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Genome-wide screen to identify genetic loci associated with cognitive decline in late-life depression

D. C. Steffens,[1] M. E. Garrett,[2] K. L. Soldano,[2] D. R. McQuoid,[3] A. E. Ashley-Koch,[2] and G. G. Potter[3]

[1]*Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA*
[2]*Department of Medicine, Duke University Medicine Center, Durham, NC, USA*
[3]*Department of Psychiatry, Duke University Medicine Center, Durham, NC, USA*

ABSTRACT

Objective: This study sought to conduct a comprehensive search for genetic risk of cognitive decline in the context of geriatric depression.

Design: A genome-wide association study (GWAS) analysis in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study.

Setting: Longitudinal, naturalistic follow-up study.

Participants: Older depressed adults, both outpatients and inpatients, receiving care at an academic medical center.

Measurements: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery was administered to the study participants at baseline and a minimum of twice within a subsequent 3-year period in order to measure cognitive decline. A GWAS analysis was conducted to identify genetic variation that is associated with baseline and change in the CERAD Total Score (CERAD-TS) in NCODE.

Results: The GWAS of baseline CERAD-TS revealed a significant association with an intergenic single-nucleotide polymorphism (SNP) on chromosome 6, rs17662598, that surpassed adjustment for multiple testing ($p = 3.7 \times 10^{-7}$; false discovery rate $q = 0.0371$). For each additional G allele, average baseline CERAD-TS decreased by 8.656 points. The most significant SNP that lies within a gene was rs11666579 in *SLC27A1* ($p = 1.1 \times 10^{-5}$). Each additional copy of the G allele was associated with an average decrease of baseline CERAD-TS of 4.829 points. *SLC27A1* is involved with processing docosahexaenoic acid (DHA), an endogenous neuroprotective compound in the brain. Decreased levels of DHA have been associated with the development of Alzheimer's disease. The most significant SNP associated with CERAD-TS decline over time was rs73240021 in *GRXCR1* ($p = 1.1 \times 10^{-6}$), a gene previously linked with deafness. However, none of the associations within genes survived adjustment for multiple testing.

Conclusions: Our GWAS of cognitive function and decline among individuals with late-life depression (LLD) has identified promising candidate genes that, upon replication in other cohorts of LLD, may be potential biomarkers for cognitive decline and suggests DHA supplementation as a possible therapy of interest.

Key words: affective disorders, dementia, genes

Introduction

The relationship between depression and cognitive function is complex. Depression, especially when occurring in later life, has long been associated with executive impairment, attentional problems, and slowed speed of information processing (Butters *et al.*, 2004; Koenig *et al.*, 2015). Other studies have identified memory impairment as a concern among older depressed patients (Lee *et al.*, 2007). Cognitive impairments (CIs) in late-life depression (LLD) may persist despite adequate treatment of mood symptoms (Lee *et al.*, 2007; Mackin *et al.*, 2014); for instance, we previously reported 2-year outcomes among older cognitively impaired, non-demented depressives that included both normal cognition and cognitive decline, the latter consisting of various forms of CI as well as dementia (Steffens

Correspondence should be addressed to: David C. Steffens, MD, MHS, Samuel "Sy" Birnbaum/Ida, Louis and Richard Blum Chair in Psychiatry, Professor and Chair, Department of Psychiatry, University of Connecticut School of Medicine, 263 Farmington Ave, Farmington, CT 06030-1410, USA. Phone: +1-860-679-4282; Fax: +1-860-679-1296. Email: steffens@uchc.edu.
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et al., 2009). This is consistent with over 30 years of epidemiological research linking depression in mid and late life to later development of Alzheimer's disease (AD) (Devanand *et al.*, 1996; Jorm *et al.*, 1991; Kokmen *et al.*, 1991; Speck *et al.*, 1995; Steffens *et al.*, 1997; Saczynski *et al.*, 2010). Other studies have found an association between LLD and development of vascular dementia (Alexopoulos *et al.*, 1993; Diniz *et al.*, 2013). The heterogeneity of cognitive trajectories of LLD presents a challenge for early detection and treatment of what may be both distinct and overlapping etiologies of disease. Given the rapid aging of populations, there is a pressing scientific need for approaches that help elucidate unique and shared variance in trajectories of cognitive decline associated with LLD.

