knopman et al. 2004) in those under the age of 65. Neuroanatomical and clinical profiles for both diseases are summarized in **Table 1**.

Although other neurodegenerative diseases (e.g., corticobasal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis, and dementia with Lewy bodies) may also affect

**Table 1** Alzheimer’s disease (AD) and frontotemporal dementia (FTD) have distinct neuroanatomical and clinical profiles

Neurodegenerative disease	Typical brain atrophy	Characteristic cognitive symptoms	Characteristic emotional and behavioral symptoms
AD	Medial temporal lobe (entorhinal cortex and hippocampus) Parietal lobe (precuneus) Posterior cingulate cortex	Episodic memory Language Visuospatial functioning	Anxiety Dysphoric mood Apathy
FTD	Frontal lobe (anterior insula, anterior cingulate cortex, orbitofrontal cortex) Anterior temporal lobe and amygdala	Executive control	Apathy Disinhibition Euphoric mood Loss of empathy



cognition, emotion, and behavior, they have been the focus of much less relevant research and thus are not included in this review.

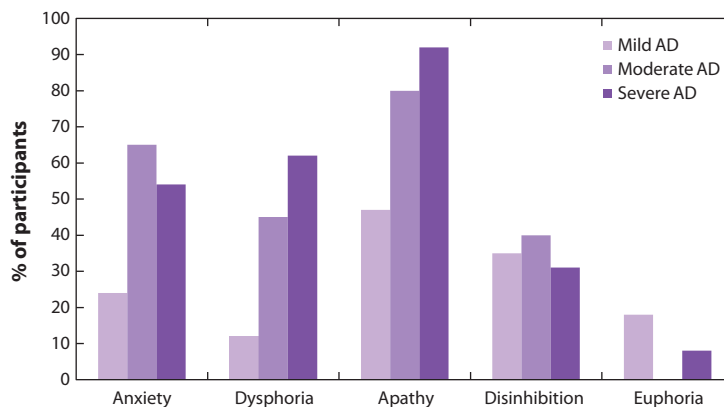
## Alzheimer's Disease

In AD, one of the earliest sites of pathology is in the medial temporal lobe (for a review of AD's molecular pathology, see Jagust 2013). Progressive accumulations of  $\beta$ -amyloid plaques and tau tangles in the brain are thought to begin in the entorhinal cortex and hippocampus and gradually progress to other limbic and then cortical structures (Braak & Braak 1995, Jack et al. 2013). The hippocampus, with connections to precuneus, posterior cingulate cortex, medial prefrontal cortex, lateral prefrontal cortex, and lateral temporoparietal cortex, is a key hub in the default mode network (Raichle et al. 2001), a network that supports episodic memory processes (Buckner et al. 2008). In AD, deterioration of default mode network connectivity is accompanied by the emergence of cognitive symptoms including episodic memory impairment (Buckner et al. 2005) as well as declines in visuospatial processing, language, and executive functioning (Mendez 2012).

Social behavior is often preserved in AD, and patients may retain their social graces and interpersonal relationships even late into the disease (Sturm et al. 2011). This preservation may result from a disjunction between network changes. As intrinsic connectivity declines in the default mode network in AD, connectivity may actually increase in the emotional salience network (anterior insula, anterior cingulate cortex, and thalamus, among others), which is devoted to affective stimulus detection and visceromotor emotion generation (Seeley et al. 2007, Zhou et al. 2010). These changes can result in a large number of behavioral changes, some of which can be considered as positive (e.g., preservation of emotional reactivity) and others that are quite troublesome (e.g., apathy, anxiety, dysphoric mood; e.g., Balthazar et al. 2013, Mega et al. 1996 ). In **Figure 1**, prevalence rates for common symptoms of psychopathology in AD are depicted.

## Frontotemporal Dementia

FTD is a clinically heterogeneous disease characterized by gradual neurodegeneration of the frontal and anterior temporal lobes. Pathologically, FTD is most often caused by abnormal aggregation of tau or TDP-43 proteins (Dickson et al. 2011, Josephs et al. 2011). Although many



**Figure 1**

Prevalence estimates for symptoms of psychopathology in Alzheimer's disease (AD) patients reported by caregivers using the Neuropsychiatric Inventory (Cummings 1997). Data from Mega and colleagues (1996). Mini Mental State Examination scores for mild AD: 21–30; moderate AD: 11–20; and severe AD: 0–10.

cases are sporadic, occurring without known cause, an increasing number of cases are associated with known genetic mutations (Cohn-Hokke et al. 2012).

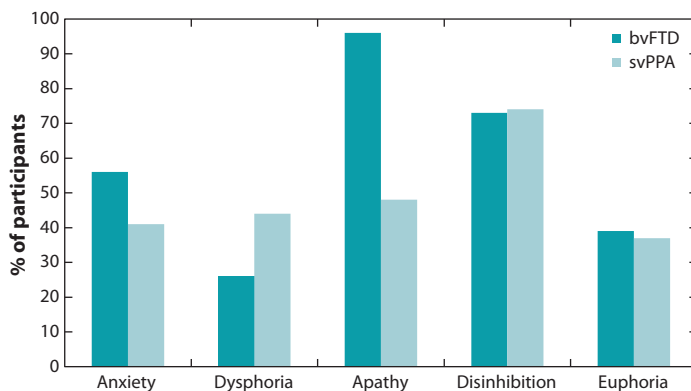
FTD is an umbrella term that includes three clinical subtypes: (a) behavioral variant FTD, (b) semantic variant primary progressive aphasia, and (c) nonfluent variant primary progressive aphasia (Gorno-Tempini et al. 2011, Rascovsky et al. 2011). In behavioral variant FTD, impairments in social behavior and emotion are common early features. Patients have dramatic declines in their interpersonal functioning and exhibit empathy deficits, disinhibition, compulsive behavior, apathy, aberrant motor behavior, and executive dysfunction (Neary et al. 1998, Rascovsky et al. 2011). These early behavioral changes are often accompanied by neurodegeneration of salience network structures that are essential for social behavior and emotion including right anterior insula, pregenual anterior cingulate cortex, and amygdala (Seeley et al. 2008). Deterioration of this salience network may hinder patients' ability to detect relevant affective cues, monitor their own emotional behavior, respond empathically, and interact appropriately with others (Banks & Weintraub 2008, Eslinger et al. 2005, Rankin et al. 2005, Snowden et al. 2003).

