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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.

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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; Hesser 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 (Spiegelhalter 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.

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

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.

Table 2

Different categories of risk represented by MDD for later AD.

MDD	AD
Common predisposition (genetic, environmental)	MDD and AD as stages of a progressive disorder
Event during MDD subtype	Predisposition for later AD (same factor)
Event during MDD subtype	Sensitization to second hit (different factor)
Predisposition to MDD, or event during MDD	Accelerated progression of AD

MDD also represents a risk, but of an indirect kind. It is important to distinguish the various categories of risk (Table 2).

Postulating a link between MDD and AD at a neural level requires a firm understanding of the pathogenesis of AD. This presents problems. The accumulation of β -amyloid is associated with AD, but there is continued debate on its role, the specific forms of β -amyloid involved, their subcellular or intraneuronal localization and biochemical properties. Variants in the amyloid precursor genes are known to be responsible for the comparatively rare cases of early-onset, familial AD, but the argument against β -amyloid being the root cause of sporadic AD rests principally on two findings: (i) that β -amyloid can be present in high amounts in the brain without AD being evident, and (ii) that removal of β -amyloid using different methods has not, so far, led to either improvement of cognitive function or attenuation of established AD (Herrup, 2015).

However, neither is fatal for the proposition that a neurodegenerative ‘cascade’ follows β -amyloid accumulation (Hardy and Higgins, 1992) – which is suggested to include release of extra-synaptic glutamate from astrocytes, activation of microglia and NMDA receptors, NO formation, hyper-phosphorylation of tau, caspase-3 activation and, most recently, inactivation of a neuronal Na/K-ATPase (Bloom, 2014; Talantova et al., 2015; Ohnishi et al., 2015). If the stages of this cascade are themselves individually variable or controllable, then it is possible that there are those in whom β -amyloid can accumulate but without the rest of the cascade necessarily following. Similarly, if the cascade has already been activated or there are activators other than β -amyloid (Clark and Vissel, 2015), then removal of β -amyloid would not necessarily inhibit progression. Furthermore, there may be those in whom only a relatively small accumulation of β -amyloid can precipitate the cascade. So it is possible to agree that β -amyloid represents a risk for AD, rather than the disease itself, without abandoning the central tenet that it is a necessary though not sufficient cause. On this basis, MDD could either promote β -amyloid accumulation, or even potentiate the subsequent events of the neurodegenerative cascade that follows its accumulation (e.g. p-tau aggregation). However, it has to be acknowledged that uncertainties over the exact nature of the neurodegenerative process in AD or MDD hamper defining exact links between the two conditions.

4. Common genetic factors

If there were common genetic variants that predicted both MDD and AD, then this would strengthen the case for a common pathological origin, rather than MDD representing an independent risk for AD. Although it is known that MDD, like other psychiatric disorders, has a genetic basis, studies aimed at providing precise information on the nature of such a basis have been unrewarding. For example, a recent GWAS study based on around 10,000 cases and corresponding controls failed to find any significant SNP variations associated with MDD (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013). A different

approach yielded evidence linking MDD with genes associated with BDNF (see below) but also with many other factors (including ephrin receptors and GABA-related genes) (Chang et al., 2014). Studies on other disorders (e.g. schizophrenia), which have revealed more definite genetic components, show that these overlap considerably with other diagnoses, suggesting either that clinical assessment is inaccurate, or that susceptibility to mental disorder may not be specific at a genetic level (Gratten et al., 2014; Zhu et al., 2014; Cross-Disorder, 2013). Genetic studies are necessarily large, but nearly always omit any measure of environmental events, either early in life, during adolescence or more proximate to the onset of MDD, even though all are well-known to contribute to risk of this disorder (Brown, 1998; St Clair et al., 2014). Since these events, even though they are difficult to define and measure, may contribute around 50% of the overall risk for both MDD and AD (and even the link between them), their omission in such studies is a serious handicap (Kendler et al., 1999).

The candidate gene approach to MDD, which relies on selecting genes that have been identified on the basis of clinical or experimental evidence, has also not been very successful so far. Since SSRIs have been the recent mainstay in the treatment of MDD, with the consequent assumption – highly dubious (Cowen and Browning, 2015) – that low serotonin activity is a direct cause of MDD (rather than a risk for it – the two are not the same: see above), the focus has been on genes related to serotonin receptors or uptake modulators (Fabbri et al., 2013). Earlier studies, mostly comparing small numbers of patients with controls, were either negative or were not replicated (Fabbri et al., 2013). However, a landmark study that did combine environmental adversity with measures of a copy number variation of a 44 bp repeat in the promoter region of the serotonin re-uptake receptor (5HTT, SLC6A4) showed a highly significant interaction between the ‘short’ form of this receptor (5HTTLPR) and the occurrence of adverse life events as a positive predictor of subsequent MDD (Caspi et al., 2003). Subsequent replications have been inconsistent, though a recent meta-analysis supports the original finding (Karg et al., 2011). Methodological problems, particularly associated with defining and measuring the incidence or timing of adversity or stressful events, may have contributed to variations in the literature (Hammen et al., 2010; Uher and McGuffin, 2008); for example, the influence of 5HTT variants may be particularly potent on childhood adversity as a predisposition for later MDD. It is also apparent that, as for symptoms, this and other serotonin-related genetic variations are not to be associated specifically with one disorder (Yildirim and Derksen, 2013). This would be expected given the widespread action of serotonin on neural and behavioural functions, including reactivity to external events. The susceptibility of childhood adversity as a risk factor for MDD is also increased by variants in corticotrophin (CRH) receptor and GC related genes (CRHR1 and FKBP5) (Binder et al., 2008; Bradley et al., 2008). It is important to emphasize that genetic analysis is incomplete without careful additional assessment of the contribution of both the early and current social and physical environment, even though these are difficult to define and quantify.

Since precise information about the genetic basis of MDD is still incomplete, it is difficult to assess whether or not there are similar genetic risk factors for MDD and AD that could explain their connection. Twin studies show the heritability of AD (Raiha et al., 1996). But those genetic variations that have been identified as risk factors differ from those associated with MDD. Unlike MDD, much of the genetic risk for AD is attributable to a few genes (around 20) with large effects (Gratten et al., 2014; Lambert et al., 2013). A major contributor is the well-known APOE ϵ 4 variant (possibly more influential in women) (Strittmatter et al., 1993; Karch and Goate, 2015), but this has never been implicated as a risk for MDD, or for depression associated with AD (Locke et al.,

2013). Conversely, the 'short' variant of the serotonin transporter (5HTT) is not included in the list of known genetic risks for AD (Lambert et al., 2013). Indeed, none of the variants identified so far as contributing to the risk for AD have been implicated in MDD. Such comparisons do not exclude possible interactions between genetic variants (epistasis) or unknown gene–environment interactions which could represent common risk factors, but these are entirely speculative. Genes associated with the immune system are being identified as risk factors for AD (Karch and Goate, 2015) as well as in MDD (see below). It is possible that commonalities in genetic risk related to inflammation or immunity are still to be uncovered. Since inflammatory processes (themselves made up of numerous cell types and mediators) are being associated with a wide range of neurological and psychiatric disorders, a specific link is unlikely to be found in this context as in the others already mentioned (see below).

As well as genetic variations that may alter the likelihood of the occurrence of either MDD or AD, there may be those that either increase or inhibit the risk of MDD predisposing to later AD without necessarily altering the individual risk for either condition. None has so far been found, neither are there any reports of their being investigated. There are parallels in other contexts: for example, the APOEε4 variant increases the risk of AD following head injury (Sundstrom et al., 2007). There is increasing interest in the contribution that *de novo* mutations make to psychiatric disorders (i.e. variants that are not inherited but arise in the patient). Most attention has been focused on schizophrenia and autism (Gratten et al., 2013; Rovelet-Lecrux et al., 2015), rather than mood disorders (Van Den Bossche et al., 2012). Such *de novo* variants might occur that characterize a particular subtype of MDD that poses a risk for later AD, or increase that risk should the patient experience a bout of MDD. None have, so far, been described.

