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The neuroscience of depressive disorders: A brief review of the past and some considerations about the future

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Abstract

Depression is a common and debilitating mental health condition whose underlying aetiology and pathophysiology is still relatively poorly understood. In this article, we first turn to the past and briefly review what neuroscientific investigations have taught us so far about depression. In doing so, we cover neurochemical, neuroendocrine, immunological, functional and structural anatomical, and cognitive levels of description. We then turn our attention to the future and discuss where the field might be moving in the years to come. We argue that future developments may rely on three important lines of enquiry: first, the development of an integrated neuroscientific model of depression and its treatment in which different levels of description can be mechanistically linked, and in which distinct pathophysiological trajectories leading to depressive symptomatology can be identified. Second, the continued search for potentially overlooked pathophysiological factors, especially outside the immediate boundaries of the brain. And third, the improvement in translation of neuroscientific insights to aid and advance clinical practice and research.

Keywords

Depression, antidepressant, neurochemistry, brain imaging, hypothalamic–pituitary–adrenal axis, cognition, emotion

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Introduction

Depressive disorders (particularly their main representative 'major depressive disorder') constitute one of the leading causes of disability worldwide (Friedrich, 2017). Clinically, depressive disorders are characterised by the prolonged presence of specific somatic and cognitive abnormalities in combination with sad, empty or irritable mood, or anhedonia (American Psychiatric Association, 2013).

In the past decades, different lines of neuroscientific enquiry have been pursued in order to better understand the aetiological and pathophysiological factors that contribute to the development and maintenance of depressive symptoms. These research efforts have yielded important insights on multiple levels of description, linking depression with abnormalities in genes, neurotransmitter systems, neuroendocrine systems, functional and structural brain anatomy, and cognition.

In this short essay, we will first turn to the past and briefly review what neuroscientific investigations have taught us so far about depression. Based on this, we then turn our attention to the future and discuss potential lines of enquiry that could take the field forward over the coming years.

Understanding depression: where have we got so far?

Depressive disorders are complex neurobiological conditions, and it is clear now that they are associated with a wide range of physiological and cognitive abnormalities. The large number of pathological features that have been identified in the last decades has stimulated the development of a whole array of (mutually not necessarily exclusive) theories of depression which explain the development of clinical symptoms in terms of dysfunctions on different levels of neuroscientific description.

The neurochemical level of description

From a clinical perspective, the most influential neurobiological discoveries related to depression have probably been neurotransmitter-related ('neurochemical') abnormalities, with the monoamines (serotonin, noradrenaline and dopamine) having received most attention. Early observations of the ability of tricyclic antidepressants to (a) relieve depressive symptoms and (b) potentiate serotonin and noradrenaline activity triggered a wide range of

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neurochemical investigations in patients with depression (Cowen, 2015).

Although first reports of impaired monoaminergic function in depression were rather limited by the methodologies on which they were based (e.g. measurements of the levels of neurotransmitters, their precursors or their metabolites in plasma, cerebrospinal fluid or post-mortem brain tissue), they have more recently been complemented by studies using improved methodologies, such as brain imaging with radiolabelled receptor ligands (Cowen, 2015). It could thus be shown, for example, that depression is associated with decreased serotonin transporter binding in the midbrain and amygdala (Gryglewski et al., 2014), decreased 5-HT1A receptor binding in frontal, temporal and limbic regions (Sargent et al., 2000) and increased density of monoamine oxidase A (Meyer et al., 2006), and all these findings are consistent with the idea of some sort of monoaminergic dysfunction.

Notably, some abnormalities in monoamine function have not only been reported in patients during acute depressive episodes, but also in remission (Cowen, 2015). This observation has led some authors to postulate that they might actually represent the neurobiological correlates of some trait-like vulnerability, or of 'scars' left by previous depressive episodes, rather than representing markers of acute depression (Bhagwagar et al., 2008; Cowen, 2015; Wichers et al., 2010).