In semantic variant primary progressive aphasia, predominantly left-hemisphere atrophy in the temporal pole leads to decline in single-word object knowledge. In nonfluent variant primary progressive aphasia, predominantly left-hemisphere atrophy in the inferior frontal gyrus and anterior insula disrupts motor-speech output and syntax (Gorno-Tempini et al. 2011, Grossman et al. 2013). Each of the clinical subtypes of FTD is initially characterized by a somewhat unique constellation of symptoms and anatomy. However, as the disease progresses, regions involved in socioemotional regulation become affected, and behavioral changes become increasingly common (Rosen et al. 2002, Seeley et al. 2005). In **Figure 2**, prevalence rates are depicted for common symptoms of psychopathology in FTD.

**Clinical subtypes of FTD:** (a) behavioral variant FTD, (b) semantic variant primary progressive aphasia, and (c) nonfluent variant primary progressive aphasia

## NEUROPATHOLOGY AND FIVE MAJOR SYMPTOMS OF PSYCHOPATHOLOGY

Traditional DSM diagnoses (e.g., schizophrenia, major depressive disorder) are notorious for heterogeneity of symptoms, both within and across syndromes. As an example of within-syndrome heterogeneity, some patients diagnosed with schizophrenia have primarily negative symptoms



**Figure 2**

Prevalence estimates for symptoms of psychopathology in frontotemporal dementia patients reported by caregivers using the Neuropsychiatric Inventory (Cummings 1997). Data on behavioral variant frontotemporal dementia (bvFTD) and semantic variant primary progressive aphasia (svPPA) from Liu and colleagues (2004).

## METHODOLOGICAL CHALLENGES IN THE MEASUREMENT OF SYMPTOMS

Many of the existing studies on symptoms of psychopathology in neurodegenerative disease are based on caregiver reports (Teng et al. 2009). These studies use scales that measure emotional and behavioral symptoms such as apathy, agitation, and dysphoria (e.g., Cohen-Mansfield Agitation Inventory, Neuropsychiatric Inventory, Apathy Inventory, Behavioral Pathology in Alzheimer's Disease Rating Scale, Behavior Rating Scale for Dementia). Although caregivers have unique insights into the everyday functioning of patients, their assessment of symptoms can be negatively biased, especially when their own well-being is compromised (Schulz et al. 2013). For example, prevalence rates of certain symptoms (e.g., apathy) in AD vary from 29% using reports from trained personnel such as psychometricians and nurses (Lyketsos et al. 2000) to 72% using caregiver reports (Mega et al. 1996).

(e.g., social withdrawal, emotional blunting) whereas others have primarily positive symptoms (e.g., hallucinations, delusions). That such widely disparate symptoms would have a common underlying neural circuitry seems highly unlikely. As an example of across-syndrome heterogeneity, the same symptom (e.g., anxiety or sleep disturbance) can appear in multiple disorders (e.g., Harvey et al. 2004). Together, these two kinds of heterogeneities powerfully argue against DSM diagnoses serving as the appropriate level of analysis for linking psychopathology with underlying neural circuitry.

For this review, we adopt a different approach, emphasizing specific symptoms rather than DSM diagnoses (see also sidebar Methodological Challenges in the Measurement of Symptoms). The five symptoms associated with psychopathology that we have chosen (anxiety, dysphoric mood, apathy, disinhibition, and euphoric mood) have some overlap with constructs in the current version of RDoC (Cuthbert & Insel 2013) but are not identical. RDoC was designed to be a dynamic system, with the behavioral constructs evolving over time to reflect new knowledge (Insel et al. 2010). We believe that these five symptoms are ones for which we can make a strong case for associated neural circuitry based on brain-behavior links using data from patients with neurodegenerative diseases. Only time will tell whether the constructs in the current RDoC, the ones we will be describing, or others yet to be proposed will be most useful for understanding the neural substrates of psychopathology.

### Anxiety

Anxiety reflects uncontrolled feelings of apprehension and persistent worry or concern (Brown & Barlow 2009). It is a prime exemplar of a symptom that appears in multiple DSM disorders. For example, focal forms of anxiety can arise in response to specific triggers including social situations (social phobia), animals or objects (specific phobia), traumatic memories (posttraumatic stress disorder), or fear of contamination (obsessive-compulsive disorder). There is also a more diffuse, pervasive, and nonspecific variant that appears in generalized anxiety disorder. Despite the great variability in the specific triggers that can cause anxiety and in the duration and intensity of the anxiety response itself (i.e., a sudden panic attack versus chronic unease), an overlapping characteristic that unites all anxiety disorders is dysregulation of fear (Ohman & Mineka 2001). When operating in a functional manner, fear is an extremely useful emotion that arises in response to threatening stimuli, mobilizes needed physiological resources (e.g., somatic and autonomic), and helps protect us from danger (Levenson 2003). When fear is out of control or occurs in response to nonthreatening cues, however, it can be debilitating, creating unneeded physiological activation and dramatically interfering with normal functioning.

Anxiety is a common symptom in multiple neurodegenerative diseases, with prevalence estimates ranging from 5% to 21% for anxiety disorders and from 8% to 71% for anxiety symptoms (see review in Seignourel et al. 2008). In mild cognitive impairment (MCI; cognitive impairment that exceeds expected age-related changes but is less profound than that seen in dementia) and AD, the majority of patients have anxiety symptoms (Apostolova & Cummings 2008, Spalletta et al. 2010). Common manifestations of anxiety in patients with AD include worried appearance, fearfulness (e.g., fear of being left alone), tension, restlessness, and fidgeting (Ferretti et al. 2001). Although there is some debate as to whether these symptoms reflect a psychological reaction to cognitive and functional decline or a biological change in emotion-relevant neural circuits, there is strong evidence for the latter. This includes findings of heightened intrinsic connectivity in the salience network in AD (Balthazar et al. 2013) and hypometabolism in the medial temporal lobe, superior temporal gyrus, and insula (Hashimoto et al. 2006), both associated with attendant increases in anxiety. In FTD, anxiety is more variable, with some studies suggesting lower prevalence rates than in AD (de Vugt et al. 2006, Liu et al. 2004) and others reporting higher rates (Porter et al. 2003). The anatomical correlates of anxiety in FTD have not been as well established. Although one study found that anxiety is more common in patients with FTD with predominantly frontal (compared to temporal) damage (Liu et al. 2004), another suggested that anxiety was associated with temporal hypometabolism (Mendez et al. 2006b). One challenge with FTD is determining whether behavioral symptoms that are often associated with anxiety in other patient groups (e.g., aberrant motor behavior) are actually associated with subjective feelings of anxiety when manifest by patients with FTD.

