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COMMENTARY TO SPECIAL ARTICLE

Neurotic depression as the missing link: old wine with a new twist on anxiety and major depressive disorder

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The findings in this study about anxiety and depression from Kessler and colleagues extend and reinforce an important association with profound clinical and neurobiological implications. They found that lifetime anxiety disorders and their persistence predict the persistence of major depressive disorder (MDD). Additionally, the development of anxiety disorders temporally preceded the development of MDD in two-thirds of respondents, signifying anxiety as a potential important risk factor for the development of MDD. As noted by Kessler and colleagues, the prospective associations between temporally precedent anxiety disorders and subsequent development of MDD can be parsimoniously explained by a common latent internalising variable. This latent variable can be best described as neuroticism (Barlow *et al.* 2014*b*). Thus, these epidemiological findings may be reflective of a core neurotic syndrome that underlies anxiety and mood disorders with profound effects on fundamental aspects of emotion perception, processing and regulation (Barlow *et al.* 2014*a*).

The neurotic syndrome has been defined as 'the propensity towards increased emotional reactivity, coupled with a heightened tendency to view these experiences as aversive and attempts to alter, avoid, or control emotional responding' (Farchione *et al.* 2012). Another way to think about the neurotic syndrome is that information is more often interpreted as negatively valenced than positively valenced, preferentially activating brain networks subserving salience processing. Furthermore, that activation persists because of increased activation of negative memories along with a decreased ability to forget the negative information, preventing the decay of the negative stimuli, and forming a ruminative loop (Holtzheimer & Mayberg, 2011). In response to the ruminative loop, people use a range of strategies to cope with their response, some of which may be more adaptive (e.g. mindful meditation or exercise) with others less so (e.g. substance abuse or excessive distraction). All you have to do is recall the pain of the loss of your first romantic relationship to appreciate the pain of rumination and the blessing of forgetting.

On a molecular level, this 'forgetting' may be dependent on brain-derived neurotrophic factor (BDNF), necessary for neurogenesis in the hippocampus. (Akers *et al.* 2014) Of note, persistent stress and anxiety have been shown to directly affect Hypothalamic-Pituitary-Adrenal-axis functioning with neurotoxic effects on neurogenesis in the hippocampus, a possible precursor of depression. Thus, addressing anxiety, stress reactivity and emotion regulation may have protective effects on the subsequent development of depression. Indeed, gene expression of BDNF is increased by antidepressants, representing a possible core mechanism of antidepressant treatment effect (Malberg *et al.* 2000; Sen *et al.* 2008). Neurogenesis appears to be a key process in the ability to separate patterns in memory – e.g. to be able to discriminate between a stimulus now (a loud noise) and a memory of a loud sound from gunshots during a traumatic war experience. Deficient or failed pattern separation results in memory overgeneralisation (Clelland *et al.* 2009; Sahay *et al.* 2011; Yassa & Stark, 2011). Forgetting may also be essential for fear extinction, i.e. the ability

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to stop reacting to a previously aversive stimulus when the stimulus is subsequently not paired with the aversive stimulus (Milad *et al.* 2014) Another way to think of fear extinction is that it becomes difficult for someone to learn that something that previously induced fear is no longer a threat, and to essentially consciously 'forget' these stimulus response associations (although these associations are never fully 'forgotten') and have the ability to be reactivated, they nevertheless become less activated following successful extinction learning, a process shown to be deficient in mood and anxiety disorders. Since the neurotic syndrome includes *persistent* hyper-emotional reactivity that people experience as aversive, and aversive stimulus-response associations are continually reactivated, then the slings and arrows of daily life could be experienced as a series of unending aversive stimuli in the here and now as well as evocative of an extensive set of past experiences. Indeed, learned helplessness models of depression suggest depression may represent a sort of shutting down when no other option for relief from anxiety and stress is available.

On the level of functional brain circuitry, information (cognitive) processing is intimately integrated with emotional processing (Pessoa, 2008). Thus, if what is capturing one's attention (attentional network) and what is seen as important in one's environment (salience network) is tilted proportionally more towards negatively than positively valenced information, then the world can appear as a place full of past, current and future threat. Furthermore, the inability to flexibly and adaptively switch between salience processing (salience network), internal processing (default mode network) and goal-directed executive processing (executive control network) may lead to rigid, 'stuck' patterns of emotional processing like rumination and worry. If one has an impaired ability to try to change one's perception through rebalancing internal and external inputs with new information using executive control functions, then one's subjective experience becomes persistent negative emotional flooding. Antidepressants might bring incomplete relief to those who experience the pain of anxiety and depression, in part, by decreasing the resting state hyperfunctional connectivity between the amygdala and key nodes of the default-mode network subserving rumination that is found with MDD. (McCabe & Mishor, 2011) In contrast, when exposed to fearful faces, antidepressants increase coupling between the amygdala and regions of the prefrontal cortex important for cognitive control of emotion, as well as striatum and thalamus, important structures for reward processing (Harmer & Cowen, 2013) Thus antidepressants may function to reduce the impact of subjective emotions on executive function, thereby providing some relief to the neurotic syndrome. Indeed, successful treatment with antidepressants has been shown to directly interact with neurotic temperamental variables (Soskin *et al.* 2012). But if the antidepressants fail to shift the fundamental emotional dysregulation of the neurotic syndrome, then threat, fear and anxiety will persist, along with the experience of persistent stress – consistent with findings that anxious depression is less responsive to antidepressant than non-anxious depression.

Developing treatments that can directly target the common, core deficits in cognitive and emotion processing and emotion dysregulation that are key features of a neurotic syndrome, as opposed to targeting discrete anxiety and depression symptoms, may ultimately help to ameliorate anxiety and mood disorders. Farchione and colleagues found that overall distress and emotion dysregulation improved in patients with a range of comorbid anxiety and mood disorders using a transdiagnostic cognitive behavioural (CBT) intervention, the unified protocol (UP). The UP was developed to address maladaptive emotion processing across anxiety and mood disorders by targeting reactions to internal and external emotion stimuli and maladaptive attempts to regulate these experiences. Existing, overlearned associations between emotion-related stimuli and learned patterns of perceptions, thoughts and behaviours are identified, and maladaptive emotion regulation strategies are replaced with more adaptive strategies. In this way, new associations between emotions, cognition and behaviour are learned. (Ellard *et al.* 2010). Thus, transdiagnostic CBT can be conceptualised as retraining the flexible switching between executive control and salience processing and providing a broader range of information into constricted and constrained brain networks. As a result, transdiagnostic CBT may help to rehabilitate the maladaptive emotional reactivity inherent in the neurotic syndrome.

One of the clinical implications of Kessler and colleagues' findings is that for those with persistent depression, psychopharmacologic and psychotherapeutic interventions that address comorbid anxiety might be helpful. But perhaps more importantly, interventions that address the underlying features subserving anxiety and depression, constituting a core neurotic syndrome, may ultimately prove more beneficial.

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