Altered expression of microRNAs (miRNA) has been described in both MDD and AD. Whether these are part of the genesis of these disorders or a response to the underlying pathology is not clear. Neither is there any information on the specific proteins that might be regulated by these miRNAs. As for studies on genetic variations, there is little consensus on the patterns of altered miRNA in either condition. Increased plasma miR-132, which interacts both with BDNF and the glucocorticoid receptor (see below), has been reported in MDD, but not AD. Comparing the patterns of reported miRNAs in the two conditions reveals little overlap between them (miR-107, 146a and 155 are possible exceptions), which does not support a common miRNA landscape (Femminella et al., 2015; Geaghan and Cairns, 2015).

5. Epigenetics

One way for an environmental or pathological event to impose a long-lasting effect on a subsequent trajectory is by epigenetic modification of particular genes. If the occurrence of MDD were to result in such an epigenetic event (e.g. DNA methylation or demethylation, or histone acetylation, etc.), then it could be a basis for subsequent vulnerability for AD. This scenario requires two conditions: that epigenetic events that are stable and long-lasting occur in MDD, and that they can be suggested plausibly as contributing to later AD.

DNA methylation patterns in the blood have been associated with MDD, including genes implicated in rapid glucocorticoid (GC) signalling, IL2 responses and adrenergic pathways (Cordova-Palamera et al., 2015), but see below for a caveat. Childhood adversity (e.g. quality of maternal care or the presence of early trauma), a known risk factor for later MDD, has been linked with consequent glucocorticoid receptor (GR) methylation (Weaver et al., 2004; McGowan et al., 2009) but it is important to note that many other

genes are altered, including corticotropin-releasing factor (CRF) (McGowan et al., 2011) and FKBP5 (which regulates GR (Klengel et al., 2014), particularly in the hippocampus. Changes in global DNA methylation, GABA_A receptor promotor hypermethylation and astrocytes have been reported. However, increased GR methylation in the brain was not found in post-mortem brains from cases of MDD (Alt et al., 2010). The role of GR in the link between MDD and AD is further considered below. It should be noted that altered DNA methylation (and other epigenetic changes) may occur locally and may be transient, so patterns in the blood may not necessarily reflect persistent ones in specific areas of the brain (Kinde et al., 2015; Nemoda et al., 2015). It is clearly important to distinguish epigenetic patterns in response to stress (Schouten et al., 2013) (which may be adaptive) from those that represent a risk for, or the presence of, MDD – one (not inevitable) pathological consequence of such stressors.

Our current information on epigenetic changes in the brain in MDD is thus highly incomplete. We still do not know whether different forms of MDD are correlated with correspondingly different methylation patterns, whether this involves specific genes or regional differences in methylation in the brain. Neither do we know whether chronicity or recurrent episodes of MDD are reflected in distinct epigenetic signatures in the brain. Finally, we need to know whether altered GCs and/or cytokines in MDD relate to epigenetic brain patterns and, if they do, how they map onto the other factors mentioned in this paragraph. Alterations in patterns of daily secretion or accumulative amounts of GCs during MDD (see below) may mediate epigenetic changes. This lack of data seriously limits attempts to relate epigenetic changes in MDD with the risk of consequent AD. Whilst future, more focused, post-mortem studies may improve matters, the field really awaits methods of imaging epigenetic changes reliably in the living brain.

If epigenetic patterns in the brain associated with MDD do represent a risk for subsequent AD, then they should still be present in AD and be distinguishable from the appropriate controls. Age itself is associated with changes in DNA methylation in the brain (Yang et al., 2015), so this also needs to be taken into account since age is the strongest risk factor for AD. Information on epigenetic patterns in AD is also limited; a recent review listed the current data, and emphasized its preliminary nature (Bennett et al., 2015). There is no overall, accepted, pattern: results from different studies have been highly variable; some (often based on small numbers of subjects) report no differences between AD and controls, and analysis of positive findings is complicated by being limited to end-stage disease (De Jager et al., 2014; Van den Hove et al., 2014). One paper reports a global increase in DNA methylation in the blood of AD patients, particularly associated with the APOEε4 allele (Di Francesco et al., 2015) and another increased histone acetylation (Narayan et al., 2015). But none has, so far, implicated the same genes as those reported for MDD; in particular, those associated with the HPA axis, plasticity or the immune system. Experimentally, a number of distinct patterns of DNA methylation, acetylation and microRNA production have been identified in genetically engineered AD mice, though it remains to be determined whether they also occur in human AD (Fitzsimons et al., 2014). The current evidence suggests that there is no reason, at this point, to postulate a common epigenetic pattern for AD and MDD, though there are serious reservations because of the sparse information for both conditions. Future results may modify this conclusion.

6. Glucocorticoids as predisposing factors

A wealth of evidence shows that chronic stress or excess glucocorticoids (e.g. cortisol in humans) can either damage the brain directly (Uno et al., 1994; Sapolsky et al., 1990) or potentiate the

action of other damaging agents, including β -amyloid (Magarinos et al., 1996, 1998; Sapolsky, 1996; Goodman et al., 1996; Tombaugh et al., 1992), whereas blockade of GCs is protective. For example, the hypercortisolism of Cushing's disease decreases hippocampal and frontal lobe volume (Starkman, 2013; Starkman et al., 1992) and results in long-term reductions in white matter and impaired cognitive function long after remission (van der Werff et al., 2014; Ragnarsson et al., 2012). A reduction in hippocampal volume has been repeatedly reported in MDD, but considerable variation exists in the literature. This may relate to differences in disease duration, anatomical delineation, lateralization, early life conditions and genotype (Czeh et al., 2015; Drevets et al., 2008; Kempton et al., 2011; Takahashi et al., 2010). Whether hippocampal volume loss reflects a cause or a consequence of MDD remains unclear but lower hippocampal volumes in patients can be predicted by more extensive depressive episode duration and recurrence, the size of their integrated cortisol responses and a history of early life stress. Furthermore, a smaller hippocampal volume can predispose the development of later psychopathology (Sapolsky et al., 1990; Czeh and Lucassen, 2007; Lucassen et al., 2014).

There may be regional differences in the sensitivity of hippocampus to either stress or depressive illness. The volumes of the posterior parts of the dentate gyrus and CA3 were specifically reduced in non-medicated patients compared to controls, and this was not seen in medicated subjects (Czeh et al., 2015; Huang et al., 2013). Total hippocampal volume has been related to the duration of depression, but this was not associated with altered density of either neurons or glia, suggesting shrinkage in either cell size or neuropil, which may reflect altered plasticity (Sheline, 2011; Swaab et al., 2005). Glucocorticoids (GCs) may accentuate brain damage; GC treatment worsened the outcome of traumatic brain injury in humans (Edwards et al., 2005), and magnified the damaging effects of neurotoxins in experimental animals ('neuroendangerment') (Sapolsky, 1996). There is general agreement that it is persistent elevations of GCs, in contrast to acute ones, that can be damaging to the brain (Joels et al., 2012; McEwen, 2008). Age-dependent increases in cortisol have also been suggested to promote neurotoxic actions (Landfield, 1994).

