

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  $\alpha 2$  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.

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

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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

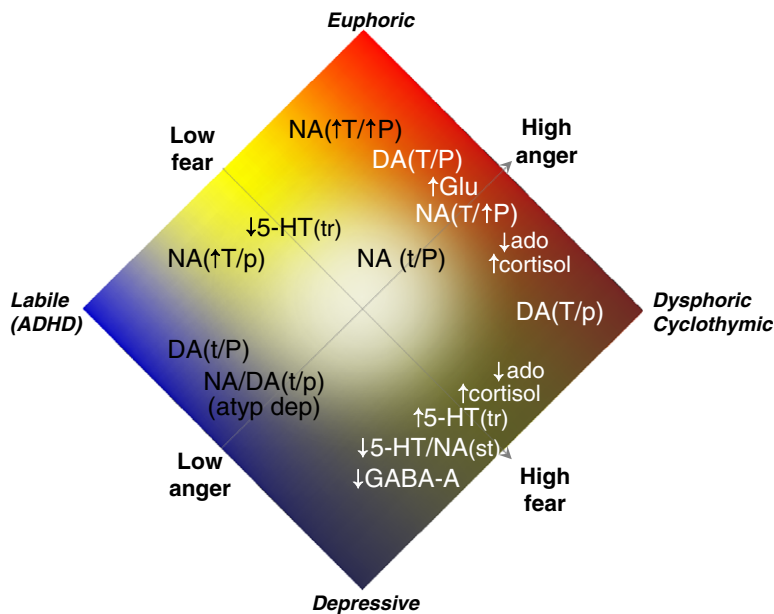


Fig. 1. Neurochemical correlates of fear and anger. The fear axis is influenced mainly by serotonergic (5-HT) and noradrenergic (NA) activity, with a predominant role of serotonin on high fear and of noradrenalin in the low fear range. Noradrenergic activity is particularly involved in attention and impulsivity ( $\uparrow$  indicates excessively high tonic (T) or phasic (P) activity; low case 't' and 'p' indicate low tonic and phasic activity, respectively). GABA also plays a role in the fear dimension. Tonic and phasic dopaminergic activity mainly influences the anger dimension ('T' and 't' for high and low tonic activity and 'P' and 'p' for high and low phasic activity, respectively). Glutamate would also be involved in anger modulation. Cortisol and adenosine (ado) may play a role in both the anger and fear dimensions.

appetite, are probably related to regions such as the hypothalamus, which are connected to the core regions of striatum and amygdala (Zahm, 1998). Also the hippocampus participates in cognitive processes, seems to be particularly vulnerable to stress and plays a special role in learned fear (but not in innate fear). A summary of the putative neuropsychobiological aspects of fear and anger is shown in Table 1. Also, some of the putative neurochemical substrates of fear and anger (and consequently the diatheses they may produce) are shown in Fig. 1 and are discussed below. Rather than a comprehensive review, we address some of the findings that regulate anger and fear traits.

### 3. Neurobiological correlates of anger

As proposed by Svrakic and Cloninger (2005), dopamine is a key neurotransmitter in the modulation of anger and novelty-seeking, but glutamate may also play a significant role. Dopamine transmission is involved in 'incentive salience', appetitive approach behavior and goal-directed behavior (Berridge and Robinson, 1998; Montague et al., 2004), which are features seen in (hypo) manic states and impulsive goal-directed (appetitive) behavior. However, recent evidence also point out a

significant role of dopamine and the nucleus accumbens in fear conditioning (learned fear rather than fear traits) and affective memory, with relevance for the development of phobic states (Pezze and Feldon, 2004). Such influence of limbic dopaminergic activity would be a central trait characteristic of the bipolar spectrum and some impulsive spectrum disorders, here considered as anger-related disorders. In contrast, in schizophrenia the negative symptoms would play the key role at the trait level, with hyperdopaminergic states and psychosis as secondary, but perhaps also associated with anger traits.

At the sensory gating level, prepulse inhibition (which is highly influenced by dopaminergic activity) has been shown to be deficient in manic patients and in pathological gambling (Perry et al., 2001; Stojanov et al., 2003). Another measure of sensory gating, the P50 paradigm, is impaired in mania but not in ADHD (Franks et al., 1983; Olincy et al., 2000), in line with high and low salience perception, respectively, that may differentiate their distractibility symptoms (see companion article).

