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From high anxiety trait to depression: a neurocognitive hypothesis

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Although exposure to substantial stress has a major impact on the development of depression, there is considerable variability in the susceptibility of individuals to the adverse effects of stress. The personality trait of high anxiety has been identified as a vulnerability factor to develop depression. We propose here a new unifying model based on a series of neurocognitive mechanisms (and fed with crucial information provided by research on the fields of emotion, stress and cognition) whereby individuals presenting a high anxiety trait are particularly vulnerable to develop depression when facing stress and adversity. Our model highlights the importance of developing prevention programs addressed to restrain, in high anxious individuals, the triggering of a dysfunctional neurocognitive cascade while coping with stress.

Introduction

Individual differences in personality traits have been associated with both resilience to stress and stress-induced depression [1]. In particular, strong evidence highlights high anxiety trait as an important risk factor for the development (onset, severity and outcome) of depression [2,3]. However, it is not yet clear which are the mediating mechanisms, processes and factors whereby an individual with a highly anxious personality eventually evolves into clinical depression. To address this question it is important to also bear in mind that there is a considerable comorbidity between depression and anxiety disorders (~40–60%) [4] that seems to follow a temporal relationship, with anxiety disorders tending to precede the onset of depressive disorders and probably increasing the risk for subsequent depression [5].

Recent work suggests that the etiological factors (i.e. genetic and environmental) that influence high anxiety trait are the same as those that increase susceptibility for anxiety disorders and major depression (for review, see Ref. [3]). Two etiological hypotheses can account for such a picture: (i) that high anxiety trait, anxiety disorders and major depression are all directly caused by common etiological factors without necessary interrelations among themselves (Figure 1a); or (ii) that the etiological factors lead to high anxiety trait, which, in turn, predisposes to anxiety disorders and depression, contemplating the possibility that the first occurrence of anxiety disorders facilitates the triggering of depression; this hypothesis also accounts for situations in which depression is directly developed from high anxiety trait (Figure 1b). Whereas the first hypothetical model proposes a direct link between etiological factors and the vulnerability to develop depression, the second model puts forward the personality trait of high anxiety as the vulnerability phenotype that mediates subsequent psychopathological developments. Given that substantial evidence indicates that high anxiety trait is a vulnerability factor to develop not only depression but also anxiety disorders [2,3,6], and that anxiety trait, therefore, might mediate some of the elevated comorbidity between anxiety disorders and depression [7], we argue in favor of the etiological model represented in Figure 1b and against the model based on a parallel causation as represented in Figure 1a. However, the model in Figure 1b implies a 'deterministic' link between high anxiety trait and the development of depression, which is at odds with emerging information emphasizing the modulatory role of stressful life events, which we reflect in the expanded model presented in Figure 2.

Although the discovery of risk factors (e.g. genetic, personality and stress) is essential to progress on the understanding of depression, it does not explain, by itself, what mechanisms mediate vulnerability to develop the disorder and its progression. Very active research in recent years has identified essential elements (e.g. neurocognitive patterns and neuroendocrine alterations) that, although representing important milestones in the field, only provide partial explanations for the understanding of how high anxiety trait predisposes to depression. Likewise, intensive work on the intricate interactions between emotion, stress and cognition has provided, in turn, important hints about the key role of such interactions for the development of depression. However, this information has so far remained rather fragmented and no unifying theory has as yet been offered.

Here, we propose a unifying model that integrates major progress on converging but independent research fields and proposes a trajectory whereby individuals presenting the vulnerability trait of high anxiety can eventually develop depression. We first go through the major neurocognitive and neuroendocrine hallmarks of depression to then examine the essential factors in high anxiety trait that promote the transition from the phenotypic predisposition provided by the personality trait to the dysfunctional alterations linked to depressive psychopathology.

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0166-2236/$ – see front matter doi:10.1016/j.tins.2009.02.004 Available online 4 May 2009

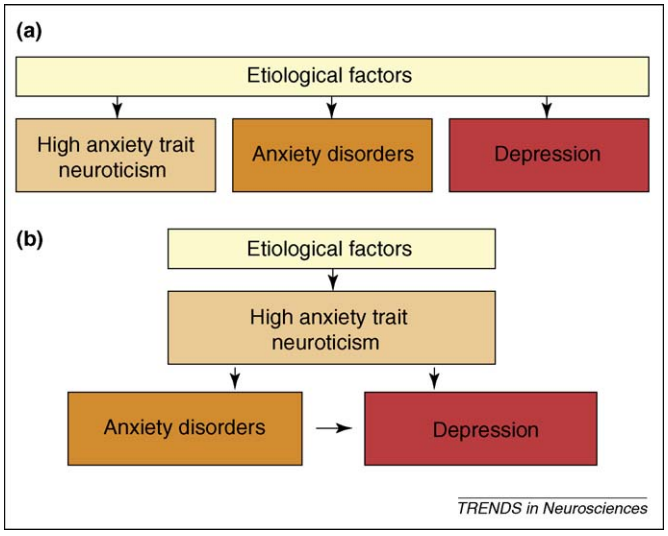

Figure 1. Alternative etiological hypotheses for the development of depression. **(a)** According to this hypothesis, high anxiety trait, anxiety disorders and major depression are all directly caused by common etiological factors without any requirement for causal influences between the personality trait of anxiety and mood and anxiety disorders. **(b)** The second hypothesis proposes a first causal relationship between certain etiological factors and the development of the personality trait of high anxiety; in turn, this personality trait will be a vulnerable phenotype for the development of depression, either directly or via a first development of an anxiety disorder. Our model is based on this second etiological hypothesis.

