GUEST EDITORIAL

Is depression really different in older people?

As politicians and pollsters are well aware, it is easy enough to get different answers to the same question by adjusting the details of the question posed. So I clarify at the outset that I am not considering depression in the broadest sense of any depression occurring in any older person. It seems self-evident that differences are present when defined this way; that is, this includes people with depression in dementia, post-stroke depression, depression in the context of other chronic illnesses and so any assessment of clinical or biological factors would yield differences (in cognition, physical symptoms, and so on) compared to a similar sample of depression in all younger adults. Rather I focus the question on unipolar major depressive disorder (MDD). This is because if there are no differences in late-life MDD compared with younger adults, then it seems unlikely that such differences are present in broader constructs of unipolar disorder (minor depression and dysthymia) and pragmatically because this more tightly defined group has been better assessed. A problem in addressing this question is that relatively few studies have directly compared aspects of depression in older and younger people. Thus, the answer will necessarily be limited and subject to a potential “absence of evidence” error. Here, three key areas of evidence where such comparisons have been made will be examined.

Clinical features of late-life depression

It is frequently said that the symptoms of depression are different in older people but reviewing the literature, Baldwin (1994) concluded that there was little evidence for phenomenological differences between older and younger depressed patients and a more recent review of phenomenology found only a few modest differences in symptoms identified using the Hamilton Depression Rating Scale (Hegeman et al., 2012). Whilst some studies have reported differences compared with younger adults, e.g. increased delusions, agitation, and appetite loss (Brodaty et al., 2001), or decreases in hypersomnia, pessimism, and irritability (Husain et al., 2005), such findings are rarely replicated and often emanate from specialist centers. Again, it is often thought that late-onset depression (LOD) has a different symptom profile but this also does not appear to be the case with three studies of inpatients reporting no differences between people with early-onset depression (EOD) and LOD (Brodaty et al., 1997; 2001; Alvarez et al., 2011). The only clinical features repeatedly reported as different in late-life MDD are aspects of neurocognitive impairment, especially impairment in information processing, memory, and executive function, e.g. (Butters et al., 2004; Kohler et al., 2010a; Vasudev et al., 2012), though such cognitive impairments are of course not symptoms used in the diagnosis of depression. A systematic review of the literature comparing the neuropsychological profile of LOD and EOD and healthy controls found that the MDD groups were impaired in all domains versus controls but that LOD had greater deficits in executive function and processing speed compared with EOD (Herrmann et al., 2007). This raises the question as to whether this greater severity of cognitive impairment is simply due to aging effects, since the domains characteristically impaired in depression also decline with age. This does not seem to be the case. Studies which have carefully excluded people with early dementia and compared older and younger adults with MDD matched for depression severity have found that even after controlling for the age-related increase in impairment adults with late-life depression have more severe impairments in memory and executive functions (Lockwood et al., 2002; Thomas et al., 2009). However, apart from these neurocognitive deficits the clinical features of late-life MDD do not seem to be different in older people.

Neurobiology of late-life depression

In a few areas, researchers have examined key neurobiological aspects of MDD and made comparisons between younger and older adults. The genetic contribution to late-life depression is often said to decrease with age. However, whilst earlier clinical studies comparing LOD with EOD have usually reported that the former has fewer relatives with depression (reviewed in Levinson (2006)), a twin study found no change in the heritability of depression with increasing age (Johnson et al., 2002) and neither did a Genome Wide Association Study (GWAS) of over 3,500 participants (Demirkan et al., 2012). Whilst some studies have
et al., 2011). Thus, it is unclear whether late-life MDD does have a lower genetic contribution. Many studies have demonstrated that MRI white matter hyperintensities (WMH) are more severe in late-life depression and this is especially the case for LOD (Herrmann et al., 2008). Postmortem studies have confirmed that these lesions are ischaemic (Thomas et al., 2002; 2003) and they have been related to the neurocognitive impairments characteristic of depression (Sheline et al., 2008). Structural studies have identified specific areas of the prefrontal cortex as reduced in volume, and functional imaging has confirmed that these areas have reduced activity and/or blood flow in depression. However, studies have not examined differences by age, although a few have reported that LOD has greater volume reductions (Parashos et al., 1998; Andreescu et al., 2008). This neuroimaging evidence has led to post-mortem neuropathological investigations seeking to identify the cellular correlates of these abnormalities. In younger adults, such studies have consistently reported reductions in gial density in MDD but, in contrast, studies of late-life MDD have reported no evidence of reduced gial density in prefrontal and subcortical areas but have found abnormalities in pyramidal neurons (Khundakar and Thomas, 2009; Khundakar et al., 2011a; 2011b). These prefrontal pyramidal neurons are mainly glutamatergic and, as well as projecting to other cortical areas, also project to the striatum, and it may be that ischaemic WMH affect the axons of these neurons inducing these subtle changes. So these different lines of research show WMH are definitely more severe in late-life depression and there may be cellular and volumetric changes in key frontal–subcortical areas which could be related to these.