At the molecular level, TaqI A1 allele of the D2R has been correlated with novelty-seeking, impulsivity, antisocial personality and alcohol dependence (Bowirrat and Oscar-Berman, 2005). Dopamine D4R-knockout mice also show reduced novelty-seeking behavior

Table 1  
Implications of the fear and anger model on neuropsychobiological domains

|                                    | Fear  | Anger  |
|------------------------------------|---|--|
| Behavior and style                 | Towards compulsivity<br>Security-seeking<br>Behavioral inhibition   | Towards appetitive impulsivity<br>Pleasure-seeking<br>Learned fear-aversion for displeasure (conditioned avoidance)<br>Eccentric, dramatic, intense, aggressive, paranoid  |
| Cognition<br>(information process) | Innate fear leading to avoidant behavior<br>Shy, dependent, avoidant, obsessive<br>Negative bias, high risk perception<br>(Low fear leads to positive bias and low risk perception)   | High salience bias (both positively and negatively charged; all-or-nothing thoughts, overgeneralization)<br>Psychosis-prone  |
| Neuroanatomy                       | Primary: amygdala<br>Secondary: cingulate, hippocampus, prefrontal cortex   | Primary: nucleus accumbens<br>Secondary: prefrontal cortex   |
| Neurochemistry                     | ↑ 5-HT activity, ↓ GABA activity (high fear), noradrenalin (low fear), corticosteroids (dystrophic effects on neurons), BDNF (?), ↓ adenosine activity, stathmin, vasopressin, others | ↑ dopamine activity (+D2R), ↑ glutamate activity (+AMPA), DeltaFosB, corticosteroids and opioids (dopamine releasing effect), ↓ adenosine activity, others   |
| Psychopharmacology                 | ↓: Serotonergic and noradrenergic antidepressants, 5-HT2 blockade, lamotrigine, benzodiazepines and other GABAergic drugs;<br>↑: Lithium and α2 agonists may 'reduce low fear'        | ↓: D2R antagonists, glutamate inhibitors (sodium channel antagonists, AMPA receptor antagonists), lithium (?), lamotrigine (?), allopurinol (?)<br>↑: Dopamine agonists (direct and indirect), 5-HT2 blockers (indirect), T4 (?) |
| Putative non-genetic risk factors  | Stress, poor parental care, trauma  | Drugs of abuse, excessive environmental stimulation, trauma  |
| Putative genetic risk factors      | 5-HTTPR(short), NRTK2, BDNF   | TaqI A1 allele of D2R, DAT, D4R polymorphisms (?)  |

Note: some of these characteristics would be opposite or absent in low fear and low anger, whereas medium fear and anger would be associated with intermediate expression.

(Dulawa et al., 1999) and D4R polymorphisms may be involved in novelty-seeking temperament (Savitz and Ramesar, 2004). Intracellularly, the transcription factor DeltaFosB seems to mediate some actions of dopamine and response to psychostimulants in the nucleus accumbens (Levine et al., 2005; Zachariou et al., 2006).

Anger traits undergo considerable changes in time, with relevance for the onset and course of anger-related disorders. The time course for the onset of mania/bipolar disorder, impulsive and substance use disorders (all anger-related disorders) coincides with dopamine D2R availability and novelty-seeking traits, which are higher in adolescence/early adulthood and progressively decrease with age (Cloninger et al., 1994; Ichise et al., 1998; Pelissolo and Lepine, 2000; Kennedy et al., 2005). This ~10% decay of D2R binding potential per decade may also contribute to age-related maturity (e.g. less impulsivity) and improvement of cluster B personality disorders (Zanarini et al., 2004; Svrakic and Cloninger, 2005). Regarding course, the process of behavioral sensitization, which has been suggested to account for increased cycling in bipolar disorders, is also related to the dopaminergic/nucleus accumbens substrate (Post, 2005). Accordingly, rats that express high novelty-seeking traits and conditioned avoidance

behavior (learned fear) are particularly sensitive to repeated psychostimulant administration (Corda et al., 2005). Also, stress has been shown to increase this dopaminergic sensitization (Nikulina et al., 2004), which is in line with evidence that a history of stressful events is related to earlier onset of bipolarity or mood episodes (Hlastala et al., 2000; Hillegers et al., 2004). Finally, the female gender is also associated with increased sensitization both in rodents and humans (Becker et al., 2001; Strakowski et al., 2001), which is probably associated with higher cycling in women (see companion article for a broader discussion on the course of mood disorders).

The contribution of the anger domain to some mood states may be related to the tonic and phasic balance of dopaminergic activity. Similarly to what has been proposed by Grace (2000) regarding drug addiction, euphoric states may be associated with high tonic and high phasic dopamine activity, whereas dysphoria may be related to increased tonic activity but decreased phasic activity due to presynaptic D2R desensitization (Fig. 1). Euthymia would represent balanced and flexible tonic and phasic dopaminergic activity, whereas in ADHD patients (low anger), there would be a trend toward decreased tonic activity and increased phasic activity.

Possibly low tonic and phasic dopaminergic activity may contribute to the state seen in atypical depression.