Recent studies suggest that the variance in the presentations of CI and LLD may be explained by genetic polymorphisms (Brzezinska *et al.*, 2020). Large-scale genetic studies to identify loci or genes associated with increased risk of cognitive decline or dementia in the context of depression have been limited. One strategy employed has been to examine genes and alleles known to increase AD risk, including the epsilon-4 allele of Apolipoprotein E gene (*APOE* ϵ4) (Saunders *et al.*, 1993). Another candidate gene approach has been to examine genes associated with risk for depression where there is a plausible scientific basis supporting a link with AD risk, for example, single-nucleotide polymorphisms (SNPs) of genes encoding cholinergic muscarinic receptors, which have been related to depression (Chee and Cumming, 2018). Other studies have found genetic loci common to depression and AD that were related to inflammatory, serotonergic, neurotrophic, and immune pathways (Kang *et al.*, 2015; Kitzlerova *et al.*, 2018; Lutz *et al.*, 2020), and the angiotensin-converting enzyme gene (Zettergren *et al.*, 2017). Genetic polymorphisms of brain-derived neurotrophic factor, interleukin 1-beta, and methylenetetrahydrofolate reductase confer increased risk to both LLD and AD (Ye *et al.*, 2016). Despite these findings, some have suggested that a common genetic predisposition for depression and AD may be unlikely (Herbert and Lucassen, 2016).

In comparison to candidate gene approaches, which are hypothesis driven, genome-wide association studies (GWAS) may help identify putative genes that increase the risk for cognitive decline and dementia among depressed individuals in an unbiased manner. GWAS analyses that sought to identify genetic loci linking depression and cognitive change have implicated genes related to cerebrovascular disease (Rutten-Jacobs *et al.*, 2018), presynaptic function (White *et al.*, 2017), and the complement pathway (Hamilton *et al.*, 2012). However, one GWAS study found no evidence to support a common polygenic structure for AD and major depressive disorder (MDD) (Gibson *et al.*, 2017).

To date, there has not been a GWAS of cognitive decline in the context of geriatric depression, which may be due to a lack of a consensus on how to conceptualize "cognitive decline" as a phenotypic target. One approach is to define cognitive decline clinically based on the established diagnostic criteria that characterize it. An example of this is a consensus diagnostic approach that has been used in many population-based studies (Plassman *et al.*, 2006; Plassman *et al.*, 2007). However, because diagnoses of CI share common neuropsychological deficits with LLD (Zihl *et al.*, 2010), an alternative approach is to track decline on an objective index of cognitive function. To address the former issue, we examine cognitive decline as a clinical diagnosis based on expert consensus; to address the latter issue, we examine change on a validated neuropsychological battery, such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) instrument (Morris *et al.*, 1989). The CERAD Total Score (CERAD-TS) has been shown to be a valid global measure of AD progression and of annualized change between AD and control groups (Rossetti *et al.*, 2010). As such, change in the CERAD-TS may be a useful phenotypic target for GWAS. We hypothesize that cognitive decline within a geriatric depressed cohort may represent distinct underlying genetic risks and pathways than simply geriatric depression alone. Moreover, these genetic risk factors may lay the path for subsequent neurodegenerative disorders in the same individuals.

We undertook a GWAS analysis in Neurocognitive Outcomes of Depression in the Elderly (NCODE), a longitudinal study of older depressed adults that characterized the incidence of cognitive decline and development of cognitive disorders including AD. We examined both by clinical diagnosis, as well as by a neuropsychological phenotype. We hypothesized that this approach would identify genetic markers that might be candidates for future genetic studies of CI and cognitive decline in LLD.

