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RESEARCH ARTICLE

Models of depressive pseudoamnestic disorder

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All study procedures have been conducted in New York State Psychiatric Institute (NYSPI)/Columbia University Medical Center and Duke University Medical Center. Analyses were performed at NYSPI.

Abstract

Objective: Little effort has been made in the past to validate depressive pseudodementia based on hypothesis-driven approaches. We extended this concept to individuals with amnestic Mild Cognitive Impairment and Major Depression, that is, pseudodepressive amnestic disorder. We tested two hypotheses consistent with the presentations and mechanisms associated with this potential syndrome: improvements in cognition would be significantly correlated with improvements in depression after treatment (Hypothesis 1), and if not confirmed, the presence of such an association could be identified once moderator variables were taken into account (Hypothesis 2).

Methods: Within a clinical trial, 61 individuals received open label serotonin reuptake inhibitor (citalopram or venlafaxine) treatment over a 16-week period. Selective Reminding Test and Hamilton Depression scale were conducted serially to measure change in memory and depression, respectively. Magnetic resonance imaging, other cognitive measures (Alzheimer's Disease Assessment Scale–Cognitive and speed of processing tests), and additional depression measure (Beck Depression Inventory [BDI]) were also administered.

Results: No significant associations between improvement in depression and improvement in cognition were observed. Sensitivity analyses with other cognitive measures, the BDI, and exclusion of possible "placebo" responders were negative as well. There were no significant moderation effects for baseline Hamilton Rating Scale for Depression as a measure of symptom severity or age. *APOE* ε4 genotype and white matter hyperintensity burden yielded counter-intuitive, albeit marginally significant results.

Conclusions: Negative findings cast doubt on the frequency of depressive pseudoamnestic disorder in older populations with documented depression and memory impairments.

KEYWORDS
Clinical trial, depression, memory, mild cognitive impairment, pseudodementia

1 | INTRODUCTION

The concept of depressive pseudodementia has a known history. It was initially proposed by Kiloh in 1961 and reached prominence in the 1970s when it was applied to a variety of diagnoses.[1] Depressive pseudodementia in particular refers to memory impairments and functional status compromises, mainly in depressed older individuals, that improve with treatment of depression. Thus, they are reversible. This view is complicated but not negated by the fact that older individuals have increased risk for both depression and dementia and that about 51% of Alzheimer's disease (AD) cases may initially present with apathy, memory problems, and mood changes that can be viewed as "depressive."[2–5] There are also cognitive concomitants of depression, including executive function, speed of processing, and memory, that may not completely resolve after an episode. Additionally, late-life depression may differ from depression in younger individuals due to findings implicating small vessel disease in the brain that may contribute to late-life cognitive impairments.[6,7] While some older studies validated the concept of pseudodementia, most were conducted in the 1960s and 1970s when tricyclic antidepressants were a first-line antidepressant. These are known to have anticholinergic effects that might reduce cognitive gain. Furthermore, patients were generally younger (<70 years), carried various diagnoses including psychosis, and received limited cognitive assessments.

Recent studies of depressive pseudodementia have reached contrasting or equivocal conclusions. Butters et al.[8] found that older depressed patients did not show greater improvement on multiple cognitive tests than a non-depressed control group despite large improvements in depression. However, their second study demonstrated an improvement on the Dementia Rating Scale's initiation/perseveration and conceptualization in the depressed group, though performance was not normalized.[9] Nevertheless, Butters et al. went on to suggest that pseudodementia was a rare occurrence. In contrast, Barch et al.[10] found evidence for state-related changes in cognition in older depressed individuals treated with sertraline. The largest improvements were in measures of memory and executive function. However, given the nature of the tests used (word lists and stories; card sorting) practice effects were likely unavoidable.

