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Cognitive Performance in First-Degree Relatives of Individuals With vs Without Major Depressive Disorder
A Meta-analysis

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Supplemental content

IMPORTANCE Findings of cognitive impairment in major depressive disorder (MDD), including remitted MDD, raise the question whether impaired cognition is part of preexisting vulnerability rather than a consequence of MDD or its treatment. To our knowledge, no meta-analyses have been published on cognitive impairment in first-degree relatives of individuals with MDD.

OBJECTIVE To compare cognitive performance between individuals with and without family history of MDD.

DATA SOURCES Medline/PubMed, PsycINFO, and Embase using combinations of search terms for *depression*, *first-degree relatives*, and *cognition* from January 1, 1980, to July 15, 2018.

STUDY SELECTION Original articles that reported data on cognition in first-degree relatives of individuals with MDD compared with controls with no family history of major mental illness.

DATA EXTRACTION AND SYNTHESIS Means and SDs were extracted, and standardized mean differences (SMD) between relatives and controls were calculated for each measure of cognitive performance. The relative-control differences in overall cognition and in specific cognitive domains were synthesized in random-effects meta-analyses with robust variance estimation that allows including multiple correlated measures of cognition within each study. Heterogeneity was quantified with τ^2. Publication bias was assessed with funnel plots and Egger intercept.

MAIN OUTCOMES AND MEASURES Performance on cognitive tests.

RESULTS Across 284 measures of cognition in 54 nonoverlapping samples including 3246 relatives of people with MDD (mean age 15.38 years, 57.68% females) and 5222 controls (mean age 14.70 years, 55.93% females), relatives of people with MDD performed worse than controls across all measures of cognition (SMD = −0.19; 95% CI, −0.27 to −0.11; $P < .001$). Domain-specific meta-analyses showed similar size of relative-control difference in most domains of cognition, including Full-Scale IQ (SMD = −0.19), verbal intelligence (SMD = −0.29), perceptual intelligence (SMD = −0.23), memory (SMD = −0.20), academic performance (SMD = −0.40), and language (SMD = −0.29). Study characteristics were not significantly associated with observed between-group differences. There was no evidence of publication bias.

CONCLUSIONS AND RELEVANCE A general impairment in cognition is a feature of familial disposition for MDD. Cognition may contribute to early identification of risk for depression and may be examined as potential target for early intervention.

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Major depressive disorder (MDD) is a psychiatric disease with lifetime prevalence of 20%.[1] Cognitive impairments are common in individuals with MDD[2,3] and persist after remission.[4,5] Some prospective studies suggest that impaired cognition predates the onset of MDD,[6,7] but others raise the possibility that cognitive impairment may be a consequence of depression, its comorbidity, or its treatment.[8,9] One method of answering the question about the origin of cognitive impairments in depression is the study of unaffected relatives. First-degree relatives of people with MDD share half of the genetic variants that contribute to MDD risk and are at an increased risk of developing MDD themselves.[10,11] Presence or absence of cognitive impairment in unaffected relatives of individuals with MDD would be strong evidence that impaired cognition is a precursor or consequence of MDD respectively. However, investigations of cognition in first-degree relatives of individuals with MDD have provided inconsistent results, with some studies finding impaired cognitive performance compared with controls[12-15] and others finding no difference between groups.[16,17] It is likely that small sample sizes have limited the ability of previous investigations to detect small to moderate effect sizes in this nonpatient population owing to lack of statistical power. To our knowledge, there has been no meta-analysis of cognitive performance in first-degree relatives of individuals with MDD.

The present study seeks to clarify the association between family history of depression and cognition in a meta-analysis of a large composite sample that provides adequate statistical power to investigate cognition in unaffected first-degree relatives of individuals with MDD. Our aim was to compare first-degree relatives of individuals with MDD with controls to quantify the difference in their overall cognitive performance and in specific cognitive domains.

Key Points

Question Is cognitive impairment present in relatives of individuals with depression?

