

Hypercortisolaemia and Neurobiological Structural Alterations During Depression: How do Current Treatments Fit?

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Abstract

Although several treatment options exist for mild, moderate and severe depression, few reports have closely linked the sequence of neuroendocrinal and regional brain structural and connectivity alterations which accompany depression with the therapeutic processes underlying a range of common treatments. By examining the neurobiological correlates of depression (particularly Major Depressive Disorder), and then discussing the underlying causal mechanisms of common treatments, this review suggests that only tangential links may be found between these two sets of variables. (German J Psychiatry 2010; 13 (2): 104-115).

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Introduction

Clinical and subsyndromal depression damage physical health, relationships and cognitive performance (Druss & Rosenheck, 1999; Judd, Paulus, Wells & Rapaport, 1996; Lyness et al., 2006; Nutt, 2004). In addition, depression has recently been shown to represent as great a risk for mortality as does smoking, even when related health factors such as blood pressure, alcohol intake, cholesterol and social status are taken into account (Mykletun et al., 2009). It is no surprise, therefore, that depression is the principal contributor to the Total Disease Burden (Ustun et al., 2004) and predicted to become the second leading cause of mental illness by 2020 (Murray & Lopez, 1997; WHO, 2001). With up to 13% (Europe) and 17% (USA) of people experiencing a major depressive episode at some time in their lives (Alonso et al., 2004; Kessler et al., 1994; Kessler et al., 2005), effective treatment thus remains a consideration of major importance.

Sub-types (and causes) of depression

Although depression is often defined as a number of related disorders (APA, 2000; WHO, 2007), this paper focuses on unipolar depression. One distinction among unipolar depressive subtypes which has been supported by factor analytic studies is that between melancholic and non-melancholic depression (Leventhal & Rehm, 2005). Melancholic depression is marked by anhedonia, psychomotor difficulties, excessive guilt or hopelessness, suicidal features and disturbances of appetite or weight, and these symptoms distinguish patients suffering from this subtype of depression from those who exhibit general distress (Clark & Watson, 1991; Leventhal & Rehm, 2005; Marcos & Salamero, 1990). Melancholic patients also have distinct biological features that are associated with psychological concomitants. These biological features may include dysfunction of: (i) the hypothalamic-pituitary-adrenal (HPA) axis (Du et al., 2009; Fiocco et al., 2006; Gillespie et al., 2004), which is related to emotional and sympathetic nervous system problems such as excessive guilt and hopelessness; (ii) the thyroid axis (related to psychomotor abnormalities, weight loss and sleep disturbances: Thase & Howland, 1995); (iii) REM (Rush et al.,

1997), which may also reflect changed circadian rhythms that are found in melancholic patients; and (iv) left dorsolateral prefrontal cortex activity (Galynker et al., 1998), which is associated with mood problems.

These wide-ranging biological concomitants of depression underline the importance of including genetic and biological agents (that may contribute to the development of depression) when considering treatment options. Although not the focus of this paper, several genetic links with depression have been reported, including the presynaptic protein PCLO (Sullivan et al., 2009), the GAD1 gene (which expresses glutamic acid decarboxylase: Hettema et al., 2006) and at least six other genes (Lopez-Leon et al., 2007). Some gene-linked biological factors reduce the functionality of the neurotransmitters serotonin (Muller & Schwartz, 2007) and dopamine (Chowdary et al., 2005), thus impairing cognitive performance and directly contributing to depressive symptomatology. These findings are reflected in a direct relationship between likelihood of developing major depression and familial incidence of that disorder (Kendler et al., 2009).

In turn, environmental stress has been shown to influence gene expression that is associated with the antecedents of depression (Phillips, 2005). For example, adverse experiences and chronic stress during early life have been shown to predict HPA hyperactivation measured via elevated salivary cortisol and thereby contribute to the incidence of major depression in adolescents (Rao et al., 2008). Similarly, adversity during early life has been shown to decrease expression by the gene for Brain-Derived Neurotrophic Factor (which mediates neural plasticity in the prefrontal cortex and hippocampus: Roth et al., 2009). Environment-gene interactions can reduce neurogenesis in the hippocampus (an area which is centrally involved in emotional expression), thereby contributing to lowered mood and depression (Mirescu & Gould, 2006). These findings support the “Diathesis-Stress hypothesis” (Barlow & Durand, 1995; Bear et al., 2007), which argues that the gene-environment interaction, plus resulting neurobiological changes to the brain, hold the key to a fuller understanding of mood disorders (Charney & Manji, 2004; Nestler et al., 2002; Uhlir, 2008).