Among other modulators of anger, the glutamate system, especially related to AMPA receptors, has also been implicated in aggressive behavior (Munoz-Blanco et al., 1986; Swann, 2003; Vekovischeva et al., 2004) and in drug addiction (Park et al., 2002; Di Ciano and Everitt, 2004).

In summary, we submit that the anger dimension is highly influenced by dopaminergic activity. High anger may result from enhanced postsynaptic response to dopamine and/or presynaptic characteristics leading to increased synaptic dopamine concentration (e.g. decreased dopamine uptake), yet to be clearly characterized in humans. Within the dopaminergic system, the neurobiological substrate for excessive or deficient anger may involve synthetic enzymes, ion channels, synaptic proteins and/or intracellular signaling and messenger systems. However, key alterations may be found in other neurotransmitter or neuromodulatory systems (e.g., glutamatergic, opioid, adenosinergic, cholinergic, orexin) that interact with and regulate the dopaminergic system, which may be a common final pathway for behavioral expression of anger and its related features.

#### 4. Modulation of fear by serotonin, noradrenalin and GABA

The serotonergic system seems to play a major role in fear as shown by the blunted response to serotonergic stimulation in individuals with high harm avoidance or fear traits (Hennig et al., 2000; Weijers et al., 2001). At the genetic level, increased prevalence of the 5-HTTLPR short allele (theoretically related to higher synaptic serotonin levels) was associated with amygdala activation and fear traits in healthy individuals (Hariri et al., 2005; Pezawas et al., 2005; Gonda et al., 2006) and to depression when exposed to stressful and low support situations (Caspi et al., 2003; Eley et al., 2004; Kaufman et al., 2004; Grabe et al., 2005; Kendler et al., 2005). Accordingly, both genetic and early (childhood) pharmacological manipulation leading to higher serotonin levels in the synapse predispose to an anxious phenotype in mice (Ansoorge et al., 2004) whereas low serotonin metabolites predict impulse dyscontrol in primates (Higley and Linnoila, 1997). Altogether, these lines of evidence suggest that an increased serotonergic tone predisposes to high fear traits (Fig. 1) and a low serotonergic tone is associated with reckless impulsivity (low fear), contrary to early predictions based on the effects of serotonergic antidepressants (see Pezawas et al. (2005) for discussion). Therefore, trait reckless impulsivity associated with low

serotonergic tone may respond to serotonin uptake inhibitors; however, depending on anger traits as well as additional mechanisms of action that modulate fear and anger (e.g. noradrenergic, dopaminergic), care should be taken not to induce a manic switch. In contrast to high fear trait conditions associated with a high serotonergic tone, stress-induced depression may be associated with reduced serotonergic (as well as noradrenergic) function (Lechin et al., 1996; Charney, 2004).

Noradrenalin is another important modulator of the fear axis, but would be particularly relevant in the low fear range (Fig. 1). The noradrenergic system works mainly in the phasic and tonic modes, with distinct cognitive and behavioral correlates (see Aston-Jones and Cohen (2005) for review). The high tonic mode is associated with high distractibility and poor performance on tasks that require focused attention. Such mode is associated particularly with false-alarms in attention tasks, which can be attributed to reckless impulsivity, disinhibition, or low fear in the present model. Therefore, a trend towards increased noradrenergic tonic mode can be associated with ADHD and partly with the increased distractibility seen especially in hyperthymic bipolar disorder, possibly being the common terrain seen in ADHD/bipolar disorder comorbidity. In contrast, an increased phasic mode of the noradrenergic system (with moderate tonic activity) is associated with a task-related performance or a goal-directed activity. Therefore, the noradrenergic system in a predominantly phasic mode can to some extent contribute to high anger and appetitive impulsivity. We also posit that an overall increased noradrenergic activity (high tonic and phasic activities) may take place in euphoric manic states (with both distractibility and goal-directed behavior) and an overall decrease (low tonic and phasic activities) may be associated with atypical depression (Fig. 1). Alternatively, high tonic noradrenergic activity accounts for distractibility, whereas a high dopaminergic tone underlies increased goal-directed behavior.

A robust body of evidence also supports the role of the GABAergic system in modulation of anxiety (for review, see Nemeroff (2003)) and in fear traits (Crestani et al., 1999). Neurotrophic factors may also play a role in temperament, as recently found for the association of BDNF receptor NTRK2 with harm avoidance (Ribases et al., 2005).