Previous studies conducted in both animals and humans have delineated a neural circuit that supports fear. These neuroanatomical models emphasize the amygdala (central nucleus in particular) as a key structure in fear reactivity (LeDoux 2000). This framework has served as the foundation for more elaborate models in humans that propose that anxiety may be due to a combination of hyperactivity in emotion-generation systems and hypoactivity in emotion-regulation systems that help to modulate the fear response. Consistent with this hypothesis, multiple functional magnetic resonance imaging studies have found that individuals with anxiety disorders have higher activity in the amygdala, insula, anterior cingulate cortex, and ventromedial prefrontal cortex in response to negative emotional cues (Etkin & Wager 2007, Freitas-Ferrari et al. 2010). Analyses of intrinsic connectivity in individuals with anxiety have also found heightened intrinsic connectivity between the amygdala and anterior cingulate cortex and other emotion-generating structures (Pannekoek et al. 2013) and decreased coupling between emotion generators (e.g., amygdala) and regions that promote emotional control, including orbitofrontal and dorsolateral prefrontal cortex (Etkin et al. 2009, Hahn et al. 2011). Structural neuroimaging analyses, which measure regional brain volumes, have found mixed results as to whether individuals with anxiety have smaller or larger brain volumes in emotion-relevant structures. For example, smaller volume in left middle and superior temporal gyri and pregenual anterior cingulate cortex has been reported in anxiety disorders broadly (van Tol et al. 2010), and larger volume in the central nucleus of the amygdala has been found in individuals with generalized anxiety disorder (Etkin et al. 2009). Similarly, smaller volume in the temporal lobes and bilateral amygdala (but normal hippocampal volume) has been reported in individuals with panic disorder (Massana et al. 2003, Vythilingam et al. 2000). Both types of findings lend themselves to plausible explanations. For example, findings of larger volume in emotion generators can be interpreted as indicating greater neural support for mounting fear responses. On the other hand, findings of smaller volume in these structures can be interpreted as resulting from the accumulated wear and tear associated with chronic activation of the fear system over time. The influences of symptom severity and duration, medication and psychological treatment, and other biological and lifestyle factors likely also contribute to these differing results.

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**Mild cognitive impairment (MCI):** a clinical condition in which cognitive decline exceeds normal age-related changes but does not severely disrupt daily functioning; often precedes Alzheimer's disease

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**Laboratory studies:**

laboratory studies of emotion examine emotion processes (reactivity, regulation, and empathy), types (positive, negative, and self-conscious), and response systems (experience, behavior, physiology, and language)

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## Dysphoric Mood

In recent years, our understanding of the mood changes that accompany DSM depressive disorders has been evolving. Whereas at one time depression was thought to largely consist of high levels of sad affect (perhaps accompanied by other negative emotions such as anger), the emerging picture is more complex. Of course, sad mood is often seen in major depressive disorder, but laboratory studies have found a profile of affective responding that is “context insensitive.” In these studies, depressed patients have been shown to have blunted emotional reactivity to both positive and negative stimuli (Bylsma et al. 2008). Moreover, when they become emotionally activated, they may have trouble recovering from negative emotional events (Salomon et al. 2009), suggesting problems with downregulating negative emotion. As with so many DSM syndromes, we expect that the depressive disorders encompass multiple dysfunctional processes that are associated with different neural circuitry. In this regard, symptoms of overwhelming sadness seem likely to be dissociable from symptoms of blunted reactivity, apathy, and social withdrawal.

In neurodegenerative disease, symptoms of depression are common. Although the depressive symptoms experienced by individuals with dementia are quite similar to those seen in depressed older adults who are cognitively normal (Chemerinski et al. 2001), there is some indication that certain symptoms (e.g., irritability and social isolation) may be more common than others (e.g., diminished interest in activities) in depressed individuals with dementia (Olin et al. 2002). Some studies of depression in dementia do not specify the particular symptoms that are present, but those that do indicate that sadness, crying spells, and hopelessness commonly occur in depressed patients with MCI (Apostolova & Cummings 2008, Gabryelewicz et al. 2004, Lopez et al. 2005) and that feelings of sadness are also common in depressed patients with AD (Engedal et al. 2011, Spalletta et al. 2010). The picture in FTD is quite different. Depression is often reported in FTD (de Vugt et al. 2006), but it is not as common as in AD (Levy et al. 1996). Importantly, when depression is reported in FTD, it is more likely to be associated with apathy and social withdrawal (Blass & Rabins 2009) and less likely to be associated with sadness (Suzuki et al. 1999). In our work with patients with FTD, we have been struck by how often they are described by clinicians as being relatively happy, which may reflect an absence of sadness (and anxiety).

Influential models of the neurobiology of depression have proposed that altered connections between emotion-generating and emotion-regulating systems underlie mood symptoms. Consistent with this, individuals with depression have been shown to have heightened intrinsic connectivity in visceromotor emotion generators including subgenual anterior cingulate cortex and thalamus (Greicius et al. 2007) and reduced dorsolateral prefrontal cortex metabolic activity (Bench et al. 1992, Rogers et al. 2004) at rest and in response to emotional stimuli (Davidson et al. 2003). They also exhibit greater (Davidson et al. 2003) and sustained (Siegle et al. 2002) activity in the amygdala to emotional cues, a pattern that abates with successful treatment (Mayberg 2009, Sheline et al. 2001). Some authors have concluded that depression involves an inability to modulate amygdala reactivity to changing emotional cues (Anand et al. 2005, Sheline et al. 2001), a hypothesis that is consistent with findings of context-insensitive emotional responding. Structural neuroimaging studies of patients with depression have found volume reductions in regions important for both emotion generation and regulation including the pregenual anterior cingulate cortex, dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, hippocampus, and thalamus (Bora et al. 2012, Du et al. 2012). Although there is some evidence for a relationship between disease duration and smaller volume in these structures (Bora et al. 2012, Sheline et al. 1996, van Tol et al. 2010), intrinsic connectivity analyses have found that longer mood episodes are associated with greater connectivity in subgenual anterior cingulate cortex (Greicius et al. 2007). Of course, it is difficult to know the direction of causality in these relationships; anatomical

differences may reflect pre-existent vulnerabilities or may result from disease processes, medications, and other factors.

