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Neurocognitive disorders and depression – complex interrelationships

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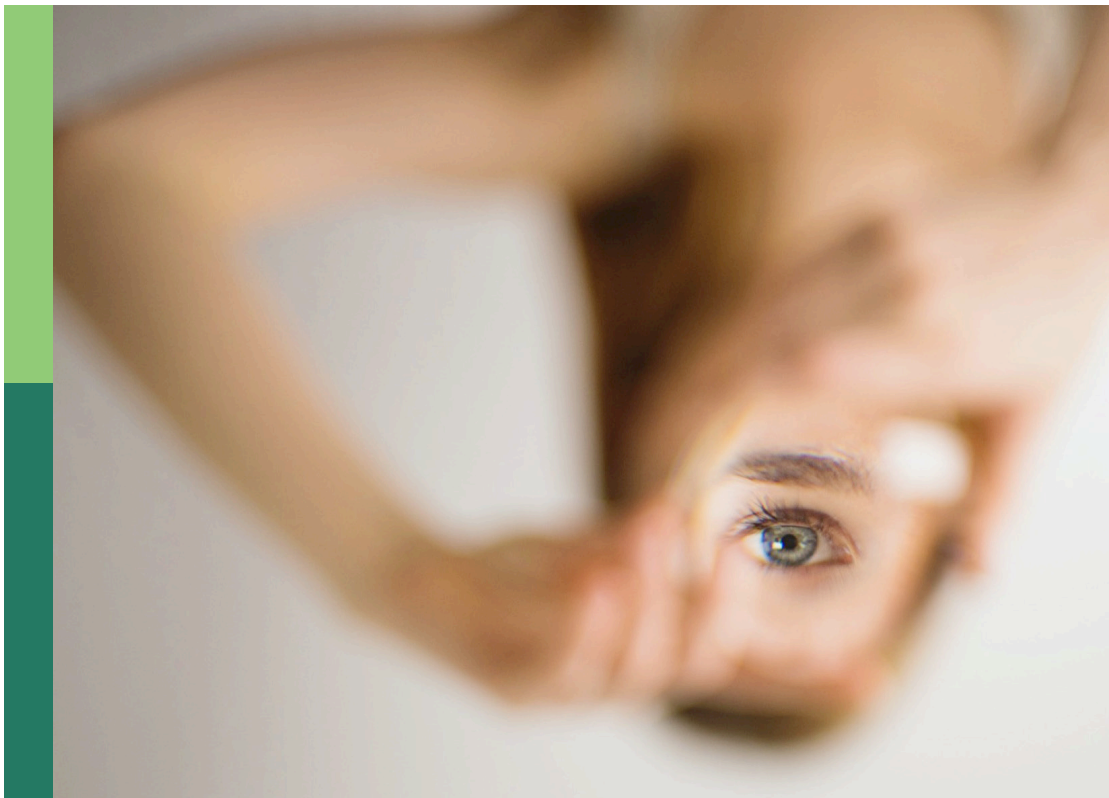

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Neurocognitive disorders and depression – complex interrelationships

Topic editors

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Editorial: Neurocognitive disorders and depression—Complex interrelationships

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Editorial on the Research Topic
Neurocognitive disorders and depression—Complex interrelationships

Cognitive impairment and depressive symptoms often coexist especially in older adults, however depression may be associated with signs of cognitive decline at any age. The complex relationships between cognitive disorders and depression may be viewed from biological, neuropsychological, medical, and social perspectives. Untangling these interrelationships may facilitate diagnostic precision, choice of individually tailored treatment options, and development of practice oriented recommendations.

There are many trajectories linking depression and cognitive decline. Depressive symptoms might precipitate the onset of Alzheimer's disease (AD) and other dementias, depression may also develop in the course of previously diagnosed neurocognitive disorder due to neurodegenerative or vascular causes. Cognitive decline resulting from major depression is often related to as "pseudodementia" and cognitive problems diminish over the course of antidepressant treatment. On the other hand, depressive disorders increase the risk for cognitive impairment in the future.

In older adults, mental health problems are often underdiagnosed and undertreated, therefore societies such as Alzheimer's Association[1] and Alzheimer's Europe[2] promote early diagnosis of depressive symptoms in individuals with Alzheimer's disease.

The optimal therapeutic approach to neurocognitive disorders and depression includes medications, diet, psychological therapy, art therapy, and social support. Increasing evidence points to treatments based on understanding underlying mechanisms (e.g., increased inflammatory status) such as probiotics (Dobielska et al., 2022).

The Research Topic addresses the issue of neurocognitive disorders and depression from various and exciting standpoints. It includes six original research articles, one review, and two systematic reviews written by 61 outstanding authors.

Masse et al. present a very interesting and useful approach to differentiating results of neuropsychological assessment between normal aging, late life depression (LLD) and mild AD including the following domains: verbal episodic memory, executive skills, mental processing speed, constructional praxis, and semantic memory. Impairment in one cognitive domain was relatively frequent in healthy older adults, low scores in two domains prevailed in LLD,

1 https://www.alz.org

2 https://www.alzheimer-europe.org

while decline in at least three domains was characteristic for AD. These findings provide important clues for clinical practice such as regular follow-up of cognitive performance in patients with LLD.

