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Special review article

Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: II. Implications for neurobiology, genetics and psychopharmacological treatment

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Abstract

Current psychiatry relies on a purely categorical paradigm for diagnosis of mental disorders that profoundly impacts research and clinical practice. However, high comorbidity rates and relative non-specificity of family history for psychiatric disorders suggests that this categorical approach fails to identify the underlying diathesis. As an attempt to overcome such limitations, we developed a bidimensional model based on fear and anger traits or temperaments which does not preclude the use of a categorical approach. As a result, it is hypothesized that mood, behavioral and personality disorders share a neurobiological substrate according to combinations of fear and anger traits. Both fear and anger, when excessive or deficient, lead to increased risk for mental disorders and should be considered in genetic, neurobiological and neuroimaging studies. Fear traits are much influenced by the amygdala and the serotonergic, noradrenergic and GABAergic systems, whereas anger seems to be mostly regulated by the nucleus accumbens and the dopaminergic and glutamatergic systems. Pharmacological treatments with antidepressants and anxiolytics can be considered as essentially restraint on fear, whereas lithium and α2 noradrenergic agonists would attenuate fear deficiency. Dopaminergic antidepressants and psychostimulants are anger enhancers and antipsychotics and mood stabilizers, such as divalproate and carbamazepine, may share antianger effects. Drugs effective for manic and depressive phases probably have both antianger and antifear effects. This framework may lead to a better understanding of the neurobiological basis of mental health and disease, providing an integrative approach for future research.

Keywords: Temperament; Fear; Anger; Bipolar disorder; Depression; Anxiety; Antipsychotic; Antidepressant; Mood stabilizer

Contents

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1. Introduction

The current model of psychiatry relies on supposedly distinct mental disorders or entities to address neurobiological, genetic and pharmacological issues. The significant consequences of this assumption include the exclusion of patients with comorbidities from samples and promote the notion that neurobiological findings and effective treatments may be specific for a given disorder. It also produces idiosyncrasies in labeling drug classes, since e.g. 'antidepressants' can treat a range of anxiety disorders, 'mood stabilizers' can treat psychosis, 'antipsychotics' can treat non-psychotic mania and depression, and these drug classes are also effective against a range of impulsive and anxiety disorders.

Although differences between disorders surely exist, we attempt to create a bidimensional model based on fear and anger traits that aim to address the basic diatheses for mood, behavioral and personality disorders. The clinical evidence for this model as well as the clinical implications for this framework are reviewed in the companion article. In brief, fear and anger dimensions are conceived within an orthogonal framework (Figs. 1 and 2). With schizophrenia, schizoid personality disorder and pervasive developmental disorders as the main exceptions, we hypothesize that most psychiatric disorders (with schizophrenia, schizoid personality disorder and pervasive developmental disorders as the main exceptions) would emerge from excessive or deficient fear and/or anger traits. The combination of low and high fear and anger traits would create the basic temperaments of hyperthymic, cyclothymic, depressive and labile individuals (Figs. 1 and 2; see also companion article). Moreover, excessive fear is proposed as the common basis for anxiety disorders, depression and cluster C personality disorders, whereas low fear (with reckless impulsivity) would be the basis for the hyperactivity seen in hyperthymic bipolar patients, monopolar mania, ADHD, and some disruptive disorders. Excessive anger is suggested to be the common basis of bipolar disorders, (appetitive) impulsive disorders, cluster B personality disorders, and most of the diathesis for substance abuse, whereas low anger would be a main substrate for inattention and the reduced focus of ADHD and would contribute to unipolar depression. Moderate or balanced fear and anger traits would predispose to euthymia and low risk for psychiatric disorders.

2. Neuroanatomical correlates of fear and anger

The emotions of fear and anger are clearly primitive and ancient from an evolutionary perspective (Cloninger et al., 1993). Therefore, they should be based on ancient limbic regions, whereas well-developed cortical regions, such as the prefrontal cortex, would have a modulatory rather than a primary role. Several studies point to the amygdala as central for fear detection and perception of stimuli valence (Merali et al., 2003; Pezawas et al., 2005). The amygdala has been shown to be particularly active in emotionally arousing experiences (for review, see McGaugh (2004)) and in those with high fear traits, even without history of psychiatric disorders (Bishop et al., 2004; Pezawas et al., 2005; Hariri et al., 2005).

For 'anger', which is here conceptually related to appetitive impulsivity, drive, motivation, pleasure, psychoticism and (as the amygdala) salience of stimuli, the main region is the nucleus accumbens or limbic/ventral striatum (Salamone et al., 2005). Neuroimaging evidence for this comes from recent studies showing increased activity in amygdala and ventral striatum in bipolar depression (Ketter et al., 2001; Bauer et al., 2005), with consequent decreased activity with mood improvement (Bauer et al., 2005). Therefore, the amygdala and the ventral striatum are probably the core regions in temperament, mood and behavior, along with the cingulate cortex, and connections with prefrontal cortex seem to be regulatory. However, the focus on these limbic regions does not preclude cortical involvement in the pathophysiology of mood and behavioral disorders leading to dysregulation of limbic regions. Neurovegetative symptoms, such as altered sleep and