Furthermore, studies exploring the effects of experimental manipulations of monoaminergic pathway activity, for example, through restricting the availability of the serotonin precursor tryptophan, report that only those who had previously suffered from depressive episodes or who have a family history of depression develop depression-like symptoms in response to impaired monoamine function (Ruhé et al., 2007). The inability to induce depression in those without a vulnerability to the disorder thus suggests that impaired monoamine pathway activity alone is probably not sufficient to cause depressive episodes (Cowen, 2015).

Despite the main focus having been on monoamines in the last decades, there is also accumulating evidence for changes in other neurotransmitter systems associated with depression, specifically the gamma-aminobutyric acid (GABA) system (Croarkin et al., 2011; Sanacora, 2010) and the glutamate system (Sanacora et al., 2008).

For instance, in the plasma and cerebrospinal fluid of depressed patients, GABA levels have been repeatedly reported to be lowered (Sanacora, 2010). Furthermore, there have been reports of decreased density of specific GABAergic interneurons in prefrontal and occipital cortical regions of patients with depression (Maciag et al., 2010; Rajkowska et al., 2007) and magnetic resonance spectroscopy studies have suggested a decrease in GABA in occipital cortex and anterior cingulate cortex (Cowen, 2015; Sanacora et al., 1999).

Abnormalities of glutamate in plasma, serum, cerebrospinal fluid and brain tissue have also been described in patients with depression (Sanacora et al., 2008) and magnetic resonance spectroscopy imaging has yielded some evidence for decreased levels of glutamate especially in anterior brain regions (Cowen, 2015; Yüksel and Öngür, 2010). Furthermore, ketamine, an antagonist at the glutamatergic N-methyl-D-aspartate (NMDA) receptor, has repeatedly been shown to exert rapid antidepressant effects (Kishimoto et al., 2016).

The neuroendocrine level of description

Neuroendocrine investigations have also revealed interesting associations between endocrine functioning and clinical depression.

It has long been noted by clinicians that patients suffering from various endocrine disorders (e.g. Cushing's disease) often develop depressive symptoms (Cowen, 2015). In turn, patients with depression have been observed to exhibit a number of abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis, most notably subtle signs of cortisol hypersecretion. For instance, depression has been associated with elevated 24-h blood cortisol levels, decreased suppression of cortisol secretion after dexamethasone administration, increased waking salivary cortisol, increased volumes of the adrenal glands and decreased numbers of glucocorticoid receptors both in the brain and in the periphery (Cowen, 2015). Furthermore, depressive disorders frequently go along with comorbidities (e.g. diabetes mellitus and cardiovascular disease) and long-term consequences (e.g. hippocampal volume reduction and cognitive impairments) that are consistent with increased long-term glucocorticoid exposure (Brown et al., 2004). Highly interesting in this context is also the finding that increased early life stress (a known risk factor for depression) could potentially cause hyperactivity of the HPA axis that persists into adulthood (Pariante and Lightman, 2008).

As with neurochemical abnormalities, some HPA axis–related abnormalities (e.g. increased waking salivary cortisol) have been reported not only in individuals suffering from acute depression (Bhagwagar et al., 2005) but also in those at risk for the disorder (Mannie et al., 2007; Portella et al., 2005), which could suggest that they also represent more of a trait-like vulnerability factor.

More recently, other endocrine systems (e.g. vasopressin, oxytocin or melatonin) have also been implicated in the development of depressive symptoms (Cowen, 2015; Neumann and Landgraf, 2012; Valdes-Tovar et al., 2018). However, neither their pathophysiological role nor their clinical relevance has been clarified in detail.

