Depression and neurological disorders

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Purpose of review

Clinical studies support a bidirectional link between depression and neurological diseases. Here we review the most recent findings supporting the hypothesis that major depression is a medical illness of the brain which can be elicited by neurological illnesses.

Recent findings

In the last year major improvements in brain-imaging techniques allowed correlations to be demonstrated between functional and structural brain abnormalities in specific brain areas (prefrontal cortex, hippocampus, cingulate gyrus) and the presence and severity of affective disorders, thus suggesting a neural basis for their onset and progression. Similar lesions, caused by neurological diseases, have been found to correlate with the presence of depression in neurological illnesses, but literature on the topic is still lacking. Depression in neurological disorders responds to the same treatments available for idiopathic major depression, but patients seem to have different sensitivities to side effects depending on their specific neurological syndrome. Most available data come from case reports and open trials.

Summary

'Psychiatric' and 'neurologic' depression seem to share common abnormalities in specific brain areas, but sound brain-imaging studies of the neural correlates of depression in neurological disorders are still lacking. Available treatments are efficacious, but no clear-cut guidelines about the best drugs and dosages can be defined because double-blind placebo-controlled studies are still scarce.

Keywords

brain imaging, depression, neurological disorder

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Abbreviations

MS	multiple sclerosis
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
WMH	hyperintensity in the white matter

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Introduction

The traditional boundary between primary affective disorders, as 'diseases of the mind', and depressive syndromes secondary to neurological conditions, as 'diseases of the brain', has been challenged since advances in brain imaging techniques have shown correlations between functional and structural brain abnormalities and the presence and severity of affective disorders, thus suggesting a neural basis for their onset and progression. The most recent studies focusing on hippocampus [1] and anterior cingulate cortex [2•] are clear examples of a new way of considering depression as a medical illness.

Consistent findings have linked the presence of major depression with a hippocampal volume reduction. Compared with healthy individuals, patients affected by recurrent major depression exhibited a decrease in hippocampal volume that was proportional to the duration of untreated depression, thus suggesting that the disease process may cause neurologic damage resulting in grey matter volume loss. Tentative explanations of this degenerative process, which seems to parallel the recurrence of mood episodes, point to the neurotoxic effects of persistently elevated glucocorticoids on hippocampal neurons [3]. In animal models, prolonged increased concentrations of glucocorticoids lead to a variety of brain insults, including direct damage to CA3 pyramidal neurons, reduced development of granule cell neurons, and an overall disruption of neuronal dendritic trees [4,5]. In depressed patients, the known hyperactivity of the hypothalamic–pituitary–adrenal axis could result in similar damage, as suggested by high-resolution structural brain imaging and confirmed by preliminary neuropathologic observations that found apoptosis and decreased dendritic arborization in hippocampi of patients affected by both unipolar and bipolar depression [6]. It should be noted that an increase in brain-derived neurotrophic factor is a neurochemical effect shared by all antidepressants, and possibly linked to their mechanism of action [7], thus suggesting a protective role for these substances against the prolonged neuronal stress. This still open area of research suggests a neurodegenerative correlate of mood disorders that could explain some of the subtle and still controversial neuropsychological deficits that have been described in affective patients.

Classical twins and adoption studies confirmed the heritability of affective disorders, thus suggesting a critical role for susceptibility genes leading to neurodevelopment and

brain structured function [8]. The search for a brain anatomic correlate of the susceptibility to affective disorders has recently led to the definition of a structural grey matter endophenotype of bipolar disorder. Both patients affected by the illness and their unaffected first-degree relatives shared a decrease in the grey matter of the anterior cingulate cortex proportional to the genetic liability for the disorder [2•]. Brain metabolic changes in this area have been described in depression, depression recovery (both after pharmacological and nonpharmacological treatments), and transient sadness in healthy individuals [9–11]. Blood oxygen level dependent functional magnetic resonance imaging confirmed the involvement of these brain regions in the processing of emotional stimuli and in the cognitive generation of affects, and showed different patterns of activation in depressed and healthy individuals [12]. These findings provided a conceptual frame for the study of the neural correlate of depression and for the development of new theoretical models, and suggest that specific brain abnormalities, due to yet undefined pathogenetic mechanisms, could be linked to the presence of mood disorders.

Following this line of reasoning, neurologic conditions could lead to changes in brain structure and function that are similar to those occurring in the natural history of mood disorders, and could then cause identical changes in mood and cognition. These specific mechanisms rather than a maladaptive reaction to the neurologic disabilities, could explain the well documented increased prevalence of depression in neurologic populations.