Because exposure to stressful life events is a central element of the model, the latter is fed with essential information provided by research in the fields of emotion, stress and cognition, with a particular emphasis on an escalation of neuroendocrine and cognitive dysfunctions. The resulting neurocognitive model (Figure 3) enables the making of specific, testable predictions about which could be the most relevant therapeutic interventions at the different steps of the trajectory from high anxiety trait to depression.

Neurocognitive and neuroendocrine hallmarks of depression

Mood disturbances have been traditionally emphasized as core symptoms in depression, whereas cognitive alterations are considered to be simply epiphenomena (i.e. of age, poor motivation, inattention or response bias). However, this traditional view has been challenged by recent suggestions that cognitive deficits are intrinsic expressions of the brain changes occurring in depressive illness [8] and by evidence showing that depression severity is correlated with the magnitude of cognitive deficits under some psychopathological conditions [9].

In fact, cognitive theories of depression have proposed now for some time [10] that negative cognitions are essential for the etiology and progression of the disorder. Cognitive disturbances in depressive patients are characterized by (i) enhanced negative cognitions (i.e. mood-congruent biases, which are related to a predisposition to form and particularly retrieve memories for negative information) and (ii) several cognitive deficits (in attention, executive function, working memory, and in both the short- and long-term memory formation) that might be instrumental for the expression of depression [8,11].

Another important feature in depression is a dysregulation of the hypothalamus–pituitary–adrenocortical (HPA) axis [12]. Many depressed subjects display enhanced cortisol secretion as a consequence of an overactive HPA axis [13], and enhanced activity of corticotropin-releasing-factor (CRF) systems in limbic regions has been related with increased depression-like symptomatology [14].

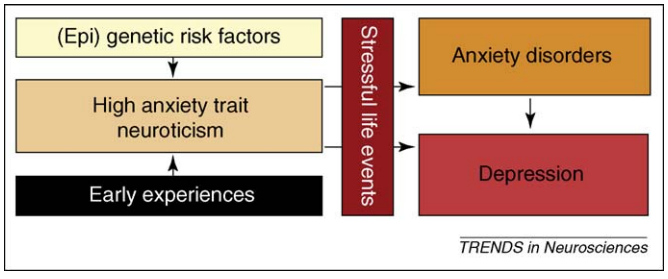

Figure 2. From high anxiety trait to depression: the etiological model. This figure depicts the factors that, according to our model, should converge for increased vulnerability to develop depression. Etiological factors [(epi)genetic and environmental (mainly early experiences)] first have a key role in defining the high anxiety trait phenotype. This personality trait confers a psychobiological vulnerability but does not necessarily cause, by itself, depression. The convergence of major stressful events will be the trigger (required factor in our model) that leads with a higher propensity in high anxious individuals than other personality types to develop depression, either directly or via a first development of an anxiety disorder.

Neurocognitive characteristics of high anxiety trait

Recent progress on the characterization of the neurocognitive profile corresponding to high anxiety trait reveals important neuropsychological features [15] that can partly explain why this trait represents a vulnerable phenotype to develop depression.

At the cognitive level, highly anxious individuals show a distinctive cognitive style characterized by alterations in the processing of threat, including bias in selective attention towards threat-related stimuli, interpretation of emotionally ambiguous stimuli as negative and enhanced fear conditioning responses [15]. Note the similarity between these cognitive alterations and a part of those characteristic of depressive patients, as mentioned in the previous section. In anxiety disorders, neuropsychological deficits have been reported at the level of executive function, attention, working memory and new learning [11].

At the level of functional neural dynamics, emphasis has concentrated on two types of abnormalities presented in high anxious subjects while processing emotional information: one related to the activation of the amygdala and the second related to amygdala coupling with other brain structures.

Neuroimaging studies initially observed a particular sensitivity of the amygdala to be activated when individuals from the general population are confronted with emotionally arousing material, with activation intensity correlating with the emotionality rate given to the material [16,17]. Other sets of studies also noted enhanced amygdala activation when individuals were exposed to unattended, masked or perceptually suppressed threat-related stimuli, implicating the amygdala in the rapid preattentive detection of threat [15,18]. In both research lines, studies relied on group analyses and, therefore, suggested that amygdala activation is a response usually shown