Other developments have made pseudodementia conceptually problematic. First, there is an increasing realization that mild cognitive impairment (MCI) may represent a transitional phase of AD and so cognitive impairments found in the context of depression in late life may be related to neurodegeneration. Second, depression itself is a risk factor for AD and may be present 15 to 20 years prior to a dementia diagnosis.[11] Additionally, depression and its concomitant symptom apathy are frequent comorbidities of AD; depression has been also related to amyloid pathology.[12]

Here, we extend this line of work to what we term pseudodepressive amnestic disorder. The current study was therefore implemented in a group of patients with Major Depressive Disorder and psychometrically and clinically diagnosed amnestic MCI who were assessed longitudinally. Such patients do not have the more generalized and severe impairments in cognition and function that AD patients demonstrate. This may increase the likelihood that improvements in mood and cognition might be both observed and correlated. In this study we take a hypothesis-driven approach to validate what may be implicit assumptions that are contained in previous literature. Thus, we evaluated whether changes (improvements) in depression covary with changes (improvements) in cognition among the MCI participants with depression during serotonin reuptake inhibitor (SRI) or selective SRI (SSRI) treatment. We further examined multiple potential moderators of this relationship. Last, we examined whether cognitive improvements were present, general, and not consistent in their profile with a practice effect.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional (e.g., PubMed) sources, references in recent papers, and their own knowledge. While there is an older literature on depressive pseudodementia, there were no studies on what we term depressive pseudoamnestic disorder, that is, major depression in individuals with amnestic mild cognitive impairment (MCI). Relevant citations to the broader field, including critical reviews, are made.
2. **Interpretation**: Our study was hypothesis-driven as we examined evidence for a systematic relationship between changes in depression level and cognition in this MCI group. We did not find such a relationship, casting doubt on the utility of the concept.
3. **Future Directions**: Our study proposes a framework to study depressive pseudodementia and pseudoamnestic disorder. We recommend use of a placebo control group and better control of practice effects to further refine work in this area.

2 | METHODS

2.1 | Participants

The trial was conducted at New York State Psychiatric Institute (NYSPI)/Columbia University Medical Center (N = 41) and Duke University Medical Center (N = 40). Among the 81 patients aged 55 to 95 years with depression and cognitive impairment, two patients did not complete baseline procedures, leaving a sample of 79 patients. The trial was registered on clinicaltrials.gov (identifier: NCT01658228) and the study was conducted from October 2012 to August 2016. Inclusion criteria for participants were the following: (1) met diagnosis for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV major depression or dysthymic disorder by SCID-P evaluation, with a minimum score of 14 on the 24-item Hamilton Rating Scale

for Depression (HAM-D); (2) presented with subjective memory or other cognitive complaints; (3) had a score of ≥21 on the Folstein Mini-Mental State Exam (MMSE), with memory score meeting amnestic MCI criteria (≤11 on the Logical Memory-II subscale from the Wechsler Memory Scale-Revised; or ≥1.5 standard deviations [SDs] below norms on the Selective Reminding Test [SRT, immediate or delayed recall]); (4) received 0.5 from the Clinical Dementia Rating; and (5) were willing and capable of giving informed consent.

Patients were excluded if they had other serious major pre-existing mental or neurological disorders, including dementia, schizophrenia, schizoaffective disorder, psychotic depression, other psychosis, bipolar I disorder, alcohol or substance abuse or dependence in the past 6 months, active suicidal ideation or suicide attempt, use of medications known to cause cognitive impairment, any acute medical illness, uncontrolled hypertension, current use of effective antidepressants, current use of cholinesterase inhibitors or memantine, and electrocardiogram QTc interval greater than 460 msec. The overall trial design is described in a previous paper.[13]

2.2 | Measures

The assessments for depression, HAM-D and Beck Depression Inventory-II (BDI), were collected at each study visit for a total of 10 ratings from baseline to the week 16 endpoint. Response to treatment was defined as ≥50% decrease in HAM-D scores in the 16 weeks.

The three primary outcome measures were the Free and Cued SRT (a test of verbal list learning 12-item 6-trial version) total immediate recall score, modified Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog; 13-item version that assays multiple cognitive domains including verbal memory [free recall and word recognition], visual motor abilities, verbal comprehension, praxis, and naming) total score, and MMSE total score. These three measures were administered at baseline and the week 16 endpoint. The following are secondary measures used in exploratory analyses: Letter and Animal verbal fluency (VF) test, which measures word generation in a 60 second time period; Wechsler Adult Intelligence Scale—Third Edition, Digit Symbol subtest, used to evaluate processing speed (involving using a key to code numbers and symbols); Trail Making Test A (Trails A), which served as an estimate of attention and speed of processing (in which numbers on a page had to be connected in order); and Trail Making Test B (Trails B), a measure of speed and executive function (in which numbers and letters must be connected in alternating sequence).