## Apathy

Apathy is a multifaceted construct that refers to a constellation of cognitive, behavioral, and affective symptoms including emotional blunting, lack of motivation, and lack of interest in pursuing goal-directed activities (Marin 1991, Robert et al. 2002). Because many patients do not endorse feelings of apathy, most studies of apathy rely on informant reports (e.g., Eslinger et al. 2012, Robert et al. 2002). Apathy has also been reported in studies of schizophrenia (Bonilha et al. 2008). In addition, a number of related symptoms have been reported in major depressive disorder (including psychomotor retardation, diminished interest or pleasure, and diminished ability to think or concentrate) and in schizophrenia (flat affect, alogia, anhedonia, and avolition). Apathy and this constellation of related symptoms span the domains of cognition, behavior, and affect and are related to problems in motivation, emotional responsiveness, social and intellectual interest, and self-initiated activity.

Apathy is one of the most common behavioral symptoms in neurodegenerative disease and is one of the most distressing symptoms for family members (de Vugt et al. 2006, Massimo et al. 2009). Apathy is quite common in AD, with prevalence rates ranging from 55% to 80% (Mega et al. 1996, Spalletta et al. 2010, van Reekum et al. 2005). Apathy may be even more ubiquitous in FTD (Liu et al. 2004, Massimo et al. 2009) and is one of the core diagnostic criteria of behavioral variant FTD (Rascovsky et al. 2007). Most studies evaluate apathy in dementia quite broadly, using instruments that are not designed to tease apart its various components. Nonetheless, there is emerging evidence that different dementias are characterized by different forms of apathy. For example, apathy in AD is more likely to be associated with dysphoric mood than in FTD (Chow et al. 2009). Conversely, apathy in FTD is more likely to be characterized by diminished motor activity than in AD (Shinagawa et al. 2006).

Given the substantial heterogeneity in the definition and measurement of apathy across studies, it is not surprising that there is also significant variability in the neuroanatomical regions that have been associated with it. Apathy, broadly defined, has been associated with lesions in a neural system that includes anterior cingulate cortex, ventral striatum, and thalamus (Bonelli & Cummings 2007). In FTD, atrophy in many of these regions (e.g., anterior cingulate cortex caudate and ventral striatum) in addition to ventromedial prefrontal cortex and temporoparietal junction, among others, has been associated with greater apathy (Eslinger et al. 2012, Levy & Dubois 2006, Rosen et al. 2005). In AD, there is a similar pattern of results, with apathy being related to hypoperfusion in anterior cingulate cortex, inferior frontal gyrus, and orbitofrontal cortex (Benoit et al. 2002, Migneco et al. 2001). In terms of more specific apathy symptoms, lack of initiative and interest has been associated with hypoperfusion in anterior cingulate cortex in AD (Robert et al. 2006).

Taken together, the emotional component of apathy in dementia appears to be associated with deficient activation of medial frontal systems that support reward responsivity and positive emotional reactivity. A similar conclusion can be drawn from functional imaging studies of patients with schizophrenia that focused on specific symptoms. Thus, in schizophrenia, negative symptoms such as flat affect, avolition, anhedonia, and social withdrawal have been associated with medial frontal hypoactivity (Mazza et al. 2013) and less activation in the ventral striatum during reward anticipation (Simon et al. 2010).

## Disinhibition

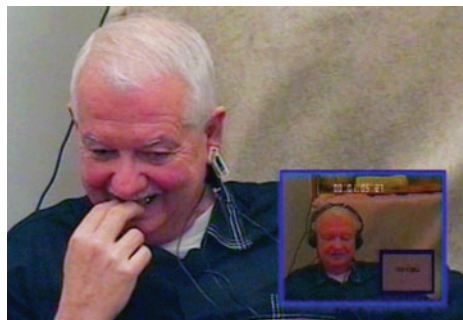
Disinhibition refers to the presence of unwanted actions, thoughts, and feelings (see sidebar Laboratory Approaches to the Study of Emotion in Neurodegenerative Disease). As control systems



## LABORATORY APPROACHES TO THE STUDY OF EMOTION IN NEURODEGENERATIVE DISEASE

Laboratory-based approaches for assessing emotional functioning that were developed in basic affective science are an effective way to identify areas of functional loss and preservation in neurodegenerative disease (Levenson 2007). These approaches often distinguish between different emotion processes (i.e., emotion reactivity, regulation, and recognition), different emotions and emotion families (e.g., positive, negative, and self-conscious), and different emotion response systems (e.g., peripheral and central physiology, facial expression, body posture, voice tone, emotional language, and subjective experience). One example paradigm that we have used in the laboratory is the karaoke task. Participants sing a song (“My Girl”) over instrumental background music with lyrics presented on a monitor. Afterward, without warning, participants are shown a recording of their just-completed singing performance, and their emotional response is assessed. For healthy participants, the karaoke task is a highly effective elicitor of self-conscious emotional (e.g., embarrassment). Patients with FTD, in contrast, show deficits in physiological responding and self-conscious emotional behavior while watching themselves singing. Impairment in self-conscious emotion likely contributes to key behavioral symptoms in FTD such as disinhibition and social inappropriateness. (See **Figure 3**).

that are involved in self-monitoring, impulse control, and emotion regulation fail, behavior becomes dysregulated, inappropriate, and error prone. In social contexts, these deficits lead to poor maintenance of social boundaries and violations of social norms. These kinds of problems are often seen in patients with bipolar disorder, who tend to be impulsive and have problems with decision making regardless of whether they are in the euthymic or manic phase of their illness (Henry et al. 2013, Mazzola-Pomietto et al. 2009, Swann et al. 2003). They are also seen in Axis II disorders such as borderline personality disorder, where difficulties with interpersonal boundaries are common (Linehan & Kehrer 1993), as well as in narcissistic and histrionic personality disorders.