Adenosine is an interesting neuromodulator to be further studied in psychiatry, since it can modulate many neurotransmitter systems (Fredholm et al., 2005). Caffeine, which non-selectively blocks A1 and A2 receptors, can induce or aggravate a range of symptoms from both the fear and anger domains, such as anxiety, panic attacks (Fredholm et al., 2005) and possibly hypomania or mixed

states. Knockout mice of A1 and A2A receptors also show that reduced adenosinergic activity can increase anxiety and aggressive behavior as well as produce emotional instability (Ledent et al., 1997; Gimenez-Llort et al., 2002; Lang et al., 2003). Conversely, in preclinical models adenosine agonists exert anxiolytic, antiaggressive and antipsychotic-like effects (Fredholm et al., 2005). A2A receptors have also been shown to be involved in amphetamine sensitization (Bastia et al., 2005) and in alcohol sensitivity and consumption (Naassila et al., 2002). Also, alcohol seems to increase adenosine signaling by inhibiting the nucleoside transporter, affecting both alcohol intoxication and preference (Choi et al., 2004). Unfortunately, drugs that directly enhance the adenosine function are not yet available for human use, but indirect enhancers, such as allopurinol, show promising results for the treatment of aggression and psychosis (Lara et al., 2000, 2003; Brunstein et al., 2005).

Cortisol is another putative modulator of both fear and anger. Corticosteroids may induce manic features, which may be related to its acute enhancing effect on dopaminergic activity, especially in individuals with hyperthymic or cyclothymic temperaments. Corticosteroids can also induce depressive states due to its chronic effect of decreasing dopaminergic activity as well as its neurodystrophic effects (Pacak et al., 2002).

Other recently identified modulators of fear in rodents include vasopressin (Wigger et al., 2004) and stathmin (Shumyatsky et al., 2005).

### 5. Pharmacological evidence and implications for treatment of mood, behavioral and personality disorders

If mood and behavior were mostly regulated by fear and anger traits, it would be expected that drugs known to modulate excesses and deficiencies of these temperaments should also modulate mood and behavior and vice versa. A summary of the treatment directions based on fear and anger is shown in Fig. 2.

Regarding the anger dimension, dopamine D2R antagonists ('antipsychotics') reduce anger, novelty-seeking and mania (Swann, 2003; Svrakic and Cloninger, 2005; Post, 2005). Accordingly, euthymic bipolar patients (with high anger in temperament) show increased mood and behavioral changes following an amphetamine challenge (Anand et al., 2000), further suggesting that the bipolar diathesis is related to hypersensitivity to catecholamines. Valproate can also reduce dopamine related behaviors (Ralph-Williams et al., 2003) and dopamine parameters in neuroimaging of bipolar patients (Yatham et al., 2002), but possibly have other independent antimanic/

antianger effects associated with neuronal depolarization. Importantly, in the present model, excessive anger is the core of the manic state (the 'sunny' euphoric tone in mania results from low fear) and accounts for irritable mood, aggressive behavior, pleasure-seeking behavior and psychosis or psychoticism. Therefore, it makes sense that antipsychotics are antimanic (or mood stabilizers) and some mood stabilizers (e.g. divalproate) treat psychotic symptoms of manic episodes, since these drugs particularly affect the anger dimension. It is also reasonable that they should be more effective in treating mood elevations than depressions, as indeed is the case for most 'antianger' mood stabilizers (Geddes et al., 2004; Swann, 2005). Clearly, carbamazepine and oxcarbazepine (blocking sodium channels and inhibiting glutamate-induced depolarization) as well as topiramate (blocking AMPA receptors) can also treat some impulsive or anger-related behaviors (Post, 2005). Finally, D2R blockade facilitates the extinction of conditioned fear in mice (Ponnusamy et al., 2005), further suggesting the role of anger/dopamine in learned fear. As a result, antianger treatments could potentially be useful for treating learned fear in patients with simple phobia, PTSD and/or borderline personality disorder.

Dopaminergic enhancers, such as methylphenidate and cocaine, can also elevate mood, probably by acting on the same substrates of anger, but their noradrenergic effects could also lead to a positive or optimistic bias in the fear dimension. The milder dopaminergic/noradrenergic agent bupropion is an antidepressant that seems to be less frequently associated with euphoric switches, although it may be as effective as other antidepressants or possibly more effective in bipolar and atypical (usually pseudounipolar) depression (Goodnick et al., 1998). As bupropion does not directly act on serotonin, which is a major substrate of fear, euphoric characteristics associated with lowering fear may be less common. The therapeutic effect of bupropion would be due to its ability to act on the substrate of downward anger dysregulation, which may be more associated with atypical depression or a 'worn-out' type of depression (see companion article). However, depressions of cyclothymics (dysregulation of fear and anger) may be treated with dopaminergic agents (acting on anger downward dysregulation) and/or serotonergic strategies (with antifear and antistress effects) associated with mood stabilizers, possibly with a similar efficacy. A low dose of amisulpride or sulpiride can be particularly effective for dysphoric states by targeting presynaptic D2 receptors (putatively desensitized in dysphoric states). Pramipexole is another dopaminergic compound (direct agonist at D2 receptors) with antidepressant properties

