Neuroscience and Biobehavioral Reviews 75 (2017) 129–139

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Systematic review and meta-analysis of genetic studies of late-life depression

Ruby S.M. Tsang[a,*], Karen A. Mather[a], Perminder S. Sachdev[a,b], Simone Reppermund[a,c]

[a] Centre for Healthy Brain Ageing, School of Psychiatry, UNSW Medicine, University of New South Wales, Sydney, Australia
[b] Neuropsychiatric Institute, Prince of Wales Hospital, Barker Street, Randwick, NSW, Australia
[c] Department of Developmental Disability Neuropsychiatry, School of Psychiatry, UNSW Medicine, University of New South Wales, Sydney, Australia

ARTICLE INFO

Article history:
Received 3 June 2016
Accepted 23 January 2017
Available online 27 January 2017

Keywords:
Late-life
Geriatric
Depression
Genetics
Systematic review
Meta-analysis

ABSTRACT

Late-life depression (LLD) is thought to be multifactorial in etiology, including a significant genetic component. While a number of candidate gene studies have been carried out, results remain inconclusive. We undertook a systematic review of all genetic association studies of depression or depressive symptoms in late life published before February 2016, and performed meta-analyses on polymorphisms investigated in three or more independent studies. A total of 46 candidate gene studies examining 56 polymorphisms in 23 genes as well as a genome-wide association study (GWAS) were included. Meta-analyses were conducted for four polymorphisms using random effects models, of which three (*APOE*, *BDNF*, *SLC6A4*) were associated with LLD. These genes are implicated in hippocampal plasticity and stress reactivity, suggesting that dysregulation of these pathways may contribute to LLD. Despite using a large sample, the only GWAS published to date identified only one genome-wide significant locus in the 5q21 region. In the future, larger genetic studies specifically examining LLD, including non-hypothesis-driven GWAS, are required to further identify genetic determinants of LLD.

Contents

* Corresponding author at: Building R1f, Randwick Campus, University of New South Wales, UNSW Sydney NSW 2052 Australia.
E-mail address: ruby.tsang@unsw.edu.au (R.S.M. Tsang).

http://dx.doi.org/10.1016/j.neubiorev.2017.01.028
0149-7634/

1. Introduction

Depression is a common neuropsychiatric disorder during the life course. While major depression is relatively uncommon among older adults, epidemiological studies suggest clinically significant depressive symptoms affect between 7% and 49% of community-dwelling older adults (Blazer, 2003; Riedel-Heller et al., 2006). Depressive symptoms in late life are associated with poorer wellbeing such as higher levels of anxiety, psychological distress and lower satisfaction with life (Reppermund et al., 2011); it also aggravates medical comorbidities, and is associated with greater disability and mortality, as well as an elevated risk of cognitive impairment (Diniz et al., 2013).

The etiology of late-life depression (LLD) is believed to be multifactorial, involving complex interactions of genetic and non-genetic factors. Twin studies have reported low to moderate heritability of late-life depressive symptomatology, with genetic influences estimated to explain 14%–55% of the variance, and remaining variability attributed to non-shared environmental influences (Carmelli et al., 2000; Gatz et al., 1992; Jansson et al., 2004; Johnson et al., 2002). There is also some evidence that heritability increases in late adulthood (Carmelli et al., 2000; Gatz et al., 1992). However, despite the many genetic association studies being conducted, limited susceptibility genes for LLD have been identified and results across studies were not consistently reproducible. These inconsistencies may likely be explained by methodological differences such as the definition of depression and sampling strategies employed. Another possible reason is that many studies had small sample sizes and therefore inadequate statistical power to detect modest genetic effects.