**Figure 3**

The karaoke singing task elicits self-conscious emotion in healthy participants but not in patients with frontotemporal dementia (FTD). The photograph shows a normal control participant watching himself singing karaoke style (the inset is taken from the videotaped recording of the control singing “My Girl,” which was recorded earlier in the laboratory testing session). This participant exhibits a classic embarrassment response, as indexed by a controlled smile, gaze aversion, and face touching. Patients with behavioral variant FTD generally have no difficulty complying with the instructions but exhibit a diminished embarrassment response during this task. Note: The participant provided consent for his videotape to be used in scientific and public presentations.



Disinhibition is more common in FTD than AD (Hirono et al. 1999, Liu et al. 2004) and is one of the core diagnostic criteria of behavioral variant FTD (Rascovsky et al. 2011). Clinical reports suggest that disinhibited patients with FTD often approach others without concern for negative consequences, commit social faux pas without feelings of embarrassment, and are overly familiar with strangers. This pattern of behavior may reflect underlying deficits in the ability to generate embarrassment and other self-conscious emotions (e.g., shame and guilt), which normally signal violations of social norms and motivate corrective behaviors (Sturm et al. 2006, 2008).

Behavioral, cognitive, and emotional control all rely on a network that has hubs in ventrolateral prefrontal cortex and orbitofrontal cortex and connections with dorsal anterior insula, anterior mid-cingulate cortex, dorsolateral prefrontal cortex, medial frontal cortex, frontal pole, and lateral parietal cortex (Aron 2007, Dosenbach et al. 2007). In patients with dementia, disinhibition is associated with orbitofrontal cortex damage, which may alter connections with basal ganglia and thalamus (Bonelli & Cummings 2007). Consistent with this, disinhibition in FTD relates to dysfunction in orbitofrontal cortex and inferior frontal gyrus (Hornberger et al. 2010, Massimo et al. 2009, Peters et al. 2006, Possin et al. 2012), regions that are less vulnerable in AD (Liu et al. 2004, Whitwell et al. 2008). Studies with psychiatric patients that focus on particular symptoms also converge on this circuitry. For example, in patients with bipolar disorder, hypoactivation in these regions has been linked to higher error rates on response inhibition tasks (Mazzola-Pomietto et al. 2009).

### **Euphoric Mood**

We close this section by discussing a fifth important symptom of psychopathology, euphoric mood. However, in contrast to the symptoms discussed previously, evidence about the associated neural circuitry is largely derived from studies of psychiatric rather than neurological patients. Feelings of euphoria and elation reflecting an elevated positive emotional state are the hallmark symptom of bipolar disorder. Among DSM disorders, bipolar disorder may be least vulnerable to criticisms of heterogeneity. The hallmark symptoms of intermittent elation and euphoria found in bipolar disorder are not found in many other diagnoses. Moreover, bipolar disorder is one of the few DSM disorders that has a fairly unique pharmacologic treatment (i.e., lithium and other mood stabilizers). For these reasons, neuroimaging studies of patients with bipolar disorder may be much more useful in detailing the associated neural circuitry of euphoric mood than is the case with more heterogeneous DSM disorders. This is fortunate because there are not many studies of euphoric mood in neurodegenerative disease to draw upon.

A diagnosis of bipolar disorder requires at least one episode of mania, a period of elevated or irritable mood that is accompanied by symptoms including decreased need for sleep, increased activity, racing thoughts, extreme self-confidence, and pursuit of rewards with disregard of associated risks (Johnson et al. 2012). Although depression may also occur intermittently in bipolar disorder, it has been proposed that persistent elevations in positive emotion (even between manic or depressive episodes) are central to this illness (Gruber 2011). At one time, positive emotion was not seen as highly differentiated as negative emotion (which includes sadness, fear, anger, disgust, and contempt). However, positive emotion is being increasingly viewed as a family of emotions that includes amusement, attachment love, awe, contentment, enthusiasm, and nurturant love (Griskevicius et al. 2010). These positive emotions serve important interpersonal functions, facilitating approach behavior, fostering the development of new relationships, and supporting creativity and expansiveness (Fredrickson 2004, Shiota et al. 2011). Moreover, they serve valuable functions in quelling physiological arousal produced by negative emotions (Fredrickson & Levenson 1998). Arguably, enthusiasm is the hallmark positive emotion in bipolar disorder, but this has not been

established empirically. Individuals with bipolar disorder place high value on reward (with disregard for negative consequences), have elevated levels of positive emotional experience, and have high levels of vagal tone and reactivity (a measure of parasympathetic nervous system activity that has been linked with positive emotion; Gruber et al. 2008, 2011; Johnson et al. 2012). Together, these findings suggest that there may be elevated positive emotional experience in bipolar disorder that promotes reward-seeking and approach behaviors and puts people at risk for manic episodes.

In most neurodegenerative diseases, euphoric mood is relatively rare (Teng et al. 2009). However, euphoric mood is relatively common in FTD (Hirono et al. 1999), with prevalence rates of up to 40% (Liu et al. 2004). Patients with FTD often exhibit accentuated positive affect (e.g., smiling and laughing, overfamiliarity, jocularity, and silliness) and increased reward-seeking behaviors (e.g., overeating, risk taking, gambling, and excessive use of drugs and alcohol; Mendez et al. 2006a, Woolley et al. 2007). Given the substantial symptom overlap with bipolar disorder, it is not surprising that patients with FTD who display high levels of positive affect are often diagnosed as having bipolar disorder (Woolley et al. 2007, 2011).

Functional neuroimaging studies of individuals with bipolar disorder have found hypermetabolism in structures important for appraisal and emotion generation (e.g., pregenual and subgenual anterior cingulate cortex, parahippocampal gyrus, gyrus rectus, and medial and inferior temporal lobe). In addition, hypometabolism has been found in emotion-regulating systems (e.g., dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, superior temporal gyrus, and precuneus) during mania (Brooks et al. 2010). Other studies have found smaller volumes in emotion regulatory structures (e.g., orbitofrontal cortex) to be associated with greater amygdala reactivity to emotional stimuli (Foland et al. 2008, Foland-Ross et al. 2010). Volumetric analyses have found atrophy in emotion-relevant structures including dorsal anterior insula, ventrolateral prefrontal cortex, and pregenual anterior cingulate cortex that is somewhat attenuated with pharmacotherapy (Bora et al. 2010, Ellison-Wright & Bullmore 2010). Importantly, these are some of the same regions that are affected in FTD (Seeley et al. 2008), which may account for the overlapping symptomatology and the frequent diagnostic confusion.