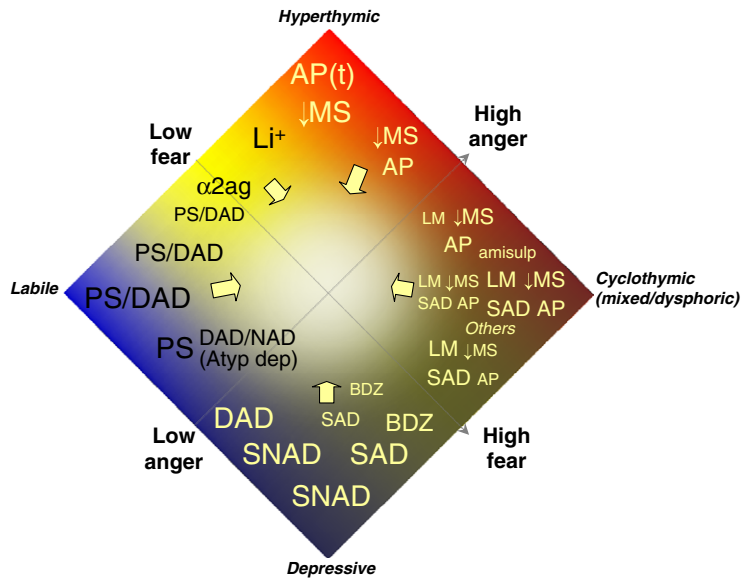


Fig. 2. Psychopharmacological treatment based on the bidimensional model of fear and anger. The main pharmacological classes are shown according to their putative efficacy to treat the high fear and anger substrates. Dosages are proportional to letter size.  $\downarrow$ MS = 'top-down' mood stabilizers, such as valproates, carbamazepine and oxcarbazepine;  $\text{Li}^+$  — lithium; AP — atypical antipsychotics, (t) — also typical antipsychotics; DAD — antidepressants with dopaminergic action, such as bupropion, MAO inhibitors and pramipexole; amisulip = low-dose (50 mg) amisulpride or sulpiride; LM = lamotrigine; SAD = serotonergic antidepressant mechanism of action, such as in SRIs, nefazodone, trazodone, mirtazapine, tianeptine and atypical antipsychotics; NAD — antidepressants that include a noradrenergic action at reuptake level, such as reboxetine, venlafaxine, nortriptyline, duloxetine, minalcipran or  $\alpha 2$  receptor antagonists, such as mirtazapine and mianserin; BDZ — benzodiazepines; SNAD — dual or triple agents (most tricyclics, venlafaxine, duloxetine or IMAOs) or combination of antidepressants. Others: benzodiazepines, gabapentin, topiramate, T4, eicosapentanoic acid (EPA).

in bipolar disorders (Goldberg et al., 2004). In line with our unifying model, dopaminergic antiparkinsonian drugs can also induce pathological gambling at higher doses since this behavioral disorder would be related to high anger (Driver-Dunckley et al., 2003; Avanzi et al., 2004).

In patients with low fear and high anger (hyperthymics) with predominantly (hypo)manic episodes, anti-anger medications (antipsychotics, valproate and carbamazepine) alone could stabilize mood (downward right to left shift along the anger axis in Fig. 2). We also postulate that lithium mainly attenuates the positive bias of deficient or low fear (downward left to right shift along the fear axis in Fig. 2), rather than directly reducing excessive anger (although some effect on anger is also plausible). This notion would be compatible with the fact that predictors of lithium response (euphoric mania, low cycling, absence of comorbid anxiety disorder, Yatham et al., 2005) are what we postulate as features related to low fear, whereas predictors of non-response are related to high anger (psychotic symptoms, drug abuse, sensitization leading to dysphoria or cycling) or high anger and fear (high cycling and anxiety). In contrast, the atypical antipsychotics valproate and carbamazepine show higher

efficacy in those with psychotic symptoms, dysphoric states, high cycling and comorbidity with anxiety disorders (Yatham et al., 2005), possibly because they might work mainly on the neurobiological substrates of high anger but also to a lesser degree by reducing fear. Typical antipsychotics, however, act only by reducing the anger domain, with no primary effect on the fear domain. Given the different response profiles between lithium and anticonvulsant mood stabilizers, searching for a common antimanic mechanism relies on the assumption that mania is a unidimensional or uniform process, which does not seem to be the case (Angst et al., 2005). Although they may share a single mechanism (e.g. inhibition of phosphoinositol metabolism or PKC inhibition), consideration of two dimensions (low fear and high anger in pure or classic mania) may lead to a better understanding of the differences among antimanic treatments as well as rational drug combinations and drug designs that differentially affect both dimensions.