Disturbances in cortisol or, more accurately, the activity of the hypothalamo–pituitary–adrenal axis (HPA), are well established in some cases of MDD (Cowen, 2010; Stetler and Miller, 2011; Herbert, 2013). These are of several kinds, and do not necessarily occur together: furthermore, the impact they have on brain function will differ (Herbert, 2013; Herbert et al., 2006). (Fig. 1)

- (i) There is normally a surge in plasma cortisol 30–60 min after awakening (Pruessner et al., 1997). Increased size of this surge predicts MDD, is elevated during depressive episodes and persists after recovery (Vrshek-Schallhorn et al., 2013; Bhagwagar et al., 2005). Despite much speculation, the functional significance of the awakening effect, if there is one, is still not known (Law et al., 2013).
- (ii) The daily and ultradian cortisol rhythms are altered in MDD: characteristically, evening levels (which normally fall) remain elevated (Sachar et al., 1973; O'Brien et al., 1994; Christensen et al., 1985; Goodyer et al., 1996). This has two distinct consequences: it removes the signalling function of the rhythm (i.e. the brain is exposed to a relatively constant amount of cortisol rather than an intermittent daily surge), and the total amount of cortisol reaching the brain is increased (Guazzo et al., 1996); in some cases, this can approach levels recorded in Cushing's disease. Higher cortisol levels are negatively related to cognitive function in MDD (Hinkelmann et al., 2009). The way each of these parameters changes will vary in different patients (i.e. they may repre-

Fig. 1. The categories of HPA axis dysfunction in depression. (A) The awakening effect on cortisol in depressed or control subjects. Redrawn from Bhagwagar et al. (2005). (B) Daily cortisol rhythms in depressed and control subjects. Drawn from data in O'Brien et al. (2004). (C) The dexamethasone suppression test in depressed or control subjects. Cortisol values are those at awakening before or after 0.5 mg dexamethasone the previous evening. Redrawn from Jarcho et al. (2013).

sent distinct subtypes of MDD), but it is important to reiterate that the effect they have on neural function are also very different (Young et al., 2004; Conway-Campbell et al., 2010; Karatsoreos et al., 2011).

- (iii) The HPA axis becomes resistant to feedback inhibition in some cases of MDD; a dose of dexamethasone in the evening, which normally reduces plasma cortisol next morning to below 50 ng/ml, becomes ineffective (Carroll, 1986) and has been associated with changes in the glucocorticoid receptor (GR) (Anacker et al., 2011), possibly related to the immunophilin protein FKBP51 and other stress-related genes (Wohnik et al., 2005). Note that all these alterations in HPA activity occur only in a proportion of cases of MDD.

Defining 'excess' glucocorticoid activity is not straightforward, though most authors do so in a binary fashion by comparing the target group with matched controls. But it is well-known that opti-

mal levels of cortisol vary both between individuals and within the same individual under different circumstances. For example, Addisonian patients (who suffer from adrenal insufficiency and need replacement cortisol treatment) have to increase their dose if they suffer an infection or other stressful events. So a simple measurement of cortisol levels may not reflect accurately 'optimal' or 'excess' amounts in individual cases (Herbert, 2013). Nevertheless, a proportion of MDD cases show disturbed secretion of cortisol. Since this exposes the brain to abnormal amounts or patterns of cortisol, altered rhythms or increased overall levels of cortisol are features that may well contribute to later AD, and impaired feedback may reflect pathologically significant changes in corticoid receptors (Anacker et al., 2011; Wochnik et al., 2005).

Stressful 'life events' are known to precede many cases of MDD (see above). But only a proportion of those experiencing such events subsequently develop MDD (Brown et al., 1987). Since stress and elevated cortisol levels have been identified as a common provoking factor for both MDD and AD (Sotiropoulos et al., 2008; Machado et al., 2014; Harris et al., 2000), the magnitude and characteristics of the cortisol response to stress can have implications for later AD without an intervening bout of MDD (Aznar and Knudsen, 2011). Furthermore, depressed patients show an enhanced cortisol response to further stress (Burke et al., 2005). It should be noted that 'stress' is a generic term, incorporating many forms of physical or psychological demand and challenges, and that to equate 'stress' solely with 'cortisol' is to underestimate the complexity of the biological response to stress and to coping with it. Exposure of animals to stressors is commonly used to 'model' depression in humans (see below), but there is considerable confusion in the literature between changes in the brain that represent responses to stress (and thus possibly adaptations to it) and those that are thought to model depression (Menard et al., 2015); the two are clearly not the same.

But can we implicate altered cortisol in the risk for AD? As is the case for depressive symptoms, raised blood and CSF cortisol are also features of AD (Armanini et al., 2003; Ferrari et al., 2000; Gil-Bea et al., 2010), and cortisol levels may also be dexamethasone (i.e. feedback)-resistant (Davis et al., 1986) so the recurrent problem remains of distinguishing risk factors from co-morbidity (see above). In contrast to MDD, daily cortisol rhythms seem not to be flattened in AD (Hatfield et al., 2004; Hartmann et al., 1997), and GR expression (in the hippocampus) is not altered in AD or with age (Seckl et al., 1993; Wang et al., 2013). Cortisol tends to rise during normal ageing (Lupien et al., 1998, 2009) so one explanation is that raised cortisol in AD is an accentuation of the expected pattern (Landfield, 1994). The co-existence of MDD in AD is not necessary for cortisol to be raised (Hoogendijk et al., 2006) so this is not an epiphenomenon of MDD in AD. Whether or not cortisol is increased in mild cognitive impairment (MCI) is not agreed (Arsenault-Lapierre et al., 2010; Popp et al., 2009), though this has a bearing on whether cortisol levels could be a prodromal indicator of incipient AD, or even a trigger for its onset or progression.

But do pre-morbid levels of cortisol predict subsequent AD? A large prospective study suggested that they did not (Schrijvers et al., 2011). This has to be contrasted with evidence that cortisol levels are positively associated with cognitive decline in aged humans without AD (Lupien et al., 1998) and with a report that higher levels of cortisol predict more rapid cognitive decline in those with early AD (Huang et al., 2009), suggesting that cortisol is associated with ongoing pathology. Older non-demented subjects with an APOE ϵ 4 genotype had higher CSF cortisol levels than those with APOE ϵ 2 (Peskind et al., 2001): since the former is a major risk factor for AD (see above), there may be a more subtle and complex association between cortisol and the risk for AD waiting to be explored. Experimentally, stress or GC treatment acceler-

ated the formation of both β -amyloid and p-tau in mouse models of AD (Gil-Bea et al., 2010; Marlatt and Lucassen, 2010), whereas mifepristone, a glucocorticoid-receptor blocker, reduced the formation of both β -amyloid and phosphorylated tau (p-tau) in the 3xTg-AD mouse (Baglietto-Vargas et al., 2013). GC treatment of a rat neuronal cell line engineered to express human tau increased the APP protein C99 and stabilized p-tau (Sotiropoulos et al., 2008); but these were only short-term studies, and β -amyloid 40 and 42 were not altered. It remains highly plausible that raised cortisol levels observed in AD could potentiate the neurodegenerative cascade.

If GCs are implicated in AD, then mechanisms that regulate their activity should also have a role. The metabolism of glucocorticoids at a neuronal level is regulated by enzymes (11 β -hydroxysteroid dehydrogenases: 11 β -HSD) that convert cortisol to its inactive metabolite (cortisone), or vice versa. 11 β -HSD type2 protects cerebellar neurons from the damaging actions of GCs (Holmes et al., 2006) and inhibiting 11 β -HSD type1 improves cognition in ageing men (55–75 yr) (Sandeep et al., 2004). A rare variant of the 11-HSD type1 gene (reducing its action) has been linked with a 6-fold increase in the risk for AD; apparently type 1 can remove potentially damaging GCs (Quervain et al., 2004). This adds to the weight of evidence that glucocorticoids are a significant contributor to the onset of AD. But it is clear that a sufficiently long and substantial follow-up study on the role of life-time cortisol levels, and how these relate to genetic variants in 11 β -HSD, as a risk for AD has not yet been carried out. In particular, there is no information on whether those cases of MDD that also present with altered cortisol have an added risk for later AD in contrast to cases without such disturbances.

7. Sites and mechanisms of glucocorticoids promoting AD: hippocampal neurogenesis

The hippocampus and perihippocampal (entorhinal) cortex are curiously highly susceptible to anoxic and toxic damage (Kirino et al., 1985) and to the effects of stress (McEwen et al., 2015). Some of the earliest signs of AD pathology occur in the hippocampus, well before symptoms appear (Douaud et al., 2013) and the closely-related medial temporal entorhinal cortex is a site of early amyloid deposition (Villemagne and Rowe, 2013). The hippocampus, together with the prefrontal cortex and amygdala, is also highly sensitive to the damaging actions of corticoids (Leuner and Shors, 2013), and excess corticosterone is well-known to impair spatial and episodic memory, a prominent function of the hippocampus and a core symptom of AD (de Quervain et al., 1998).