Van den Bossche and Schoenmakers analyzed affiliate stigma in relatives of people living with dementia diagnosis and its impact on caregivers' mental health. Interestingly, many caregivers' characteristics including age, sex, and education were correlates of the impact of stigma on caregivers' life. The results of the study are important for creating an inclusive environment for people living with dementia and their family members.

Cao et al. report on the psychological consequences of acute myocardial infarction treated with percutaneous coronary intervention. Of note, symptoms of post-traumatic stress disorder were present in substantial percentage of patients 3 months after the event.

Hall et al. studied cognitively normal older adults in terms of neurobehavioral symptoms known as risk factors for cognitive decline such as depression, apathy, anxiety, worry, and disordered sleep in relationship to blood-based biomarker of neurodegeneration (plasma total tau, t-tau). T-tau was not a predictor of any of the assessed symptoms, however, additional analysis revealed that in individuals with the highest quintile of t-tau, the above neurobehavioral symptoms were significantly related to the biomarker level. These results are important clues for further research, as blood-based biomarkers are an exciting alternative to cerebro-spinal fluid (CSF) and PET imaging assessment of tau burden in the brain.

Egglefield et al. applied magnetic resonance imaging to assess cortical thickness and hippocampal volume in patients with or without vascular changes in the brain and undergoing pharmacological treatment for depression. Vascular depression (VD) was defined as presence of deep white matter hyperintensities (DWMHs) on T2-weighed FLAIR sequence. Interestingly, no differences were found between VD and non-VD in terms of gray matter characteristics.

Wang et al. assessed psychological mechanisms underlying depression in young adults with special consideration of resilience, attentional bias, and neuroticism. Depressive symptoms were frequent in college students which indicated a urgent need for preventive and therapeutic strategies to promote mental health across lifespan.

The review by Hammar et al. focuses on neurocognitive profiles of major depressive disorder. The authors describe three hypotheses crucial to understanding cognitive decline in depression, namely state, scar, and trait hypotheses. Clinical implications of residual cognitive symptoms as well as potential preventive strategies are discussed.

Ma et al. provide thorough insight into relationship between interleukin 6 (IL-6) level, depression, and cognitive-behavioral therapy (CBT) for depression. The authors analyzed the results of 10 studies and found that peripheral IL-6 levels were significantly lower after CBT. The authors discuss potential modulating anti-inflammatory effects of CBT.

Carbone et al. provide a systematic review on psychological consequences of COVID-19 pandemic for people living with dementia and their caregivers. As suspected most studies under review showed increased psychological burden and physical strain in caregivers as well as increased anxiety and general decline, fatigue, and cognitive impairment in people living with dementia. Severely decreased access to health care and social services due to lockdown was definitely among culprits of psychological consequences of the pandemic. A positive notion is related to technological advances enabling video-consultations.

COVID-19 pandemic poses significant threats to health care systems, but also opens new possibilities of integrated care. How these options will develop in the future and whether the post-COVID era will be friendly toward people suffering from neurocognitive disorders and depression is an open question.

Author contributions

KB is the lead author of the manuscript, PG and M-CG-N commented and revised the draft. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Cortical Thickness and Hippocampal Volume in Vascular and Non-vascular Depressed Patients

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Background: Reduced cortical thickness and hippocampal volume are prevalent markers of late life depression as well as mild cognitive impairment (MCI) but are conspicuously absent in the vascular depression (VD) literature. The present study aimed to determine differences in cortical thickness and hippocampal volume between VD and non-VD patients.

Methods: Participants were enrolled in an 8-week open treatment antidepressant trial. Forty-one depressed individuals aged 50 and older underwent brain magnetic resonance imaging at baseline and were classified as VD or non-VD. Cortical thickness values for the left and right entorhinal, parahippocampal, and precuneal cortices, as well as left and right hippocampal volume, were linearly regressed on VD status to determine mean differences between VD and non-VD. Covariates included site, age, sex, and mean thickness or intracranial volume.

Results: No statistical differences were found between VD and non-VD patients in cortical thickness of the bilateral precuneal, entorhinal, or parahippocampal cortices, or hippocampal volume ($p > 0.001$).

Conclusions: The absence of statistical differences in gray matter between VD and non-VD patients raises several diagnostic, etiological, and developmental possibilities, namely that VD may not be connected with other late-life psychiatric illnesses such as MCI or dementia and that vascular disease may not be a common etiological risk factor for depression and dementia. Larger datasets, prospective longitudinal studies, and cognitively intact controls are needed to further address these types of questions.

Keywords: vascular depression, white matter hyperintensities, cortical thickness, hippocampal volume, mild cognitive impairment

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INTRODUCTION

Depression in late life is often associated with cognitive impairment and has been shown to increase risk for developing dementia (1), but the heterogeneity of late life depression (LLD) complicates a complete understanding of this relationship (2). One strong possibility is that depression is a causal risk factor or else moderator of neurodegenerative processes leading to Mild Cognitive Impairment (MCI) and dementia. Consistent with this possibility is that while some depressed patients remain

cognitively normal, others experience neuropathology associated with Alzheimer's Disease (AD), and later convert to MCI or AD (2). On the other hand, it is possible that the apparent depression-dementia causal relationship is confounded by vascular disease, as vascular disease is a risk factor for and common comorbidity in both disorders (3). Vascular depression (VD) has traditionally been proposed as a subtype of LLD (4) defined by cerebrovascular disease (5, 6) (manifested by the presence of deep white matter hyperintensities (DWMHs) on MRI) and characterized by executive dysfunction (5, 7–9). The VD hypothesis proposes that vascular risk factors lead to DWMHs which disconnect prefrontal cortical regions from subcortical regions, resulting in the onset of depressive symptoms, executive dysfunction, and poor response to antidepressant treatment (6, 10).