The apolipoprotein E (*APOE*) genotype was determined by Prevention Genetics using blood samples processed by the Columbia University Human Genetics Resource Core.

Magnetic resonance imaging (MRI) scans were acquired on a Signa 3 Tesla whole body scanner (GE Medical Systems, Milwaukee, WI) using an identical model at the two sites (Columbia, Duke). As described elsewhere in detail,[12] sequences involved a T1 spoiled gradient recalled acquisition in steady state aligned to the long axis of the hippocampus, and T2 fluid-attenuated inversion recovery (FLAIR). Hyperintensity volumes on axial FLAIR images were measured on a semiautomated version of the Fazekas scale that included deep white matter intensities (WMH), subcortical gray matter hyperintensities in the basal ganglia, and periventricular hyperintensities using MRIcro software.[14] We dichotomized the total hyperintensity volume into high and low burden using a median split of the data.

2.3 | Treatment

In 16 weeks of open-label antidepressant therapy (a pre-phase for a randomized clinical trial), citalopram was started at 10 mg and raised to 20 mg daily after 2 weeks in 36 of the participants. If there was lack of antidepressant response by 8 weeks, citalopram was switched to venlafaxine 37.5 mg daily, with the dose raised weekly over 4 weeks to reach 225 mg daily or the maximum tolerated dose in 25 of the participants. Twenty participants began the trial on venlafaxine and remained on it. Other antidepressants were prescribed for patients with non-response or intolerability to citalopram and venlafaxine. We found 18 patients who switched antidepressant drugs from baseline to week 16: thirteen from citalopram to venlafaxine, three from citalopram to another drug, and two from venlafaxine to another drug. Other drugs included fluoxetine, escitalopram, duloxetine, and bupropion.

A second phase of the trial involving the cholinesterase inhibitor donepezil was not analyzed here as it was not relevant to the focus of this study and has been reported elsewhere.[15]

2.4 | Statistical analyses

The study will test the following two hypotheses. First, as Hypothesis (Hyp) 1, improvements in cognition would be significantly correlated with improvements in depression. Multiple sensitivity analyses could examine whether cognitive domains might be differentially sensitive to antidepressant efficacy and that changes in cognition and depression are differentially imparted by drug type (SSRIs vs. norepinephrine/serotonin SRIs), depression severity, or exclusion of participants who demonstrated an early and large expectancy response (hereafter called "placebo" responders). Second (as Hyp 2), other factors (e.g., *APOE*, WMH, age, depression severity at baseline) might moderate such systematic changes in both depression and cognition. WMH may be associated with or cause late life depression and might modulate the relationship between depression symptom change and cognition change. Age is also a crucial variable in pseudodementia given that the earlier literature showed that cognitive improvements were greater in younger individuals.[16]

This study has 80% power to detect r = .35 (moderate) correlation at the 5% significance level. We reported regression coefficients with 95% confidence intervals (CIs) since a 95% CI contains all the null hypotheses that would not be rejected at the 5% level. Descriptive statistics for demographic and clinical variables at baseline across the whole sample were reported. The chi-square and the two-sample *t*-test were used to compare the group differences between 61 participants who completed the 16-week open-label antidepressant treatment and

TABLE 1 Demographic characteristics and cognition for included and excluded participants at baseline (n = 79)