Epilepsy

Depression is common among people with epilepsy, being, along with anxiety disorders, the most frequent psychiatric condition in these patients. Recent publications raise concerns of undercognition and undertreatment of psychopathology among patients with epilepsy [13•].

The relationship between depression and epilepsy is two-directional, because patients with major depression also have a higher frequency of epilepsy. Mood changes may occur before, during or after a seizure. Among potential biologic risk factors for interictal depression, a number of studies have demonstrated a significant correlation with the diagnosis of temporal lobe epilepsy [14]. Other studies, using different methods of investigation (e.g. functional imaging techniques, neuropsychological assessments), have demonstrated the association in depressive patients between temporal lobe epilepsy and frontal lobe dysfunction [15,16].

A growing literature provides compelling evidence that the presence of brain metabolism abnormalities increases the risk of depression in persons with epilepsy. Serotonin positron emission tomography imaging studies indicate abnormalities in 5HT receptor binding in brain regions distant from the epileptogenic zone [17•] and a decreased volume of distribution in the epileptogenic regions in temporal lobe epilepsy and also in areas distant from the presumed seizure onset area [18].

Current recommendations for the antidepressant treatment are selective serotonin reuptake inhibitors (SSRIs) or cognitive therapy, considering potential medical interaction such as the inhibition of the metabolism of some antiepileptic drugs by SSRIs and the potential lowering of the seizure threshold by tricyclic antidepressants (TCAs) and SSRIs. Recent studies [19,20] prospectively evaluated 100 consecutive epilepsy outpatients started on sertraline (up to 200 mg/day) to determine safety and effectiveness: 54% achieved complete resolution of their psychiatric symptoms and sertraline was well tolerated in the majority of patients. A retrospective analysis of 75 patients with temporal lobe epilepsy and major depression found no difference in efficacy between three antidepressants (mirtazapine, citalopram and reboxetine) [21]. Although TCAs are not as well tolerated as SSRIs, some authors [22] suggested their potential usefulness as adjunctive agents in patients who have incomplete response to SSRIs.

Vascular disease and stroke

High rates of depression have been described after stroke. A precise pattern of brain localization responsible for depression has not been found yet. Involvement of left anterior lesions was initially suggested, but it has been questioned by a recent metaanalysis [23,24]. A link between subcortical lesions and depression has recently been discussed [25], and needs further assessment.

Recent developments point toward the definition of the relationship between the small and silent brain insults due to a general vascular disease, of whatever etiology, and the development of depression. The evidence of an association between vascular disease and depressive symptoms in elderly people is well known, and supported the use of the term 'vascular depression' to address such patients [26]. Hyperintensities in the white matter (WMHs) and deep grey matter of the basal ganglia are the most replicated neuroimaging abnormalities in these conditions. Recent studies have confirmed that depression shows a strong association with lesions in the frontal lobes and basal ganglia [27–29]. Neuropathological studies indicate that WMHs reflect different pathologies, with smaller lesions usually standing for dilated perivascular spaces, while larger lesions represent patches of ischemic damage [30]. Thomas *et al.* [31] have investigated the neuropathological basis of WMHs in depression with a neuroimaging–neuropathological correlational study. Evidence of ischemia was much stronger in the

WMHs of depressed patients compared with controls, and lesions showed a marked specificity for the white matter at the level of dorsolateral prefrontal cortex in depressed patients.

Several studies investigated the effectiveness of antidepressant drugs in these conditions, but we still lack converging findings to support the use of a specific therapeutic strategy for vascular depression. A recent review of published studies found no evidence to support the routine use of antidepressants for the prevention of post-ictal depression or to improve recovery from stroke [32•].

Parkinson's disease

Psychomotor retardation, anhedonia, apathy, and neurovegetative disturbances are symptoms of Parkinson's disease that overlap with the psychiatric syndrome of major depression, and prospective assessment showed that Parkinson's disease patients experience severe mood fluctuations that occur within minutes and several times a day. Common abnormalities of monoaminergic function could explain the similar clinical picture. Though these were once thought to be restricted to dopamine depletion, monoaminergic abnormalities in Parkinson's disease are now known to involve extensive cell loss in nucleus coeruleus and morphological alterations in raphe nuclei [33].

This suggests that antidepressant drugs enhancing monoaminergic functions should produce benefits in Parkinson's disease, but the lack of randomized controlled trials hampers the evaluation of this issue. A 2003 Cochrane review [34] concluded that data about effectiveness and safety of any antidepressant therapy for Parkinson's disease are not sufficient to draw definite indications and, since then, not much has changed.

Clinical practice must for the present rely on open or uncontrolled trials, which gave the following indications.