There is significant phenomenological and neuropathologic overlap between the vascular subtype of LLD and MCI. Clinically, an individual presenting with characteristic symptoms of vascular depression could also be conceptualized as being diagnosed with a subtype of MCI with depression, particularly non-amnestic single-domain MCI (11). Reduced cortical thickness and hippocampal volume are salient features of MCI and AD that often predate symptom onset (12–15). Specifically, the medial temporal lobe (12) and precuneus gyrus (14, 16) are among the first areas to deteriorate in cognitively normal individuals who later convert to MCI or dementia. Gray matter atrophy in similar brain regions is also apparent in LLD: depressed older adults compared to healthy controls show bilateral cortical atrophy in the frontal, parietal, and temporal lobes, as well as lower hippocampal volumes (17, 18). Poor antidepressant treatment response in geriatric depressed patients is associated with smaller hippocampal volumes (19) and poor response to psychotherapy is associated with thinner bilateral parahippocampal and left precuneal cortices, among other regions (20).

Of note, comparing LLD patients to healthy controls leaves open the possibility that findings of reduced cortical thickness and hippocampal volume observed in LLD patients may be driven by the component of the sample with vascular subtype of LLD. To help clarify whether volumetric brain changes associated with MCI/dementia are more related to the presence of a mood disorder or rather the presence of significant vascular disease, a sample of patients with the vascular subtype of LLD would need to be compared to depressed individuals without vascular risk. If reduced cortical thickness in medial temporal brain regions and hippocampal atrophy were to be observed among individuals with vascular depression compared to depressed patients without vascular lesions, this would suggest a common causal model of the depression-dementia relationship in which vascular disease leads to both conditions.

As studies of cortical thickness and hippocampal volume have been conspicuously absent in VD research, a comparison of these features between VD and non-vascular depressed patients could further elucidate the VD construct as well. Toward this end, evaluating structural brain differences between these two groups of late life depressed patients across different definitions of vascular depression could be very informative. Thus, the goal of this study was to evaluate the presence of gray matter atrophy in VD compared to non-vascular LLD (non-VD). In keeping with the idea that vascular disease may play a critical etiologic role in both VD and MCI, the present study hypothesized that VD patients will show decreased cortical thickness in the entorhinal and parahippocampal (medial temporal lobe regions) and precuneal cortices, and lower hippocampal volumes, compared to non-VD patients.

MATERIALS AND METHODS

Participants

Patients from two sites, New York State Psychiatric Institute and Harlem Hospital Center, participated in an 8-week open antidepressant medication trial (escitalopram or duloxetine) for older adults with depression. Patients underwent a comprehensive neuropsychological evaluation at baseline and week 8 as well as received baseline imaging. The full study protocol has been described elsewhere (9). Patients were eligible if they were 50 years or older; had a current diagnosis of major depressive disorder, dysthymia, or depression not otherwise specified; and had a Hamilton Rating Scale for Depression (HRSD) score of $\geq$14 at their initial screening, corresponding to at least a moderate level of depressive severity. Patients were excluded from participating in the study if they had other Axis I diagnoses such as bipolar disorder, obsessive compulsive disorder, psychotic disorder, or current substance abuse or dependence within the past year; were actively suicidal or had a past suicide attempt within the last 6 months; or had a Mini Mental Status Exam (MMSE) score lower than 24.

MRI and Cortical Thickness

Patients underwent structural MRI at baseline. Images were acquired on a GE Signa 3 Tesla whole body scanner with the following sequences: (1) 3-Plane localizer repetition time (TR) = 23.4 ms, echo time (TE) = 1.7 ms, flip angle = 30°, bandwidth = 31.3 MHz, field of view (FOV) = 24 × 24 cm, thickness = 5.0 mm, Spacing = 1.5 mm, nine slices per volume (three axials, three sagittals, three coronals), matrix 256 × 128, (2) 3D SPGR anatomical sequence TI 500 ms, TR 5 ms, TE minimum (1.3 ms), flip angle 11°, bandwidth 31.25 MHz, FOV 26 × 26, slice thickness 1.1 mm, spacing 0.0, 128 slices per volume, one NEX images × two (acquisitions averaged off line), matrix 256 × 256 coronal oblique orientation, aligned to the long axis of the hippocampus, and (3) T2 fluid-attenuated inversion recovery (FLAIR): 2D IR axial images, TR = 10,000 ms, TE = 122 ms, TI = 2,000 ms, FOV = 24, matrix = 320 × 256, NEX = 1, slice thickness = 5 mm, 31 slices.