	Excluded (n = 18) Mean (SD) or Freq (%)	Included (n = 61) Mean (SD) or Freq (%)	*P*	Overall at Week 0 (n = 79) Mean (SD) or Freq (%)
Sex				
Female	7 (38.9%)	31 (50.8%)	.53	38 (48.1%)
Male	11 (61.1%)	30 (49.2%)		41 (51.9%)
Age (years)	65.8 (9.53)	69.8 (8.66)	.12	68.9 (8.97)
Race				
Black/African-American	4 (22.2%)	8 (13.1%)	.48	12 (15.2%)
Caucasian	13 (72.2%)	45 (73.8%)		58 (73.4%)
Hispanic	1 (5.6%)	8 (13.1%)		9 (11.4%)
Education (years)	15.1 (2.41)	15.4 (2.88)	.64	15.3 (2.77)
APOE ε4 allele[a]				
No	12 (85.7%)	39 (65.0%)	.24	51 (68.9%)
Yes	2 (14.3%)	21 (35.0%)		23 (31.1%)
HAM-D	23.6 (4.02)	22.9 (5.40)	.57	23.0 (5.10)
BDI Total Score	26.9 (10.5)	20.3 (8.14)	.02	21.8 (9.10)
Folstein MMSE Total Score	28.1 (1.97)	27.8 (1.96)	.58	27.9 (1.95)
Modified ADAS-Cog Score	11.9 (3.35)	13.0 (5.34)	.33	12.7 (4.96)
SRT Total Recall	45.2 (8.02)	41.8 (10.7)	.15	42.6 (10.2)
WAIS-R Digit Symbol Test	43.9 (8.95)	41.4 (13.0)	.35	42.0 (12.2)
Trails A Time	45.4 (17.2)	47.0 (21.0)	.75	46.6 (20.1)
Trails B Time	113 (34.3)	135 (70.5)	.083	130 (64.5)
Fluency Animal Total	20.1 (4.32)	16.7 (4.50)	.01	17.5 (4.65)

Abbreviations: *APOE*, apolipoprotein E; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; BDI, Beck Depression Inventory; HAM-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Exam; SRT, Selective Reminding Test; WAIS-R, Wechsler Adult Intelligence Scale, revised.
[a]Five participants (4 were excluded and 1 was followed) had missing values.

18 subjects who did not complete it. Similar analyses were performed to examine the differences between the 12 placebo responders (at least 50% decrease in HAM-D scores in the first 2 weeks) and 49 non-placebo responders, and to examine the differences between *APOE* ε4 carriers versus non-carriers. Additionally, pre-post changes in the depression and cognitive measures were tested using paired Wilcoxon's signed rank test to minimize outlier effects.

For Hyp 1, separate linear regressions were used to estimate the association between each change in depression measures (primary: ΔHAM-D; secondary: ΔBDI) and changes in cognition measures (primary: ΔMMSE, ΔADAS-cog, ΔSRT total recall; secondary: ΔDigit Symbol, ΔTrails A, ΔTrails B, ΔVF). The predictor was ΔHAM-D and the dependent measures were ΔSRT Total recall, ΔADAS-Cog, and ΔMMSE. We also examined whether antidepressant response (binary variable indicating ≥ 50% reduction in HAM-D from baseline) over 16 weeks was associated with the change in cognition measures. The same linear regression models were performed on the sample without placebo responders (N = 12), that is, those individuals who evinced a large very rapid antidepressant response, as inclusion might influence the opportunity to observe antidepressant biological effects as a sensitivity analysis. Last, we examined ΔBDI as a secondary analysis. All models were adjusted for each baseline cognition measure, as well as for age, gender, race, education, and antidepressant medication at baseline. For effect size comparison, standardized coefficients were reported.

For Hyp 2, we then examined a series of variables that could act as moderators of the relationship. For these, we examined the moderator as a main effect and, critically, as an interaction term with ΔHAM-D. Moderators were separately examined with *APOE* ε4, WMH, baseline HAM-D, and continuous and dichotomized age (> 69 vs. < = 69). For the significant moderators, we performed a post hoc contrast analysis to quantify the effect of ΔHAM-D by moderator groups.

3 | RESULTS

3.1 | Demographic characteristics

Seventy-nine participants were enrolled in the study, and 61 participants completed the 16-week open-label antidepressant treatment and were included for the analysis. We focused on these individuals with complete data in order to minimize modeling or imputation and to allow for correlational analyses. Additionally, these patients went on to participate in the randomized trial of donepezil. The 61 participants had lower BDI (Table 1, *P* = .02) and had lower animal fluency total (Table 1, *P* = .01) at baseline compared to the 18 participants

