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The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features

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ABSTRACT

As the population ages, the economic and societal impacts of neurodegenerative and neuropsychiatric disorders are expected to rise sharply. Like dementia, late-life depressive disorders are common and are linked to increased disability, high healthcare utilisation, cognitive decline and premature mortality. Considerable heterogeneity in the clinical presentation of major depression across the life cycle may reflect unique pathophysiological pathways to illness; differentiating those with earlier onset who have grown older (early-onset depression), from those with illness onset after the age of 50 or 60 years (late-onset depression). The last two decades have witnessed significant advances in our understanding of the neurobiology of early- and late-onset depression, and has shown that disturbances of fronto-subcortical functioning are implicated. New biomedical models extend well beyond perturbations of traditional monoamine systems to include altered neurotrophins, endocrinologic and immunologic system dysfunction, inflammatory processes and gene expression alterations. This more recent research has highlighted that a range of illness-specific, neurodegenerative and vascular factors appear to contribute to the various phenotypic presentations. This review highlights the major features of late-life depression, with specific reference to its associated aetiological, clinical, cognitive, neuroimaging, neuropathological, inflammatory and genetic correlates. Data examining the efficacy of pharmacological, non-pharmacological and novel treatments for depression are discussed. Ultimately, future research must aim to evaluate whether basic biomedical knowledge can be successfully translated into enhanced health outcomes via the implementation of early intervention paradigms.

Contents

Abbreviations: 5HTTLPR, serotonin transporter gene; 5-HT, serotonin; ACC, anterior cingulate cortex; AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; BOLD, blood oxygen level dependent; Cho, choline; CM, cerebral metabolism; CNS, central nervous system; Cr, creatine; CVD, cardiovascular disease; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; ECT, electroconvulsive therapy; EoD, early-onset depression; FA, fractional anisotropy; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; HDL, high density lipoprotein; HMPAO, hexamethyl-propylene amine oxime; HPA, hypothalamic pituitary axis; LLD, late-life depression; LoD, late-onset depression; MCI, mild cognitive impairment; MD, major depression; MEG, magnetoencephalography; mI, myoinositol; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTHFR, methylenetetrahydrofolate reductase; MTR, magnetization transfer ratio; NAA, N-acetyl aspartate; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; PiB, Pittsburgh B; rCBF, regional cerebral blood flow; RCT, randomised controlled trial; SPECT, single photon emission computed tomography; SSRI, selective serotonin reuptake inhibitor; VRFs, vascular risk factors; WMLs, white matter lesions.

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1. Introduction

As the population ages, the economic and societal impacts of neurodegenerative and other neuropsychiatric disorders are expected to rise sharply (Access Economics, 2009; Bloom et al., 2011; Smith, 2011). While dementia is emphasized, late-onset depressive disorders are also common and disabling (Hickie and Scott, 1998; Naismith et al., 2007). Hence, these conditions are now the focus of considerable public health and clinical attention (Hickie et al., 2006; Highet et al., 2002; Kessler et al., 2010; Naismith et al., 2009b; Ustun et al., 2004). The prevalence of clinically significant depressive syndromes in those people over 60 years of age (i.e. 'late-life depression' or LLD) ranges from 9% to 18% and incidence rates of 19.3 per 1000 person years have been reported (Beekman et al., 1995; Luijendijk et al., 2008; Mulsant and Ganguli, 1999). LLD has been linked to increased rates of suicide and premature mortality (Gareri et al., 2002) and more frequent use of health care with significantly higher health care costs (Katon, 2003).

The core symptoms of major depression (MD) are persistently depressed mood or anhedonia (i.e. loss of pleasure in normal daily activities). Typically patients also report cognitive impairment (slowed reaction time, poor concentration and memory), dysfunctional thoughts (e.g. inappropriate guilt, worthlessness, suicidal ideation), appetite disturbance or weight change, loss of libido, sexual dysfunction, non-localized pain, low energy, altered sleep–wake cycle and daytime fatigue. Indeed, disturbances of sleep appear to be linked directly to cognitive impairment (Cho et al., 2008; Dew et al., 1997; Naismith et al., 2009b, 2011b). Hence, new treatments recognise the significance of incorporating sleep and circadian realignment into disease management (Hickie and Rogers, 2011).

There is considerable heterogeneity in the clinical presentation of MD across the life cycle (Hickie et al., 2009). Younger patients may have clinical profiles characterized by high trait anxiety and quite variable patterns of circadian, sleep, energy and appetite disturbance (Hansell et al., 2011). Those in mid-life present the more stereotypic picture of anhedonia in combination with sleep disturbance, weight loss and cognitive and motor impairments (American Psychiatric Association, 1994). In later-life, clinical phenotypes are again more variable (Blazer, 2003). This may well reflect different neuropathological pathways to illness – largely differentiating those with earlier onset who have grown older from those who are experiencing clinical depression for the first time. Certainly, modelling of genetic and environmental risk factors over the life course suggest distinctly differing pathways in early, mid and later-life (Gillespie et al., 2004). It would appear that the relevance of genetic risk to vascular risk factors particularly