Regarding the fear domain, serotonergic drugs are antidepressants, can induce (hypo)mania, and decrease harm avoidance or fear traits (Joyce et al., 1994; Allgulander et al., 1998; Abrams et al., 2004; Svrakic and Cloninger, 2005; Post, 2005). In the case of pure major

depression, dysthymia (with high fear and low anger) and anxiety disorders with low anger, serotonergic (or dual) antidepressants alone can be an effective strategy (Haykal and Akiskal, 1999). However, the higher the fear traits, the more aggressive should be the treatment. This is in accordance with findings that very high harm avoidance is associated with worse response than moderate–high harm avoidance scores (Joyce et al., 1994; Abrams et al., 2004; see also Yu et al., 2002) and with the need for high doses of serotonergic agents to treat disorders with very high fear traits, such as low anger social phobia and OCD. In these patients, ‘antifear’ treatment may also take longer to produce therapeutic effects (Stein, 2005) since they would be acting on a trait or a diathesis rather than only a state. In contrast, stress-induced depressions of subjects with moderate to low fear traits should improve in a few weeks with regular doses of antidepressants. These patients may also be less likely to require a longer term of treatment than those with high fear traits. Conversely, hyperthymic bipolar patients (low fear) may respond too much and faster — (hypo)manic switch (Henry et al., 2001). Intermediate cases of ‘hyperthymic’ switches in pseudodysthymic individuals (usually with a bipolar family history, Haykal and Akiskal, 1999) may occur by reduction of fear traits in predominantly depressive cyclothymic individuals.

Specifically regarding OCD, it should be noted that repetitive behavior due to stereotypes (with a hyperdopaminergic substrate in the basal ganglia), along with high salience perception (with a hyperdopaminergic substrate in the nucleus accumbens) may resemble obsessive–compulsive symptoms and should be treated with high potency D2 receptor blockers (Berridge et al., 2005) rather than with serotonergic antidepressants.

In cyclothymic patients (high fear and high anger), combinations of antianger and antifear strategies may be necessary to stabilize mood, even if within the same drug, as may be the case of atypical antipsychotics, such as quetiapine (moderate D2 blockade attenuates anger, 5-HT<sub>2</sub> and  $\alpha$ 2 receptor blockade reduces fear, Celada et al., 2004) and valproate (sodium channel blockade as antianger and GABAergic effects as antifear, Owens and Nemeroff, 2003). Likewise, we speculate that the minority of patients with bipolarity who benefit from continuous antidepressant treatment (Altshuler et al., 2003) are possibly cyclothymic individuals with higher fear traits.

Antidepressants may have some pro-anger effect as they increase novelty-seeking scores in social phobics (Allgulander et al., 1998), possibly by inducing D2R sensitization (Collu et al., 1997; Willner et al., 2005), but this may also reflect the fact that novelty-seeking scores in Cloninger’s model are partly influenced by the fear

dimension (see companion article). Interestingly, carbamazepine as well as a D2R antagonist counteracted such D2R sensitization induced by antidepressants (D’Aquila et al., 2001; Willner et al., 2005), whereas lithium did not (D’Aquila et al., 2000). This also suggests that lithium does not work robustly or as directly on anger as other mood stabilizers. Moreover, corticosteroids (increased in stress) can induce presynaptic dopamine sensitization (Deroche et al., 1995), therefore putatively acting to contribute to induce mania, cycling or to underlie some mood enhancement by risky attitudes. Since the GABAergic system does not seem to directly regulate anger, GABA enhancers are not expected to have significant antimanic effects, as indeed is the case for the anticonvulsants phenobarbital, gabapentin, tiagabine, benzodiazepines and others (Yatham et al., 2005; Post, 2005). However, increasing the GABAergic activity may contribute to reduce fear related symptoms.

Noradrenergic modulation of fear dimension also occurs and is compatible with the action of noradrenergic drugs on depression. Interestingly, a noradrenergic antidepressant increased positive emotional bias more than decreased fear perception, whereas a serotonergic antidepressant mainly reduced fear perception (Harmer et al., 2003, 2004). This difference on fear attenuation may underlie the distinct efficacy of serotonergic compared to noradrenergic drugs on a range of anxiety disorders, but both seem to contribute to the dimension of fear. Thus, serotonin would be a main modulator of fear in the high fear range, whereas noradrenalin would play a more important role in the low fear range. The partial and additive contribution of these two neurotransmitters would be compatible with observations of increased manic switch rates with antidepressants with dual action or including a noradrenergic action (Yatham et al., 2005).