Methods

The sample

The methods of the NCODE study, including a description of the sample, have been previously described (Steffens *et al.*, 2004). In brief, the NCODE sample consists of participants originally enrolled in the Conte Center for the Study of Depression in the Elderly, a National Institute for Mental Health (NIMH)-supported study of depressed and non-depressed older adults (age 60 and above) at Duke University Medical Center. Some individuals were

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enrolled beginning in 1995 into the NIMH-supported Clinical Research Center at Duke and have subsequently agreed to continue participating in the longitudinal study associated with the Conte Center, spanning a study period from 1995 to 2011. As part of the enrollment evaluation, a geriatric psychiatrist interviewed each depressed participant and assessed depression symptoms with several standardized clinical assessments (Steffens *et al.*, 2004). Depressed participants met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive episode. Depressed participants entering the study with a Mini-Mental State Exam less than 25 were followed clinically to assess cognition and determine whether a diagnosis of baseline dementia warranted exclusion. In the present analysis, based on the clinical judgment of the study geriatric psychiatrist following established study protocol, clinically evident dementia was excluded at or close to baseline in all participants.

Participants with psychotic depression were included, as were those with comorbid anxiety disorders, as long as major depression was deemed by the treating geriatric psychiatrist on the study to be the primary psychiatric disorder.

The sample for the current study initially consisted of 271 individuals meeting criteria for major depressive episode on NCODE study entry who were referred to a series of Consensus Diagnostic Conferences (see below). The study was approved by the Institutional Review Board at Duke University Medical Center, and the study procedures were explained to all participants, who then provided written informed consent to participate.

Clinical follow-up of depressed participants

The NCODE study operates in a naturalistic treatment milieu using treatment guidelines established by the Duke Affective Disorders Program (Steffens *et al.*, 2002a). Treatment modalities available included antidepressant medications, electroconvulsive therapy, and individual and group cognitive-behavioral psychotherapy. Treatment was monitored to ensure that clinical guidelines were followed appropriately. Patients were evaluated when clinically indicated and at least every 3 months for the duration of study participation. The protocol recommends that participants receive continuation treatment for at least 1 to 2 years (some indefinitely) once they achieve remission. Each participant was thus assured to receive the most appropriate care we were able to provide.

Referral of participants with CI

Participants had the option of referral to the Memory Disorders Clinic at Duke University Medical Center when (1) they self-reported cognitive complaints, (2) family members reported cognitive concerns to the study geriatric psychiatrist, or (3) the psychiatrist had a clinical suspicion of CI or dementia. The study sought to obtain copies of medical records from these referrals when they occurred.

Neuropsychological battery

The neuropsychological test battery was administered to depressed participants at baseline while still symptomatic and then annually regardless of depression status. A trained psychometric technician supervised by a licensed clinical neuropsychologist administered testing. The full battery is described elsewhere (Steffens *et al.*, 2004), while the current study focuses on the tests in the battery that constitute the CERAD-TS. The CERAD-TS was computed based on the original publication by Chandler et al. (Chandler *et al.*, 2005) and includes score ranges from Animal Naming (0–24); 15-item Boston Naming Test (0–15); Constructional Praxis (0–11); and Word List Learning (0–30), Delayed Recall (0–10), and Recognition Memory Discriminability (true positives – false positives: 0–10). The CERAD TS is the sum of these individual tests and ranges from 0 to 100. Longitudinal CERAD-TS was utilized to assess cognitive change. Participants with baseline CERAD-TS and two or more CERAD TS over the first three annual follow-up evaluations were included ($N = 145$).

Consensus diagnostic conference

Clinical diagnoses were made by a consensus panel of experts in dementia, based on a model developed in several epidemiological studies of dementia (Plassman *et al.*, 2006; Plassman *et al.*, 2007). The panel consisted of a core group of experts, including three to four geriatric psychiatrists, a cognitive neuroscientist, one to two neuropsychologists specialized in memory disorders, and a neurologist specialized in memory disorders. Panel members reviewed the following information for each participant presented: (1) initial and most recent clinical depression study notes, (2) neuropsychological testing profiles and provisional diagnoses for all participants who underwent testing, and (3) neurological consultations when available. The treating study psychiatrist briefly presented the case, and a neuropsychologist summarized the neuropsychological findings to the group. Discussion among the panel members would ensue until a consensus clinical diagnosis was assigned. Panel members chose among several clinical diagnoses (Steffens *et al.*, 2004). Dementia diagnoses were based on criteria from the DSM-IV (American Psychiatric Association, 1994). For AD diagnoses featured in the present study, we used published criteria for diagnoses of probable and possible AD

