International Psychogeriatrics (2013), 25:11, 1739–1742 © International Psychogeriatric Association 2013
doi:10.1017/S1041610213001038

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., 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 postmortem neuropathological investigations seeking to identify the cellular correlates of these abnormalities. In younger adults, such studies have consistently reported reductions in glial density in MDD but, in contrast, studies of late-life MDD have reported no evidence of reduced glial 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

https://doi.org/10.1017/S1041610213001038 Published online by Cambridge University Press

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.

ALAN THOMAS

Institute for Ageing and Health, Newcastle University, Biomedical Research Building, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK
Email: alan.thomas@ncl.ac.uk

Acknowledgment

The research supported by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at The Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. The views expressed are those of the author and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

Alexopoulos, G. S. *et al.* (1996). Recovery in geriatric depression. *Archives of General Psychiatry*, 53, 305–312.

Alexopoulos, G. S. *et al.* (2000). Executive dysfunction and long-term outcomes of geriatric depression. *Archives of General Psychiatry*, 57, 285–290.

Alexopoulos, G. S. *et al.* (2008). Microstructural white matter abnormalities and remission of geriatric depression. *American Journal of Psychiatry*, 165, 238–244.

Alvarez, P., Urretavizcaya, M., Benlloch, L., Vallejo, J. and Menchon, J. M. (2011). Early- and late-onset depression in the older: no differences found within the melancholic subtype. *International Journal of Geriatric Psychiatry*, 26, 615–621.

Andreescu, C. *et al.* (2008). Gray matter changes in late life depression – a structural MRI analysis. *Neuropsychopharmacology*, 33, 2566–2572.

Baldwin, R. C. (1994). Is there a distinct type of major depression in the elderly? *Journal of Psychopharmacology*, 8, 177–184.

Brodaty, H. *et al.* (1997). Increased rate of psychosis and psychomotor change in depression with age. *Psychological Medicine*, 27, 1205–1213.

Brodaty, H. *et al.* (2001). Early and late onset depression in old age: different aetiologies, same phenomenology. *Journal of Affective Disorders*, 66, 225–236.

Butters, M. A. *et al.* (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry*, 61, 587–595.

Demirkan, A. *et al.* (2011). Genetic risk profiles for depression and anxiety in adult and elderly cohorts. *Molecular Psychiatry*, 16, 773–783.

Hegeman, J., Kok, R., van der Mast, R. and Giltay, E. (2012). Phenomenology of depression in older compared with younger adults: meta-analysis. *British Journal of Psychiatry*, 200, 275–281.

Herrmann, L. L., Goodwin, G. M. and Ebmeier, K. P. (2007). The cognitive neuropsychology of depression in the elderly. *Psychological Medicine*, 37, 1693–1702.

Herrmann, L. L., Le Masurier, M. and Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: a systematic review. *Journal of Neurology, Neurosurgery and Psychiatry*, 79, 619–624.

Hickie, I., Scott, E., Wilhelm, K. and Brodaty, H. (1996). Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression-a longitudinal evaluation. *Biological Psychiatry*, 42, 367–374.

Husain, M. M. *et al.* (2005). Age-related characteristics of depression: a preliminary STAR*D report. *American Journal of Geriatric Psychiatry*, 13, 852–860.

Johnson, W., McGue, M., Gaist, D., Vaupel, J. W. and Christensen, K. (2002). Frequency and heritability of depression symptomatology in the second half of life: evidence from Danish twins over 45. *Psychological Medicine*, 32, 1175–1185.

Kalayam, B. and Alexopoulos, G. S. (1999). Prefrontal dysfunction and treatment response in geriatric depression. *Archives of General Psychiatry*, 56, 713–718.

Khundakar, A. and Thomas, A. J. (2009). Morphometric changes in early and late-life major depressive disorder: evidence from postmortem studies. *International Psychogeriatrics*, 21, 844–854.

Khundakar, A., Morris, C., Oakley, A. and Thomas, A. J. (2011a). Morphometric analysis of neuronal and glial cell pathology in the caudate nucleus in late-life depression. *American Journal of Geriatric Psychiatry*, 19, 132–141.

Khundakar, A., Morris, C., Oakley, A. and Thomas, A. J. (2011b). A morphometric examination of neuronal

and glial cell pathology in the orbitofrontal cortex in late-life depression. *International Psychogeriatrics*, 23, 132–140.

Kohler, S., Thomas, A. J., Barnett, N. A. and O'Brien, J. T. (2010a). The pattern and course of cognitive impairment in late-life depression. *Psychological Medicine*, 40, 591–602.

Kohler, S., Thomas, A. J., Lloyd, A., Barber, R., Almeida, O. P. and O'Brien, J. T. (2010b). White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *British Journal of Psychiatry*, 196, 143–149.

Levinson, D. F. (2006). The genetics of depression: a review. *Biological Psychiatry*, 60, 84–92.

Lockwood, K. A., Alexopoulos, G. S. and van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry*, 159, 1119–1126.

Mitchell, A. J. and Subramaniam, H. (2005). Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *American Journal of Psychiatry*, 162, 1588–1601.

O'Brien, J., Ames, D., Chiu, E., Schweitzer, I., Desmond, P. and Tress, B. (1998). Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. *BMJ*, 317, 982–984.

O'Connor, M. K. *et al.* (2001). The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *American Journal of Geriatric Psychiatry*, 9, 382–390.

Parashos, I. A., Tupler, L. A., Blitchington, T. and Krishnan, K. R. (1998). Magnetic-resonance morphometry in patients with major depression. *Psychiatry Research*, 84, 7–15.

Reynolds, C. F. *et al.* (1996). Treatment outcome in recurrent major depression: a *post hoc* comparison of elderly ("young old") and midlife patients. *American Journal of Psychiatry*, 153, 1288–1292.

Sheline, Y. I. *et al.* (2008). Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *American Journal of Psychiatry*, 165, 524–532.

Sneed, J. R., Rindskopf, D., Steffens, D. C., Krishnan, K. R. R. and Roose, S. P. (2008). The vascular depression subtype: evidence of internal validity. *Biological Psychiatry*, 64, 491–497.

Sneed, J. R. *et al.* (2011). MRI signal hyperintensities and failure to remit following antidepressant treatment. *Journal of Affective Disorders*, 135, 315–320.

Tew, J. D., Jr. *et al.* (1999). Acute efficacy of ECT in the treatment of major depression in the old-old. *American Journal of Psychiatry*, 156, 1865–1870.

Thomas, A. J., Perry, R. H., Barber, R., Kalaria, R. and O'Brien, J. T. (2002). Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Annals of New York Academy of Sciences*, 977, 333–339.

Thomas, A. J., Perry, R., Kalaria, R. N., Oakley, A., McMeekin, W. and O'Brien, J. T. (2003). Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *International Journal of Geriatric Psychiatry*, 18, 7–13.

Thomas, A. J. *et al.* (2009). A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychological Medicine*, 39, 725–733.

Vasudev, A. *et al.* (2012). Relationship between cognition, magnetic resonance white matter hyperintensities, and cardiovascular autonomic changes in late-life depression. *American Journal of Geriatric Psychiatry*, 20, 691–699.

Whyte, E. M. *et al.* (2004). Time course of response to antidepressants in late-life major depression: therapeutic implications. *Drugs and Aging*, 21, 531–554.