Recently, lamotrigine and quetiapine have been shown to be effective in bipolar depression (Muzina et al., 2005; Calabrese et al., 2005). Lamotrigine works on various ion channels, inhibits glutamate release and was recently shown to decrease dopamine and serotonin basal levels in rats (Hahn et al., 2004; Ahmad et al., 2005). These are all substrates of anger and fear, but the precise action to produce its therapeutic effect is not clear yet. In contrast, quetiapine’s mechanism of action has been ascribed to its moderate to high blockade of 5-HT<sub>2</sub>R and moderate to low blockade of D2R, which would be only transient (Kapur et al., 2000; Gefvert et al., 2001) with the protocol used for bipolar depression of a single administration at night (Calabrese et al., 2005). This combined action may attenuate anger (transient D2R blockade — downward right to left shift as shown in Fig. 2) and reduce fear (5-HT<sub>2</sub>R blockade and  $\alpha$ 2 receptor blockade — upward



right to left shift in Fig. 2). The differential effect of typical and atypical antipsychotics on fear and anger substrates is also compatible with some reports of (hypo)mania induced by atypicals only (Rachid et al., 2004) and depressive symptoms with typicals (Bressan et al., 2002; Yatham et al., 2005).

In line with this unifying model, anger-related disorders such as bipolar, some impulsive and cluster B personality disorders, as well as drug abuse, comorbid or not, may improve with antianger drugs (antipsychotics and mood stabilizers) (Hollander et al., 2003, 2005a; Steiner et al., 2003; Svrakic and Cloninger, 2005; Salloum et al., 2005). Lithium may have been more effective than placebo in pathological gamblers (Hollander et al., 2005b) by reducing positive bias and reckless impulsivity related to low fear. Conversely, antifear drugs (e.g. antidepressants) are effective for major depression, anxiety and cluster C disorders (Schatzberg, 2000; Svrakic and Cloninger, 2005) as well as some behavioral and cluster B personality disorders with high anger and fear, but may leave anger traits mostly untreated.

Regarding ADHD, treatment with psychostimulants would increase tonic dopaminergic activity and consequently decrease phasic activity, thereby ameliorating salience and goal-directed behaviors (Volkow et al., 2001), here suggested as related to the anger domain. Inhibiting tonic noradrenergic activity with the  $\alpha$ 2R agonist clonidine may decrease distractibility and reckless impulsivity associated with low fear. Since we propose that hyperactivity (low fear) would be a shared feature of hyperthymic bipolar patients and ADHD, and that lithium may act mainly by decreasing fear deficit, it is interesting that Dorrego et al. (2002) found similar efficacy of lithium and methylphenidate for the treatment of adults with ADHD in a preliminary study. Similarly, clonidine can be effective in both ADHD and mania (Hardy et al., 1986; Pliszka, 2003). Lithium may reduce positive bias or correct fear deficiency (rather than increasing fear or negative bias) in mania by reducing the noradrenergic tone (Swann et al., 1987; Kovacs and Hernadi, 2002), although other relevant mechanisms and therapeutic effects (e.g. trophic effects) are likely to play a role.

## 6. Implications for neurobiological and genetic studies of mood, behavioral and personality disorders

Progress in understanding the neurobiological and genetic basis of mental illness heavily depends on the concepts employed in clinical diagnosis. Current fragmented models may fail to address the commonalities between disorders, which are evident by the high

comorbidity rates and partially non-specific family history of psychiatric disorders. If mood, behavioral and most personality disorders are influenced by high or low fear and/or anger traits, then the neurobiological substrates and genes that regulate these basic trait emotions are likely to be important predisposing and shared factors for most psychiatric illnesses. As pointed out by Cloninger (1999), it would be surprising to find genes for specific diagnostic categories as presently conceived in diagnostic manuals. If this principle is correct, samples of patients with mood disorders should also be stratified according to temperament dimensions. For example, hyperthymic and cyclothymic subjects may share the neurobiology and genetics for anger, but may be opposite regarding fear, and familiar trends for psychiatric disorders from cyclothymic subjects should be relatively different from those of hyperthymics. Genetic data supporting this view is emerging (Winokur et al., 1993; Perugi et al., 2001; Kelsoe, 2003; Kesebir et al., 2005; Evans et al., 2005). In particular, temperaments have been shown to correlate with familial risk for a mood disorder, being proposed as endophenotypic markers (e.g. cyclothymic temperament — Chiaroni et al., 2005). These results provide a preliminary genetic validator for the unifying bidimensional model based on fear and anger traits. This model also offers insights for the selection of control subjects based on temperament, rather than just not meeting criteria for psychiatric diagnoses. However, the present model does not exclude the possibility that other regulatory genes not directly related to fear and anger play a role in the genetics of psychiatric disorders. Another advantage of this model is that one can compare opposite extremes (e.g. low and high fear) with normal controls (medium fear), a process that would increase the chance of finding relevant genes. Such an approach is not possible using solely the current nosology.