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(McKhann *et al.*, 1984); diagnoses of other types of dementia were based on currently accepted criteria (McKeith *et al.*, 1996; Roman *et al.*, 1993; The Lund and Manchester Groups, 1994). Individuals with CI not meeting criteria for dementia were included a broad category of CI, no dementia (CIND). Diagnosis of CIND was based on prior work (Plassman *et al.*, 2000, 2006), defined as mild cognitive or functional impairment that does not meet criteria for dementia, such as performance on neuropsychological measures that was below expectation based on the individual's premorbid history, and scores at least 1.5 standard deviations (SDs) below published norms on any test. Finally, individuals with no CI were diagnosed as cognitively normal (CN). As mentioned previously, all participants in this study met criteria for major depression at the time of study enrollment. For the purposes of the current study, we used the following diagnostic groups at the time of censure, which was 5 years from the time of study enrollment: (1) CI, which encompasses diagnoses of CIND, AD, and non-AD dementias; (2) AD only, and (3) CN, which reflects with no diagnoses of CI during the study period.

Genotyping

DNA was extracted from whole blood using the Puregene system (Gentra Systems, Minneapolis, MN, USA). A total of 576 samples were genotyped with the Infinium PsychArray-24 v1.3 BeadChip (Illumina, San Diego, CA, USA), which included 552 study samples (271 depressed and 381 non-depressed), 12 replicates, and 12 internal quality control (QC) samples. Resultant genotype data were analyzed using the GenomeStudio software (Illumina) in order to call individual genotypes. Samples with whole genome amplified DNA were removed ($n = 18$). Several QC methods were employed including call rate > 98% ($n = 4$ samples excluded) and exclusion of gender discrepancies ($n = 6$ samples excluded). Cryptic relatedness was performed using PLINK (Purcell *et al.*, 2007), which resulted in the exclusion of one duplicate and two first-degree relatives of other study samples. Identity by descent estimates for all replicates and their matched study sample was 1, as expected. Principal component analysis was run using the smartpca program from the software package EIGENSOFT (Patterson *et al.*, 2006) in order to identify remaining outliers ($n = 0$ excluded) and calculate eigenvectors to use as covariates in the statistical analysis. Finally, we required probes to have a call rate > 97% and display no deviation from Hardy–Weinberg Equilibrium (HWE) in the control samples (p-values > 10^{-6}). In total, 521 samples and 398,317 probes passed genotyping QC checks.

Imputation

To increase genomic coverage, we imputed missing genotypes using a global reference panel from the 1000 Genomes Project (www.1000genomes.org). Samples were pre-phased using SHAPEIT (Delaneau *et al.*, 2011) and genotypes imputed using IMPUTE2 (Howie *et al.*, 2009). Imputed probes with certainty < 90% were zeroed out for specific individuals and were subsequently removed from the entire data set if the call rate was < 97% in all samples. Imputed probes were also removed if HWE p-values were $<10^{-6}$ in controls or if the minor allele frequency (MAF) was <5%. A subset of genotyped calls were masked and imputed to determine the average imputation accuracy. The concordance between imputed and true genotype was 98.3%. After all QC steps, 3,730,665 autosomal probes were available for statistical analysis.