Cortical thickness analyses were obtained using Freesurfer 5.3, a fully automated program for obtaining cortical thickness and volume. Bilateral entorhinal, parahippocampal, and precuneus cortices, as well as left and right hippocampal volume were selected as ROIs a priori using the Desikan-Killiany atlas. **Figure 1** presents a normalized brain with these ROIs highlighted. Cortical thickness was computed as the distance between the white matter surface and pial surface at each location along the cortex. Hippocampal volume was also extracted using this procedure.

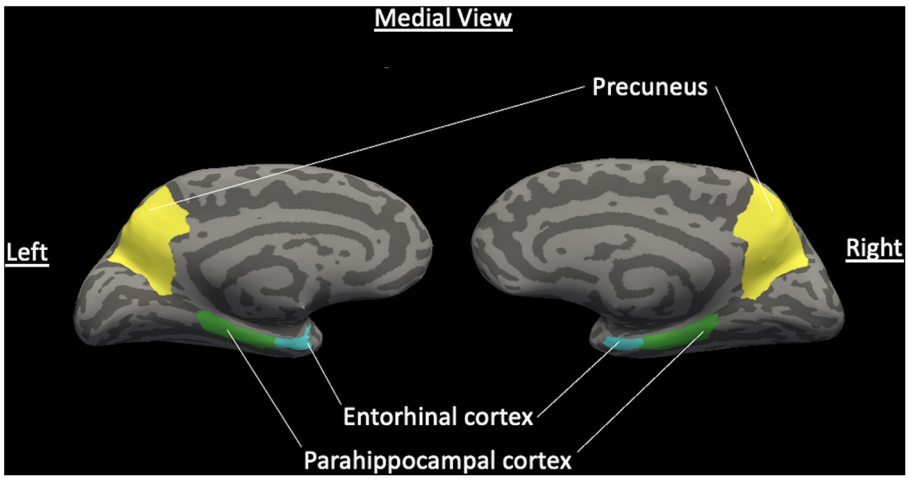

FIGURE 1 | Normalized brain with ROIs of hypothesized cortical thickness differences. Medial view of a normalized brain with highlighted hypothesized regions of interest of decreased cortical thickness between VD and non-VD patients for the left and right hemispheres: entorhinal cortex, parahippocampal cortex, and precuneus gyrus. Light gray features are sulci and dark gray features are gyri (Color should be used in print for this figure).

VD Classification

T2-weighted FLAIR were evaluated for the presence of DWMHs. The severity of lesions was rated by a neuroradiologist using the Fazekas modified Coffey Rating Scale for signal hyperintensities (21). DWMHs were defined as abnormalities in the frontal, parietal, temporal, or occipital lobes and scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluence of foci). Patients were classified as having MRI-defined VD if they received a score of two or higher on their DWMH (6, 22). Lesion volume estimates were calculated using MRIcro for quantitative evaluation of DWMH. The full procedure for calculation using this method has been described elsewhere (8). Patients were classified quantitatively as having VD if they fell in the highest quartile of the distribution for WMH volume scores, which is consistent with previous research (8, 23, 24).

Missing Data

The multiple imputation procedure in SPSS (25) was used to accommodate missing cortical thickness and hippocampal volume data (34.1%). This procedure replaces missing data with a set of plausible values on the basis of all variables in the data set, including demographic, clinical outcome, and neuropsychological test variables. This report is based on 20 imputed data sets ($m = 20$), which is satisfactory in obtaining excellent results unless rates of missing data are extremely high (26). The imputed datasets were analyzed using standard statistical analyses and the results of these analyses are combined using Rubin's rules (25).

Statistical Analyses

Baseline differences in demographic and clinical variables were compared using independent *t*-tests for continuous variables and chi-square analyses for categorical variables. Cortical thickness and hippocampal volume of each hemisphere were linearly regressed on qualitative and quantitative VD status to determine differences between VD and non-VD. Cortical thickness analyses were then adjusted for site, age, sex, and mean thickness, and hippocampal volume analyses were adjusted for site, age, sex, and total intracranial volume (ICV).

Statistical Significance

Due to the use of multiple tests, a more stringent significance value of $p \leq 0.003$ was used to determine statistical significance. This value was calculated in line with the Bonferroni correction method, which suggests dividing the critical alpha by the number of comparisons being made (27). As such, using the traditional significance value of $p < 0.05$, we divided this number by 16 (the number of comparisons necessitated by hemispheric ROIs for cortical thickness and hippocampal volume) to set an appropriate significance value to reduce the chances of obtaining false positives.

Human Subjects Research

The investigation in this study was carried out in accordance with the 2013 version of the Declaration of Helsinki. The study design was review by IRB Ethics Committees at Queens College, Columbia University and the New York State Psychiatric Institute, and Harlem Hospital Center. Informed consent was obtained from all participants in the study.

RESULTS

Descriptive Statistics

Forty-six participants met inclusion criteria and forty-one received structural MRI at baseline. **Table 1** presents demographic and clinical data for the whole sample ($n = 41$) as well as divided into MRI-defined VD ($n = 15$) and non-VD ($n = 26$) patients (using the categorical Fazekas scale). The sample had an average age of 62.3 (SD = 9.55) years old (minimum age

TABLE 1 | Baseline demographic and clinical characteristics.