The HPA axis as a link between environment, genes and depression

As mentioned above, genetic disposition may be a factor in individuals developing hyperresponsivity of the HPA axis under stressful environmental conditions, leading to depression (Du et al., 2009; Fiocco et al., 2006; Gillespie & Nemeroff, 2005; Segerstrom & Miller, 2004). Up-regulation of the HPA axis instigates hypercortisolaemia, which can induce organic changes to several brain regions that are associated with cognitive processing of the threat valence of environmental demands and the selection of rational *vs* emotional responses to those demands (Chrousos, 2009). In this way, organic changes to the brain have been linked to the eventual development of the withdrawal behaviours that have been suggested to underlie depressive symptomatology (Bolling et al., 1999; Kanfer et al., 2008). These organic changes include alterations to the volumes of certain brain

regions such as the amygdala (van Eijndoven et al., 2009), prefrontal cortex (Levin et al., 2007) and hippocampus (MacQueen et al., 2008). There are also alterations to the connectivity of those regions of the brain (e.g., amygdala-prefrontal: de Almeida et al., 2009; amygdala-hippocampus: Fu et al., 2008). These findings will be described below in greater detail, plus the possible causal links between hypercortisolaemia and these changes that are associated with depression.

Brain areas and connectivity alterations during depression

A great deal has been written about the association between various brain areas and the general experience of depression. For example, Siegle et al. (2007) found that blood flow increased in the amygdala and decreased in the dorsolateral PFC in depressed patients compared to non-depressed subjects, and Quirk and Gehlert (2006) noted that there were four potential pathways between amygdala malfunction and psychopathological states. However, as well as these general findings about depression, the accepted symptomatology of depression (i.e., DSM, ICD) highlight the specific presence of apathy and anhedonia as central to any diagnosis. These states have been localized to the reward circuits in the limbic system, specifically the loop between the nucleus accumbens, the ventral globus pallidus and the anterior cingulate gyrus, and are heavily involved with dopaminergic communication systems (Lieberman, 2006). Nestler et al. (2002) referred to this loop as the “neural circuitry of depression” (p. 16), emphasising the central role which these regions (and their interconnectivity) play in depression. In addition, Nitschke and Mackiewicz (2005) found that apathy in depression involved the dorsolateral PFC as well as the anterior cingulate cortex, implicating this decision-making region in this central symptom of depression. Because apathy prevents depressed persons from taking action to reduce their depressive behaviour via more productive problem-solving and lifestyle strategies (APA, 2000), down-regulation of these key areas may be the neurobiological causal mechanism which prevents melancholic depressive patients from self-activated treatment and from being able to put psychotherapy-based cognitive strategies into action (Nitschke & Mackiewicz, 2005). This hypothesis has been supported by a study of dysregulation in the influence of the dorsolateral PFC on the anterior cingulate cortex, which is observed in depressed persons (Schlosser et al., 2008).

These findings suggest a model of Major Depressive Disorder (MDD) in which a circuit including the prefrontal cortex, amygdala and hippocampus influences not only mood regulation, but also learning and contextual memory processes (Maletic et al., 2007). Specifically, during MDD, the ventromedial prefrontal cortex (VMPFC) and lateral orbital prefrontal cortex (LOPFC) are hyperactivated and the dorsolateral prefrontal cortex (DPFC) is hypoactivated (Drevets, 1998). These changes are consistent with the symptoms of MDD because hyperactivation of the VMPFC is associated with sensitivity to pain, anxiety, depressive rumination and tension; and hypoactivity of the DPFC is associated with