Findings In this meta-analysis of 54 studies including more than 8000 individuals, first-degree relatives of people with depression performed consistently less well on cognitive tests compared with individuals with no family history of major mental illness. Cognitive impairment generalized to most cognitive domains tested.

Meaning General cognitive impairment may be associated with familial risk for depression.

Methods

Literature Search

We searched Medline/PubMed, PsycINFO, and Embase using combinations of search terms for depression (*depression*, *mood disorder*, *major depressive disorder*), first-degree relative (*cognitive endophenotype*, *unaffected relatives*, *family/familial high-risk*, *genetic high-risk*, *first degree relative*, *siblings*, *twins*, *offspring*, *parent*), and cognition (*cognition*, *neurocognition*, *intelligence*, *intellectual functioning*, *memory*, *working memory*, *verbal memory*, *visual memory*, *attention*, *sustained attention*, *controlled attention*, *executive function*, *cognitive flexibility*, *stroop*, *facial recognition*, *emotional processing*, *affective biases*, *learning*, *reward learning*, *theory of mind*, *visual processing*, *social cognition*, *motor*, *verbal fluency*, *psychomotor speed*, *processing speed*). In addition, we searched the bibliographies of identified eligible articles and of a recent review.[18] We included articles published between January 1, 1980 (corresponding with the publication of the *Diagnostic and Statistical Manual of Mental Disorders* [Third Edition]),[19] and July 15, 2018. We contacted the corresponding authors of included studies to request unpublished data.

Eligibility Criteria

We included studies that reported original data on cognition in first-degree relatives of individuals with MDD and in a control group without a first-degree relative diagnosed as having MDD, bipolar disorder, or schizophrenia, established by a validated diagnostic instrument. We included studies with participants 69 years and younger to analyze cognitive performance independent of cognitive decline associated with aging. We excluded samples matched on cognitive performance (eg, Full-Scale IQ [FSIQ]) and cognitive tests without clear direction of better vs worse performance (eg, attention bias to specific emotion). We excluded overlapping data from the same sample unless different publications presented data on different domains of cognition (eg, we excluded overlapping FSIQ but retained executive function data that was published in a separate publication). If there was more than 1 publication from the same sample reporting overlapping data, we included the publication with the largest number of participants. For studies that involved an intervention, we included only the preintervention test scores. When studies assessed cognition longitudinally with no intervention, we included the time point with the largest sample size.

Publications in languages other than English were not excluded; however, no publications in languages other than English met inclusion criteria. We contacted authors for additional information when it was not clear whether the study met inclusion criteria. We excluded the data if we did not resolve the discrepancies by contacting the authors.

Data Extraction

Citations from systematic search of databases were imported into Covidence systematic review platform (Cochrane). Title and abstract screening was completed by the first author (L.E.M.). Full-text review was completed to determine full eligibility criteria by all authors (L.E.M., R.U., and B.P.). Discrepancies were resolved in consensus meetings with all authors.

We extracted the following information from the individual publications: author, year of publication, geographic region, method of recruiting relatives, method of recruiting controls, the number of individuals in the relatives group, the number of individuals in the control group, type of first-degree relative, type of validated instrument for diagnosis of mental disorders, whether the relatives and controls were matched on socioeconomic status, age, number of male and

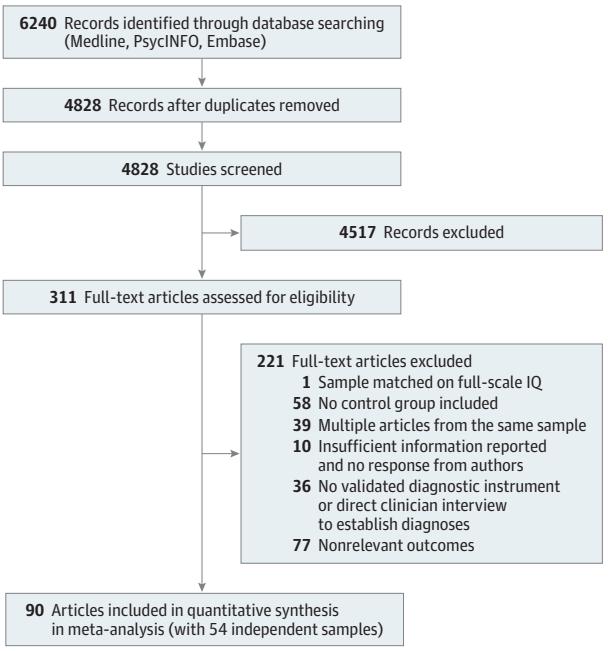
female individuals in the first-degree relative group and control group, their age (mean and SD), cognitive domain, cognitive test used, the cognitive performance of the relatives group (mean and SD), and the cognitive performance of the control group (mean and SD). When required data were not included in the original publication, we contacted the authors for more information.