Variable	Total sample ($n = 41$)	MRI-defined VD ($n = 15$)	Non-VD ($n = 26$)	t/Chi square statistic
	M (SD) or *n* (%)	M (SD) or *n* (%)	M (SD) or *n* (%)	
Site (%)*				$\chi^2 = 9.90$, $p = 0.002$
HHC	17 (41.5%)	11 (73.3%)	6 (23.1%)	
NYSPI	24 (58.5%)	4 (26.7%)	20 (76.9%)	
Age (years)	62.29 (9.55)	63.13 (11.06)	61.81 (8.87)	$t = -0.42$, $p = 0.672$
Women (%)	23 (56.1%)	11 (73.3%)	12 (46.2%)	$\chi^2 = 2.85$, $p = 0.091$
Race (%)*				$\chi^2 = 12.69$, $p = 0.013$
Caucasian	19 (46.3%)	2 (13.3%)	17 (65.4%)	
African American	18 (43.9%)	11 (73.3%)	7 (26.9%)	
Hispanic	2 (4.9%)	1 (6.7%)	1 (3.8%)	
Education*	14.95 (2.98)	13.47 (2.85)	15.72 (2.76)	$t = 2.58$, $p = 0.014$
Age at depression onset (years)	41.65 (21.16)	37.43 (23.45)	43.92 (19.93)	$t = 0.91$, $p = 0.364$
FH mood disorder*	22 (55.9%)	4 (28.6%)	20 (75%)	$\chi^2 = 7.20$, $p = 0.007$
HRSD	23.32 (5.64)	23.40 (7.21)	23.27 (4.66)	$t = -0.07$, $p = 0.944$
CIRS-G total score	3.91 (3.30)	4.92 (2.84)	3.33 (3.47)	$t = -1.34$, $p = 0.180$
MMSE	28.49 (1.33)	28.40 (0.99)	28.54 (1.50)	$t = 0.36$, $p = 0.722$
DWMH volume*	1.09 (1.79)	2.65 (2.22)	0.18 (0.24)	$t = -4.28$, $p < 0.001$

**HHC, Harlem Hospital Center; NYSPI, New York State Psychiatric Institute; FH, family history; HRSD, Hamilton Rating Scale for Depression; CIRS-G, Cumulative Illness Rating Scale—Geriatrics; MMSE, Mini Mental Status Exam; DWMH, deep white matter hyperintensity.*

= 50, maximum age = 83) and was 56.1% female. There were no differences in age, sex, age of depression onset, depressive symptom severity, cumulative illness score, or cognition as measured by the MMSE. VD patients were significantly more likely to be African American, have fewer years of education, and have a lower likelihood of having a family history of a mood disorder.

Cortical Thickness and Hippocampal Volume Between Groups

Tables 2, **3** present the comparison of group means between VD and non-VD patients, with VD status defined qualitatively (Fazekas) and quantitatively (WMH volume). Analyses of group means showed no statistical differences in cortical thickness in the precuneal, entorhinal, and parahippocampal cortices regardless of hemisphere between VD and non-VD patients ($p > 0.003$). Similarly, differences in group means for left and right hippocampal volume did not meet statistical significance.

TABLE 2 | Comparison of mean cortical thickness and hippocampal volume between MRI-defined VD and non-VD patients (Fazekas rating scale).

ROI	VD ($n = 15$) Mean (SD)	Non-VD ($n = 26$) Mean (SD)	*B* (SE)	Effect size (Cohen's *d*)
L entorhinal	3.00 (0.29)	3.17 (0.33)	−0.19 (0.14), $p = 0.181$	0.55
R entorhinal	3.37 (0.43)	3.37 (0.53)	0.001 (0.20), $p = 0.998$	0.00
L parahippocampal	2.54 (0.26)	2.58 (0.28)	−0.02 (0.12), $p = 0.888$	0.15
R parahippocampal	2.49 (0.31)	2.53 (0.27)	−0.02 (0.12), $p = 0.836$	0.14
L precuneus	2.22 (0.16)	2.21 (0.16)	0.01 (0.06), $p = 0.843$	0.06
R precuneus	2.21 (0.12)	2.21 (0.17)	−0.01 (0.06), $p = 0.863$	0.00
L hippocampal volume	3544.09 (475.09)	3442.92 (372.03)	100.09 (133.71), $p = 0.454$	0.24
R hippocampal volume	3725.11 (483.14)	3588.29 (417.23)	135.98 (143.37), $p = 0.343$	0.30

**ROI, region of interest; L, left hemisphere; R, right hemisphere; VD, vascular depression; non-VD, non-vascular depression. Unadjusted values did not change when adjusted for age, gender, site, mean thickness, and total intracranial volume.*

TABLE 3 | Comparison of mean cortical thickness and hippocampal volume between quantitatively-defined VD and non-VD patients (DWMH volume).