psychomotor retardation, apathy, and deficits in working memory and attention (Maletic et al., 2007). Studies of the connectivity between these areas have also suggested that decreased communication between the amygdala and anterior cingulate complex (ACC) occurs in MDD (Anand et al., 2005). Because the ACC acts to inhibit emotional regulation (Whittle et al., 2006), decreases in the communication between it and the amygdala could be involved in the irregularity of mood that is a symptom of MDD (Malatic et al., 2007). When connectivity is disrupted between the integrative and executive functions of the lateral orbital PFC, rostral PFC, medial PFC, dorsolateral PFC and dorsal ACC on one hand, and the emotional/visceral functions of the ventral ACC and ventral medial PFC plus the hippocampus, amygdala and nucleus accumbens on the other hand, the brain undergoes a decrease in regulatory feedback from the former “rational” regions to the latter “emotional” regions (Roosendahl, 2009). This allows the latter to dominate control of the hypothalamus and consequent neuroendocrine activity, leading to further stress responses and sympathetic nervous system (SNS) dominance (Chrousos, 2009), plus increases in fear and consequent withdrawal by the fearful/depressed person from their physical and social environment (Bolling et al. 1999; Kanter et al., 2008).

However, there are functional differences within the “emotional” regions listed above (i.e., ventral ACC, ventral medial PFC, hippocampus, amygdala and nucleus accumbens). Unlike the amygdala, which is activated during threat and which stimulates the hypothalamus for fight-or-flight responses, the hippocampus has an inhibitory effect upon the hypothalamus (Maletic et al., 2007). Additionally, the ventral region of the hippocampus is involved in inhibition of the SNS and subsequent reduction of anxiety behaviours (Whittle et al., 2006). Anxiety is not only often comorbid with depression (Coryell et al., 1988), there is also major overlap in the symptomatology for both disorders (Zinbarg et al., 1994). For example, several studies of depression and anxiety among prostate and breast cancer patients, as well as university students, have shown that it is difficult to disentangle the two disorders, their factor structures and their underlying symptomatology (e.g., Sharpley & Christie, 2007a, b), as well as the environmental events which initiate each of these disorders (Sharpley et al., 2009, 2010). These links between hippocampal inhibition of anxiety and the amygdaloid activation of fear via hypothalamic neuroendocrine secretions may represent a “balance” of efforts by these two regions that has the effect of allowing the individual to manage threat effectively (Roosendahl et al., 2009). A key to understanding how this change in the relative balance of influence upon the hypothalamus occurs (and effects anxiety and depression) is the mechanism by which the hippocampus and amygdala alter their functioning. Studies of changes to the volumes of these regions (and the PFC) can offer this key, and the next section will briefly review some of the literature regarding links between these changes and depression.

Brain region volume change

Some reports have indicated that the anterior cingulate cortex (ACC) reduces in volume during *bipolar* depression (Chiu

et al., 2008), and the rostral ACC decreases in volume in normal healthy children with depressed mood and *subsyndromal depression* (Boes et al., 2008), as well as in adolescents with *borderline personality disorder* (Whittle et al., 2009). However, the major foci of research into volumetric changes of specific brain regions associated with MDD have been the amygdala and the hippocampus.

Widespread reductions in glucose use and cerebral blood flow have been demonstrated in MDD (Kumar et al., 1998). While the whole brain volume of persons with MDD has not been found to be significantly smaller than that of non-MDD control subjects, PFC volumes are smaller (Kumar et al., 1998). In addition, a significant linear relationship between severity of depression and PFC reduction has been reported (Kumar et al., 1998), suggesting that this change may be causally linked with the intensity of the depressive symptomatology. Hippocampal volume has also been shown to be reduced in MDD patients compared to non-depressives (Nemeroff, 1998). In addition, the size and direction of these brain region changes have been shown to predict susceptibility to favourable outcome from antidepressant treatment (Costafreda et al., 2009). Several agents have been suggested as having a causal role in changes to these brain regions during depression, including growth factors and Brain-Derived Neurotrophic Factor, alterations in all of which may be initiated by elevated glucocorticoids or cytokines (Hayley et al., 2005; Rot et al., 2009).