Cognition was separated into the following domains: FSIQ, verbal IQ, perceptual IQ, attention, memory, processing speed, executive function, hot cognition, psychomotor skills, academic performance, and language. All cognitive performance variables were coded so that a higher score reflected a better performance.

Statistical Analysis

For each cognitive test, we computed the standardized mean difference (SMD) between the first-degree relatives of people with MDD and controls through dividing the mean difference by pooled SD. We combined effect sizes across studies to provide overall estimates and their 95% CIs using random-effects meta-analysis with robust variance estimation that accounts for the dependence of effect sizes from the same study,[20] implemented through the robumeta[21] macro in Stata (version 15; StataCorp). This method allows the inclusion of multiple test results from the same study. We first performed a meta-analysis of overall cognition including all directional measures of cognitive ability. Then we proceeded to complete domain-specific meta-analyses of cognitive domains that were measured in at least 4 independent samples. We report pooled effect sizes as SMDs with their 95% CIs and *P* values. Negative SMDs indicated worse performance in first-degree relatives of individuals with MDD than in controls. We quantified statistical heterogeneity with the τ^2 statistic, which reflects the between-study heterogeneity variance in SMD between relatives and controls on cognitive measures. In addition, we calculated I^2 as the proportion of variance due to heterogeneity between studies.[22] We tested the association of study characteristics (type of relatives [offspring vs other first-degree relative], age, socioeconomic status, publication year, geographic region) with relatives-controls differences in cognitive performance using random-effects meta-regressions with robust variance estimation.[20,21] We also used the robust random-effects meta-regressions to test if any domain of cognition is associated with greater or smaller relatives-controls difference. We report the results of meta-regressions as the standardized regression coefficients (β), their 95% CIs, and *P* values. Finally, we carried out a series of sensitivity analyses to probe whether the results generalize to subsets of studies with more stringent methodology (ie, those that only included relatives without mood disorders, those that matched relatives and controls on socioeconomic status only, and those that matched relatives on socioeconomic status and age) or studies of specific subgroups (relatives of patients with severe/chronic depression, offspring of affected parents, individuals 7 years or older, or samples recruited from the community). Since only 1 test of overall cognition was carried out, we consider a result with $P < .05$ as statistically significant. For domain-specific meta-analyses, we report both nominal significance ($P < .05$) and significance corrected for the number of cognitive domains tested (11 domains, corrected *P* threshold value = .0045). We assessed the likelihood of publication bias through visual inspection of funnel plots and the Egger intercept test.

Figure 1. Flow Diagram of Study Selection and Inclusion



Results

Search Results and Sample Characteristics

Our systematic search identified 4828 articles, of which 4517 articles were excluded after title and abstract screening. After full-text screening of the remaining 311 articles, we identified 90 eligible articles that comprised 54 nonoverlapping samples[12-17,23-70] with 3246 first-degree relatives (1872 female [57.68%]) and 5222 controls (2921 female [55.93%]) (**Figure 1**). The mean (SD) age of first-degree relatives was 15.38 (13.66) years, and the mean (SD) age of the controls was 14.70 (12.37) years. Thirty-four of 54 samples (63.0%) were recruited in North America. Of the 54 samples included in the meta-analysis, 39 (72.2%) consisted of offspring of parents with MDD, 12 (22.2%) included any first-degree relatives, and 3 (5.6%) were siblings or twin samples. See eTable 1 in the Supplement for details of the included studies.