Depressive disorders have also been associated with abnormalities in the immune system especially an increase in levels of inflammatory biomarkers (e.g. C-reactive protein, tumour necrosis factor alpha or interleukin 6) (Cowen, 2015). Furthermore, it is also known that treatment with immune system modulating drugs (e.g. interferon alpha) can induce depressive symptoms (Bonaccorso et al., 2002; Capuron and Miller, 2004). One causal mechanism by which inflammatory processes have been hypothesised to lead to the development of depression is via the induction of a tryptophan-metabolising enzyme (indoleamine 2,3-dioxygenase), causing decreased availability of the serotonin precursor tryptophan and increased production of the potentially neurotoxic metabolite quinolinic acid (Cowen, 2015; Dantzer et al., 2008). In line with these considerations, clinical trials using anti-inflammatory treatments in patients with depression have been conducted, and in some cases have indeed yielded promising results (Köhler et al., 2014).

The anatomical level of description

From an anatomical perspective, depression is associated with structural and functional abnormalities in the limbic-cortico-striato-pallido-thalamic pathway which includes the orbitofrontal

cortex, the anterior cingulate cortex, the basal ganglia, the hippocampus, the parahippocampus and the amygdala (Disabato et al., 2016).

Structural anatomical abnormalities in depressed individuals have been described for both grey matter and white matter. Consistently reported grey matter abnormalities associated with depression are decreased volumes of the hippocampus, the prefrontal cortex, the orbitofrontal cortex, the (subgenual) anterior cingulate cortex and basal ganglia structures (Bora et al., 2012; Campbell et al., 2004; Disabato et al., 2016). It is unclear to date what exactly causes these decreases in grey matter volume, however, increased neuronal and glial cell death as well as diminished adult neurogenesis presumably play a role (Duman, 2004).

White matter lesions are especially prominent in late-life depression and are conceptualised to be mainly of ischemic origin (Disabato et al., 2016; Herrmann et al., 2008). A dominant theory suggests that these white matter lesions can cause depressive symptomatology by interrupting limbic projections to the frontal cortex that are crucially involved in mood regulation (Disabato et al., 2016; Herrmann et al., 2008). Interestingly, higher levels of white matter lesions have been associated with later onset of depression, greater clinical severity, poorer clinical outcome and specific clinical symptoms (e.g. apathy and psychomotor retardation) (Cowen et al., 2012), which has led some researchers and clinicians to consider them the substrate of a pathophysiologically special type of depression.

Functional imaging studies of patients with depression have examined task-related and resting-state brain activity patterns. Abnormalities of cerebral blood flow (and/or metabolism) – as measured with single-photon emission tomography (SPET), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) – are relatively consistently reported for the prefrontal cortex (orbitofrontal, dorsolateral and dorsomedial cortex), the anterior cingulate cortex (especially the subgenual region), the amygdala, the thalamus and basal ganglia structures (Cowen et al., 2012; Disabato et al., 2016).

Furthermore, functional connectivity studies have revealed evidence for various connectivity abnormalities in patients with depression, in line with the idea that network-level deficits may also play an important pathophysiological role. The limbic-cortico-striato-pallido-thalamic circuit encompasses several distinct functional networks, including the cognitive control network, the default mode network, the affective network and the salience network, and abnormalities have been found both within and between these networks in depressed patients (Disabato et al., 2016).

In the cognitive control network, for instance, decreased task-related activity and increased resting-state functional connectivity have been reported (Disabato et al., 2016). In the affective network, both increased task-related activity and increased resting-state functional connectivity have been described (Disabato et al., 2016). In the default mode network, increased task-related activity has been found (Whitfield-Gabrieli and Ford, 2012). Furthermore, there have been reports of decreased functional connectivity between the salience network and the default mode network, and increased functional connectivity of the dorsomedial prefrontal cortex with the default mode network, the cognitive control network and the affective network (Disabato et al., 2016; Sheline et al., 2010).

