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Helplessness: A systematic translational review of theory and evidence for its relevance to understanding and treating depression

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ABSTRACT

Helplessness is a major concept in depression and a major theme in preclinical and clinical depression research. For example, in rodents and humans, the learned helplessness (LH) effect describes a specific deficit in behaviour to control aversive stimuli that is induced by prior exposure to uncontrollable aversive stimuli. The LH effect is objective and valid in that the cause of the behavioural deficit, namely uncontrollability, is clear; furthermore, the deficit induced is underlain by emotional, motivational and cognitive processes that are relevant to depression psychopathology. As a further example, helplessness, hopelessness, external locus of control and causal attribution are inter-related and major themes in psychological theories (primarily cognitive theories) of depression. Despite this broad interest in helplessness, it can be argued that its potential usefulness as a scientific and clinical concept has so far not been investigated optimally, including with respect to its application in research aimed at development of improved anti-depressant pharmacotherapy. The first aim of this review was to describe and integrate the psychological evidence and the neurobiological evidence for the LH effect in rodents and healthy humans and for helplessness in depressed patients. The second aim was to conduct three systematic reviews, namely of rodent studies of the LH effect, rodent studies of effects of psychopharmacological agents on the LH effect, and human studies of efficacy of pharmacotherapeutic and psychotherapeutic treatment on helplessness in depressed patients. With respect to the first aim, the major findings are: the specificity of the LH effect in otherwise non-manipulated rodents and healthy humans has been under-estimated, and the LH effect is a specific learned aversive uncontrollability (LAU) effect. There is theoretical and empirical support for a model in which a specific LAU effect induced by a life event of major emotional significance can function as an aetiological factor for generalised helplessness which can in turn function as an aetiological and maintenance factor for depression. However, to date such models have focused on cognitive mediating processes whereas it is emotional–motivational–cognitive processes (as proposed for the LAU effect) that need to be invoked and understood. The evidence is for analogous neural processes underlying the LAU effect in rodents and healthy humans and helplessness in depression, with the ventro-medial prefrontal cortex exhibiting aversive uncontrollability-dependent activity. With respect to the second aim, the major findings are: the LAU effect is demonstrated quite consistently using a number of different paradigms in rat but is poorly studied in mouse. The rat LAU effect can be reversed by chronic administration of monoamine reuptake inhibitors. The effects of antidepressants on human helplessness have been scarcely studied to-date. The major conclusion is that the LAU effect and generalised helplessness constitute major neuropsychological concepts of high value to future translational research aimed at increased understanding of depression and development of novel, improved antidepressant treatments.

Contents

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1. Introduction

1.1. Background

Mood disorders, especially unipolar depressive disorders, such as major depressive disorder (MDD) and dysthymia, are among the most prevalent mental disorders (Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005; Kessler, Demler, et al., 2005). They place substantial burden on individuals with these disorders and on society (Lopez et al., 2006), and their prevalence is still increasing (Mathers & Loncar, 2006). Moreover, whilst mental disorders are strongly associated with suicidal behaviour worldwide, mood disorders are the strongest predictor of suicide ideation and attempts in developed countries and suicide is among the leading causes of death (Fawcett et al., 1990; Nock et al., 2008; Nock et al., 2009). MDD is more common in women than in men, although the gender difference is decreasing as gender roles become more equable in society (Seedat et al., 2009). Depressive disorders affect individuals across all age groups, including children (Merikangas et al., 2010) and the aged (Byers et al., 2010; Kessler, Birnbaum, et al., 2010).

In the majority of cases, depression shows a high rate of recurrence and substantial chronicity, indicating that the disorder is frequently not treated adequately (Gonzalez et al., 2010). Even in a primary care setting, only about one-quarter of identified patients with MDD achieved and maintained full remission for 18 months, whilst another quarter failed to remit at all. The remaining patients suffered either from residual symptoms or recurrences during follow-up (Vuorilehto et al., 2009). Randomised clinical trials show some efficacy of several types of interventions, including cognitive behavioural therapy or selective serotonin reuptake inhibitors (Gelenberg et al., 2010). However, given the substantial percentage of subjects who do not respond to treatment or who relapse after treatment discontinuation (Gelenberg et al., 2010), a better understanding of the psychopathology and pathophysiology, and their bi-directional interaction, of depressive disorders is essential. In turn, this should facilitate new and more efficacious preventative and therapeutic treatments (Belmaker & Agam, 2008).