ROI	VD ($n = 10$) Mean (SD)	Non-VD ($n = 31$) Mean (SD)	*B* (SE)	Effect size (Cohen's *d*)
L entorhinal	3.00 (0.30)	3.13 (0.35)	−0.14 (0.15), $p = 0.374$	0.41
R entorhinal	3.33 (0.50)	3.38 (0.47)	−0.05 (0.21), $p = 0.806$	0.11
L parahippocampal	2.60 (0.27)	2.57 (0.28)	0.03 (0.12), $p = 0.837$	0.09
R parahippocampal	2.58 (0.32)	2.51 (0.28)	0.08 (0.12), $p = 0.534$	0.26
L precuneus	2.22 (0.17)	2.22 (0.16)	0.01 (0.07), $p = 0.918$	0.04
R precuneus	2.20 (0.12)	2.20 (0.15)	−0.003 (0.06), $p = 0.963$	0.02
L hippocampal volume	3520.57 (429.96)	3467.35 (409.62)	53.22 (150.75), $p = 0.724$	0.13
R hippocampal volume	3700.68 (433.14)	3617.76 (449.34)	82.93 (162.13), $p = 0.609$	0.19

**ROI, region of interest; L, left hemisphere; R, right hemisphere; VD, vascular depression; non-VD, non-vascular depression. Unadjusted values did not change when adjusted for age, gender, site, mean thickness, and total intracranial volume.*

Significance levels did not change when adjusting for site, age, sex, and mean thickness or ICV. Despite not reaching statistical significance, the difference between left entorhinal thickness in VD vs. non-VD yielded a medium effect size (defined categorically, Cohens $d = 0.55$; defined continuously, Cohens $d =$

0.41), suggesting that VD patients have decreased left entorhinal thickness compared to non-VD patients.

CONCLUSIONS

To our knowledge, this is the first study directly comparing cortical thickness and hippocampal volume in depressed older adults with and without MRI-defined vascular disease. No significant differences were found between vascular and non-vascular depressed patients in cortical thickness or hippocampal volume. The lack of statistical differences in thickness of medial temporal structures and precuneus gyrus and hippocampal volume in this study raises a number of diagnostic, etiological, and developmental possibilities. Of course, larger datasets, prospective longitudinal studies, and cognitively intact controls are needed to address these questions.

One possible reason for the lack of statistical differences observed is that VD is a valid subtype of LLD, etiologically distinct from other late-life psychiatric disorders. Atrophy of the medial temporal lobe and precuneus manifest prior to onset of cognitive impairment and predict later conversion to MCI and dementia in cognitively normal individuals (12, 13, 15). Since reduced cortical thickness and hippocampal volume are hallmarks of other late life diagnostic entities like MCI and dementia, the lack of statistical differences suggest that these entities are non-overlapping and lends support to the credence that VD is a distinct diagnostic entity (28). The problem with this interpretation, however, is that both groups in this sample (VD and non-VD) likely have decreased cortical thickness relative to healthy controls, as cortical thickness has been used to differentiate depressed from non-depressed elderly (17–19). Thus, without a healthy control group, conclusions cannot be drawn as to whether both groups have reduced thickness and hippocampal volume consistent with a pre-dementia profile or appropriate values of thickness and volume for depressed elderly. Additionally, it may be more challenging to identify differences between VD and non-VD as they might both be in a pre-dementia phase where differences in thickness and volume would later become more detectable.

Another possibility is that vascular disease may not be a common causal mechanism in the depression-dementia relationship. As no statistical differences in cortical thickness or hippocampal volume were found between VD and non-VD patients, data from this study are not consistent with the idea that vascular lesions are a critical etiological factor for depression and dementia. Indeed, when LLD patients are matched for vascular risk to non-depressed older adults, LLD patients show thinner frontal lobes and lower hippocampal volumes (19), suggesting the possibility that gray matter brain changes may be more related to the presence of a mood disorder than the presence of vascular disease.

It is also conceivable that no significant differences were observed between the VD and non-VD groups because white matter changes predate gray matter deterioration. The presence of elevated regional WMHs has been observed up to 20 years before symptom onset of autosomal AD (29), whereas cortical atrophy has been observed up to 11 years prior to symptom onset in AD (12). This leaves a gap of 9 years in which VD could manifest. The temporal relationship between white matter and gray matter changes in cognitively normal adults is unclear, with some studies suggesting associations between WMHs and cortical thickness (30) and others suggesting no association (31). Interestingly, healthy controls and AD patients show inverse associations between WMHs and cortical thickness, such that higher WMH volume is associated with decreased cortical thickness, but MCI patients show a positive association between the presence of WMHs and cortical thickness, such that higher WMH volume is associated with an increase in cortical thickness values (30). This demonstrates a contradictory relationship during the transition between intact cognition and conversion to AD, which may be due to neuroinflammation stimulated by WMHs or AD pathology (30). Thus, it is plausible that VD may be a prodromal phase occurring somewhere between white matter deterioration and gray matter atrophy. The cross-sectional nature of the data in the study does not allow us to test for this possibility.