Hippocampus

Focussing specifically on the hippocampus, several studies have reported that decrease in hippocampal volume during depression occurs via cell apoptosis (e.g., Fuchs et al., 2004; Fuchs et al., 2006; Hastings et al., 2004; Sapolsky, 2000). While the prime causal agent for this neuronal apoptosis is probably elevated cortisol due to exaggerated hypothalamic-pituitary-adrenal axis activation during prolonged periods of chronic stress (Chrousos, 2009), which perhaps interferes with mitochondrial function within neurons and leads to their death (Du et al., 2009), there are also data which suggest that genetic predisposition may play a causal role (Ballmaier et al., 2008; Lloyd et al., 2004). Of further causal significance, remission of depressive symptoms has been associated with return to non-depressed state hippocampal volumes (Caetano et al., 2004; MacQueen et al., 2008). In addition, antidepressant treatment (Balu & Lucki, 2009; Lucassen et al., 2004) and activation of mineralocorticoid receptors (to lower levels of circulating glucocorticoids) have reversed hippocampal apoptosis (Crochemore et al., 2005) and relieved depressive symptoms. It has also been established that adverse early life experiences significantly predict vulnerability to hippocampal apoptosis when the individual is under chronic stress later in life (Weavey et al., 2006), underlining the environmental and epigenetic aspects of this brain region change that is associated with depression.

Prefrontal cortex

As suggested above, reduced PFC activity is integral to depression (Kumar et al., 1998; Levin et al., 2007). Reductions in PFC volumes have been significantly associated with

depression (Bremmer et al., 2002; Radley et al., 2004; Rajkowska et al., 1999), and these data support the argument that these reductions in volume are associated with impairment of feedback and control of the limbic system (Maletic et al., 2007), which then dominates cognition and (for the depression-vulnerable individual) exacerbates negative interpretation of events and depressive symptomatology, including withdrawal from social support sources and previously-available pleasurable activities (Bolling et al., 1999).

Amygdala

Contrary to the observed decreases in hippocampal and PFC volumes during depression, MDD patients show increased glucose metabolism in the amygdala when compared to healthy non-depressed persons (Drevets et al., 1992; Ho et al., 1996). Further, increased cerebral blood flow and glucose metabolism in the amygdala are directly related to depression severity (Abercrombie et al., 1998). Enlargement of the amygdala has been reported to occur even within the first episode of MDD (Frodl et al., 2002; van Eijndhoven et al., 2009), suggesting that this change is either very fast or is an antecedent for the onset of depressive symptomatology. At the other end of the disease-treatment period, there is some disagreement as to whether patients who are in remission continue to show enlarged amygdala volume (Lorenzetti et al., 2009) or have amygdala that are not significantly different in size to healthy non-depressed subjects (Bremner et al., 2000; Caetano et al., 2004; Frodl et al., 2008; van Eijndhoven et al., 2009). In a challenge to the observed relationship between depression and enlarged amygdala, Hamilton et al. (2008) conducted a meta-analysis of 13 studies published between 1985 and 2008, and found that the often-reported enlarged amygdala in depressed patients was a function of them having received antidepressant treatment. By contrast, non-treated depressed persons showed reduced amygdala volumes compared to control subjects. Clearly, this finding is contentious and, if replicated, may challenge the model of the enlarged amygdala as a consequence of elevated serum cortisol that produces neurogenesis within the amygdala and is hypothesised to be associated with (if not an antecedent for) development of depression (Roozendaal et al., 2009).