Major depressive disorder presents as a disorder of feelings, thoughts and somatic functions that debilitate daily functioning and, as stated above, can be life threatening. The symptoms are heterogeneous and include emotional, cognitive and somatic dysfunctions that are used to make a nosological diagnosis. As for other mental disorders, two nosological classification systems exist for depression, and these are the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition, text revision (DSM-IV, 1994) and the International Classification of Diseases (ICD), 10th edition, chapter V: Classification of Mental and Behavioural Disorders (ICD-10, 1994). Both DSM and ICD recognise several forms of depressive disorder and grades of severity within these forms. According to DSM, MDD is the most common form of depression, and an approximate equivalent of MDD in ICD is (recurrent) depressive episode. According to DSM, MDD will be diagnosed if the clinical course is one or more major depressive episodes, with each such episode characterised by five (or more) symptoms during a minimum 2-week period, where at least one of the symptoms is either depressed mood (sadness, emptiness) or anhedonia (loss of interest or pleasure in (almost) all activities). According to ICD-10, (recurrent) depressive episode will be diagnosed if the clinical course is one (or more) episodes during a minimum 2-week period of at least two of three typical/core symptoms i.e. depressed mood, loss of interest and enjoyment, reduced energy leading to increased fatigability and diminished activity, and at least three (preferably four) common symptoms.

Based on describable and observable symptoms, the DSM and ICD nosologies allow for relatively clear diagnosis of and communication about MDD. However, the clinical entity MDD is not based on its neuropsychopathology, i.e. the changes in psychological processes, brain circuitry, and inter-cellular and intra-cellular brain functions, which causally underlie the symptoms of MDD. As such, there is incompatibility between the current diagnostic system and psychological and neurobiological research that would aim to increase understanding of MDD neuropsychopathology and, based on this, could lead to development of novel, improved treatments. Commensurate with this problem, some integration of the focus on specific symptoms and their underlying pathology — a dimensional diagnostic approach — is under consideration for the upcoming revision of the DSM (Hyman, 2007). Clearly, integration and translation across a number of disciplines in the clinical, social and biological sciences is needed to achieve the goal of a neuropsychopathology-based system of diagnosis and treatment in psychiatry.

The core/typical symptoms of depression can be viewed as disrupted emotional–motivational–cognitive states. Emotions e.g. sadness, helplessness, grief, relief, pleasure, are distinct psychological states that vary in intensity and that arise in response to environmental stimuli or events that are either aversive or rewarding, as processed by the brain's punishment system and reward system (Rolls, 2000). The punishment system and reward system are the bases of emotions, and emotions are the bases of mood; therefore, the punishment and reward systems are also the bases of mood. Cognitive processes enable the individual in her/his emotional categorisation of environmental stimuli/events, and also allow an environmental event to be re-experienced, or ruminated on, in the absence of its physical presence. The MDD core symptom of depressed mood therefore constitutes dysfunction(s) in the brain's punishment system, that manifests as chronic hyper-sensitivity to aversive events and is associated with symptoms/states such as sadness, pessimism, helplessness (Elliott et al., 2002). The MDD core symptom of reduced interest and pleasure constitutes dysfunction(s) in the brain's reward system that manifests as chronic hypo-sensitivity to rewarding events (Haber & Knutson, 2010). In this sense, MDD shifts from an absolute, abnormal emotional–cognitive nosological entity, to several emotional–cognitive states that are each at the extreme end of their continuous distribution (Hyman, 2007).

Emotional–cognitive assessment of environmental stimuli/events is not absolute, neither within individuals across time nor between individuals. For each individual, the emotional response to a stimulus/event is determined by: his/her alleles for genes that regulate emotional responsiveness (Pezawas et al., 2005); the expression levels of these alleles and their products in the specific brain regions that contribute to emotional–cognitive circuits (Choudary et al., 2005); and his/her life history with respect to prior emotional experiences (Caspi & Moffitt, 2006; Jacobs et al., 2006). Thus, the extent to which an aversive stimulus