Neurogenesis in the dentate gyrus (DG) of the adult hippocampus is well-established to occur in both rodents and humans. About 700 new neurons are formed per day in man (Spalding et al., 2013) within a population of around 15 million (Amaral et al., 2007). The relative rate in rats is much higher. Newly-formed neurons project to CA3, which then projects to CA1 and thence to the entorhinal cortex. A consequence is that the addition of only a few, highly excitable, new neurons to the otherwise relatively silent circuit of the DG can exert significant effects in the CA3 subregion, that can amplify to the CA1 and cortex. Thus, even though the newborn cells are present in small numbers, they have considerable impact on hippocampal function. The rate of neurogenesis declines with age in both rats and humans, though somewhat less in the latter (Siwak-Tapp et al., 2007).

Neurogenesis is powerfully regulated by numerous hormonal and environmental factors, including stress, exercise and enriched environmental housing that can all modify one or more stages of the process of forming new neurons (Koehl, 2015). Changes in neurogenesis have been implicated in specific brain disorders such as

depression, epilepsy and AD and their experimental models (Mu and Gage, 2011; Thompson et al., 2008), and drugs of abuse or antidepressant medication also modify neurogenesis. While MDD and stress-related disturbances were thought traditionally to involve neurochemical (mainly monoaminergic) disturbances at the synaptic level, more recent studies indicate that impairments in structural plasticity contribute to the volumetric changes and pathophysiology of these disorders. Various candidate cellular substrates, such as dendritic retraction, neuronal loss or glial changes have been proposed, most of which are stress-sensitive. However, it remains uncertain whether changes in these substrates can be considered truly 'pathological' or whether they reflect more dynamic adaptations to stress, that can, at least to some extent, be transient, and/or reversible (Czeh and Lucassen, 2007; Lucassen et al., 2014; Sapolsky, 2000).

There is ongoing debate about whether decreased dentate gyrus neurogenesis underlies depression and if recovery depends on its restitution. Initially, this was based on the fact that drugs used as anti-depressants stimulated the mitotic rate of the dentate progenitor cells in rats, though this has not always been confirmed (Jacobs et al., 2000; Malberg et al., 2000). But the word 'anti-depressant' defines a drug (e.g. fluoxetine) by its selective clinical use, not its pharmacological mechanism, which is largely related to serotonin. Serotonin has many actions on the brain, so to relate any effect specifically to MDD on the basis of clinical use of such drugs is not logical. The evidence that neurogenesis is reduced in MDD is inconsistent, but better scanning methods are needed for reliable assessments of neurogenesis in living subjects suffering from depression (Manganas et al., 2007). Post-mortem studies have shown increased formation of dividing neuronal cells (Boldrini et al., 2009) (the numbers in this study were small) and immature (double-cortin: (DCX) staining) neurons in the dentate gyrus following anti-depressant therapy, the latter only in younger, female patients (Epp et al., 2013). There is more agreement that hippocampal volume is decreased in MDD but only limited evidence that enhanced neurogenesis is required for the anti-depressant effects of drugs (Lucassen et al., 2014, 2015; Miller and Hen, 2015; David et al., 2009; Surget et al., 2011). Although decreased progenitor proliferation has been found in the dentate gyrus of elderly depressed patients, this did not change with anti-depressant treatment (Lucassen et al., 2010). As already mentioned, cortisol levels are raised in some cases of MDD, and on the basis of experimental (animal) evidence this would be expected to reduce neurogenesis in the dentate gyrus in these cases at least. Studies on the relation between MDD and hippocampal neurogenesis carried out post-mortem have been unable, so far, to take (pre-mortem) cortisol levels or patterns of secretion into account.

8. Corticoids and the hippocampus

Experimentally, corticoids have two structural actions on the hippocampus: the dendritic fields of the pyramidal neurons of CA3 atrophy (Magarinos et al., 1998; Alfarez et al., 2009), and the mitotic activity of neurogenic cells and maturation of newly-formed neurons in the dentate gyrus is markedly repressed (Cameron et al., 1998). It is not clear whether these effects are linked, though CA3 is the major output for the granular neurons of the dentate gyrus, and lesions of CA3 reduce dentate neurogenesis (Liu et al., 2011). CA3 projects to CA1 (via the Schaffer collaterals), the area implicated in initial AD. Neurogenesis is altered in mouse models of AD (Rodríguez et al., 2008). During the initial stages, when early (mostly oligomeric) amyloid precipitates start to form, hippocampal stem cells show increases in proliferation, whereas at older ages, and at later stages of pathology develop-

ment, when amyloid plaque deposition is prominent, proliferation is decreased in most models (Marlatt and Lucassen, 2010; Hamilton et al., 2010), though there have been discrepancies (Krezymon et al., 2013). Neurogenesis is reduced by amyloid precursor protein (APP) (Wang et al., 2014). It is also reduced by knocking down presenilin-1, a gene known to be involved in some cases of AD, and which impairs pattern recognition and memory (Bonds et al., 2015). These models are based on genetically engineered abnormalities: since these are known in only a very small proportion of human AD, their relevance may be limited.

However, similar events appear to take place in human AD brain where increases in cell cycle and proliferation markers were reported in the AD hippocampus (Mu and Gage, 2011; Arendt et al., 1996; Boekhoorn et al., 2006; Jin et al., 2004; Ekonomou et al., 2015). So far, little is known about the actual phase of neurogenesis in AD brain (Fitzsimons et al., 2014) – partly because neurogenesis is a rare event in the aged human brain and partly because it is often difficult to make accepted rodent neurogenesis markers work on human postmortem brain. For example, double-cortin (DCX), a marker of immature neurons, is very sensitive to degradation during post-mortem delay (Boekhoorn et al., 2006) and may also label a subset of astrocytes (Verwer et al., 2007).

There is increasing evidence for epigenetic control of hippocampal neurogenesis (Fitzsimons et al., 2014), but no indication, so far, that this relates to MDD or its risk for later AD. Reduced hippocampal neurogenesis is postulated to be an important critical early event in human AD (Mu and Gage, 2011) – though this is not universally agreed – but measuring mitotic cells in postmortem brain has given inconsistent results. It has been suggested that whilst progenitors decrease, there is compensatory increased differentiation into new neurons (Fitzsimons et al., 2014). Elevated cortisol, such as that occurring in some cases of MDD – particularly if it is persistent – may thus contribute either to the development of AD or to its progression (Perry et al., 2012) and its suppression of hippocampal neurogenesis is one plausible mechanism. Loss of episodic memory is a prominent feature of AD, and this is reproduced experimentally by corticosterone treatment (Darcet et al., 2014). Restoration or stimulation of neurogenesis in one such model also restored spatial memory, and could delay AD pathology (Richetin et al., 2015; Hsiao et al., 2014).

The glucocorticoid receptor (GR) is central to the regulation of the HPA axis; it has also been implicated in MDD. It has a complex gene structure. Two of its nine exons are variable: those in exon 9 result in two splice variants (GR α and β) but there are also multiple alternative promoters (Alt et al., 2010). Some of these sites are regulated by epigenetic methylation (see above). These variants alter the ability of GCs to bind to GR, or the latter's ability to translate and activate downstream genes. So considerable variation in GR activity can occur in different individuals (Stevens et al., 2004), different tissues, and in the same tissue (e.g. brain) according to circumstances (e.g. the environment) (Cao-Lei et al., 2011). Furthermore, the GR may have many other actions in addition to those on downstream genes (Yudt and Cidlowski, 2002), and the contemporaneous activity of the mineralocorticoid receptor (MR) may also be important for the brain's response to corticoids (de Kloet et al., 2007). Alterations in the GR have been postulated as central both to the onset of MDD and its response to anti-depressants (Anacker et al., 2011; de Kloet et al., 2007), though it should be recalled that GCs also have rapid, non-genomic actions on the brain (Joels et al., 2012; Dallman, 2005). It is not clear whether particular patterns of GR are associated with AD.