## DISCUSSION

There is striking overlap in the cognitive, emotional, and behavioral symptoms produced by psychiatric disorders and neurodegenerative disease. In this review, we examined five core symptoms of psychopathology (anxiety, dysphoric mood, apathy, disinhibition, and euphoric mood) that also appear in two common neurodegenerative diseases, AD and FTD. Our goal was to explore the neural circuitry associated with these symptoms in neurodegenerative diseases and, when possible, to compare this to available evidence about the neural circuitry associated with these symptoms in psychiatric diseases. AD and FTD are particularly useful in this regard because they are common, well characterized behaviorally, and have quite different clinical presentations. Importantly, they also have different anatomical features, including their patterns of atrophy, breakdowns in intrinsic neural connectivity, and neuropathology. AD is a disease that targets more posterior neuroanatomical systems important for episodic memory and other cognitive functions; in contrast, FTD is a disease that targets more anterior systems important for social and emotional behavior. Together they present opportunities to study some of the most important symptoms of psychopathology in the realms of cognition, emotion, and social behavior and their associated neural circuitry.

Our analysis takes advantage of the fact that neurodegenerative diseases have much more clearly discernible patterns of neural atrophy than those typically associated with psychiatric symptoms. New understanding about the patterns of atrophy in neurodegenerative diseases suggests that they

are not random but rather target major structural and functional networks in the brain (Seeley et al. 2009). This emphasis on specific behaviors and symptoms is consistent with RDoC's basic tenet that greater progress in the treatment and prevention of mental illness will come from a symptom-centric approach than a more traditional syndrome-centric approach (Cuthbert & Insel 2013). Our review is also consistent with the RDoC emphasis on underlying neural circuitry. In our approach, when a neurodegenerative disease with a well-characterized pattern of damage to neural circuits creates a symptom that closely resembles a psychiatric symptom, we consider the circuit associated with the neurodegenerative disease likely to be critically involved in producing the psychiatric symptom. Although we are fully cognizant of the logical leaps involved and the viability of alternative hypotheses, when appropriate data are available from both neurodegenerative and psychiatric populations, the overlap has been impressive (see, for example, our previous discussion of neural circuits related to symptoms of disinhibition in FTD and bipolar disorder). Arguably, this can be considered to provide a preliminary proof of concept for this approach. Nonetheless, much more research clearly needs to be done before the final verdict is known.

### Sharpening the Behavioral Phenotypes

The exploration of brain-behavior relationships lies at the very heart of psychology, psychiatry, neuroscience, and neurology. In the past decade, our ability to characterize the brain side of these relationships has improved dramatically, with the advent of magnetic resonance imaging representing the breakthrough technology. Since then, there have been continuing and dramatic improvements in the methodologies available for quantifying imaging information in ways that enable characterization of many important aspects of brain structure and function. Ironically, our ability to characterize the behavioral side of these relationships has lagged behind. In recent years, as funding at NIMH has shifted away from basic behavioral science toward more translational and disease-centric science (Nat. Inst. Mental Health 1999), human and nonhuman animal research that could have provided deeper understanding of basic cognitive, social, and emotional processes and better ways to measure these functions has suffered. Simply stated, when twenty-first-century brain science is coupled with twentieth- (and nineteenth-) century behavioral science, the result is destined to sink to the lowest common denominator. Moreover, these mismatches are destined to hinder progress in other areas of psychopathology research involving biobehavioral relationships (e.g., linking genes with behavior; linking proteins and molecules with behavior).

RDoC clearly throws down the gauntlet in favor of much finer-grained behavioral analysis. Attempting to match specific circuits, molecules, and genes with broad, heterogeneous DSM syndromes (e.g., schizophrenia, depression, and autism) is rejected in favor of building links with more specific behaviors. But how are these behaviors to be measured and quantified? Focusing on clinical symptoms rather than syndromes is clearly a step toward greater behavioral precision. However, such symptoms are still quite complex, likely involving a number of different emotional, cognitive, and motor processes, each mediated by different neural mechanisms. The symptom of apathy explored previously in this review illustrates this problem. Apathy is a highly heterogeneous behavioral construct that can arise from the disruption of cognitive, emotional, or motor systems (Marin 1991, Robert et al. 2002). Studies of apathy describe its behavioral features using a panoply of descriptors including remoteness, disinterest, passivity, mental sluggishness, boredom, social withdrawal, social avoidance, lessened drive, lessened motivation, less caring, less concern, self-centeredness, loss of awareness, and asponaneity (Merrilees et al. 2013). This raises the question of whether some or all of these terms actually refer to the same underlying process and thus share a common underlying neural circuitry or whether they refer to different processes with different associated neural circuitry.

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#### Symptom-centric approach:

an approach to understanding psychopathology (e.g., Research Domain Criteria; RDoC) that conceptualizes mental illness as involving particular behaviors that can become dysfunctional. For these behaviors to be included in RDoC they must be associated with a plausible neural circuit

#### Syndrome-centric approach:

the traditional approach to classifying psychopathological disorders (e.g., *Diagnostic and Statistical Manual of Mental Disorders*), which conceptualizes mental illness as being categorical entities

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In our literature review, we encountered the related problem of how to determine whether a given symptom said to occur in both a neurodegenerative disease and a psychiatric disorder was really the same symptom. Thus, for example, how similar is the disinhibition shown by a patient with FTD to the disinhibition shown by a patient with bipolar disorder? Framed in another way, if skilled observers blind to diagnosis were shown thin slices of apathy behavior in a group of patients with either schizophrenia or FTD, would they be able to match the behavior samples with the patient diagnosis? The frequent misdiagnosis of FTD and bipolar disease by experienced clinicians indicates that this would not be an easy task, suggesting that the symptoms are actually quite similar in the two diseases. However, this is only anecdotal evidence, underscoring the need for serious research on symptom equivalency.

Addressing issues of symptom equivalency would also greatly benefit from detailed descriptions and reliable, well-validated measures of symptoms in neurological and psychiatric patients. There was a time when richly detailed observations of psychiatric symptoms by skilled clinicians were relatively common (e.g., Shapiro 1965); however, these promising descriptive forays did not lead to the development of measures with sound psychometric properties. As a result, the literature is replete with data on symptom intensities and frequencies but less well endowed with the kinds of information that enables determination of symptom equivalency.