The lack of statistical differences noted also speaks to the heterogeneity of how VD has been defined. The VD hypothesis was first formulated based on patients with depression onset past the age of 60 and clinical evidence of vascular disease (score $\geq$ 1 on vascular scale of Cumulative Illness Rating Scale—Geriatrics) (4). Steffens & Krishnan defined VD as depression onset after age 50 with a DWMH qualitative rating $\geq$2 or neuropsychological impairment (executive dysfunction) (5). Alexopoulos and colleagues broadened their VD criteria into Depressive-Executive Dysfunction (DED) Syndrome, where participants were diagnosed solely on the presence of depression and executive dysfunction (32). Krishnan et al. later proposed a diagnosis of MRI-defined subcortical ischemic depression (used in the present study), where the only criteria was depression and a DWMH rating $\geq$2 or a subcortical gray hyperintensity (SGH) rating of 3 (22), for which both internal (6) and external (8) validity have been provided. Quantitative approach to classification using lesion volume, as used in this study, has also been advocated (23, 24). Despite the heterogeneity of this construct, supplemental analyses were run using these five definitions of VD and results were consistent between definitions, indicating no significant differences in thickness or hippocampal volume between VD and non-VD patients (see **Supplementary Tables 1, 2**). Similarly, significant associations were not found between MMSE score, MRI-defined VD status, DWMH lesion volume, or left entorhinal thickness (see **Supplementary Data** and **Supplementary Table 3**).

Of further consideration is that although WMHs and executive dysfunction are predictive factors in antidepressant treatment non-response, the VD hypothesis does not establish a mechanistic explanation for treatment non-response. The known mechanisms of action for Selective Serotonin Reuptake Inhibitors (SSRIs) relates to salutary modulation of hyperactive limbic structures (33) and stimulation of neurogenesis (34), and SSRIs are effective in preventing and treating post-stroke depression (35). Therefore, it is unclear why vascular damage to frontostriatal tracts would prevent SSRIs from working

effectively, when they are effective in treating post-stroke depression. The level of specificity in terms of the mechanism of antidepressant non-response, the diagnostic overlap between VD, MCI, and those diagnosed with MCI and depression, the measurement of components that define the construct, and the complexity of the syndrome as it is currently understood, as well as the interaction between these components, require more precision if we are to determine the causal mechanism of VD.

This study was limited in the size of the sample. Because of this, it is important to consider effect sizes in addition to statistical significance. Notably, the difference in left entorhinal thickness values between VD and non-VD yielded a medium effect size (Cohens $d = 0.55$), suggesting that VD patients showed decreased thickness in the left entorhinal cortex compared to non-VD. This is consistent with the hypothesis that VD may be a transitional state between white matter and gray matter deterioration, as decreased entorhinal thickness has been suggested as a biomarker for AD in the prodromal phase (36), and the majority of studies investigating cortical thickness in MCI/dementia implicate the left hemisphere as opposed to bilateral thinning (12, 14, 37). This medium effect sized difference between VD and non-VD in the left entorhinal cortex supports the possibility that VD may in fact be a prodromal phase of MCI or AD.

Another limitation of this study is the young patient population, encompassing individuals over the age of 50, as opposed to more traditional older adult populations of 60+ or 65+, which may be more consistent with the MCI literature. The use of ages >50 in this study reflects the common use of age >50 in the VD literature (5, 21). Additionally, gray matter atrophy is but one measure used in addressing conversion to MCI or AD, and this study was not able to evaluate other contributing variables prevalent in this population, such as amyloid-beta and tau retentions. Additional longitudinal research is required to supplement these limitations, as the cross-sectional nature of this study does not allow for investigation of diagnostic conversion. These limitations are potentially offset by important methodological strengths, including examination of gray matter atrophy in a population where these variables have not been traditionally studied, and half of the sample consisting of African Americans, who have been shown to be at greater risk for VD than Caucasians (9). Unfortunately, the small sample size limits an investigation into the role of race in VD. Nonetheless, this is one of the first studies to date using cortical thickness and hippocampal volume to compare vascular and non-vascular depressed geriatric patient profiles.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB Ethics Committees at Queens College, Columbia University and the New York State Psychiatric Institute, and Harlem Hospital Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DE was responsible for data analyses. DE, SS, BR, and JS are responsible for data interpretation and drafting the manuscript with input from all authors. JM and AG are responsible for the generation of cortical thickness and hippocampal volume data. JS was responsible for study conception and design. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.697489/full#supplementary-material

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Cognitive Impairment in Late-Life Depression: A Comparative Study of Healthy Older People, Late-Life Depression, and Mild Alzheimer's Disease Using Multivariate Base Rates of Low Scores

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Late-Life Depression (LLD) is often associated with cognitive impairment. However, distinction between cognitive impairment due to LLD and those due to normal aging or mild Alzheimer's Disease (AD) remain difficult. The aim of this study was to present and compare the multivariate base rates of low scores in LLD, mild AD, and healthy control groups on a battery of neuropsychological tests. Participants (ages 60–89) were 352 older healthy adults, 390 patients with LLD, and 234 patients with mild AD (i.e., MMSE $\geq$ 20). Multivariate base rates of low scores (i.e., $\leq$5th percentile) were calculated for each participant group within different cognitive domains (verbal episodic memory, executive skills, mental processing speed, constructional praxis, and language/semantic memory). Obtaining at least one low score was relatively common in healthy older people controls (from 9.4 to 17.6%), and may thus result in a large number of false positives. By contrast, having at least two low scores was unusual (from 0.3 to 4.6%) and seems to be a more reliable criterion for identifying cognitive impairment in LLD. Having at least three low memory scores was poorly associated with LLD (5.9%) compared to mild AD (76.1%) and may provide a useful way to differentiate between these two conditions [$\chi^2_{(1)} = 329.8$, $p < 0.001$; Odds Ratio = 50.7, 95% CI = 38.2–77.5]. The multivariate base rate information about low scores in healthy older people and mild AD may help clinicians to identify cognitive impairments in LLD patients, improve the clinical decision-making, and target those who require regular cognitive and clinical follow-up.