**Treatment response in late-life depression**

Studies directly comparing response and remission to antidepressants in older and middle-aged depressed adults have not found any overall differences (Alexopoulos et al., 1996; Reynolds et al., 1996), though people with LOD seem to have a slower response (Alexopoulos et al., 1996; Whyte et al., 2004). One review of the literature reached the same conclusion (Whyte et al., 2004) and another agreeing that depression remitted as frequently in later life found that it was associated with a higher relapse rate (Mitchell and Subramaniam, 2005). However, these findings may only be valid in older adults who are healthy and cognitively intact, i.e. biologically like younger adults, since these were the type of participants included in the relevant trials. Other evidence demonstrates that WMH are associated with a poorer response to antidepressants (e.g. Alexopoulos et al., 2008; Sneed et al., 2011), poorer longer term outcome and increased relapse rates (Hickie et al., 1996; O’Brien et al., 1998), and persistent cognitive impairment up to four years (Kohler et al., 2010b). Since WMH are associated with cognitive impairment this too is associated with a poorer response to antidepressants and increased relapse rates (Kalayam and Alexopoulos, 1999; Alexopoulos et al., 2000). Studies have also directly compared electroconvulsive therapy (ECT) by age and similarly, in selected patients typical of those receiving ECT, reported ECT to have at least as large a benefit in older adults with no age-associated increase in adverse effects (Tew et al., 1999; O’Connor et al., 2001). Thus, in the absence of cognitive impairment and/or WMH, people with depression in old age appear to respond as well to antidepressants and ECT. The situation is likely to be the same for psychological treatments.

**Is depression really different?**

The editorial title is ambiguous and is actually two different questions, which are often conflated like this. It can mean: “is it true, as is often stated, that depression in older people is different from depression in younger people?” Or it could mean: “assuming depression is different, is this difference in depression in older people substantial, that is clinically important?” For core depressive symptoms, there do not seem to be any differences and even if there are such differences, these appear to be clinically unimportant. An important caveat is that the symptom profile examined may be one characteristic of depression in younger adults and there may be other symptoms, e.g. apathy or agitation, which are not used in diagnosis and so have not usually been assessed but which are more prominent in older people. Thus, neurocognitive deficits, which are not diagnostic clinical features and are the only ones adequately studied, are more severe in older adults. These clinical differences in neurocognitive deficits are related to the most robust neurobiological difference, a higher burden of MRI WMH. But are these “really different?” Determining what constitutes a clinically important difference is open to debate but cognitive deficits were of moderate effect size (0.56 for executive function, 0.58 for processing speed, and 0.44 for episodic memory versus controls (Herrmann et al., 2007)) and similar or larger effect sizes were found for the increased burden of WMH (Herrmann et al., 2008). This strongly suggests they are clinically important and this is supported by the evidence demonstrating that both WMH and these related cognitive deficits are associated with a poorer treatment response and worse clinical
outcomes. Thus, in this way MDD is “really different” in older adults. But in the absence of a significant burden of WMH and these deficits, MDD in older adults appears to be similar to MDD in younger adults. Such an answer begs the question of what is a “significant burden of WMH,” since WMH are nearly universal in older people, and how much cognitive impairment needs to be present to adversely affect outcomes. One study found it was those in the highest quartile of WMH burden who had poorer response to antidepressants (Sneed et al., 2011). However, this is difficult to translate into regular clinical practice and a more pragmatic answer is that a WMH score of 2 or more on the modified Fazekas rating scale distinguished between “vascular” and “non-vascular” subgroups of late-life MDD (Sneed et al., 2008) and may represent this poorer outcome subgroup. For executive dysfunction, the problem of translating into clinical practice is more acute since regular clinic “bedside” tests do not provide a detailed enough assessment to relate to research findings. In conclusion, whilst evidence supports a real and important difference in at least a subgroup of depression in older people, it is difficult at the current time to translate these findings into routine clinical practice.

Conflict of interest

None.

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References