## 7. Environmental influences on fear and anger domains

The neurobiology of fear and anger traits can be greatly influenced by non-genetic factors (Svrakic and Cloninger, 2005). Early-life conditions (stressful events, poor care) are predisposing factors for a range of mood, behavioral and personality disorders (Joyce et al., 2003a; Chapman et al., 2004; Bandelow et al., 2005), producing neuroendocrine dysregulation and neuronal dysfunction from the synaptic to the chromatin level (Fish et al., 2004; de Kloet et al., 2005). Time, duration and type of early-life events are certainly crucial, but the basic constitution of fear and anger may also define whether or not such events will anticipate a clinical picture with

panic attacks, generalized anxiety, unipolar depression, bipolar disorders or type of personality disorder (Joyce et al., 2003b). Evidence for such nature/nurture interaction has emerged in biological terms (reviewed in Moffitt et al. (2005)). Such early-life events can influence the biological substrates that regulate anger and fear traits, i.e., these events may participate in the non-genetic influence on temperament. Environmental influence can also be therapeutic by regulating fear traits and states alone (e.g. use of psychotherapy, social support and placebo effect), and both fear and anger states or traits (e.g. aerobic exercise).

In the present model, the combination of high fear and high anger traits without major life stressors could lead to cyclothymic bipolar disorder, whereas the presence of early chronic stressors/low support would be more associated with borderline personality disorder, and acute intense stress would result in PTSD. Therefore, due to the shared biological diathesis in terms of extreme traits, the coexpression of high fear and anger is quite possible and the optimal pharmacological approach to treat these disorders should target both dimensions effectively. However, somewhat specific treatments are not ruled out, e.g., opioid antagonists as adjunctive particularly for borderline personality disorder.

It is the clinical impression of some experts that anger-related disorders have been growing in prevalence more than the changes in diagnostic issues can explain. We speculate that the presence of higher environmental stimulation in modern societies may play a role, since environmental enrichment in rats increases anger-related traits as well as consumption of alcohol and a sweet drinking solution (Fernandez-Teruel et al., 2002). However, low functional fertility in individuals with high HA and low NS (Fassino et al., 2002; Steimer and Driscoll, 2005) and [or?] higher sexuality of hyperthymic individuals could be a contributing factors driving for selection of 'stronger temperaments'.

## 8. Relevance for development of animal models of mood and behavioral disorders

The present model can also lead to animal models of unipolar and bipolar mood disorders that take into account fear and anger traits. We submit that the natural expression of such traits may better reflect the real biological composite of these disorders than using a genetic knockout model for a selective protein. For example, exploratory behavior of the central arena of an open-field can be used to select high exploratory (low fear and high anger or hyperthymic temperament) from low exploratory mice (high fear and low anger or

depressive temperament), which behave differently in a variety of behavioral and cognitive tasks (Kazlauskas et al., 2005). Importantly, chronic lithium and valproate treatment, as well as chronic stress, have been shown to reduce exploration of this central arena (Rao et al., 1991; Wood et al., 2004), whereas chronic treatment with the SSRI citalopram increases central arena exploration (Kugelberg et al., 2002). This suggests that the exploration of the open-field central arena is also a putative index of mood in animals. Therefore, temperament selection based on exploratory behavior or in specific tasks for fear and anger traits are potentially useful for studying the biological substrates for these disorders and the impact of non-genetic factors. Changes in such exploratory pattern on the open-field or specific behaviors related to fear and anger should also have predictive validity for identification of new drugs. Also, pre-selection of animals according to their temperament may increase sensitivity and specificity for predictive models (Liebsch et al., 1998; Keck et al., 2005).

## 9. Concluding remarks

The present bidimensional model based on fear and anger traits offers a synthetic framework to be used in parallel with current or future categorical approaches. This model predicts the range of disorders that may be interconnected and their response to a given pharmacological strategy. Thus, this model may offer a paradigm in which mood, behavioral and personality disorders can be studied in an integrated manner, contrary to the present diagnostic classifications. The focus on temperament, which is relatively stable, also has the advantage of minimizing the confounding effect of time, since patients often develop new psychiatric disorders or recover as they grow older (e.g. a bulimic patient who develops bipolar II disorder and later, pathological gambling or alcohol abuse, but recovers from bulimia) according to their basic diatheses. Also, the severity of clinical presentations and the number of comorbidities may be predicted by severity of temperamental dysregulation. This model is particularly useful to understand patients often missed by current approaches, who have both high anger and fear traits, and may suffer from various mood and behavioral symptoms.

This bidimensional concept also provides a framework to be tested regarding pharmacological interventions, with particular relevance for combined therapy. Rather than producing only superficial symptomatic relief, psychopharmacological treatment can be regarded as targeting deficient or excessive fear or anger traits, leading to more balanced temperaments as seen in mentally healthy individuals.

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