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The cognitive neuropsychological model of antidepressant response

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It has been hypothesised that, at a neuropsychological level, the direct action of antidepressants is to remediate negative biases in affective processing and that these actions occur early in treatment prior to an improvement in mood. Here we discuss the latest evidence for the cognitive neuropsychological model of antidepressant response as well as the clinical applications and limitations of the model. The majority of research has been conducted using antidepressants predominantly affecting serotonin or noradrenaline activity. Future research must focus on replicating these effects in larger samples with antidepressants influencing different neurotransmitter systems, such as dopamine and glutamate.

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1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and is associated with substantial disability. MDD accounted for 4.4% of total disability adjusted life years in 2000 and is predicted to become the second leading contributor to global disease burden by 2020 [1]. This burden is exacerbated by limitations in current understanding of and treatments for MDD. Among outpatients starting first-line antidepressant treatment for MDD, approximately only half will respond and only one third will achieve remission [2,3]. Therefore, the development of more broadly effective or patient-specific treatment strategies should be a priority.

The acute neuropharmacological actions of antidepressants are now well characterised, with the majority acting to enhance either serotonin (5-HT) and/or noradrenaline (NA) neurotransmission. Whilst these actions are detectable immediately after the administration of an antidepressant, repeated administration over a number of weeks is required before a clinically important therapeutic effect is observed. It is thought that this delayed onset of clinical effect is the result of a cascade of downstream neuroadaptive changes, such as downregulation of 5-HT or NA transporters or desensitisation of 5-HT or NA autoreceptors [4,5]. More recently, the focus has been on antidepressant-induced activation of second messengers and subsequent changes in gene expression leading to increased production of neurotropic factors with roles in synaptic plasticity and hippocampal neurogenesis, such as brain-derived neurotropic factor (BDNF) [6–10]. However, these purely neurobiological models of antidepressant response are limited in that they cannot explain how these actions relate to an improvement in mood and overall symptomatic relief [11,12]. Indeed, antidepressants do not elevate mood in healthy individuals [13•,14] and psychostimulant drugs that act to immediately elevate mood have no clinically important therapeutic effect in depressed individuals [15] suggesting that antidepressants may not be acting as direct mood enhancers.

Therefore, this review summarises recent evidence for the cognitive neuropsychological model of antidepressant response, which, through the integration of the neuropharmacology and cognitive psychology of MDD, could provide the missing link between the acute neuropharmacological actions of antidepressants and mood improvement.

2. The cognitive neuropsychological model of antidepressant response

It has been hypothesised that, at a neuropsychological level, the direct action of antidepressants is to remediate negative biases in affective processing, that is, the tendency to extract negative rather than positive affective information from a variety of social and affectively valenced stimuli, and that these actions occur early in treatment prior to an improvement in mood [16–18,19•]. The importance of such negative affective biases in the aetiology and maintenance of MDD has long been known and they are believed to critically fuel the low mood and negative views about oneself, the world and the future observed in MDD [20].

2.1. The role of negative affective biases in depression

Numerous studies have shown that both MDD patients [18•,21–23] and those at high risk for MDD [18•] reliably

display negative biases in both emotional and reward processing across a range of cognitive domains. MDD patients tend to perceive ambiguous information as negative, preferentially attend to negative affective information and better recall negative information. For example, in a facial expression recognition task, MDD patients are more likely to interpret ambiguous facial expressions as negative, whilst their sensitivity to happy facial expressions is reduced [24]. MDD patients also display an attentional bias towards negatively valenced words or faces, which may represent a difficultly in disengaging attention from negative affective information [25,26]. Finally, following encoding of self-descriptive words in a classification task, MDD patients have a tendency to recall negative rather than positive self-descriptive words [27].

