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Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis – What do we need to know?

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ABSTRACT

Depression (MDD) is prodromal to, and a component of, Alzheimer's disease (AD): it may also be a trigger for incipient AD. MDD is not a unitary disorder, so there may be particular subtypes of early life MDD that pose independent high risks for later AD, though the identification of these subtypes is problematical. There may either be a common pathological event underlying both MDD and AD, or MDD may sensitize the brain to a second event ('hit') that precipitates AD. MDD may also accelerate brain ageing, including altered DNA methylation, increased cortisol but decreasing DHEA and thus the risk for AD. So far, genes predicting AD (e.g. APOEε4) are not risk factors for MDD, and those implicated in MDD (e.g. SLC6A4) are not risks for AD, so a common genetic predisposition looks unlikely. There is as yet no strong indication that an epigenetic event occurs during some forms of MDD that predisposes to later AD, though the evidence is limited.

Glucocorticoids (GCs) are disturbed in some cases of MDD and in AD. GCs have marked degenerative actions on the hippocampus, a site of early β-amyloid deposition, and rare genetic variants of GC-regulating enzymes (e.g. 11β-HSD) predispose to AD. GCs also inhibit hippocampal neurogenesis and plasticity, and thus episodic memory, a core symptom of AD. Disordered GCs in MDD may inhibit neurogenesis, but the contribution of diminished neurogenesis to the onset or progression of AD is still debated. GCs and cytokines also reduce BDNF, implicated in both MDD and AD and hippocampal neurogenesis, reinforcing the notion that those cases of MDD with disordered GCs may be a risk for AD. Cytokines, including IL1β, IL6 and TNFα, are increased in the blood in some cases of MDD. They also reduce hippocampal neurogenesis, and increased cytokines are a known risk for later AD.

Inflammatory changes occur in both MDD and AD (e.g. raised CRP, TNFα). Both cytokines and GCs can have pro-inflammatory actions in the brain. Inflammation (e.g. microglial activation) may be a common link, but this has not been systematically investigated. We lack substantial, rigorous and comprehensive follow-up studies to better identify possible subtypes of MDD that may represent a major predictor for later AD. This would enable specific interventions during critical episodes of these subtypes of MDD that should reduce this substantial risk.

1. Epidemiological evidence

At first sight, it seems a simple matter to decide whether or not major depression (MDD) represents a significant risk factor for later Alzheimer's disease (AD). Retrospective studies of those diagnosed with AD ought to reveal greater prevalence of previous MDD than controls; and prospective studies of cases of MDD should exhibit a greater incidence of subsequent AD than controls, both taking any confounding variables into account. But there are complications: depressive symptoms are prominently associated with current AD (Benoit et al., 2012; Olin et al., 2003) so it is a comorbid condition. The onset of MDD in elderly subjects predicts heightened likelihood of AD within one year – that is, it can also be a prodromal event (Geerlings et al., 2000; Heser et al., 2013). To complicate matters further, those with a premorbid history of MDD are more likely to exhibit depressive symptoms if they subsequently develop AD (Harwood et al., 1999).

So it is critically important to distinguish MDD as a prodromal or an associated set of symptoms of imminent or current AD from the prior occurrence of MDD as a distinct and independent risk factor for subsequent AD. The occurrence of MDD even 10–25 years previously is associated with later AD (Green et al., 2003; Speck et al., 1995), which suggests that MDD can be a predictor or a risk

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factor rather than an accompaniment of AD. But it is known that pathological changes in the brain (including the accumulation of β-amyloid) can be detected many years before the onset of clinical AD (Kantarci et al., 2011; Price and Morris, 1999) so another interpretation is that the onset of even early MDD is a reflection of the beginning of a lengthy and progressive neuropathological process leading to ultimate AD (Heun et al., 2002).

A meta-analysis of the relation between MDD and AD over the lifespan concluded that MDD was an independent risk factor for AD, rather than a prodromal symptom, since the association of the time interval between the first onset of MDD and later AD was found to be independent (or positive) (Ownby et al., 2006). It is noteworthy that, of the 20 cohort or case-control studies that were examined, the majority (95%) reported an increased risk for AD in those with a history of MDD. Another large study concluded that late-life MDD is a prodromal symptom of AD, whereas mid-life MDD is an independent risk factor for subsequent AD (Barnes et al., 2012). A 6 year epidemiological study on 2.4 million Danish subjects aged 50 or over showed that a history of MDD increased the risk for all-cause dementia in both those aged less than 65 (HR1.78) but even more after age 65 (HR 2.93). Though risk rose sharply for diagnoses of MDD within one year of dementia (implying a prodromal component), it remained relatively high even for cases occurring more than 10 years earlier, implying that MDD represented an independent risk, though this was greater for vascular dementia than AD (Katon et al., 2015). The current consensus, therefore, is that MDD during earlier parts of the life span seems to be a risk factor for subsequent AD, with an overall odds ratio of around 1.5–2 (Green et al., 2003; Rodrigues et al., 2014). Why should this be the case?