Implications for treatment options

Psychotherapy

Various forms of psychotherapy are effective for mild and moderate depression (i.e., CBT, behavioural activation treatment, psychodynamic approaches, problem-solving therapy, interpersonal psychotherapy and social skills training; Cuijpers et al., 2008). A major review about a decade ago concluded that psychological therapies were not as effective for MDD patients as medication (Thase & Friedman, 1999), although other data have suggested that Cognitive Therapy is as effective as medication in reducing some acute depressive symptomatology (e.g., DeRubeis et al., 1999), and that Interpersonal Therapy (IPT) is equally effective as Cognitive

Behaviour Therapy in decreasing depression inventory scores for patients with MDD (Luty et al., 2007). However, other data have shown that, while medication had a demonstrated statistically significant superiority over placebo when administered to MDD patients, Cognitive Therapy did not (DeRubeis et al., 2005). However, those data were collected on patients who were classified as not having an “immediate risk” for suicide (p. 410) and therefore this patient group may not be congruent with the common definition of MDD (APA, 2000). Further, March et al (2004) reported that *Fluoxetine* was superior to CBT for adolescents with a DSM-IV diagnosis of MDD. These comparatively weaker outcomes from psychological therapies applied to MDD compared to medication may be due to the type (i.e., melancholia *vs* non-melancholia) of depression. That is, the principal effective components of CBT for depression are (1) the building of a close and rapport-inducing relationship between therapist and patient (Hawley et al., 2006; Weisz et al., 2009) and (2) those behavioural homework activities which are recommended by therapists to help patients re-experience pleasure in daily activities (Jacobson et al., 1996). Melancholic patients have a biologically-based restriction upon their experience of pleasure, and so it may be difficult to motivate them to undertake or continue the homework activities required. Additionally, the cognitive techniques in CBT require patients to identify their negative thoughts while experiencing negative mood (Beck, Rush, Shaw & Emery, 1979), but melancholic patients have difficulty experiencing such negative emotions, instead remaining apathetic (Leventhal & Rehm, 2005).

Notwithstanding some limitations in the effectiveness of psychotherapy for MDD, there is a logical link between the effects of psychotherapy and alleviation of the kinds of endocrinal and neurobiological changes mentioned above that accompany depression. For example, the experience of psychotherapy provides a powerful one-on-one interpersonal nurturing situation for the patient, unlike that available in most other social interactions in terms of its intensity and duration. This nurturing relationship may reduce hypercortisolaemia, a major factor in the causal chain between stress and depression, as described above. Supporting this hypothesis, CBT (Mommersteeg et al., 2006) and IPT (Brody et al., 2001) have both reversed the blunting of the “awakening cortisol response” (i.e., collected within minutes of waking from overnight sleep: Fries, Dettenborn & Kirschbaum, 2009) that has been associated with depression (Huber et al., 2006). In addition, daily salivary cortisol has been reduced by psychoanalysis (Eiler et al., 2005) and CBT (Antoni et al., 2000), and even by non-therapy imagery tasks which were focussed upon compassion (Rockliff et al., 2008). An analogy may be drawn between the hypercortisolaemia observed in depression and that brought about by a lack of maternal stimulation and care given to neonates who consequently develop HPA-axis hyperactivation (Weaver, 2009). This elevated circulating cortisol has been linked to depression in childhood via dampening of the hippocampal glucocorticoid receptor gene *Nr3c1* in infant humans who have had adverse nurturing experiences (Weaver, 2009), leading to impaired negative feedback to the hypothalamus regarding circulating cortisol (Bear et al., 2007). Although this deprivation of nurturance instigates elevated cortisol, hippocampal apoptosis and depression, hippocampal neurogenesis occurs

when maternal nurturance is reinstated (Weaver et al., 2006). Similarly, the intense verbal support and attention that is provided during the psychotherapy interview may thus present a parallel “maternal” nurturing experience for depressed patients who may previously have lost most sources of social reinforcement (Dougher & Hackbert, 1994; Ferster, 1973). This hypothesis is supported by findings that fear of being rejected by others significantly predicted elevated cortisol and depression in young women (Tops et al., 2008). This hypothesis requires further exploration before the link between psychotherapy and neurobiological remediation can be fully accepted.