Cognition in First-Degree Relatives of People With MDD and Controls

Based on 54 samples, including 3246 first-degree relatives and 5222 control relatives, the overall cognitive performance of first-degree relatives of individuals with MDD was worse than the performance of controls (SMD = −0.19; 95% CI, −0.27 to −0.11; $P < .001$) (**Table 1** and **Figure 2**), with moderate heterogeneity between studies ($\tau^2 = 0.100$, $I^2 = 0.296$).

Table 1. Cognitive Performance in First-Degree Relatives of People With Major Depressive Disorder Compared With Controls

	No.				Robust Meta-analysis, Multiple Effect Sizes Within Study		
Cognitive Domain	Effect Sizes	Relatives	Controls	Studies	SMD (95% CI)[a]	*P* Value	τ^2
Overall cognition	284	3246	5222	54	−0.19 (−0.27 to −0.11)	<.001	0.100
Full-scale IQ	35	2016	3304	32	−0.19 (−0.31 to −0.08)	.001	0.041
Verbal IQ	14	1349	1534	11	−0.29 (−0.56 to −0.03)	.03	0.120
Perceptual IQ	16	519	428	9	−0.23 (−0.41 to −0.05)	.02	0.029
Attention	26	247	270	6	−0.20 (−0.49 to 0.09)	.13	0.055
Memory	22	580	558	8	−0.20 (−0.35 to −0.05)	.02	0.071
Processing speed	40	302	232	8	−0.14 (−0.38 to 0.10)	.22	0.062
Executive function	47	349	273	9	−0.22 (−0.49 to 0.05)	.10	0.109
Hot cognition	48	321	278	9	−0.18 (−0.47 to 0.11)	.20	0.098
Psychomotor skills	8	247	237	6	−0.30 (−0.63 to 0.03)	.06	0.030
Academic performance	8	149	134	4	−0.40 (−0.66 to −0.14)	.02	0
Language	11	287	450	6	−0.29 (−0.55 to −0.04)	.03	0.007

Abbreviation: SMD, standardized mean difference.

[a] 95% CI of lower bound to upper bound.

When compared with controls, first-degree relatives of individuals with MDD performed significantly worse in a number of domains of cognition, including FSIQ (SMD = −0.19; 95% CI, −0.31 to −0.08; *P* = .001), verbal intelligence (SMD = −0.29; 95% CI, −0.56 to −0.03; *P* < .05), perceptual intelligence (SMD = −0.23; 95% CI, −0.41 to −0.05; *P* < .05), memory (SMD = −0.20; 95% CI, −0.35 to −0.05; *P* < .05), academic performance (SMD = −0.40; 95% CI, −0.66 to −0.14; *P* < .05), and language (SMD = −0.29; 95% CI, −0.55 to −0.04; *P* < .05) (Table 1). The difference between controls and first-degree relatives in FSIQ remained statistically significant when corrected for multiple comparisons. The differences between the performance of first-degree relatives of individuals with MDD and controls in attention (SMD = −0.20; 95% CI, −0.49 to 0.09; *P* = .13), processing speed (SMD = −0.14; 95% CI, −0.38 to 0.10; *P* = .22), executive function (SMD = −0.22; 95% CI, −0.49 to 0.05; *P* = .10), hot cognition (SMD = −0.18; 95% CI, −0.47 to 0.11; *P* = .20), and psychomotor skills (SMD = −0.30; 95% CI, −0.63 to 0.03; *P* = .06) did not reach nominal statistical significance (Table 1). See eTable 2 in the Supplement for details of the tests used to measure the individual cognitive domains.