Statistical analysis

After removing participants with missing clinical data, 271 depressed participants were analyzed. To reduce genetic heterogeneity, the primary analyses were conducted in 222 depressed participants of Caucasian ancestry. Potential covariates were examined with respect to two diagnoses: AD and the broader definition of any CI; each of these groups was separately compared with the reference group of individuals with the CN diagnosis using chi-square tests for categorical covariates and t-tests for continuous covariates in SAS v9.4 (SAS Institute, Cary, NC, USA). Trajectories of CERAD decline were obtained from beta estimates of CERAD-TS regressed on time (years) for each participant. To assess how well the beta estimate fit the longitudinal data, we examined the distribution of root-mean-square error (RMSE). Three participants were excluded from this analysis due to RMSE values more than three SDs from the mean, indicating the trajectory of CERAD decline was not linear for those participants. Genome-wide SNPs were assessed for association with AD and CI compared to (CN) participants using logistic regression with an additive genetic model implemented in PLINK. In addition to dichotomous outcomes, linear regression models were used to investigate the associations between genome-wide SNPs and baseline CERAD-TS or CERAD decline scores. Several relevant variables were considered for inclusion as covariates in the regression models: age, sex, race, years of education, and the cumulative illness rating scale (CIRS) total score. Due to significant confounding among several pairs of these variables, only age, sex, and two genome-wide principal components were included as covariates. Additionally, baseline CERAD-TS was covaried in the models of CERAD decline. In an effort to reduce genomic

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Table 1. Participant characteristics

	AD ($N = 12$)	CI ($N = 31$)	CN ($N = 111$)	p-Value (AD vs. CN)	p-Value (CI vs. CN)
% Female	67.74%	65.22%	61.45%	0.5045	0.5439
Age at enrollment (mean, SD)	73.35 (7.09)	71.97 (6.75)	66.82 (5.93)	<0.0001	<0.0001
% Caucasian	86.67%	80.22%	82.68%	0.5885	0.6198
Years education (mean, SD)	13.45 (3.25)	13.39 (3.22)	14.78 (2.28)	0.0058	<0.0001
CIRS total score (mean, SD)	4.24 (2.10)	5.00 (2.84)	4.87 (3.2)	0.3106	0.7456
CERAD-TS (mean, SD)	60.77 (13.37)	63.20 (10.66)	79.29 (8.46)	<0.0001	<0.0001
3-year CERAD decline score (mean, SD)	− 1.73 (4.94)	− 0.09 (3.97)	0.87 (2.41)	0.0022	0.0935

Comparisons for AD vs.CN and CI vs. CN groups used chi-square tests for categorical covariates and t-tests for continuous covariates.

redundancy, linkage dysequilibrium clumping was performed on the Caucasian subset in PLINK using previously reported thresholds (p1 = 1, p2 = 1, $r^2 = 0.25$, 500 kb window) (Ripke *et al.*, 2014). False discovery rate (FDR) q-values were calculated, and quantile–quantile plots were generated using the R packages *qvalue* and *qqman*, respectively.

Results

Among the 271 depressed NCODE participants, 123 experienced cognitive decline over time; 31 (14.76%) were assigned a diagnosis of AD and 92 (33.95%) were assigned diagnoses related to CI, including those with AD and other dementias. As shown in Table 1, compared with CN participants, those with AD were older at time of enrollment and completed fewer years of education. There was no difference in the proportion of females or Caucasian ancestry or in mean CIRS total score between AD and CN participants. As expected, those with AD had significantly lower average CERAD-TS at baseline compared with CN participants. Of interest, CERAD-TS for depressed AD participants declined at a faster rate compared with depressed CN participants. Results for CI participants compared with CN participants yielded similar results (Table 1).

Many potential covariates were correlated with each other, and therefore, they were not all included in the subsequent GWAS analyses. Younger participants completed more years of education ($p = 0.0048$) and had a lower CIRS total score ($p = 0.0016$). Males and those of Caucasian ancestry completed more years of education ($p = 0.0005$ and 0.0006, respectively). 90% of males were of Caucasian ancestry, while 77% of females were Caucasian ($p = 0.0019$). Because 82% of the participants were Caucasian, we limited the GWAS analysis to Caucasians ($N = 222$).

Clinical diagnosis

Among the depressed individuals, we were interested in identifying genetic variants that significantly predicted AD vs. CN (Figure 1a) and CI vs CN (Figure 1b). None of these analyses resulted in a genome-wide significant result. Again, we note that CI is a broad construct that incorporates dementia including AD.