A related problem is found when symptom-related terminology is used by different investigators in very different ways. A good example is “emotion regulation,” a critical locus of dysfunction in a number of neuropathologies and psychopathologies. In many studies, emotion regulation is assessed using self-reports and other-reports, which ultimately reflect respondents’ beliefs about how, how often and how well they or others regulate their emotions. However, in other studies, emotion regulation is assessed by measuring performance (e.g., placing the individual in a situation that elicits emotion and measuring how quickly they can restore emotional equilibrium; e.g., Bloch et al. 2013). Furthermore, within performance measures, some studies assess spontaneous performance (regulation that occurs without explicit instructions; e.g., Bloch et al. 2013), whereas others assess instructed performance (telling participants how and when to regulate; e.g., Shiota & Levenson 2009). And finally, the actual kind of regulation assessed (e.g., upregulation versus downregulation; suppression versus numerous kinds of reappraisal) often differs between studies (for a more extensive discussion of these issues, see Levenson et al. 2013). As noted previously, heterogeneity of symptoms within broad DSM diagnoses has long worked against establishing reliable bio-behavioral links. Heterogeneity of behaviors (and RDoC behavioral constructs) can create similar kinds of problems.

Finally, it is important to note that, when it comes to emotion, neurological and psychiatric diseases may not affect all kinds of emotions equally. Thus, for example, phobias may be associated with hyperreactivity in emotions such as fear and disgust in response to the phobic object, but they may not have much effect on sadness. Depression may be more associated with elevations in sadness and anger and less with fear and disgust. Similarly, neurological diseases can target particular emotions (e.g., deficits in disgust generation and recognition in Huntington’s disease; Sprengelmeyer et al. 1997) and emotion-related behaviors (e.g., laughing and crying in pseudobulbar affect in amyotrophic lateral sclerosis; Olney et al. 2011). Although there has been a lively debate in the affective science literature about the existence of separable neural circuitry for different emotions in the mammalian brain (Barrett et al. 2007, Izard 2007, Panksepp 2007), a great deal of the discussion rightfully centers on the quality of existing empirical evidence. For purposes of linking emotional behaviors with neural circuits, it seems prudent to make sure that studies that are being aggregated are well-matched in terms of the particular emotions (e.g., fear, anger), emotional dimensions (e.g., valence, arousal), and/or emotion families (positive, negative, self-conscious) that have been studied.

To summarize, in studying bio-behavioral links related to psychopathology and neuropathology, there is a pressing need for greater precision and care in specifying the behaviors, constructs, and symptoms that are candidates for linkage with neural circuits (and genes and molecules). Equivalencies among measures, procedures, and paradigms that purport to assess particular behaviors, constructs, and symptoms (including, but not limited to, those reviewed in the present article) cannot be assumed but rather must be established empirically.

## Implications for Etiology, Diagnosis, and Treatment

Identifying neural circuits associated with core symptoms of psychopathology will surely contribute greatly to our fundamental understanding of the brain, of functional and dysfunctional behaviors, and of brain-behavior relationships. However, in public health-relevant initiatives such as RDoC, there is a clear expectation that studying these relationships will have significant applied and practical benefits as well, leading to palpable advances in diagnosis, prevention, and treatment that will help relieve the enormous burden and suffering associated with mental illness. Envisioning how the latter might work requires a bit of extrapolation and conjecture.

In the realm of diagnosis, it is highly likely that future assessments (now largely based on structured interviews, questionnaires and rating scales, and behavioral observations) will be expanded to include more detailed assessment of the status of key neural circuits in the brain. This may include measures of brain structure (e.g., evidence of neurodegeneration and tract integrity obtained from highly sensitive structural scans) as well as measures of brain function (e.g., assessments of intrinsic connectivity and of activation in response to standardized behavioral probes). These kinds of assessments may be particularly helpful for diagnosing symptoms of mental illness, for identifying preclinical vulnerabilities, and for suggesting targets for early preventive interventions.

The ultimate utility of improved assessment methods will dramatically increase when there are more specific treatments available that target different disorders. When thinking about biological treatments for mental illness, pharmacologic approaches loom prominently. Currently available psychiatric drugs may target particular neurotransmitters and specific neurotransmitter mechanisms but are still relatively broad in action. When administered using current delivery systems, these drugs affect large areas of the brain and many different neural circuits (some producing the desired beneficial effects and some creating unwanted side effects). A great deal of research is being devoted to improved drug delivery systems. As these delivery systems improve, pharmacological treatments may become much more effective in targeting particular circuits in particular brain regions.

Biological treatments that directly target particular brain circuits are likely to include both electrical and surgical approaches. As with pharmacological treatments, there is a pressing need for greater precision in these approaches. Methods with long histories, such as electroconvulsive therapy and psychosurgery (e.g., lobotomy), although much improved in precision in recent incarnations, are still very broad in their action. Newer approaches that are more focused in action are already starting to be utilized in the treatment of mental illness. These include deep brain stimulation of particular neural tracts (Holtzheimer et al. 2012), transcranial magnetic stimulation (e.g., Mosimann et al. 2000), and biofeedback (providing subjects with information about the level of activation in particular brain regions).

In thinking about the implications of an increased focus on neural circuits in the assessment and treatment of psychopathology, it is important to note that this approach can be quite agnostic as to the original cause of circuit dysfunction and the type of treatment that will be most effective. Thus, for example, a problem that is thought to involve hyperreactivity in the emotional salience network might have been caused by some combination of biological and psychosocial factors

including disease (e.g., inflammation, infection), injury (e.g., early or recent brain trauma), genes (e.g., inherited vulnerabilities), environments (e.g., poverty, toxins, childhood adversity), life stress, and faulty learning. Similarly, treatment aimed at improving function of the affected circuitry might include some combination of biological, pharmacologic, psychosocial (e.g., psychotherapy targeting quite specific dysfunctional behaviors), and environmental interventions.