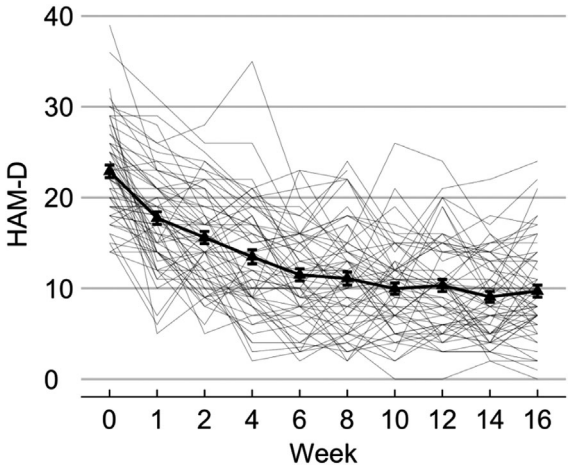

FIGURE 1 Hamilton Rating Scale for Depression (HAM-D) change over time

who did not complete the trial. The two groups did not otherwise differ in age, sex, race, education, *APOE* ε4 status, and other cognition measures. Among the participants included in the study (n = 61), there were no differences between *APOE* ε4 positive and negative groups in either demographics or cognition (Table S1 in the Supporting Information). Change in ADAS-Cog was associated with years of education (Table S2, r = −0.35, $P < .01$). In contrast, changes in other cognition and depression measures were not associated with other demographic variables.

3.2 | General trends

First, the general trends in ΔHAM-D from baseline and every 4 weeks thereafter until 16 weeks are shown as a spaghetti plot in Figure 1. BDI showed a similar improving pattern (data not shown). We also show the ΔSRT from baseline to 16 weeks, as well as other cognitive measures, in Table 2.

Cognitive improvement across measures was variable, but none worsened. MMSE, ADAS-Cog, SRT Total Recall, Digit Symbol, and Trails B improved significantly (Table 2). Improvements in other cognitive measures involving speed of processing and/or fluency (Trails A and fluency measures) were non-significant.

Examination of effect sizes demonstrated a stepwise profile in which SRT Total Recall gains were largest (Cohen's d = 0.34) and speed of processing gains (in timed tests including digit symbol, verbal fluency, and Trails A and B) were smallest (Cohen's d = 0.18). ADAS-Cog improvement was intermediate (Cohen's d = .20).

3.3 | Hyp 1: Association between change in cognition and change in depression for primary outcomes

Small and non-significant correlations were found between ΔHAM-D or antidepressant responder status and changes in primary cognitive measures (ΔMMSE, ΔADAS-Cog, and ΔSRT Total Recall, Figure 2A–C, all $|r| < 0.07$). No associations were found when we adjusted for baseline cognitive score, age, gender, race, education years, and antidepressant medication at baseline in multiple regression models (Table 3). Beyond our main cognition measures, we measured multiple tests assaying domains such as speed of processing, executive function, and semantic fluency. Consistently, no associations were found between change in these secondary measures and either change in depression measures or antidepressant efficacy (Table S3).

TABLE 2 Depression and cognitive measures at baseline and week 16

	Baseline (n = 61)	Week 16 (n = 61)	
	Mean (SD)	Mean (SD)	*P*-value[a]
HAM-D	22.9 (5.40)	9.69 (5.21)	<.001
BDI	20.3 (8.14)	10.3 (6.55)	<.001
Folstein MMSE Total Score	27.8 (1.96)	28.4 (1.93)	.018
Modified ADAS-Cog Score	13.0 (5.34)	11.8 (6.06)	.045
SRT Total Recall	41.8 (10.7)	45.6 (11.2)	<.001
WAIS-R Digit Symbol Test[b]	41.4 (13.0)	42.6 (12.9)	.035
Trails A Time	47.0 (21.0)	43.7 (19.3)	.17
Trails B Time	135 (70.5)	120 (62.2)	.009
Verbal Fluency Total	16.7 (4.50)	17.5 (5.37)	.18

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; BDI, Beck Depression Inventory; HAM-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Exam; SRT, Selective Reminding Test; WAIS-R, Wechsler Adult Intelligence Scale, revised.

[a]Wilcoxon's rank sum test was conducted on the change score.

[b]One outlier was identified at week 0, although the assessment was legitimate. If we exclude that subject, the means (SD) of weeks 0 and 16 changed to 40.567 (11.197) and 42.683 (13.018) with $P = 0.01$.

3.4 | Sensitivity analyses

We next conducted an analysis after excluding possible placebo responders (n = 12), that is, those who had a 50% improvement in HAM-D scores in the first 2 weeks. These participants had worse baseline depressive symptoms compared to the non-placebo responders (n = 49) (Table S3, all $P < .001$), but there were no differences in depression or cognition change scores. After excluding them, 29 (59%) of the 49 subjects remaining at week 16 had shown a response to open-label antidepressant treatment. We found no relationships between either change in depression measures or antidepressant responder status and change in cognitive measures (Table S3) in this refined group.