AD vs. CN

The most significant SNP in the analysis of AD compared with CN was rs754804 with an MAF of 0.06, located in an intergenic region of chromosome 1 ($p = 1.25 \times 10^{-5}$). Individuals with the T allele were 32 times more likely to have AD than be CN. The most significant SNP in a gene was rs17851751, which is a nonsynonymous variant in *ZMAT4* on chromosome 8 ($p = 7.1 \times 10^{-5}$). Individuals with the C allele were 6.5 times more likely to have AD than be CN.

CI vs. CN

The most significant SNP when comparing CI to CN participants was rs79966641 located in an intron of *DMXL1* on chromosome 5 ($p = 5.4 \times 10^{-6}$). Individuals with the A allele were 6.3 times more likely to be CI than CN.

Neuropsychological phenotype

We explored whether there were genetic variants influencing CERAD score, both at baseline and decline.

Baseline cognitive analyses

The GWAS of baseline CERAD-TS revealed a significant intergenic SNP on chromosome 6, rs17662598, that surpassed adjustment for multiple testing ($p = 3.7 \times 10^{-7}$, FDR $q = 0.0371$). For each

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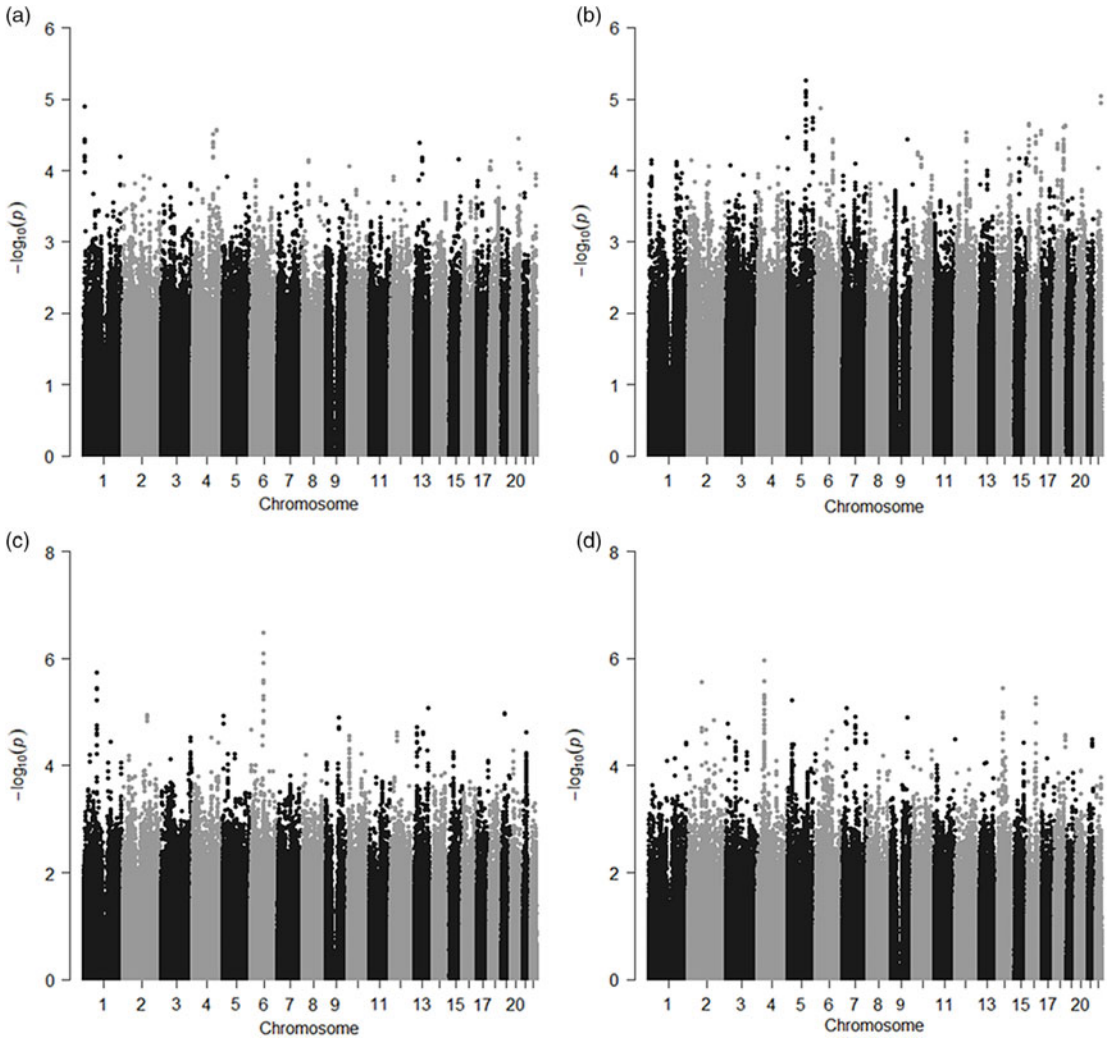