Meta-regression of Sample Characteristics

Based on the meta-regressions, type of relative (offspring vs other first-degree relative) (β = −0.10; 95% CI, −0.28 to 0.07; *P* = .25; τ^2 = 0.11), participants' age (β = 0; 95% CI, −0.07 to 0.07; *P* = .96; τ^2 = 0.12), group matching on socioeconomic status (β = −0.18; 95% CI, −0.43 to 0.07; *P* = .14; τ^2 = 0.11), the year when the study was published (β = 0.01; 95% CI, −0.09 to 0.12; *P* = .77; τ^2 = 0.11), or geographical region where sample was recruited (β = 0.11; 95% CI, −0.06 to 0.28; *P* = .19; τ^2 = 0.10) had no significant association with the difference between the overall cognitive performance of the first-degree relatives of people with MDD and the controls. Additionally, no type of individual cognitive domain tested had a significant association with the difference between the overall cognitive performance of the first-degree relatives of people with MDD and controls (**Table 2**).

Sensitivity Analyses

Sensitivity analyses restricted to healthy relatives, relatives of people with severe and chronic MDD, samples in which the MDD diagnoses were established by experts using a semistructured interview, offspring group only, relatives 7 years and older, relative and control group matched on socioeconomic status as well as socioeconomic status and age, and relative and control groups recruited from community estimated effect sizes similar to the main result (effect sizes ranging between −0.13 and −0.22; eTable 3 in the Supplement).

Publication Bias

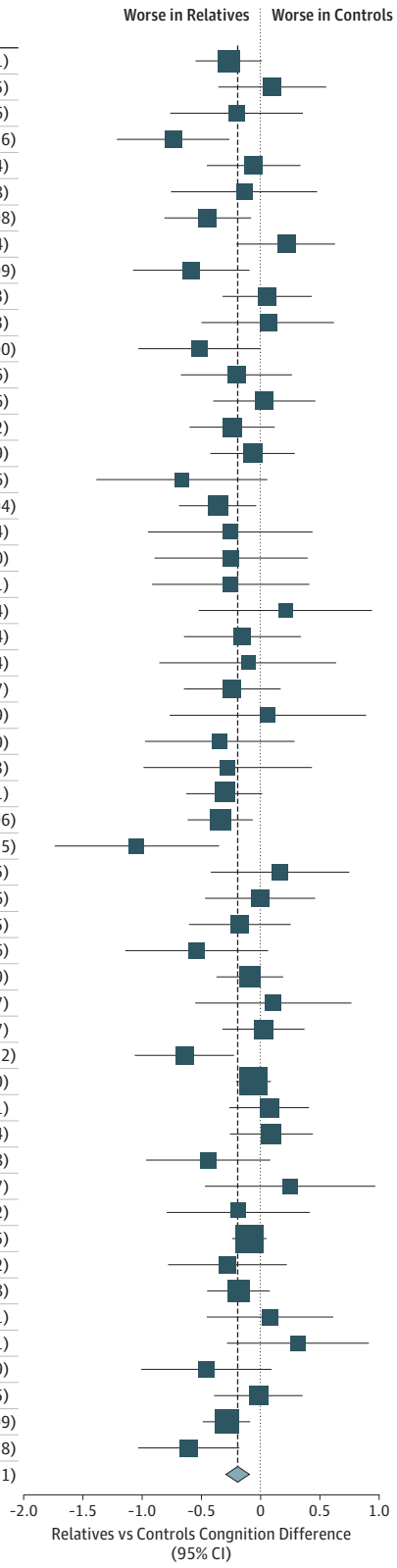
Visual examination of the funnel plot revealed no indication of publication bias. Quantitative investigation of publication bias, using Egger intercept, was nonsignificant (β = −0.37; SE = 0.35; 95% CI, −1.07 to 0.33; *P* = .29). The funnel plot is shown in eFigure in the Supplement.