Such negative affective biases in MDD have been shown to be associated with aberrant activity in limbic and striatal circuitry involved in the initial appraisal and memory of affective stimuli [22,28]. For example, MDD patients exhibit exaggerated activity within the amygdala, ventral striatum and insula in response to negative facial expressions [29–33] and reduced activity within the amygdala, thalamus, putamen and hippocampus to positive facial expressions [34,35]. A similar pattern is also observed in extrastriate brain regions involved in attention and higher-order control of affective processing, such as the fusiform gyrus and the ventromedial prefrontal cortex [32,34]. Reduced neural activity, particularly in the anterior cingulate cortex, has consistently been shown to be predictive of treatment response [36].

MDD patients have also been shown to display aberrant responses to reward, punishment and performance feedback [37,38]. For example, MDD patients display blunted responsiveness to both anticipated reward and actual reward outcomes [39–41] but respond catastrophically to negative performance feedback [42–44]. This results in a failure to adjust performance following positive or negative feedback in order to maximise reward or minimise the risk of further error, respectively, as measured by trial-by-trial adjustment of reaction time (RT) [45,46]. These effects are associated with reduced function in frontostriatal systems, such as the orbitofrontal cortex, anterior cingulate and ventral striatum, including the nucleus accumbens, in depressed [45,47–50], remitted depressed [51] and at risk individuals [52••]. Furthermore, these behavioural and neural abnormalities have been found to correlate with Hamilton Depression Rating Scale [53], severity of self-reported anhedonia [45,46,54] and treatment response [55,56••].

Negative affective biases have been found to be associated with relapse [57] and exhibited by individuals at high risk of MDD by virtue of high neuroticism [58–60] and family or personal history of MDD [61–64]. Low reward sensitivity has also been found to predict the subsequent development of MDD symptoms one year after testing [65•]. Therefore, negative affective biases appear to play a role in the vulnerability to and aetiology of MDD rather than simply being a secondary consequence of low mood.

2.2. The effects of antidepressants on affective processing

The repeated, subchronic and acute effects of antidepressants on affective processing have been extensively assessed in healthy volunteers and MDD patients [16–18,19•].

Subchronic (7 day) antidepressant treatment has been found to increase processing of positive affective information in healthy volunteers. For example, 7 days treatment with the serotonin reuptake inhibitor (SSRI) citalopram or the serotonin and norepinephrine reuptake inhibitor (SNRI) reboxetine increased the recall of positive self-descriptive words and the propensity to perceive ambiguous facial expressions as happy [66]. Even a single administration of citalopram [13•] or reboxetine [67] has been found to be sufficient to increase the recognition of happy facial expressions. Subchronic or acute treatment with either citalopram or reboxetine also results in associated neural alterations, including attenuated amygdala responses to aversive stimuli [68–71], increased fusiform responses to happy vs neutral facial expressions [70] and increased or decreased frontoparietal activity during classification or recognition of positive vs negative self-descriptive words, respectively [72,73]. Importantly, all of these effects of antidepressants on affective processing occur in the absence of any significant changes in subjective mood.

A single administration of reboxetine has also been shown to restore the normal balance of positive to negative processing in facial expression recognition and the recall of self-descriptive words in MDD patients in the absence of any changes in subjective mood [74•]. The majority of functional neuroimaging studies conducted in MDD patients have investigated the long-term effects of antidepressant treatment. For example, 8 weeks treatment with the SSRI fluoxetine in MDD patients normalises hyperactive amygdala, ventral striatal and frontoparietal cortical responses to negative affective information [29,30]. Treatment with the SNRI venlafaxine for 8 weeks also normalises hypoactive anterior cingulate responses to negative affective information [75]. Repeated SSRI treatment can also normalise hypoactive responses to positive affective information [35,76]. Due to the long-term nature of these studies, it has not been clear whether these effects of antidepressants on neural activity occur prior to mood improvement in MDD patients. However, it has since been demonstrated that whilst both placebo-treated and escitalopram-treated MDD patients display similar HAM-D scores at 7 days, such short-term escitalopram