2. The heterogeneity of MDD

A critical point is that MDD is not a unitary diagnosis (Fried, 2015). It is widely recognized that there are subtypes of MDD, either defined clinically by different symptoms (for example, melancholic, atypical, anxious, psychotic), age of onset (early, late), clinical course (recurrent, chronic, etc.), context (post-bereavement, post-partum, seasonal, etc.), or treatment response (Thase, 2013). Definitions depend on measures of symptoms or outcome and there is little consensus on the existence of subtypes or the methods used to distinguish them (Fava et al., 2004; Schmidt et al., 2011) (Table 1). Since the range of symptoms incorporated into a diagnosis of MDD is so wide (A.P. Association, 2013), it is likely that there are subtypes of MDD that constitute a far higher risk for subsequent AD than is apparent from the overall odds ratio, diluted as it would be by including subtypes that do not represent such a risk. If the most risky subtype(s) were identified, then this would not only lead to advances in understanding the nature of the risk of MDD for AD, it would also offer opportunities for early intervention in such identified cases that could reduce or even eliminate the added risk for AD represented by these subtypes of MDD.

Making a number of assumptions, it is possible to estimate the possible reduction in AD if a subtype of MDD representing a risk were to be recognized, and the critical factors were, to an extent, neutralised. The average incidence of lifetime MDD is 1/6 (this takes the gender/sex difference into account). Suppose we assume that 25% have the subtype that is a risk for MDD, and this has an OR of 4.5, but that intervention only halves this risk. This would reduce the incidence of AD by 8%. Since in the UK there are c 850,000 cases of AD, there would be c 68,000 fewer. The figures for the USA would be approximately 5 times larger. These estimates, speculative as they may be, are also conservative.

Symptoms are the primary system for classifying MDD (A.P. Association, 2013), but there is general unease about the validity of diagnosing either MDD or its subtypes on the basis of symptoms alone. Current DSM-V criteria include up to nine symptoms, of which two are core, and another three additional. This wide range of symptoms, some of which overlap with each other and with those for other diagnoses, reduce confidence in the accuracy of both the diagnosis of MDD or assignment of particular cases to putative subtypes on the basis of symptoms alone (Paris, 2014). A more direct problem is that symptoms do not causally link MDD and AD, but are a reflection of underlying pathological processes, which may themselves represent causal links which, in terms of precise mechanisms, are not well understood. For example, sleep is disturbed in a proportion of cases of MDD, and is a prominent feature of AD (Spiegelhalder et al., 2013; Hatfield et al., 2004). This may reflect a common malfunction of the neural system controlling circadian rhythms or more specific disturbances in the mechanism of sleep per se. Although it is widely recognized that MDD must have a biological (i.e. neural) substrate, the current lack of knowledge about this substrate, or how it may vary with different subtypes of MDD or the contexts in which MDD may occur, severely limits attempts to relate symptoms to underlying neuropathological events in the brain. AD, as well as MDD, is a very heterogeneous condition (Karch and Goate, 2015; Chung et al., 2015). So it is possible that one or more subtypes of AD are those made more likely by a preceding history of MDD; that is, there are restricted relationships between diagnoses in both directions. Should this be the case, it would further increase the odds ratio of a particular subtype(s) of MDD as a risk for specific forms of later AD. MDD has also been identified as a risk for subsequent Parkinson's disease (PD), another neurodegenerative disorder (Gustafsson et al., 2015). It is also a risk for later cardiovascular disease (Gan et al., 2014; Barlinn et al., 2015) and thus for vascular dementia (see below). We do not know whether these risks are represented by separate subtypes of MDD.

Table 1
The heterogeneity of depression. Subtypes may be represented by combinations of the different categories of symptoms, history or clinical measures, etc.

Family history	Depression, bipolar disorder, schizophrenia, other psychoses, etc.; Relatedness
Environmental events	Early adversity, chronic difficulties, recent life events
Symptoms	Depressed mood, anhedonia, weight change, sleep disturbance, agitation (anxiety)/retardation, fatigue, low self-esteem, psychosis, suicidal ideation, etc.
Course	Age of onset, duration, severity, recurrence, response to treatment
Biochemistry	Cytokines, adrenal function, thyroid function, plasma amino-acids, diurnal rhythms, etc. (other biomarkers when available)
Genetics	Candidate polymorphisms (SNP, CNV), GWAS scans, etc.

3. The pathology of AD

If there were a common neural condition underlying at least some forms of MDD and AD, then the occurrence of the former would also be a potential cause for the latter, and one would expect that early changes characteristic of AD would be present in the brain of some MDD cases. This has been extensively studied and no indication of p-tau, β-amyloid, or related neuropathological alterations could be found (Lucassen et al., 2001; Muller et al., 2001), though earlier markers, such as intra-neuronal forms of amyloid or oligomers have not been investigated. However, if a neural event associated with MDD increased the vulnerability of the brain to a second, different, factor (independent of MDD) that directly contributes to the onset of AD, then the relevant form of