(1) TCAs can relieve mood symptoms and their anticholinergic profile is also useful for the management of motor symptoms. They can, however, worsen the cognitive impairment that often develops during the natural history of the disorder.
(2) SSRIs cause antidepressant effects with, rarely, a worsening of motor symptoms.
(3) Electroconvulsive therapy can cause a transient improvement in drug-resistant cases [35•].
(4) Total sleep deprivation transiently improves both mood and motor symptoms by causing an immediate release of dopamine in a subset of patients [36].

The most recent studies have focused on repetitive transcranial magnetic stimulation, showing that 10 applications of 40 trains of 5 s each at 15 Hz to the left dorsolateral prefrontal cortex could cause an antidepressant effect similar to fluoxetine 20 mg/day (about 35% reduction in depression ratings after 2 weeks) [37•]; and the combination of dopamine agonists to L-Dopa, showing that the prolonged administration of pramipexol ameliorated mood and motor symptoms without changing cognitive performance [38]. Finally, clinical improvement of moderate but not severe depression has been reported up to 3 years after chronic bilateral subthalamic deep brain stimulation [39•].

Multiple sclerosis

Major depression occurs at high rates among patients with multiple sclerosis (MS), and the prevalence is high even when compared with other groups with a chronic illness, thus suggesting a specific association based either upon a common pathogenetic mechanism, or on iatrogenic effects.

Most recent brain imaging studies exploited the possible depressogenic effect of lesion localization in specific brain areas. One study detected weak correlations between severity of depression and right frontal lesion load and right temporal brain volume [40]. Using careful inclusion criteria and excluding MS patients with both premorbid and family history of mood disorder, a recent study compared brain lesion localization in MS patients with or without major depression and found that depressed patients had more hyperintense lesions in left inferior medial frontal regions and greater atrophy in left anterior temporal regions [41•].

Inflammation is still considered a possible depressogenic candidate, since many proinflammatory cytokines have been associated with depression, including interleukin-6 and 8, γ-interferon, and tumor necrosis factor. A bidirectional link has been hypothesized: the immune phenomena associated with depression might exacerbate MS, or could represent a pathogenetic mechanism common to both illnesses [42–44]. Available studies are, however, correlational in nature, and do not allow one to define the direction of this intriguing interaction between mood and inflammation.

The possible depressogenic effect of interferon treatment is still highly controversial, since available studies are inconsistent and do not take into account the new findings about structural abnormalities in depressed patients without MS, and in MS patients with or without depression [45]. New research in selected samples, with brain imaging assessment, is needed to clarify the issue.

As for Parkinson's disease, treatment indications rely on open studies and case reports, and no clear-cut guidelines can be derived from the literature to choose drugs and

dosages. TCAs were widely used, but a placebo-controlled trial of desipramine showed modest beneficial effects, with side effects limiting dosage in half of the patients [46]. Studies about SSRIs are scarce, and some reports questioned the efficacy of sertraline [47] and reported a risk of exacerbation of MS symptoms with fluoxetine [48]. A recent open study in 43 interferon β-1b treated patients experiencing a major depressive episode reported a 79% response rate to fluvoxamine despite a 16% attrition rate mainly due to side effects [49•]. Intestingly, MS patients experienced the usual side effects of treatment, with nonsignificant changes in specific MS-linked disability.

Other conditions

Mood symptoms are common in Alzheimer's disease and other dementias, and the use of antidepressants has been proposed for their clinical management. Superiority over placebo was detected for the SSRIs citalopram [50] and sertraline [51], but a recent randomized placebo-controlled trial in donepezil treated Alzheimer's disease patients found only modest effects of adjunctive sertraline on clinical global impression of improvement, with no differences in common psychiatric treating scales [52]. Given that the possible effects of SSRIs in improving cognitive performance in Alzheimer's disease are controversial [53•], and Alzheimer's disease patients need specific treatment of cognitive disabilities, the combination of SSRIs and cholinesterase inhibitors seems of unproven usefulness.

Conclusion

Depression in neurological disorder and 'primary' idiopathic major depression seem to share clinical phenotype, treatment options, and possibly pathogenetic mechanisms involving multifactorial abnormalities in specific brain regions.

Directions for future research in this area will involve the definition of the precise nature of this pathogenetic overlap, and will consider the clinical need for randomized controlled trials to assess efficacy and options of antidepressant treatments. Today, the mainstay of the clinical management of depression in neurology is a drug of proven efficacy in psychiatric mood disorders, but of as yet undefined characteristics and side effects in the several neurologic syndromes that can cause depression.

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