Figure 1. Manhattan plots of GWAS results: (a) AD vs. CN, (b) CI vs. CN, (c) baseline CERAD-TS, and (d) CERAD decline score.

additional G allele, the average baseline CERAD-TS was 8.656 points lower compared to those with the AA genotype. The most significant SNP that lies within a gene was rs11666579 in *SLC27A1* ($p = 1.1 \times 10^{-5}$). Each additional copy of the G allele was associated with an average CERAD baseline score 4.829 points lower than those with the TT genotype.

Longitudinal cognitive analyses

The most significant SNP associated with CERAD decline over time was rs73240021 in *GRXCR1* ($p = 1.1 \times 10^{-6}$). However, this association did not survive adjustment for multiple testing.

Discussion

This study represents, to our knowledge, the first GWAS of cognitive decline in LLD. We compared those patients who subsequently developed AD to those who remained cognitively intact, as well as those with CI to those who remained cognitively intact. We hypothesized that a quantitative measure of cognitive decline might provide more statistical power for this analysis. Thus, we also examined GWAS of CERAD baseline cognitive performance, as well as cognitive decline, as measured by change in CERAD-TS over at least three annual time points including baseline. Analyses related to AD vs CN and CI vs CN did not reach genome-wide statistical significance, with the most significant SNPs being located in an intergenic region on chromosome 1 (rs754804, $p = 1.25 \times 10^{-5}$) and within *ZMAT4* (rs17851751, $p = 7.1 \times 10^{-5}$) for AD vs CN analyses; and in an intron of *DMXL1* (rs79966641, $p = 5.4 \times 10^{-6}$) for CI vs CN analyses. Analyses of baseline CERAD-TS revealed a genome-wide significant association with an SNP on chromosome 6, rs17662598 ($p = 3.7 \times 10^{-7}$, FDR $q = 0.0371$). We also identified an SNP lying within *SLC27A1* (rs11666579) that did not reach genome-wide significance ($p = 1.1 \times 10^{-5}$). Our analyses of CERAD-TS

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decline revealed an SNP in *GRXCR1* (rs73240021) that did not reach genome-wide significance ($p = 1.1 \times 10^{-6}$).

The most compelling association that we detected was in the GWAS of baseline CERAD-TS, which identified rs17662598, an intergenic SNP that remains significant after adjusting for multiple comparisons. This SNP has been identified as an expression quantitative trait locus (eQTL) in Genotype Tissue Expression (GTEx) database, but only in testis. There are no known candidate regulatory elements (cREs) directly overlapping rs17662598 according to the Encyclopedia of DNA Elements (ENCODE) database, but there are three cREs within 2 kb of the associated SNP (http://screen.encodeproject.org/search/?q=rs17662598&assembly=hg19&uuid=0). Additional research will be necessary to understand how this highly statistically significant association reflects underlying biology of cognitive function. An SNP in *SLC27A1* was also nominally associated ($p = 1.05 \times 10^{-5}$), though it did not reach genome-wide significance ($q = 0.2053$). *SLC27A1* is the fatty acid transport protein 1, which has docosahexaenoic acid (DHA) as a substrate. DHA is an endogenous neuroprotective compound, and decreased levels of DHA in the brain are associated with the development of AD (Ochiai *et al.*, 2019). The GWAS of CERAD decline identified an SNP in *GRXCR1*, a gene associated with autosomal-recessive nonsyndromic hearing impairment (Schraders *et al.*, 2010). This is notable, as hearing impairment has been associated with cognitive decline and depression in late life (Rutherford *et al.*, 2018).

