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Review Article

Nested positive feedback loops in the maintenance of major depression: An integration and extension of previous models

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ABSTRACT

Several theories of Major Depressive Disorder (MDD) have previously been proposed, focusing largely on either a psychological (i.e., cognitive/affective), biological, or neural/computational level of description. These theories appeal to somewhat distinct bodies of work that have each highlighted separate factors as being of considerable potential importance to the maintenance of MDD. Such factors include a range of cognitive/attentional information-processing biases, a range of structural and functional brain abnormalities, and also dysregulation within the autonomic, endocrine, and immune systems. However, to date there have been limited efforts to integrate these complimentary perspectives into a single multi-level framework. Here we review previous work in each of these MDD research domains and illustrate how they can be synthesized into a more comprehensive model of how a depressive episode is maintained. In particular, we emphasize how plausible (but insufficiently studied) interactions between the various MDD-related factors listed above can lead to a series of nested positive feedback loops, which are each capable of maintaining an individual in a depressive episode. We also describe how these different feedback loops could be active to different degrees in different individual cases, potentially accounting for heterogeneity in both depressive symptoms and treatment response. We conclude by discussing how this integrative model might extend understanding of current treatment mechanisms, and also potentially guide the search for markers to inform treatment selection in individual cases.

Contents

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1. Introduction

Major Depressive Disorder (MDD) is one of the leading causes of illness-induced disability worldwide (Ferrari et al., 2013). The psychological and biological bases of MDD, and of MDD treatment modalities, have therefore been the focus of considerable research. More recently, computational neuroscience has also offered insightful ways of potentially linking biological abnormalities observed in MDD with their perceptual, cognitive, and behavioral consequences (Friston et al., 2014; Huys et al., 2015a). In this article, we will first review existing empirically supported cognitive, neural, and computational theories of MDD. We will then focus on recent work examining interactions between brain and body in depression. We will illustrate how looping interactions between brain and body – associated with stress, autonomic reactivity, and inflammation – reinforce and extend current cognitive and computationally focused neural models. We will then highlight the plausible relations between these theories, and attempt to integrate them into a coherent multi-level model of how a depressive episode is maintained. Finally, we will conclude by presenting an integrative "nested positive feedback loop" model of the maintenance of major depression that synthesizes previous cognitive-, computational-, and biological-level thinking on MDD, and show how this integrative model can advance current thought via clarification of the plausible relations between these different levels of description.[1]

It is important to highlight, however, that the diagnostic category of MDD permits a substantial degree of heterogeneity (Diagnostic and Statistical Manual of Mental Disorders, 2013). For example, some individuals with MDD may exhibit anhedonia, while others exhibit sad or dysphoric mood, while yet others will exhibit both. Further, a person with MDD might exhibit either weight loss or weight gain (or neither), and might show sleep disturbance as either insomnia or hypersomnia (or they may show no sleep disturbance). In total, one need only to possess five out of the nine symptoms diagnostic of MDD (where one must be either anhedonia or sad/dysphoric mood) in order to count as having the disorder. Beyond diagnostic criteria, recent research has also clarified that there are sub-groups of individuals with depression that demonstrate biological phenomena not present in others (e.g., increased inflammation, distinct patterns of functional connectivity between brain regions; Felger et al., 2016), and that such individuals may also respond best to distinct treatment options (Miller and Raison, 2015; Raison et al., 2013). Due to such heterogeneity, and associated consequences, the extent to which MDD represents a "natural kind" has been questioned (Widiger and Samuel, 2005; Zachar, 2000). Further, many of the studies we review below have not taken this heterogeneity into account in their analyses, but instead simply compare groups of healthy and depressed individuals. As such, in this review we will first treat MDD as though it were a coherent category, and highlight several related processes that may act to support/maintain the cluster of symptoms it represents. It should be understood, however, that not all aspects of the models of MDD we describe apply equally to every individual with depression. Therefore, later in the review, when explicitly discussing our integrative model and its implications, we will then highlight the various model elements that may account for sources of this heterogeneity. We will ultimately describe how, despite the fact that many of the mechanisms we outline interact with one another, differences in the relative degree to which each is present/active may account for differences in individual symptom profiles.

2. The cognitive model of depression

The cognitive model of MDD has emphasized depressive schemas (Beck, 1967); these can be thought of as maladaptive, pessimistic sets of beliefs/expectations that bias perceptual/conceptual interpretations of new sensory input, as well as the subsequent predictions, judgments, and decisions these interpretations inform. Such theories therefore appeal to a strong top-down influence of prior beliefs/expectations to explain depressive symptoms; they have also inspired a range of cognitive/behavioral therapeutic approaches designed to modify these beliefs (e.g., J. Beck, 2011).

The cognitive model suggests that negative self-referential beliefs, often acquired from adverse events in early life, may be a particularly important set of schemas that create vulnerability to depression (when they are activated by a subsequent stressor). However, it is important to highlight that MDD is associated with negative expectations unrelated to the self as well (e.g., Miranda and Mennin, 2007). Such pessimistic beliefs/expectations, when used to guide attention, memory retrieval, decision-making, and interpretation of new sensory input, are thought to lead to multiple related information processing biases that are capable of both initiating and maintaining a depressive episode. First, new perceptual input will be more likely to be interpreted negatively. Second, the memories one retrieves may be more likely to include those with negatively valenced content. Third, both internal/cognitive deci-

[1] It should be highlighted that MDD is a complex disorder that includes a number of different processes/stages: (i) the onset of a depressive episode, (ii) the maintenance of a depressive episode, (iii) the spontaneous remission of a depressive episode, (iv) the remission of a depressive episode due to targeted treatment, and (v) the recurrence of a depressive episode. In order to keep the present manuscript manageable in scope, we will here focus specifically on the different factors that can maintain a depressive episode, and their implications for patient-specific treatment options. The mechanisms that lead to onset, reoccurrence, and spontaneous remission of MDD will only be briefly discussed as they relate to the multiple maintenance processes that we focus on.

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