Discussion

Across multiple measures of cognitive ability in more than 8000 individuals, we found evidence of slightly but robustly impaired cognition in first-degree relatives of people with MDD compared with those with no family history of severe mental illness. There are several possible explanations for impaired cognitive performance in first-degree relatives of individuals with MDD. The lower cognitive ability seen in relatives of individuals with MDD may reflect genetic and social factors associated with the risk of MDD. Recent large-scale studies have mapped the genetic risk of depression to several dozen loci in genes that play important roles in neuronal development, synaptic function, and plasticity.[71] For example, one of the strongest genetic association with MDD is in *NEGR1* (neuronal

Figure 2. Difference in Cognition Between First-Degree Relatives of People With Major Depressive Disorder and Controls

Study	Effect (95% CI)
Winters et al,[12] 1981	-0.27 (-0.55 to 0.01)
Goodman et al,[24] 1987	0.10 (-0.36 to 0.55)
Whiffen and Gotlib,[13] 1989	-0.20 (-0.76 to 0.36)
D'Angelo,[25] 1993	-0.74 (-1.21 to -0.26)
Murray et al,[26] 1996	-0.06 (-0.45 to 0.34)
Hirose and Barnard,[27] 1997	-0.14 (-0.76 to 0.48)
Cicchetti et al,[23] 2000	-0.45 (-0.81 to -0.08)
Taylor and Ingram,[28] 1999	0.22 (-0.20 to 0.64)
Hay et al,[14] 2001	-0.58 (-1.08 to -0.09)
Nulman et al,[29] 2002	0.06 (-0.32 to 0.43)
Traill,[30] 2002	0.06 (-0.50 to 0.63)
Milgrom et al,[31] 2004	-0.52 (-1.03 to -0.00)
Sunew,[32] 2004	-0.20 (-0.67 to 0.26)
Pine et al,[33] 2005	0.03 (-0.40 to 0.46)
Christensen et al,[15] 2006	-0.24 (-0.60 to 0.12)
Klimes-Dougan et al,[16] 2006	-0.07 (-0.42 to 0.29)
Pérez-Edgar et al,[34] 2006	-0.67 (-1.39 to 0.06)
Bohon et al,[35] 2007	-0.36 (-0.69 to -0.04)
Oberlander et al, [36] 2007	-0.26 (-0.95 to 0.44)
Firk and Markus,[37] 2008	-0.25 (-0.90 to 0.40)
Monk et al, [38] 2008	-0.25 (-0.92 to 0.41)
Evers et al,[39] 2009	0.21 (-0.52 to 0.94)
Micco et al,[40] 2009	-0.16 (-0.65 to 0.34)
McGirr et al,[41] 2010	-0.11 (-0.86 to 0.64)
Murray et al,[42] 2010	-0.24 (-0.65 to 0.17)
Feder et al,[43] 2011	0.06 (-0.77 to 0.89)
Galbally et al,[44] 2011	-0.34 (-0.97 to 0.29)
Huang et al,[45] 2011	-0.28 (-0.99 to 0.43)
Quevedo et al,[46] 2012	-0.31 (-0.63 to 0.01)
Conroy et al,[47] 2012	-0.34 (-0.62 to -0.06)
Kersten-Alvarez et al,[48] 2012	-1.04 (-1.74 to -0.35)
Lisiecka et al,[49] 2012	0.16 (-0.42 to 0.75)
Hanley et al,[50] 2013	-0.00 (-0.47 to 0.46)
Lopez-Duran et al,[51] 2013	-0.18 (-0.60 to 0.25)
van Oostrom et al,[52] 2013	-0.54 (-1.14 to 0.06)
Watters et al,[53] 2013	-0.09 (-0.37 to 0.19)
Asarnow et al,[54] 2014	0.11 (-0.55 to 0.77)
Erk et al,[55] 2014	0.02 (-0.32 to 0.37)
Hsu et al,[56] 2014	-0.64 (-1.06 to -0.22)
Kujawa et al,[57] 2014	-0.06 (-0.21 to 0.09)
Santucci et al,[17] 2014	0.07 (-0.26 to 0.41)
Eriksen et al,[58] 2015	0.09 (-0.26 to 0.44)
Fattahi Asl et al,[59] 2015	-0.44 (-0.97 to 0.08)
Frost Bellgowan et al,[60] 2015	0.25 (-0.47 to 0.97)
Hoehne et al,[61] 2015	-0.19 (-0.79 to 0.42)
Maselko et al,[62] 2015	-0.10 (-0.24 to 0.05)
Meiser et al,[63] 2015	-0.28 (-0.78 to 0.22)
Woody et al,[64] 2015	-0.19 (-0.45 to 0.08)
Young et al,[65] 2015	0.08 (-0.45 to 0.61)
Chai et al,[66] 2016	0.31 (-0.28 to 0.91)
Kluczniok et al,[67] 2016	-0.46 (-1.01 to 0.09)
Liu et al,[68] 2016	-0.02 (-0.39 to 0.35)
Begovic et al,[69] 2017	-0.29 (-0.49 to -0.09)
Singh et al,[70] 2018	-0.61 (-1.03 to -0.18)
Overall	-0.19 (-0.27 to -0.11)