We examined the influence of outliers on the primary outcomes. All five primary outcomes normally distributed with few outliers. Using the 3 × interquartile range (IQR) beyond first and third quartiles as the thresholds of the extreme outliers, there were no extreme outliers.

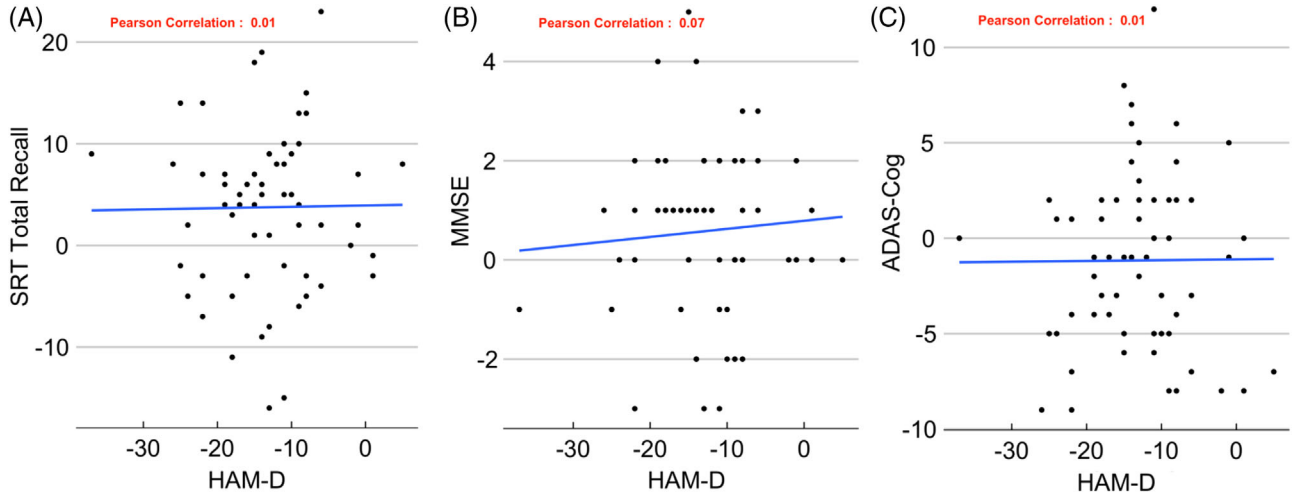

FIGURE 2 (A) Correlation between change in Hamilton Rating Scale for Depression (HAM-D) and change in Selective Reminding Test (SRT) Total Recall (unadjusted). (B) Correlation between change in HAM-D and change in Mini-Mental State Exam (MMSE; unadjusted). (C) Correlation between change in HAM-D and change in Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog; unadjusted). Note that all correlations were non-significant

Using the 1.5 × IQR beyond first and third quartiles as the thresholds of outliers, two HAM-D change scores were identified as outliers. We repeated all analyses after excluding two outliers in HAM-D, and the results were highly similar to the original analysis.

3.5 | Hyp 2: Moderator analyses

There were no moderation effects for the following variables: WMH or baseline HAM-D as a measure of symptom severity for any of the cognitive measures (Table 3, Moderator Analysis). For *APOE* ε4 we observed a significant interaction for ADAS-Cog only ($\beta = 0.61$, 95% CI = 0.07 to 1.15, $P = .028$). The post hoc contrast analysis showed that HAM-D improvements in the *APOE* e4 carriers were related to cognitive improvements ($\beta = 0.57$, 95% CI = 0.12 to 1.02, $P = .01$), while no such relationship was found in the non-carriers ($\beta = -0.04$, 95% CI = −0.33 to 0.26, $P = .80$). No significant association was found for other cognitive measures. We also found a significant interaction with WMH for ADAS-Cog ($\beta = 0.72$, 95% CI = 0.06 to 1.38, $P = .038$), such that HAM-D improvements in the patients with high WMH were related to cognitive improvements ($\beta = 0.71$, 95% CI = 0.09 to 1.33, $P = .03$), while no such relationship was found in the low WMH group ($\beta = -0.01$, 95% CI = −0.37 to 0.35, $P = 0.95$). Associations with other cognitive measures were non-significant. We further examined antidepressant response in the two WMH groups and found them to be nearly identical. Last, we did not find a significant effect for age (treated categorically after median split) as a moderator. These results are shown in Table 3.