Glucocorticoid response elements (GRE) are present in around 20% of the genome, which makes assigning links between altered cortisol and putative downstream events very difficult. In view of the possible variations in GR, these are likely to be both individual and disorder-specific. One plausible mechanism through which

GCs could promote AD or heighten the risk of early AD progressing to clinical stages involves indoleamine 2,3-dioxygenase (IDO). GCs induce IDO which promotes the metabolism of tryptophan to kynurenine and thence quinolinic acid, a known neurotoxin acting on glutamate receptors (Maes et al., 2011). This enzyme is also responsive to interleukins, a point to be discussed further below. Flattening the diurnal corticosterone rhythm in rats, which mimics that in MDD, prevented neurogenesis being stimulated by either inhibition of nitric oxide synthase (NOS), the SSRI fluoxetine or BDNF (Pinnock et al., 2007; Huang and Herbert, 2006). If this occurs in humans, it is likely to be one element predisposing to later AD.

BDNF has major enhancing actions on brain plasticity as well as on hippocampal neurogenesis, probably through the *wnt* pathway (Pinnock et al., 2010). There are suggestions that BDNF plays a principal role in MDD and in the anti-depressive actions of SSRIs, which, experimentally, increase BDNF levels in the hippocampus (Pinnock et al., 2010; Castren and Rantamaki, 2010; Duman et al., 1997). A common BDNF variant (val/66/met) has been linked with altered volumes of grey matter in the human hippocampus and frontal cortex (Pezawas et al., 2004), as well as with the risk for MDD in adolescents (in association with cortisol) and age-related cognitive decline (Goodyer et al., 2010; Hariri et al., 2003; Harris et al., 2006). There is little direct evidence for changes in BDNF in MDD; most studies measure plasma levels, which do not necessarily reflect those in the brain; but CSF levels are reduced in late-life depression (Diniz et al., 2014). Experimentally, GCs reduce the normally high levels of BDNF in the hippocampus (Pinnock and Herbert, 2008; Schaaf et al., 1998) as well as in other parts of the brain (Bennett and Lagopoulos, 2014; Pluchino et al., 2013). It is therefore probable that prolonged, elevated GCs in MDD would reduce the activity of BDNF, though no direct evidence for this is currently available. If this occurred, would it represent a risk factor for AD? Lower serum BDNF levels predicted subsequent AD in a large cohort followed for up to 10 years (but see caveat above) (Weinstein et al., 2014) and parietal cortical levels are reduced in post-mortem AD brains (Peng et al., 2005). However, the val/66/met BDNF variant which has been implicated in the risk for MDD has not been associated with AD (see above) (Kim et al., 2015). BDNF function may also be directly impaired by β -amyloid (Gan and Silverman, 2015). Since lowered BDNF is considered to play a role in synaptic loss and impaired neuronal function, reductions during MDD may predate or exacerbate those in AD.

Can glucocorticoids influence the formation or clearance of either β -amyloid or p-tau? Stress or GCs have been shown to encourage the misprocessing of amyloid precursor proteins (APP) in rodents and accumulation of β -amyloid or its clearance in astrocytes and the brain (Catania et al., 2009; Wang et al., 2011; Budas et al., 1999; Harris-White et al., 2001; Kulstad et al., 2005) (and see references above). Similar results were found for p-tau, which is increased in stressed mice (Filipczik et al., 2012). Tg2576 mice have a genetically-induced increased formation of β -amyloid, and the PS19 mouse develops p-tau. Both were increased by stress. Glucocorticoids increased the amount of β -amyloid 40 and 42 in cultured N2A cells (human neuroblastoma-derived) perhaps secondary to raised levels of amyloid precursor protein (APP), and enhanced both β -amyloid and p-tau by increasing the amount of APP and β -secretase (BACE) (Green et al., 2006) in the 3xTg-AD mouse model of AD which, similar to human AD, has elevated corticosterone. There is little parallel evidence for the human brain.

It should be recalled that abnormalities of the HPA axis include those in corticotropin-releasing factor (CRF). CRF has a widespread distribution in the brain, and a number of functions in addition to that regulating the pituitary release of ACTH; for example, it is anxiogenic (Shekhar et al., 2005; Takahashi, 2001) and has direct actions on hippocampal dendritic spine density (Andres et al.,

2013). CRF, together with vasopressin, is the main driver of the HPA axis and has been implicated in the pathogenesis of MDD (Bao and Swaab, 2010). It has also been implicated in AD. The effects of stress on β -amyloid and p-tau were prevented by blocking the CRF type 1 receptor (Carroll et al., 2011; Rissman et al., 2012, 2007; Justice et al., 2015), suggesting that CRF as well as GCs may contribute to the potentiation of AD (Joshi et al., 2012; Kang et al., 2007). It is important to remember that CRF has actions in the brain outside the HPA axis and that all the actions of the HPA axis may not be due solely to corticoids. Overall, the experimental evidence leaves little doubt that the HPA axis can have a major influence on the formation of pathological proteins associated with AD. This has direct relevance to the likelihood of MDD representing a risk for AD, and provides one intermediate mechanism for why that should be.

9. Gender (sex) differences

MDD and cortisol may also be relevant to gender (sex) differences in AD. Whilst there is agreement that the prevalence of AD is greater in women, whether or not this is a function of increased lifespan and/or altered incidence is unresolved (Mielke et al., 2014). The consensus seems to be that age-specific AD is not more common in women, so the increased prevalence is due to a longer life-span (Hebert et al., 2001; Bachman et al., 1993), though there are disagreements (Schmidt et al., 2008). Amyloid pathology as revealed by PET was associated with age but not gender (Jansen et al., 2015), but rates of cognitive decline are reported to be greater in women (Holland et al., 2013). Gender differences in MDD may account for some of these findings. MDD is more common in women (about 2–3-fold) than men (St Clair et al., 2014; Rai et al., 2013), and this might or might not include specific subtypes that predispose to AD. Adverse life events are also reportedly more common in women (Oldehinkel and Bouma, 2011), so additional stress, irrespective of MDD, could contribute. Finally, basal levels of 'free' cortisol as measured in the saliva of young, healthy females are about 20% higher than in males (Netherton et al., 2004), indicating that female brains are normally exposed to higher amounts of cortisol and thus possibly greater risk for AD. However, a study on levels of CSF cortisol (about 6% of those in plasma) showed no gender difference (Sosvorova et al., 2015). This evidence can be interpreted in several ways: one is that women are actually more resistant to the risk of AD following MDD, since several putative risk factors occur more frequently in women, but not AD; but once AD is initiated, they are more susceptible to rapid progression; that is, the neurodegenerative 'cascade' is influenced by gender. Some gender differences in AD – for example, an increased rate of deterioration in females (Herrmann et al., 2015) – could be related to corresponding differences in HPA activity.

10. MDD, cytokines and AD

There is general agreement that cytokines are elevated in the blood and inflammation is involved in some cases of MDD (Haroon et al., 2012; Maes, 2011; Patas et al., 2014; Thomas et al., 2005; Walker et al., 2014), but much less consensus about which of the many cytokines are involved, though IL1 β , IL6, TNF α and CRP are most consistently reported (Dowlati et al., 2010; Alesci et al., 2005), and whether particular subtypes of MDD or what proportion of cases are marked by elevated cytokines (some say around a third: Krishnadas and Cavanagh, 2012). Atypical MDD, characterized by increased appetite and body weight, has been associated with raised cytokines (IL6, TNF α , CRP), in contrast to melancholic MDD (decreased weight, etc.) in one study (Lamers et al., 2013) but these cytokines have been associated also with

other symptoms (Bob et al., 2010; Duivis et al., 2013). Adipose tissue is a known source of cytokines (Howren et al., 2009). A subtype of MDD with suicidal ideation had raised levels of IL1 β and IL6 in serum and brain compared to cases without this feature (Black and Miller, 2014). Chronically elevated IL1 β can act on an accessory IL1 receptor protein (the AcP/AcPb ratio) to increase the likelihood of BDNF suppression and hence reduce synaptic function in the ageing hippocampus (Prieto et al., 2015). Peripheral infusions of cytokines, or peripheral infections, result in actions on the CNS – for example, sickness behaviour – which demonstrates that peripheral cytokines can act on the brain, despite the blood–brain barrier (Dantzer et al., 2008). CSF levels of IL6 were increased in suicidal patients and correlated with their depression scores (Lindqvist et al., 2009), further emphasizing direct action on the brain.