The cognitive level of description

On a cognitive level, depressive disorders have been associated with various abnormalities in information-processing. Apart from high-level constructs postulated in psychotherapeutic models of depression (e.g. 'dysfunctional attitudes' in cognitive behavioural therapy (Beck, 2008)), abnormalities can also be observed in more basic cognitive domains such as perception, attention or memory, and these abnormalities are accessible to objective measurement in neurocognitive tasks (Elliott et al., 2011; Roiser and Sahakian, 2016; Warren et al., 2015). Broadly, cognitive abnormalities associated with depression can be distinguished in 'cold' (i.e. emotion-independent) and 'hot' (i.e. emotion-dependent) cognitive impairments (Roiser et al., 2012).

'Cold' cognitive impairments are observable in attention, executive function and memory, and seem to be more severe in individuals whose depressive disorder has a more chronic or recurrent course (Roiser and Sahakian, 2016). Interestingly, they seem to be predictive of poor treatment response (independent of baseline symptom severity) which has led to the suggestion that a subset of patients with depression might benefit from some sort of cognitive enhancement (Roiser et al., 2012; Roiser and Sahakian, 2016).

Important 'hot' cognitive abnormalities associated with depression are mood-congruent, negative biases in the processing of emotional stimuli (Roiser et al., 2012; Roiser and Sahakian, 2016), and impaired processing of reward and punishment-related experiences (Eshel and Roiser, 2010).

Negative biases are observable in behavioural tasks as differences in performance depending on whether presented stimuli have an emotionally negative or positive value. These biases have been described in various cognitive domains encompassing perception, attention, working memory and memory (Elliott et al., 2011; Harmer and Pringle, 2016; Roiser and Sahakian, 2016). Notably, biases in emotional information processing seem to be not only observable in currently depressed individuals, but also in individuals at risk for depression, such as those with a history of depressive disorder (LeMoult et al., 2009), a first-degree relative with depression (Le Masurier et al., 2007), certain genetic variants (Pérez-Edgar et al., 2010) or specific personality traits (Chan et al., 2007). An interesting phenomenon in this context is the finding that antidepressant treatments are able to dampen negative biases long before clinical effects on mood are usually measurable, which has led to the suggestion that the reversal of negative biases in emotional information processing might actually play a causal role in antidepressant treatment effects (Harmer et al., 2009, 2017).

Another 'hot' cognitive abnormality observable in depressed patients is altered reward and punishment processing (Eshel and Roiser, 2010). It has been reported, for instance, that depressed patients show impairments in reward and punishment based learning (Eshel and Roiser, 2010; Roiser and Sahakian, 2016) with hypersensitivity to negative (Elliott et al., 1997) and hyposensitivity to positive feedback (Henriques and Davidson, 2000). Furthermore, in line with clinical observations, patients with depression exhibit impaired motivation in effort-based tasks (Roiser and Sahakian, 2016). Although impairments in reward and punishment processing have just recently become a focus of interest in depression research, they might be of particular relevance for understanding the complex phenomenology of anhedonia (Roiser and Sahakian, 2016).

Understanding depression: what does the future hold?

In the first section of this essay, we have summarised a selected range of key findings yielded by neuroscientific investigations on depressive disorders in the last decades. In the paragraphs that follow, we will now highlight a few potential lines of enquiry that could take the field forward in the future.

Linking different levels of description: an integrated neuroscientific model of depression

As it has become clear from the brief outline above, previous research efforts have revealed a considerable number of insights on various levels of description. The importance of these discoveries notwithstanding, the current neuroscientific understanding of depression still faces large 'explanatory gaps' insofar as it remains for the most part silent about the mechanistic links between different physiological abnormalities, cognitive impairments, clinical symptoms and the effects of different treatments.

An important challenge for future research will therefore be to develop an overarching theoretical framework in which findings on different levels of description can be integrated. This should make clear, for example, how neurotransmitter imbalances are mechanistically linked to macroscopic decreases in hippocampal volumes, increased task-related default mode network activity and elevated salivary cortisol levels, or how treatments as different as psychotherapy, psychopharmacological manipulations and brain stimulation can all yield the same clinical effect of relieving depressive symptoms.