4 | DISCUSSION

Many prior studies of pseudodementia have not fully articulated any hypotheses. They tended to examine cognitive changes in depressed individuals grossly. Here we premised two testable hypotheses. In our primary model of depressive pseudoamnestic disorder (Hyp 1) we posited that treatment-induced changes in depression should covary with changes in cognition. In Hyp 2 we examined whether other factors might amplify or obscure such a response.

We found little support for Hyp 1, in that we did not find a significant relationship between change in depression and change in cognition. This held true irrespective of whether we examined depression change as continuous or as categorical (responders vs. non-responders) or whether we examined clinician- or patient-rated depression symptomatology. It also held true irrespective of cognitive domain (memory, global, speed) and in more sophisticated regression models with multiple adjustments for baseline demographics.

For Hyp 2, we examined potential moderators of the relationship between change in depressive symptoms and change in cognition and found non-significant results for age and depression severity. For *APOE*, results were counterintuitive in that depression and cognitive changes scores were significantly associated only in ε4 carriers, the group most likely to have features of prodromal AD and progressive neurodegenerative processes. Moreover, findings were negative for the MMSE and SRT. Age associated WMHs, including signal in deep white matter and periventricular white matter, have been linked to treatment of refractory late-life depression by a number of researchers,[17,18] though this finding has not been uniform.[7,18] In our study, individuals with a greater WMH demonstrated a significant relationship between depressive symptom change and change in ADAS-Cog, but not change in memory, MMSE, or speed measures. Both of these findings require more study to determine their validity.

We found improvement in memory (SRT), ADAS-Cog (a composite of multiple tests of memory, naming, praxis, and drawing), but not speed of processing. These are in our estimation more likely to be due to practice effects because (1) memory is the domain most susceptible to practice effects and is present even in MCI populations; (2) the dura-

TABLE 3 Association between primary cognition and depression and moderation of *APOE* ε4, WMH, baseline HAM-D, and age

			ΔMMSE			ΔADAS-Cog			ΔSRT Total Recall		
	Moderator	**Parameters**	***β***	**95% CI**	***P***	***β***	**95% CI**	***P***	***β***	**95% CI**	***P***
All participants (n = 61)	_	ΔHAM-D	−0.03	−0.26 to 0.21	.824	0.13	−0.12 to 0.39	.314	−0.06	−0.32 to 0.20	.66
		ΔBDI	0.07	−0.17 to 0.31	.553	0.04	−0.22 to 0.30	.749	−0.06	−0.32 to 0.20	.66
		Antidepressant Responders	0.31	−0.20 to 0.82	.237	−0.47	−1.02 to 0.08	.099	0.12	−0.45 to 0.68	.688
Excluding placebo responders (n = 49)	_	ΔHAM-D	−0.02	−0.28 to 0.24	.871	0.11	−0.17 to 0.39	.44	−0.05	−0.33 to 0.23	.727
		ΔBDI	0.04	−0.22 to 0.31	.754	0.05	−0.24 to 0.33	.746	−0.07	−0.35 to 0.22	.649
		Antidepressant Responders	0.32	−0.25 to 0.90	.278	−0.56	−1.17 to 0.05	.081	0.17	−0.47 to 0.80	.606
Moderator Analysis	*APOE* ε4	Δ HAM-D	0.04	−0.55	.786	−0.04	−0.33 to 0.26	.803	−0.13	−0.44 to 0.18	.401
		APOE ε4 (positive)	−0.52	−0.95	**.034**	0.56	0.07 to 1.06	**.027**	−0.49	−1.03 to 0.05	.077
		Δ HAM-D x *APOE* ε4 (Positive)	−0.36	−0.87 to 0.16	.168	0.61	0.07 to 1.15	**.028**	0.18	−0.39 to 0.76	.524
	WMH	Δ HAM-D	0.03	−0.29 to 0.35	.838	−0.01	−0.37 to 0.35	.954	−0.1	−0.45 to 0.26	.582
		WMH[a] (High)	−0.25	−0.83 to 0.32	.382	0.5	−0.15 to 1.15	.127	−0.37	−1.02 to 0.29	.261
		Δ HAM-D x WMH[a] (High)	−0.13	−0.73 to0.47	.674	0.72	0.06 to 1.38	**.038**	−0.27	−0.93 to 0.39	.424
	Baseline HAM-D	Δ HAM-D	0.04	−0.31 to 0.40	.81	0.04	−0.34 to 0.41	.846	0.05	−0.34 to 0.43	.799
		Baseline HAM-D	0.09	−0.25 to 0.44	.591	−0.06	−0.43 to 0.30	.723	0.06	−0.31 to 0.43	.758
		Δ HAM-D x Baseline HAM-D	−0.01	−0.18 to 0.17	.928	0.1	−0.09 to 0.28	.309	−0.11	−0.30 to 0.08	.234
	Age >69	Δ HAM-D	−0.1	−0.39 to 0.18	.474	0.01	−0.30 to 0.32	.966	−0.19	−0.50 to 0.11	.214
		AGE>69	0.08	−0.43 to 0.60	.744	0.12	−0.43 to 0.68	.657	0.14	−0.41 to 0.69	.622
		Δ HAM-D x AGE>69	0.28	−0.21 to 0.78	.267	0.41	−0.11 to 0.93	.125	0.41	−0.12 to 0.94	.133