Medication

Following the serendipitous discovery of the antidepressant effects of monoamine oxidase inhibitors in the 1960's, the “Monoamine” hypothesis of depression has been the predominate approach to pharmacological treatments for depression (Rang et al., 2007), with a focus upon inhibiting the neurotransmitter-reducing effects of monoamine oxidase upon 5-HT, dopamine and noradrenaline levels within the synaptic cleft. Monoamine oxidase inhibitors (MAOIs) act quickly to increase 5-HT (strongest effect), NA and DO (least effect) in the cytoplasm throughout the body, causing increases in motor activity and mood in non-depressed persons (Rang et al., 2007), although reduction of depression takes several weeks in patients and side effects may be considerable. Tricyclic and tetracyclic antidepressants (TCAs) inhibit the transporter proteins that uptake NA and 5-HT from the presynaptic nerve ending and are generally successful in treating depression, although they may also produce unwanted side effects which pass after a few weeks at about the same time as the antidepressant effect begins to take place (Rang et al., 2007). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants (Shelton & Lester, 2006), mainly due to their intensive use in primary care settings since 1998 (Olfson & Marcus, 2009), although they are nowadays used across many settings. As indicated by their name, these drugs act upon 5-HT rather than DO (Shelton & Lester, 2006), and have fewer side effects than MAOIs or TCAs (Rang et al., 2007) but may, when combined with MAOIs, cause tremor, cardiovascular collapse and hyperthermia (Rang et al., 2007), although these side effects arise from the MAOIs rather than the SSRIs. These side effects are rarer in patients treated with these newer antidepressants and so these SSRIs are better tolerated by patients than MAOIs (Olfson & Marcus, 2009). Although it has been claimed that SSRIs have been associated with an increased risk of suicide (Gunnell et al., 2005), other data on suicide rates among children and adolescents show increases in suicide when SSRI prescriptions to those groups decreased, arguing against the suggestion that SSRIs are causally linked with increased risk of suicide (Gibbons et al., 2007). The high incidence of suicide among depressed persons who are untreated adds to the argument that SSRIs may represent a more effective treatment than indicated by Gunnell et al. (2005).

However, the fact that antidepressants elevate the levels of monoamine neurotransmitters within a few days but do not

alter mood for several weeks (Anderson et al., 2000), suggests that they may be regulators of longer-term trophic effects (Rang et al., 2007) which may take the form of down-regulation of post-synaptic neurotransmitter receptors that have previously been up-regulated (perhaps by gene expression associated with vulnerability to depression) and are therefore responsible for depleted synaptic monoamines (Stahl, 2008).

There are varying opinions regarding the efficacy of these medications. For example, Stahl (2008) commented that only about two-thirds of actual (non-clinical trial) patients receiving antidepressants showed reduced depressive symptoms. A major recent meta-analytic review showed a statistically significant superiority for medication over placebo, but concluded that the difference (1.7 points on the 52-point Hamilton Depression Scale) was “clinically negligible” (Kirsch, et al., 2002, p.1; Moncrieff & Kirsch, 2005). However, this report has been criticized on the basis that it included non-suicidal MDD patients, and that meta-analyses and the randomized placebo-controlled studies on which they are based are flawed because these are not valid replicates of actual clinical practice and hold few implications for treatment (e.g., Moller & Maier, 2009). It may be that Kirsch et al.'s (2002) conclusions need to be tempered by these limitations.

Combined pharmacological and psychotherapy treatment

Parker et al. (2006) outlined the specific conditions under which psychological therapies (IPT) might be effective and argued that there is probably no universal psychological treatment for MDD, a comment supported by Thase and Denko (2008), who also added that “there are no universally effective pharmacological treatments for mood disorders” (p. 53). Therefore, *combined* psychotherapy and medication treatment models for MDD have been recommended (Friedman et al., 2006) and supported by findings that the Cognitive Behavioural Analysis System of Psychotherapy (CBASP: McCullough, 2000) was effective with those MDD patients for whom medication was ineffective, and vice-versa (Schatzberg et al., 2005). The interweaving of psychotherapy with pharmacological treatments has also been shown to prevent relapse (Casacalenda et al., 2002; de Maat et al., 2007; Frank et al., 2006; Friedman et al., 2006; Segal et al., 2003). These findings suggest the presence of an interactional relationship between psychological therapy and pharmacological treatments for MDD and raise the issue of when each might be most appropriate.