A more difficult question is whether elevated cytokines present a risk for AD. This requires long-term follow-up. Higher levels of CRP increased the risk for AD (but also vascular dementia) 25 years later (Schmidt et al., 2002). It should be noted that there are vascular changes in AD, so the distinction between the two categories may not be entirely distinct (Weller et al., 2009). The Framingham study on 668 subjects with a follow-up of around 7 years showed that AD onset (incidence 6.4%) was associated with previous blood levels of IL1 β and TNF α , but not CRP or IL6; depressive symptoms were not measured. Experimentally, IL1 β induces hippocampal inflammation, and blocking its receptor prevents memory deficits (Barrientos et al., 2012); IL1 β also reduces the action of BDNF (Cortese et al., 2011). Subjects with mild cognitive impairment (MCI) had a greater chance of later AD if their cytokines were elevated, but this may have been a prodromal event (Monson et al., 2014). However, a meta-analysis failed to show overall that either CRP or IL6 levels were risk factors for AD (Koyama et al., 2013), though most of the studies included were short-term and the results of individual papers were highly variable. Other cytokines were not analyzed. It is clear that, just as we lack adequate long-term follow-up studies of depressed subjects with deranged HPA function, so there is no convincing basis on which to decide whether altered cytokines represent a subtype of MDD that poses a specific risk for later AD. Such studies would need to differentiate between the role of MDD and that of more general stressors, since the latter can also increase cytokine levels such as IL1 β and IL6 (Steptoe et al., 2007).

11. Interactions between glucocorticoids and cytokines: inflammation

Current ideas suggest that inflammation has a pivotal role in the development or progression of AD as well as many other neurological or psychiatric disorders including MDD (Morales et al., 2014). Reactive microglia and astrocytes, together with their associated cytokines and complement factors, occur adjacent to β -amyloid plaques: the question is whether these are a secondary response to β -amyloid accumulation or a primary initiator of the AD cascade (Clark and Vissel, 2015). The latter, it is supposed, could be one consequence of chronic or repeated infections, with resultant activation of toll-like receptors (TLR), microglia and production of cytokines (including TNF α , IL1 and IL6) and other pro-inflammatory molecules (Lim et al., 2015), changes that are not necessarily specific for AD. Activated microglia can be either a response to degenerating cells or β -amyloid, or an intrinsic element of the neurodegenerative process (McGeer and McGeer, 2010, 2015; Heneka et al., 2015), and low-grade inflammation associated with ageing may contribute to AD (Michaud et al., 2013). Any postulated link between MDD and AD needs to take these ideas into account.

Is the fact that some pro-inflammatory cytokines are raised in some cases of MDD (see above) an epiphenomenon of this disorder, or does it suggest that MDD itself (or a subtype) is an inflammatory illness? In either case, if there was evidence of persistent MDD-related inflammatory processes, then this could easily be imagined to predispose to later AD, itself strongly linked to inflammatory events. It should be noted that inflammation has, so far, been discussed in the literature mostly in the context of a causative role in MDD, rather than as a contributor to the risk of MDD for subsequent AD.

Attention on inflammation (or immune reactions) as a cause or precipitant of MDD came from observations that clinical administration of either IFN α or interleukin-2 resulted in depressed mood in some cases (Dantzer et al., 2011; Maes et al., 1995; Smith, 1991; Capuron et al., 2000). A comprehensive analysis showed elevations in nine pro-inflammatory and two anti-inflammatory cytokines in the blood in MDD (Simon et al., 2008). Studies on the CSF of depressed patients, much fewer, have been less consistent (Young et al., 2014). Depression following systemic illness such as myocardial infarction or diabetes, or even after immunization in healthy subjects, has also been associated with raised cytokines (Kiecolt-Glaser and Glaser, 2002; Wright et al., 2005). Imaging studies following IFN α showed hypoactivity in the frontal cortex, but increased activity in the anterior cingulate, an area implicated in MDD by other studies (Juengling et al., 2000). Interestingly, the hippocampus and entorhinal cortex were not mentioned. Many of these results have been replicated in experimental animals, using 'sickness' or 'depression-like' behaviour (Singhal et al., 2014); but the validity of experimental models of human clinical depression is questionable, though the first is more credible than the second (see below). Both clinical and experimental studies suggest that even transient systemic inflammation – particularly in the aged – may result in microglial activation and long-lasting neural malfunction, including damage to the hippocampus and dentate gyrus (Sankowski et al., 2015). Such infections can potentiate other neurodegenerative processes, including AD (Holmes et al., 2009): so MDD (perhaps associated with raised cytokines) occurring shortly before AD may not only be prodromal, but also a trigger for incipient AD.

Although elevated cytokines during MDD are a credible signal of inflammation, what about changes in cortisol? GCs are well-established as anti-inflammation treatments and as immune suppressors, arguing against a role for them in promoting or allowing inflammation in the brain. It could even be suggested that cases of MDD with raised cortisol might be protected against future AD.

However, the actions of GCs in the brain seem to differ from those in the periphery, though even here GCs may have pro-inflammatory actions in some situations (Cruz-Topete and Cidlowski, 2015). Persistent elevations of GCs are pro- rather than anti-inflammatory in the brain (Sorrells et al., 2009). Microglia in the hippocampus, frontal cortex and substantia nigra of the rat are activated by lipopolysaccharide (LPS), and this is greatly enhanced by stress. This enhancement was reversed by the GR antagonist mifepristone, showing that it was the result of elevated corticosterone (de Pablos et al., 2014); a similar enhancement of microglial activity was observed following corticosterone treatment (Frank et al., 2011). In both cases, not only were microglial responses accentuated, but the formation of cytokines (TNF α , IL1 β and IL6) was also increased. This experimental evidence, assuming it applies to humans, is strong support for a pro-inflammatory action of GCs on the brain, and hence GCs as a highly plausible contributor to later AD-associated inflammation. It remains to be determined whether microglia are activated or cytokines released in the brain specifically in those cases of MDD associated with dysregulated GCs (and with which type of dysregulation: see above), and whether the duration or repetition of epi-

sodes of MDD is important. In particular, since some cases of MDD seem resistant to the feedback action of GCs (i.e. dexamethasone), does this also imply a similar resistance to the pro-inflammatory action of GCs in the brain? It should be noted that TNF α and many other cytokines which are increased in some cases of MDD, can de-sensitize the GR to corticoids (Pace and Miller, 2009) though, of course, they may have their own pro-inflammatory effects. One postulated mechanism is increased formation of GR β (or), but which may promote GC resistance by antagonizing GR α (Yudt and Cidlowski, 2002).

Despite elevated peripheral or even CSF levels of cytokines and related molecules, the gold standard for determining whether MDD is (or can be) an inflammatory disorder can only come from examining the brain. There are various approaches, but all have suffered to some extent from the limitations of too few samples, varied diagnoses, the effects of drugs (e.g. anti-depressants), or restrictions on the brain areas studied. Attempts to show activated microglia have given mixed results (Steiner et al., 2011); a microarray study reported increases in a range of interleukins and other inflammatory molecules in Brodmann's area 10 (medial frontal lobe) in post-mortem MDD brain (Shelton et al., 2011), but others report differently (Sibille et al., 2004). A recent in vivo imaging study, using a ligand that binds to a microglial activating molecule (translocator protein), showed widespread increases across the brain in drug-free cases of MDD (Setiawan et al., 2015), the most convincing evidence so far. But there was considerable overlap between MDD and controls, suggesting that MDD may be heterogeneous with regard to inflammation. It would not be surprising if the pathology of the brain reflected the disparate nature of depression. However, we can conclude that there is substantial evidence that some types of MDD are associated with inflammation in the brain. A precise definition of such cases remains to be determined. Since inflammation seems so pertinent to the development or progression of AD, it is plausible that these categories of MDD represent a risk for later AD.