## CONCLUSION

Neurodegenerative diseases that produce symptoms similar to those found in psychiatric disorders can provide powerful tools for exploring the neural circuitry associated with a number of the major symptoms of psychopathology. This approach takes advantage of the more clear-cut and more readily quantifiable patterns of neural loss and changes in intrinsic connectivity that accompany neurodegenerative diseases and the proclivity of these diseases to target major structural/functional networks in the brain. For this approach to be most useful in characterizing brain-behavior relationships, behavioral symptoms need to be characterized with a level of care and precision comparable to that typically applied to structural and functional brain measures. This approach is consistent with new approaches to the study of mental illness that emphasize the importance of specific behaviors and neural circuits (e.g., RDoC). Studying patients with neurodegenerative disease holds great promise for helping identify neural structures that will be important for understanding the etiology of psychopathology as well as for playing a critical role in future approaches to the diagnosis, prevention, and treatment of mental illness.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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# Contents

Advances in Cognitive Theory and Therapy: The Generic Cognitive Model <i>Aaron T. Beck and Emily A.P. Haigh</i> .....	1
The Cycle of Classification: DSM-I Through DSM-5 <i>Roger K. Blashfield, Jared W. Keeley, Elizabeth H. Flanagan, and Shannon R. Miles</i> .....	25
The Internship Imbalance in Professional Psychology: Current Status and Future Prospects <i>Robert L. Hatcher</i> .....	53
Exploratory Structural Equation Modeling: An Integration of the Best Features of Exploratory and Confirmatory Factor Analysis <i>Herbert W. Marsh, Alexandre J.S. Morin, Philip D. Parker, and Gurdinder Kaur</i> .....	85
The Reliability of Clinical Diagnoses: State of the Art <i>Helena Chmura Kraemer</i> .....	111
Thin-Slice Judgments in the Clinical Context <i>Michael L. Slepian, Kathleen R. Bogart, and Nalini Ambady</i> .....	131
Attenuated Psychosis Syndrome: Ready for DSM-5.1? <i>P. Fusar-Poli, W.T. Carpenter, S.W. Woods, and T.H. McGlashan</i> .....	155
From Kanner to DSM-5: Autism as an Evolving Diagnostic Concept <i>Fred R. Volkmar and James C. McPartland</i> .....	193
Development of Clinical Practice Guidelines <i>Steven D. Hollon, Patricia A. Areán, Michelle G. Craske, Kermit A. Crawford, Daniel R. Kivlaban, Jeffrey J. Magnavita, Thomas H. Ollendick, Thomas L. Sexton, Bonnie Spring, Lynn F. Bufka, Daniel I. Galper, and Howard Kurtzman</i> .....	213
Overview of Meta-Analyses of the Prevention of Mental Health, Substance Use, and Conduct Problems <i>Irwin Sandler, Sharlene A. Wolchik, Gracelyn Cruden, Nicole E. Mabrer, Soyeon Ahn, Abnalee Brincks, and C. Hendricks Brown</i> .....	243

Improving Care for Depression and Suicide Risk in Adolescents: Innovative Strategies for Bringing Treatments to Community Settings <i>Joan Rosenbaum Asarnow and Jeanne Miranda</i> .....	275
The Contribution of Cultural Competence to Evidence-Based Care for Ethnically Diverse Populations <i>Stanley J. Huey Jr., Jacqueline Lee Tilley, Eduardo O. Jones, and Caitlin A. Smith</i> .....	305
How to Use the New DSM-5 Somatic Symptom Disorder Diagnosis in Research and Practice: A Critical Evaluation and a Proposal for Modifications <i>Winfried Rief and Alexandra Martin</i> .....	339
Antidepressant Use in Pregnant and Postpartum Women <i>Kimberly A. Yonkers, Katherine A. Blackwell, Janis Glover, and Ariadna Forray</i> .....	369
Depression, Stress, and Anhedonia: Toward a Synthesis and Integrated Model <i>Diego A. Pizzagalli</i> .....	393
Excess Early Mortality in Schizophrenia <i>Thomas Munk Laursen, Merete Nordentoft, and Preben Bo Mortensen</i> .....	425
Antecedents of Personality Disorder in Childhood and Adolescence: Toward an Integrative Developmental Model <i>Filip De Fruyt and Barbara De Clercq</i> .....	449
The Role of the DSM-5 Personality Trait Model in Moving Toward a Quantitative and Empirically Based Approach to Classifying Personality and Psychopathology <i>Robert F. Krueger and Kristian E. Markon</i> .....	477
Early-Starting Conduct Problems: Intersection of Conduct Problems and Poverty <i>Daniel S. Shaw and Elizabeth C. Shelleby</i> .....	503
How to Understand Divergent Views on Bipolar Disorder in Youth <i>Gabrielle A. Carlson and Daniel N. Klein</i> .....	529
Impulsive and Compulsive Behaviors in Parkinson's Disease <i>B.B. Averbeck, S.S. O'Sullivan, and A. Djambidian</i> .....	553
Emotional and Behavioral Symptoms in Neurodegenerative Disease: A Model for Studying the Neural Bases of Psychopathology <i>Robert W. Levenson, Virginia E. Sturm, and Claudia M. Haase</i> .....	581



Attention-Deficit/Hyperactivity Disorder and Risk of Substance Use Disorder: Developmental Considerations, Potential Pathways, and Opportunities for Research <i>Brooke S.G. Molina and William E. Pelham Jr.</i> .....	607
The Behavioral Economics of Substance Abuse Disorders: Reinforcement Pathologies and Their Repair <i>Warren K. Bickel, Matthew W. Johnson, Mikhail N. Koffarnus, James MacKillop, and James G. Murphy</i> .....	641
The Role of Sleep in Emotional Brain Function <i>Andrea N. Goldstein and Matthew P. Walker</i> .....	679
Justice Policy Reform for High-Risk Juveniles: Using Science to Achieve Large-Scale Crime Reduction <i>Jennifer L. Skeem, Elizabeth Scott, and Edward P. Mulvey</i> .....	709
Drug Approval and Drug Effectiveness <i>Glen I. Spielmans and Irving Kirsch</i> .....	741
Epidemiological, Neurobiological, and Genetic Clues to the Mechanisms Linking Cannabis Use to Risk for Nonaffective Psychosis <i>Ruud van Winkel and Rebecca Kuepper</i> .....	767

## Indexes

Cumulative Index of Contributing Authors, Volumes 1–10 .....	793
Cumulative Index of Articles Titles, Volumes 1–10 .....	797

## Errata

An online log of corrections to *Annual Review of Clinical Psychology* articles may be found at <http://www.annualreviews.org/errata/clinpsy>