Meta-analysis is a powerful method for pooling underpowered studies to detect associations and identify sources of heterogeneity (Lohmueller et al., 2003). In recent years, comprehensive meta-analyses have been used to investigate genetic associations of psychiatric disorders (López-León et al., 2008a; Taylor, 2013; Warrier et al., 2015). While there have been over 100 candidate gene studies of LLD, no comprehensive meta-analysis has been carried out to provide an overview of the molecular genetics of LLD. To date, only two meta-analyses of genetic association studies of LLD have been conducted, which reported significant associations between the *BDNF* met allele and LLD (odds ratio $(OR)_{MetvsVal/Val} = 1.48$, 95% confidence interval (CI) 1.13–1.93) (Pei et al., 2012), and between the *SLC6A4* 5-HTTLPR short (S) allele and LLD ($OR_{SvsL/L} = 1.29$, 95% CI 1.01–1.66; $OR_{S/SvsL/L} = 1.68$, 95% CI 1.20–2.35) (Gao et al., 2014). The aim of the present study is to conduct the first systematic review and comprehensive up-to-date meta-analysis of genetic association studies of LLD, including all polymorphisms that have been studied where possible.

2. Methods

2.1. Search strategy

Studies were identified though a comprehensive search on MEDLINE, EMBASE and PsycINFO. The search strategy was based on keywords including "depress*"; "mood disorder*"; "affective disorder*"; "older"; "elder*"; "geriatric"; "late life"; "late onset"; "genetic*"; "polymorphism*"; "SNP*" and their corresponding subject headings in the respective databases (see Supplementary Table S1 for the full search strategy used in MEDLINE). Journal articles published in English before 18th February 2016 were considered. Furthermore, reference lists of eligible studies as well as reviews were hand-searched to identify additional potentially relevant studies. Citations of eligible studies were also hand-searched through the Scopus database.

2.2. Study selection

While studies have reported differences in clinical, neuropsychological and neuroimaging correlates between early-onset depression (EOD; typically with an onset in adolescence or early adulthood) and late-onset depression (LOD; typically with first symptoms emerging after the age of 50 or 60 years), which may reflect etiological differences, the majority of genetic association studies of LLD do not differentiate between the two subtypes. Hence for the purpose of this study, studies reviewed may include EOD recurrent in late life and/or LOD.

Case-control or cross-sectional studies that examined the association between one or more genetic polymorphism(s) and depression or depressive symptoms present in late life (using an age cut-off of 50 years and above), regardless of the age of onset, were selected. Case status was defined based on established psychiatric interviews or validated depression rating scales. Studies were excluded if (1) the distribution of genotypes in the control group was not in Hardy-Weinberg equilibrium (HWE) (Munafò and Flint, 2004), (2) the control group included individuals with a history of depression, (3) the sample included individuals with other psychiatric disorders or neurological disorders, or (4) there was insufficient data to estimate an effect size. Studies with individuals with psychotic depression were also excluded, as the literature suggests that psychotic depression in older adults is qualitatively different from the non-psychotic subtype and the *APOE* $\varepsilon 4$ allele is much more frequently observed in individuals with psychotic depression (Gournellis et al., 2014). We also excluded studies of depression secondary to other medical conditions (e.g., post-stroke depression, depression in Alzheimer's disease etc.) to limit phenotypic heterogeneity. The corresponding authors of studies with potentially overlapping samples (n = 5) were emailed for clarification; where studies examining the same polymorphism were found to involve substantial sample overlap, only the study with the largest sample size was included.

2.3. Data extraction

Data extraction was performed by RSMT, and checked by KAM and SR. Disagreements were resolved through consensus. The following information was extracted: first author's name, year of publication, country, ethnicity, mean and standard deviation (or range) of sample age, percentage of females, diagnostic criteria or instrument used to assess depression, genotype frequencies for cases and controls or mean depression score for each genotype group and source of sample. Authors (n = 24) were contacted for more information if study characteristics or essential data required for the meta-analyses were missing from the published articles.

2.4. Meta-analysis

Meta-analyses were conducted for polymorphisms that were examined in at least three independent published studies. Pooled ORs and 95% CIs were estimated for each meta-analysis. For studies