The forest plot shows the standardized mean difference estimate across measures of cognition in each sample (blue square) and its 95% CI (black horizontal line). The size of the blue square is proportional to the weight of each sample in the meta-analysis. The vertical dashed line and the light blue diamond show the weighted standardized mean difference in overall cognition and its 95% CI, estimated in random-effects meta-analysis with robust variance estimation across the 54 included samples. Values smaller than 0 (and symbols to the left of the gray dotted vertical line) reflect worse performance in relatives of people with major depressive disorder than in controls.

Table 2. Meta-regressions of Sample Characteristics and Cognitive Domain on Cognitive Performance

Covariate	β (95% CI)[a]	*P* Value	τ^2
Relative type (offspring)	−0.10 (−0.28 to 0.07)	.25	0.105
Age	0.00 (−0.07 to 0.07)	.96	0.115
SES	−0.18 (−0.43 to 0.07)	.14	0.109
Publication year	0.01 (−0.09 to 0.12)	.77	0.107
Geographical region	0.11 (−0.06 to 0.28)	.19	0.099
FSIQ	0.08 (−0.07 to 0.23)	.30	0.104
Verbal cognition	−0.08 (−0.49 to 0.34)	.70	0.106
Perceptual cognition	−0.06 (−0.26 to 0.15)	.53	0.104
Memory	0.05 (−0.18 to 0.27)	.63	0.105
Attention	−0.09 (−0.81 to 0.62)	.72	0.104
Processing speed	0.00 (−0.30 to 0.30)	.97	0.104
Executive function	−0.01 (−0.27 to 0.24)	.90	0.104
Hot cognition	0.08 (−0.19 to 0.35)	.52	0.105
Academic attainment	−0.14 (−0.62 to 0.33)	.31	0.104
Language	−0.03 (−0.34 to 0.27)	.75	0.105

Abbreviations: FSIQ, Full-Scale IQ; SES, socioeconomic status; β, standardized β regression coefficient.

[a] 95% CI of lower bound to upper bound.

growth regulator 1 gene) that modulates axonal extension and synaptic plasticity in the brain cortex, and the hippocampus, which are key structures involved in memory and other cognitive functions.[71] In addition, polygenic risk scores reflecting the genetic risk for MDD have shown small negative correlations with measures of cognitive ability, including memory and reaction times in a large population-based sample.[72]

Cognition in relatives may also be affected by environmental factors, such as poverty and low socioeconomic status, that may run in families alongside depression and affect even those who do not develop depressive disorders. Additionally, previous research indicates that mothers diagnosed as having MDD show decreased shared attention and vocalization with their infants and toddlers and that children of mothers with MDD speak less often to their mothers compared with controls,[73-77] which may negatively impact cognitive development in children.[78] However, results of sensitivity analyses restricted to samples in which relatives and controls were tightly matched on socioeconomic status together with sensitivity analyses restricted to offspring suggest that a genetic mechanism is a more likely determinant of cognitive deficits in unaffected relatives. In conjunction with the recent genetic findings, our results suggest that a slight reduction in general cognitive ability is part of the familial risk for depression and is likely mediated through genetically influenced neurodevelopmental mechanisms.