Of relevance to decisions about when/to whom to apply each of these treatment options, de Maat et al. (2007) reported that combined pharmacological and psychological therapy was significantly more effective than psychotherapy alone for chronic depression and for mild and moderate non-chronic depression. No data were reported from comparisons using severely depressed patients. In fact, CBT is probably unlikely to be applicable to very severely depressed MDD patients (those with melancholic disorder) for the reasons mentioned above (i.e., these patients may not be able to experience the emotions necessary for CBT to be used)

and so considerations of the place of CBT should be restricted to use with patients who suffer from non-melancholic depression. In terms of the potentially confounding effects of comorbidity, the presence of Personality Disorder has been shown to not affect the outcomes of treatment of MDD via medication, CBASP or a combination of both (Maddux et al., 2009). Fournier et al. (2009) further illuminated this issue by reporting that depressed patients who were married, unemployed and who had experienced a greater number of recent life events, were more likely to show a superior outcome from cognitive therapy than for medication.

Of interest in identifying the key ingredients in both psychological and pharmacological therapies, the relative effectiveness of cognitive therapy vis-à-vis medication has been found to rely on the level of therapist experience (DeRubeis et al., 2005). When combined with other recent findings that the neurobiological responses associated with antidepressant medication are also observed within placebo conditions (Oken, 2008), the importance of the apparent expertise of the treating agent (i.e., therapist or medication) is highlighted as an important issue for choosing treatment options.

Depressive neurobiology, psychotherapy/medication and neurological changes

As mentioned above, the effectiveness of medication for depression has been hypothesized to rely upon its trophic effects, explaining the time lag between changes to neurotransmitters and improvement of patient mood, rather than simply those increases in neurotransmitters *per se*. Psychotherapy efficacy appears to be closely linked to the apparent expertise of the therapist and the relationship between the therapist and patient (Elvins & Green, 2008; Shirk et al., 2008), and may reduce cortisol levels, thus also removing one of the principal causal agents for neural apoptosis (PFC, hippocampus) and growth (amygdala). From this perspective, both of these treatment approaches may be said to act via secondary effects upon those brain regions that have been implicated in depression.

Electroconvulsive therapy, transcranial magnetic stimulation, functional magnetic resonance imaging neurofeedback

By contrast with both psychotherapy and medication, electroconvulsive therapy (ECT) is applied directly to the brain itself, and transcranial magnetic stimulation (TMS) and functional MRI neurofeedback (fMRINF) focus on those specific brain regions that may be associated with depression. As such, these treatments may have links between their underlying therapeutic processes and remediation of those structural brain changes which are associated with depression.

ECT

Although the evidence supporting ECT as a treatment for MDD is extensive (Sackeim et al., 1995) and this treatment is especially indicated for melancholic depression (Nobler & Sackeim, 2006), no definitive or theory-based explanation exists for how ECT works (Nobler & Sackeim, 2006). Some data suggest that ECT leads to a down-regulation of β -adrenergic receptors (Kellar et al., 1981a) but increased density in 5-HT receptors (Kellar et al., 1981b). Although the latter may enhance 5-HT transmission, it does so via a different mechanism to that underlying SSRIs. One way in which ECT is considered to work is via stimulation of the deep brain structures in the HPA axis, increasing secretion of cortisol (Kronfol et al., 1991), which is in apparent contradiction to the more recent hypotheses regarding the causative effects of elevated cortisol upon depression that were reviewed earlier in this paper. Other data suggested that ECT leads to decreased activity in the PFC (Nobler et al., 2001), but neurogenesis in the hippocampus (Hellsten, Wennstrom et al., 2004; Madsen et al., 2000; Perera et al., 2007), again partly contradicting effects reported from studies of the brain changes which accompany depression.