12. Synthesis and roadmap

Revealing links between MDD and AD is bedevilled by scarcity of information in several critical areas. It is not possible at present to provide a coherent or convincing framework at a cellular level, though attempts have been made; for example, that oxidative stress could be the link (Rodrigues et al., 2014). Nevertheless, it is possible to discern promising avenues, and to define what it is we still need to know. Although corticoids, cytokines, neurogenesis and inflammation have been discussed somewhat separately, it is clear that they are closely entwined. GCs moderate the action of cytokines, and some cytokines (e.g. IL1 β) have direct stimulating actions on the HPA system (Herbert, 2013). Inflammation, by which is meant primarily the activation or priming of microglia and astrocytes (Heneka et al., 2015), is the result of, or regulated by, both corticoids and cytokines, themselves produced by microglia (and other glia). There is plentiful evidence, even though much of it is incomplete, that alterations in all three can occur in MDD, and can plausibly be associated with the pathological processes known to occur in AD. This general picture has serious limitations in detail.

The search is on for biomarkers of psychiatric and neurological disorders. Biomarkers include a range of different measures, usually in the blood, sometimes in the CSF, and may include scanning. Some have direct relevance to the pathology of either MDD or AD – for example, cytokine or β -amyloid levels, but other do not, at least at present (e.g. patterns of serum proteins, or gene expression). Large numbers of potential biomarkers for both MDD and AD have been suggested. As for genetic studies, many reports suffer from

small numbers, uncertain diagnostic criteria or specificity, low effect sizes, and lack of replication; the field is at an early stage (Scarr et al., 2015; Kalia and Costa, 2015). In the case of MDD, the hope is that biomarkers may aid diagnosis, the recognition of subtypes, or guide optimal treatment strategies (Huang and Lin, 2015). For AD, they could assist early diagnosis, or improve predictions of incipient AD (e.g. in those with MCI) (Weiner et al., 2015; Inekci et al., 2015). Reliable, reproducible and clinically useful biomarkers have not, so far, been established for either disorder, though efforts to do so continue (Bot et al., 2015; Denk et al., 2015). Furthermore, if reliable biomarkers existed for particular forms of MDD, then – together with the other diagnostic criteria listed above – they could be a valuable addition to the definition of MDD subtype(s) that represent a high risk for later AD. It is also conceivable that biomarkers may exist that, independently of their value for the diagnosis or management of either MDD or AD, are an index of the scale of the link between them, irrespective of whether or not they contributed to knowledge about the nature of that link. This field promises many new developments.

12.1. Deficiencies in the experimental evidence

It has been pointed out that lack of precise information about the pathology MDD and, perhaps to a lesser extent, AD is a serious obstruction to greater understanding of the link between them. Why has the experimental evidence not offered a greater contribution? The problem, as in many instances of neurological or mental illness, lies in the lack of convincing experimental models of a clinical disorder. The limited value of in vitro methods and genetically engineered mice as models of AD has already been mentioned. Whilst these have been valuable in elucidating the roles of specific genes in AD, most cases of human AD are not the result of mutations comparable to those created in mice, and the progression of AD-like pathology in these mice does not completely replicate that seen in humans, partly as a result of their lesser life span. The problem is even more serious in MDD (Czeh et al., 2015). Since MDD is a behavioural phenomenon, attempts have been made to replicate this in rodents and other species. The Porsolt swim test and (in mice) the tail suspension test are widely used as examples of 'depression-like' behaviour. The validity of these tests is based on two criteria: the animals are exposed to stress (which is known to precede most cases of human MDD) and the behavioural response to this stress is normalized by anti-depressant drugs (Krishnan and Nestler, 2011). Neither is convincing. Stress does not invariably induce MDD in humans (and not within 24 h), and the behavioural response (often termed 'helplessness') is not comparable to anything in human MDD, but may be an adaptation to stress rather than the pathological state of depression (Molendijk and de Kloet, 2015). The misuse of the term 'anti-depressant' has already been mentioned: the fact that these drugs alter responses in either of these tests is not support for their value as a model of depression. It has already been pointed out that serotonin, for example, has widespread effects on many, if not most, categories of behaviour. Similar problems face another model: exposure to prolonged and varied stress, which results in reduced appetite for sucrose or other sweeteners. This is often termed 'anhedonia' which is a central symptom of MDD (but not sufficient for a diagnosis). However, reduced appetite is a common adaptive reaction to stress in animals, and is replicated by administration of corticoids. Sucrose anhedonia is not a specific state, but represents one test of motivation for rewarding events. It is certainly not a specific test for 'depression'. The fact that 'anti-depressants' counteract this effect suffers from a similar caveat as for the swim test, etc. Until we have genuine experimental models of either AD or MDD, the contribution of experimental evidence to our understanding of the link between them will remain severely limited.

Table 3

Possible contributions of prior MDD to later AD.

Increased rate of accumulation of β -amyloid
Decreased clearance of β -amyloid
Increased probability of neurotoxic 'cascade' (p-tau, etc.)
Reduced protective or compensatory mechanisms
Modified activity of associated factors (e.g. reactive oxygen, increased GSK3 β , altered IGF function, etc.)
Accelerated rate of brain ageing
Precipitation of incipient AD (late life MDD)

12.2. Pathways linking MDD and AD

As already emphasized, we need to know whether there is a sub-type(s) of MDD that represents heightened risk for AD. It is likely to be those cases with altered cortisol and/or cytokines. If so, which cortisol pattern and which set of cytokines? Flattening of the diurnal rhythm is the most likely cortisol pattern, and IL1 β , IL6 or TNF α seem prominent candidates as relevant cytokines. Whether chemokines such as CCL2 or CXCL1 could be involved has not been investigated. The only method is a large study on the relation between these different patterns of cortisol and/or cytokines and the subsequent incidence of AD. This could be prospective or, if adequate data exists, retrospective. We need to know if there are high ORs (HRs) for subsequent AD of subtypes of MDD, defined principally by biochemical measures as well as symptoms. We also need to know whether repeated, or prolonged, bouts of MDD subtypes – or any case of MDD – constitute a particular risk for AD. Such studies might inevitably be complicated by the effects of drug treatment, which occurs in patients with MDD.

Assuming that a subtype of MDD is an independent risk for later AD, there are three possible links (Tables 2 and 3).

- There might be a common pathological event, such as raised IL6 or an inflammatory process, that both represented a feature of a subtype of MDD and a direct risk for later AD.
- A feature of some types of MDD (e.g. cortisol, cytokines) could represent a sensitizing or 'priming' factor for later AD, but not contribute directly to its pathology. In this case, there would need to be a second 'hit' (e.g. microglial activation) that, should it occur in the context of a previous bout of the relevant subtype of MDD, would greatly increase the risk of AD.
- MDD may accelerate ageing in the brain, and thus advance age-related accumulation of β -amyloid. Ageing itself is associated with microglial activation and increased cytokine production (Conde and Streit, 2006).

These three options are not mutually exclusive. Since they are all closely linked with cortisol, cytokines and inflammatory processes, there is no reason why they should not either occur together or represent different pathways for increased risk for AD in individual cases.