We admit that this will be a difficult task with many obstacles in the way. One major problem to overcome might be the hitherto strong reliance of researchers on relatively crude diagnostic systems which are primarily based on clinical symptomatology and therefore assign the same diagnostic label to what most probably is a range of aetiologically and pathophysiologically heterogeneous conditions. In line with the Research Domain Criteria Project launched by the National Institute of Mental Health (Insel, 2014; Insel et al., 2010), a distinguished aim in developing an integrated neuroscientific model of depression therefore has to be the separation of distinct aetiological and pathophysiological trajectories which, although eventually giving rise to a similar symptomatology, involve different distal neurobiological and cognitive mechanisms, and therefore might be differentially amenable to specific treatments. Eventually, such an approach would likely benefit the development of 'precision psychiatry', that is, the optimal matching of available treatment options to patients based on their individual characteristics.

Finding all culprits: extending the search outside the brain

Another potential line of enquiry for the future could concern the search for pathophysiologically relevant factors outside the immediate boundaries of the brain. Although mostly ignored in neuroscientific research in the past, there is now accumulating evidence for important functional relationships between the brain and other organs of the body, and dysfunctions in these relationships might play a crucial role in the development of various psychiatric disorders. Recent studies, for example, suggest a surprisingly close functional relationship between gut microbiota and the brain, implicating a whole range of bilateral signalling mechanisms (Cryan and Dinan, 2012; Mayer et al., 2014).

What is especially interesting in the context of depressive disorders is the fact that various gut-inhabiting bacteria are not only able to influence the serotonergic system and GABAergic system but also to regulate the stress response (Dash et al., 2015; Dinan and Cryan, 2013) – all of which are aspects that have been shown to function abnormally in depressed patients. Although still preliminary, there is some evidence that experimental manipulations of the gut microbiome can indeed affect emotional processes, mood and other cognitive functions in humans and animals, and these manipulations therefore might have the potential to become future treatments for depressive disorders (Cryan and Dinan, 2012; Dinan and Cryan, 2013; Mayer et al., 2014).

Last but not least: aiming at a better translation of neuroscientific insights

Finally, future research has to address the need for better translation of neuroscientific insights into clinical practice. Despite its recent progress, neuroscientific research has had surprisingly little impact on the clinical treatment of patients with depression. Future work therefore has to find opportunities to better apply already established knowledge in clinically useful ways.

Such translational efforts do not have to aim exclusively at major paradigm changes in clinical treatment (e.g. the development of a completely new antidepressant) but can also tackle comparatively 'smaller' problems whose solution, however, might still have a major impact on clinical routine and future research. To give an example, it would be highly desirable to find reliable biomarkers of antidepressant treatment response that are measurable early in the course of treatment. Such biomarkers would not only facilitate predictions whether a given antidepressant is going to be effective in an individual patient but could also prove useful in speeding up decision processes in the development of new antidepressant interventions.

Summary and concluding remarks

In this essay, we have briefly reviewed a selected range of key discoveries that neuroscientific research has made on the topic of depressive disorders in the last decades. We have shown that depression has been linked to a wide range of abnormalities on different levels of neuroscientific description ranging from molecules and cells to brain circuits and cognitive mechanisms. Based on this short overview, we have then identified three potential lines of future scientific enquiry: first, the development of an integrated neuroscientific model of depression (and antidepressant treatment) that provides mechanistic links between abnormalities (and the effects of antidepressant interventions) on different levels of neuroscientific description and that separates distinct pathophysiological trajectories leading to depressive symptomatology. Second, the continuation of the search for aetiological and pathophysiological factors implicated in the development of depression, especially outside the immediate boundaries of the brain. And third, a stronger focus on translational efforts that use

established basic neuroscientific insights to improve clinical practice and research.

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