TMS

Transcranial magnetic stimulation uses a strong pulsed magnetic field adjacent to the skull to produce an electrical current that acts to depolarize neurons within the brain (Barker et al., 1985). TMS may produce excitatory (Wu et al., 2000) or inhibitory (Chen et al., 1997) effects upon neurons and has been shown to have antidepressant effects when treatment was focused upon the left PFC (George et al., 2000; Stern et al., 2007). Use of TMS to produce deep brain stimulation upon the cingulate gyrus of depressed patients showed increases in metabolic activity and remission of depression in 35% of that sample within one month of treatment (Lozano et al., 2008). Similar reductions in depressive symptoms were reported by Friedman et al., (2008) following electrical stimulation of the ventral tegmental area. TMS has also been shown to induce hippocampal neurogenesis and (of particular relevance to the HPA-axis relationship with depression) decrease corticosteroid levels within the brain (Czeh et al., 2003). A large multi-site randomised controlled clinical trial of TMS showed it to produce significant reductions in MDD, but two randomized, controlled trials that compared ECT and TMS for MDD patients reported that ECT was superior to TMS (Erenti et al., 2007; Magg et al., 2009).

fMRINF

Functional magnetic resonance imaging neurofeedback has demonstrated efficacy in training people to control blood flow to certain parts of their brains via the use of functional MRI live feedback (for a review, see Weiskopf et al., 2004). fMRINF has been used to teach self-control of activation in the rostral anterior cingulate cortex to reduce pain (deCharms et al., 2005; Weiskopf et al., 2003), the hippocampus and limbo-thalamic-cortical pathway (Seung-Schik Yoo et al., 2008), amygdala, insula and ventral striatum (Johnston et al.,

2010). Although in its infancy, this procedure may hold significant promise for relief of depressive symptoms via alteration of blood flow and consequent brain activity in areas that are particularly relevant to depression.

Conclusion

Several conclusions may be drawn from this review. First, there are several key brain regions that have been associated with depression (amygdala, hippocampus, PFC), plus some other regions which may play a part in the alterations to mood and cognitive process which constitute depressive symptomatology. Second, there appears to be a reciprocal relationship between the increases in amygdala volume due to neurogenesis, and the reductions in hippocampal and PFC volumes (occasioned by cell apoptosis) that occur during depression. These changes produce a variation in the control of the hypothalamus so that it is more likely to respond to fearful stimuli with elevated secretion of the antecedents of cortisol. Third, this causal pathway between hypercortisolaemia and the amygdala, hippocampal and PFC structural changes seen in depression may be circular. That is, chronic stress induces hypercortisolaemia, which influences amygdala, hippocampal and PFC cells and volumes. In turn, the heightened fear state of the depressed person increases the sensitivity of the hypothalamus and thus elevates circulating cortisol. Fourth, although they appear to have significant efficacy upon mild and moderate depression (perhaps via establishment of a nurturing relationship between therapist and depressed patient), several psychotherapies have limited or very little effect upon severe depression, perhaps due to the melancholic (and biological) nature of MDD. Fifth, medication also works well for a limited subset of patients, but not via any as-yet understood and verified mechanism, and also has significant aversive side effects. Sixth, both psychotherapy and medication appear to rely on the “expertise” of their provider, thus challenging the assumptions upon which their usage lies (i.e., the monoamine oxidase inhibition effects of medication, or the cognitive and behavioural change strategies of psychotherapy). Seventh, ECT, which has impressive efficacy with severe depression, does not yet have a clear and explained causal mechanism. Finally, two treatments (TMS, fMRINF) which do have plausible causal pathways between their underlying processes and the reversal of those structural changes evident in brain regions and connectivity, remain in their infancy but hold considerable potential.

As in any review, there are limitations to the validity of the conclusions which may be drawn. Although most of the relevant literature was read and considered, space limitations meant that some papers were not included and that the details of reviewed papers were summarized for their contribution to the focus of this paper. Second, almost all the data reported herein from recent research regarding the associations between depression and brain regions have relied on neuroimaging studies of blood flow via fMRI. These studies assume that blood flow to a particular brain area is indicative

of neural activity but this may not always be true (Maier et al., 2008; Sirotin & Das, 2009).

Notwithstanding these limitations, it might be concluded that the use of the various treatments listed above for MDD is not yet soundly based upon the associations found with structural and functional changes to brain regions during depression. While some treatment efficacy can be demonstrated for all of these therapy options, further research is needed to causally link any of them to the kinds of neurobiological substrates that accompany depression.

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