We have found a small SMD between first-degree relatives of people with MDD and controls in nearly all cognitive domains. The relatively small size of the difference is expected as first-degree relatives share only 50% of genetic variants with those affected by psychiatric disorders and are typically intermediate between affected individuals and controls. The generalization of impairment across most cognitive domains suggests that familial liability to depression is associated with a broad impairment in cognition rather than a distinct cognitive profile. One exception was the finding that processing speed does not differ between first-degree relatives of people with MDD and controls. Previous findings indicate that decreased processing speed is associated with greater symptom severity and increasing patient age.[79] This pattern of findings indicates that performance on processing speed tasks does not appear to be associated with genetic or environmental susceptibility to MDD and is more likely associated with downstream effects of illness, such as duration of illness and severity of psychopathology.

Implications for Intervention and Prevention

These findings may have implications for early intervention in individuals at familial high risk for developing MDD. Early interventions could aim to remediate cognitive impairment to prevent the onset of depression in individuals at family high risk. This is supported by previous findings that intervention targeting cognitive performance in children of mothers with MDD has benefits in both child cognition and maternal mental health.[80] Early interventions may also target parenting skills and the parent-child relationship. Such intervention has previously been shown to have protective effects on children's cognitive development.[23] There are currently no data on the effect of early interventions aimed at cognitive remediation on long-term prevalence rates of MDD and the social and occupational impact of these disorders in those at family high risk, to our knowledge. Longitudinal intervention research is needed to investigate the impact of early interventions targeting cognitive development in first-degree relatives of individuals with MDD.

Strengths

To our knowledge, this is the first systematic review and meta-analysis of cognitive performance in first-degree relatives of individuals with MDD. This meta-analysis included a large number of independent samples, allowing for robust meta-analysis models. Our inclusion criteria required a validated clinical interview to establish the diagnosis of MDD in the first-degree relative and the confirmation of no severe mental illness in the first-degree relatives of the control group. We found

moderate heterogeneity between studies. Findings were robust and not significantly impacted by sample characteristics: relative type (offspring vs other first-degree relative), age, socioeconomic status, geographic region of ascertained sample, publication year, and type of cognitive domain.

Limitations

First, we were only able to include published data. However, it is unlikely that our results were influenced by publication bias, as most of the included articles did not focus on the difference in cognitive function between first-degree relatives of people with MDD and controls as their main aim. Additionally, visual inspection of funnel plots revealed no obvious indication of publication bias and statistical investigation of publication bias, using the Egger intercept, was nonsignificant. Second, it is possible that some meta-analyses of the individual cognitive domains (eg, psychomotor skills and attention) did not reach significance because they were underpowered to detect relatively small effect sizes. Third, we were not able to assess the association of several potential confounding sample characteristics with group differences owing to limited collection of this data in the original samples. For example, data on MDD course and severity in the first-degree relatives with MDD were not available in a majority of studies. In addition, we were unable to control for milder forms of psychopathology in relatives of individuals with MDD. First-degree relatives of individuals with MDD have significantly increased rates of subclinical depressive symptoms and nonsevere mental disorders[81,82] compared with controls with no family history of severe mental illness, which may impair their cognitive performance.[83-85] We were also unable to establish whether cognitive assessors were blind to the diagnostic group of relatives. Fourth, this is a meta-analysis of cross-sectional data and hence we cannot answer the question whether cognitive impairment makes first-degree relatives of people with MDD more likely to develop depression themselves.

Future Research

To investigate whether cognitive impairment in individuals at familial high-risk for MDD increases their risk of developing depression, longitudinal research is needed. Longitudinal studies should include follow-up throughout the typical onset period (adolescence and early adulthood) and adequately screened control groups with no family history of severe mental illness.

Conclusions

General impairment in cognition is a feature of familial disposition for MDD. As approximately 50 million individuals are living with MDD in the United States alone,[1,86,87] the cognitive impairment in first-degree relatives of people with MDD impacts not only a large number of families, but also imposes a substantial cost on the society. Efforts should focus on the development of early interventions for individuals with a first-degree relative with MDD.

ARTICLE INFORMATION

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