The intergenic SNP rs754804, found in the AD vs CN GWAS, is 10 kb from the gene *SLC45A1*. This gene has been previously associated with intellectual disability with neuropsychiatric features (Srour *et al.*, 2017). It is possible that variation in rs754804 is regulating expression of *SLC45A1*; however, the GTEx database shows no significant eQTLs in any tissue. Looking in the ENCODE database, there are no directly overlapping cRE, but there are five cREs within 2 kb of this SNP (http://screen.encodeproject.org/search/?q=rs754804&uuid=0&assembly=hg19). Thus, it is possible that the association with this SNP is driven by other regulatory elements. The most significant SNP that fell in a gene was a nonsynonymous SNP in *ZMAT4* (rs17851751) associated with AD. Interestingly, *ZMAT4* has previously been associated with refractive error (Fan *et al.*, 2014), which has in turn been associated with cognitive function (Ong *et al.*, 2013).

For CI vs. CN analyses, *DMXL1*, lying in a region on chromosome 5, has been associated with astrocytomas (van den Boom *et al.*, 2006), and a link has been hypothesized between AD and astrocytomas (Lehrer, 2018). *DMXL1* has also been associated with primary open-angle glaucoma (Davis *et al.*, 2011).

The strengths of our study include the careful clinical assessment and the novelty of our approach. The diagnosis of MDD was assigned by a geriatric psychiatrist based on a comprehensive standardized assessment, and participants received ongoing care. Participants completed neuropsychological testing annually, and cognitive diagnoses were assigned by an expert consensus panel based on current clinical histories. The diagnostic process using consensus diagnoses has been shown to be reliable and valid (Breitner *et al.*, 1995). In addition, this study represents the first GWAS of cognitive decline in the context of geriatric depression, which was examined across both clinical diagnosis and neuropsychological phenotype.

Despite the strengths, we also acknowledge that the study has several limitations. The most significant limitation is the sample size. Notably, most GWAS analyses are conducted in samples of several thousand individuals and our study had only a few hundred individuals. This certainly impacted the statistical power to identify associations. However, despite the small sample, we did identify one genome-wide significant association, and several other plausible candidate genes that were nominally significant. Additionally, our approach to conceptualize cognitive decline quantitatively by using annual CERAD assessments was quite novel. Nonetheless, having more CERAD assessments over a longer period of time could provide a more informative construct of cognitive decline. While our results are intriguing, they are simply a first step in understanding the genetic architecture of cognitive decline in geriatric depression. As such, we have refrained from reporting effect sizes. Future work should build upon these findings and ideally include much larger samples.

The advantage of the GWAS approach over previous candidate gene approaches is the potential to identify new genes and pathways related to the development of a particular disorder or condition. While the chip we used in this study did not include *APOE* variants, we note that we failed to find an association between *APOE* genotype and incident dementia in our prior NCODE study (Steffens et al., 2007), highlighting the importance of research that seeks to discover new genetic paths linking depression, cognitive decline, and dementia. In the present study, the results related to cognitive performance and cognitive decline are particularly intriguing and point toward DHA biology and hearing impairment as being related to baseline and longitudinal cognition in depression.

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Conflict of interest

None.

Description of authors' roles

D. C. Steffens designed the study and wrote the paper. M. E. Garrett conducted the study, analyzed the data, and assisted in writing the paper. K. L. Soldano conducted the study and reviewed the final draft of the paper. D. R. McQuoid managed the data and created data sets for analysis. A. E. Ashley-Koch supervised the genetic analyses and assisted in writing the paper. G. G. Potter conducted the study and assisted in writing the paper.

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