12.3. Common factors

Uncertainties about the neuronal basis of both MDD and AD limit speculations about cellular mechanisms. However, the ubiquitous enzyme glycogen synthase kinase 3 β (GSK3 β) has been implicated in both MDD and AD. GSK3 β hyperactivity is proposed as an element of the pathogenesis of MDD (Nho et al., 2015); it has a major controlling action on inflammation and cytokine production (Llorens-Martin et al., 2014), on the cellular actions of GCs (Spokoini et al., 2010), and suppresses hippocampal neurogenesis (by acting on the *wnt*-catenin pathway) (Sirerol-Piquer et al.,

2011). In the context of AD, GSK3 β has been shown to have a role in the formation of β -amyloid and the hyper-phosphorylation of tau (Llorens-Martin et al., 2014). Persistent hyper-activation of GSK β -dependent NF κ B is a plausible link between MDD and AD. IGF1 is an important negative regulator of GSK3 β , and also has neuroprotective and anti-oxidant functions (Yin et al., 2013) and positive effects on cognition. Obesity and diabetes are risks for AD (van Dijk et al., 2015), which has focused attention on insulin, growth hormone and their control of IGF1. There are reports that IGF1 is raised in both MDD and AD (de Bruijn et al., 2014; Kopczak et al., 2015), though the evidence is limited, but since IGF1 stimulates neurogenesis and is neuroprotective (Liquitaya-Montiel et al., 2012), this may be an adaptation to these disorders rather than a contributor to them (Cole and Frautschy, 2007). Cytokines (and other factors, including β -amyloid) may reduce IGF1 sensitivity and its role in glucose utilization by the brain by acting on its receptors (Fernandez and Torres-Aleman, 2012; O'Connor et al., 2008). However, the picture is complicated by reports that knock-out of the IGF receptor (IGF-1R) reduces β -amyloid 40 and 42 load and improves memory in a transgenic mouse model of AD, suggesting that reduced IGF signalling protects against AD (Gontier et al., 2015); it seems that IGF1 can have both protective and damaging action on the brain, depending on context (Fernandez and Torres-Aleman, 2012), and increased expression of IGF-1R has been associated with ageing of the brain, clearly relevant to the risk of AD (Puglielli, 2008).

There is experimental evidence (see above) for a direct effect of corticoids and cytokines on β -amyloid accumulation in genetically modified mice, though whether this applies to sporadic forms of human AD is questionable. If the neurodegenerative cascade typical of pre-symptomatic AD starts during certain forms or patterns of MDD, then this should, eventually, be detectable by improved scanning methods. We do not necessarily need to understand why this occurs in order to take appropriate preventive measures. Identification of the crucial element in particular subtypes of MDD (for example, altered cortisol, raised TNF α , particular epigenetic patterns) would allow interventions with the prospect of reducing risk for later AD. A common inflammatory process (e.g. microglial activation) remains a plausible explanation for the link between MDD and AD.

12.4. Priming factors

The second option is even more difficult to establish, since it requires identification not only of the priming condition (the subtype of MDD, the effect on microglia, etc.) but also the second 'hit' that, together with the initial priming event, represents the overall risk for MDD-related AD. However, reduction of the priming event itself would reduce later incidence of AD, irrespective of the detailed information about the mechanism: this could come from careful epidemiological and clinical identification of the risk-laden subtypes of MDD. If these could be related to a recognizable pathological or biochemical pattern (cortisol, cytokines, inflammation, etc.) occurring during MDD then intervention to negate these pathophysiological events would reduce consequent AD even in the absence of precise knowledge about the identity of the second 'hit'. In view of the current uncertainty over common factors in the pathogenesis of MDD and AD, this also seems a likely option. It should be emphasized that this link and the one described in the previous paragraph are not mutually exclusive.

12.5. MDD and the ageing brain

Age is a major risk factor for AD, but less is known about why this should occur or what constitutes ageing in the brain. Ageing in the brain is usually measured by changes in cognitive abilities

(e.g. memory), rather than underlying neural processes (e.g. neuronal loss or decreasing hippocampal neurogenesis). Changes in IGF signalling and pro-inflammatory cytokines have been implicated, including altered type1 interferon (e.g. IFN β) transport in the choroid plexus (Baruch et al., 2014; Stranahan and Mattson, 2012). There may be reduced ability of neurons to withstand stressors, such as oxidation, with consequent effects on BDNF (amongst other factors), though there is still much uncertainty (Yeoman et al., 2012). The increased incidence of DNA damage with age is often attributed to reactive oxygen activity, also proposed as a link between MDD and AD (Rodrigues et al., 2014); and age-related epigenetic methylation or acetylation has been linked to neurodegeneration (Lardenoije et al., 2015). If MDD accelerated ageing, then this could add to the risk of AD, but whether this occurs is uncertain: for example, there is some evidence for altered telomere length or telomerase activity resulting from MDD (Lindqvist et al., 2015) but this is still not established, though an intriguing possibility. Recently, a pattern of mRNA in blood, skin and brain has been described that distinguished young (c 25 years) from older (c 70 years) persons. Furthermore, individual differences in this pattern in older subjects predicted those who developed AD as well as longevity and other health measures (Sood et al., 2015). Whether a history of MDD modifies this pattern (e.g. accelerates that seen in 'normal' ageing) in subjects at any age remains to be determined.

There are marked age-related, but individually variable, decreases in blood levels of dehydroepiandrosterone (DHEA) (Orentreich et al., 1984). DHEA protects neurons against NMDA-induced neurotoxicity (Kimonides et al., 1998) opposes the action of corticoids (McIntosh et al., 1999) and has positive actions on declining age-related immune function (Buford and Willoughby, 2008). Levels have been reported to be lower in MDD than controls (Goodyer et al., 1996; Michael et al., 2000), though this has not always been confirmed: there may be subtypes of MDD associated with reduced DHEA. DHEA is also reported to be lower in AD (Aldred and Mecocci, 2010), but there is no evidence that DHEA plays a part in the onset of AD, or improves cognitive function in older people, though the data available is still very incomplete (Huppert and Van Niekerk, 2001). There is urgent need to bring these various aspects of neural ageing together, see how they are inter-related, and whether they contribute to the risk of sporadic AD or that following MDD.

12.6. Indirect links

MDD increases the risk for subsequent coronary heart disease and stroke (Gan et al., 2014; Barlinn et al., 2015). Since both are also risk factors for dementia (AD and vascular), there might be indirect links between MDD and AD. Though these may involve the potential risk factors described above, they are outside the scope of this review – but need to be borne in mind. It should also be noted that MDD may increase the risk for other forms of dementia, as well as AD (Diniz et al., 2013), so links between them may be either variable or non-specific, or different subtypes of MDD may predict different types of dementia.

13. Conclusions

It is clear from this review that we lack essential data to determine the exact nature of the risk posed by MDD for subsequent AD. There is also uncertainty about whether treating depression with anti-depressant drugs reduces the risk of later AD (Kessing et al., 2011), though anti-depressants may lower IL6 (Strawbridge et al., 2015). What do we need? There are various levels of investigation. The first is to determine whether there are subtypes of MDD that

actually represent most or all of the risk for AD. This needs a large long-term follow-up study, in which MD is categorized precisely at a number of levels: clinical phenotype (e.g. symptoms) and history (e.g. recurrence, severity), psychological assessment (both cognitive and emotional), environmental events (e.g. early adversity), genetic profile, endocrine function (particularly HPA axis), inflammatory and immune function (e.g. cytokines). This will allow the identification of subtypes according to the probability of later AD (but including other endpoints, such as cardiovascular disease, Parkinson's disease and vascular dementia) and their respective risk ratios, etc. Once this subtype (or subtypes) has been identified, then the search is on for the critical feature(s) that may represent the actual risk (e.g. raised cytokines, aberrant HPA function, inflammatory indices or combinations of these and other factors). Thirdly, the effectiveness on the risk of later AD of interventions (and their timing) that counteract or normalize these factors would need to be assessed. Finally, investigation (both clinical and experimental) might provide an explanation at a neural level of how these risk factors operate to increase the likelihood of AD, suggesting further pharmacological or other means of reducing that risk. The burden of both MDD and AD shows that these efforts would be worthwhile.

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