Note: Age, gender, race, and education, antidepressant medication at baseline were adjusted. Standardized regression coefficients are reported. Signficant *P*-values are in **Bold** font. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; *APOE*, apolipoprotein E; BDI, Beck Depression Inventory; HAM-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Exam; SRT, Selective Reminding Test; WMH, white matter hyperintensities.

[a]Baseline WMH was available for n = 49 participants.

tion between tests was relatively short; (3) alternate forms were not used (these have attenuated practice effects); and (4) the speed domain showed the smallest gain, and this is also the least likely to demonstrate practice effects.[19–21]

Our study adds substantively to the literature on depression-associated cognitive impairments in old age. We took a hypothesis-based approach in that we sought to determine if a principled relationship existed between gains in cognition and improvement in depressive symptoms. We also examined multiple potential moderator effects. Last, our sample was large and included only subjects who met psychometric criteria for amnestic MCI and Major Depressive Disorder. As noted, we believed this group was ideally suited to test our hypotheses about pseudodementia. We found little evidence in its favor and so view our findings as largely negative; we also suggest that this study is broadly consistent with other studies that have demonstrated that depression increases the risk for dementia and may perhaps be a very early symptom of neurodegeneration.[22,23] In a systematic review, Brodaty and Connors[2] found collectively that 38% of depressive pseudodementia patients progressed to what they termed frank dementia. In the study with the largest N and longest follow-up, Kral and Emery observed that after an initially good response to antidepressants, 89% of the large sample (N = 44) eventually progressed to dementia of the Alzheimer's type during an extended follow-up period. Many of the studies included in the Brodaty and Connors review were small and had short follow up periods compared to Kral and Emery.

This study has several limitations. First, we did not utilize biomarkers (e.g., cerebrospinal fluid, amyloid-β, or tau) to diagnose MCI. However, *APOE* ε4 may serve as a useful proxy for these.[24] Second, we did not have a placebo control group that could be directly compared to the antidepressant group on the magnitude of cognitive gains. We also did not have a depressive pseudodementia group that could be contrasted with the literature more directly.

In conclusion, we conducted this study in a group of older individuals, who by virtue of their documented memory impairment, responsivity to antidepressant treatment, and serial broad-based cognitive assessment over 16 weeks, were well-positioned to test the hypotheses about depressive pseudoamnestic disorder. Our negative findings cast doubt on the frequency of this syndrome in older populations with documented depression and memory impairments.

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CONFLICTS OF INTEREST

P. Murali Doraiswamy has received research grants (through Duke University) and advisory/board/speaking fees from several companies; P. Murali Doraiswamy owns shares in several companies and is a co-inventor on patents relating to dementia which are not discussed here. Davangere P. Devanand is Scientific Adviser to Acadia, Eisai, Genentech, and Sunovion, and is on the Data and Safety Monitoring Board for Green Valley. All other authors declare no conflicts or disclosures. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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