Keywords: late-life depression, Alzheimer's disease, older people, base rates, low scores, false positive, misdiagnosis, cognitive impairment

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INTRODUCTION

Late-life depression (LLD), defined as a major depressive episode occurring in individuals 60 years or older (Bhalla and Butters, 2011; Koening et al., 2014), independent of age at onset (O'Hara et al., 2006), is a heterogeneous mood disorder that has been found to have negative impact effect on people's health-related quality of life (Kiosses et al., 2001). In a clinical setting, patients with LLD frequently report subjective cognitive complaints (Gonda et al., 2004) and may show cognitive impairment in several neuropsychological domains including, most notably, executive function (Lockwood et al., 2002; Dybedal et al., 2013), psychomotor speed (Butters et al., 2004; Bennabi et al., 2013), and episodic memory (Herrmann et al., 2007; Dybedal et al., 2013). Visuospatial ability (Butters et al., 2004), semantic memory, and oral language (O'Hara et al., 2006) have also been found to be impaired in patients with LLD.

However, the pattern of cognitive impairment in LLD remains unclear and varies across studies due to methodological factors such as differences in patients sampled or the variety of tools used to measure cognition (Jaeger et al., 2006; Godin et al., 2007). In addition, most studies available had modest sample sizes (Dybedal et al., 2013; Roca et al., 2015) or reported cognitive functioning in terms of group means in a case-control design (Herrmann et al., 2007; Korsnes and Ulstein, 2014) that may obscure the degree of cognitive impairment in LLD (Gualtieri and Morgan, 2008; Iverson et al., 2011). An alternative approach for interpretation pattern of cognitive impairment is to determine the prevalence of low test-scores within a neuropsychological battery (Gualtieri and Morgan, 2008; Iverson et al., 2008, 2011; Brooks et al., 2011; Holdnack et al., 2017).

However, identification of cognitive impairment in patients with LLD remains difficult without taking into account normal cognitive variability in the healthy older population. Indeed, a great deal of research has demonstrated that the presence of one or more low scores was common among healthy older adults when multiple measures were considered simultaneously rather than in isolation (Palmer et al., 1998; Brooks et al., 2012; Gunner et al., 2012). For example, when considering performance across all subtests from the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological assessment battery, 60.6% of the healthy older participants (aged 49–92 years) obtained one or more score at or below the 10th percentile (Mistridis et al., 2015). Using the RAPID (Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment) neuropsychological battery, we previously found that 40.1% of the normative sample (individuals aged 50–89 years) obtained one or more test scores at or below the 5th percentile (Sylvestre et al., 2017). These findings suggest that isolated low scores may be erroneously considered impaired performances and lead to a false positive interpretation (Schretlen et al., 2008).

Many other studies (Palmer et al., 1998; Schretlen et al., 2008; Brooks et al., 2009a; Gunner et al., 2012; Oltra-Cucarella et al., 2019) also highlighted the need to consider base rates of low scores in healthy older individuals (i.e., false positive) in drawing inferences from low-test performances in patients, including those with neurological or psychiatric disorders (Brooks et al., 2009b; Karr et al., 2017). Indeed, the presence of cognitive impairment in patients with LLD may be sometimes due to the development of incipient dementia such Alzheimer's disease (AD) (Rushing et al., 2014, Ly et al., 2021). In clinical practice, the distinction of cognitive impairment related to LLD from those associated with early stage of AD is particularly difficult (Swainson et al., 2001; Foldi et al., 2003; Mazur-Mosiewicz et al., 2011; Gasser et al., 2018; Lanza et al., 2020a) and may lead to misdiagnosis in the older population (Rotomskis et al., 2015).

In view of the above mentioned, the aim of the present study was to describe the cognitive performance in patients with LLD in comparison with those with mild AD and a healthy control group. To achieve this aim, this study examines and presents the multivariate base rates of low scores on the RAPID battery in patients with LLD, mild AD, and older healthy adults. It is hypothesized that patients would have more low scores on the RAPID test battery compared with healthy older people controls. It is further hypothesized that the base rate information could help to distinguish cognitive impairments associated with LLD from those observed with mild AD or normal aging.

METHODS

Participants

The study sample consisted of a healthy older people control group and two clinical groups including patients with LLD and patients with AD.

The healthy older people control group were subjects drawn from the RAPID normative sample whose neuropsychological data had been initially collected previously (Ferreira et al., 2010). The design and methods for the RAPID normative data have been described in detail elsewhere (Ferreira et al., 2010). Briefly, to be included in the study, subjects had to speak and comprehend French, have no visual deficits or hearing loss that could interfere with the administration of neuropsychological testing, and had to live independently according to the "instrumental activities of daily living" (Lawton and Brody, 1969). Any participant with a previous medical history of a neurological disease (i.e., head trauma, stroke, dementia, Parkinson's disease, epilepsy, or brain tumor) or a psychiatric disorder (i.e., major depression, schizophrenia, bipolar disorder) was not included. As older adults represent the population of interest, individuals under 60 years of age were not included, thus the final group consisted of 352 healthy older people controls aged 60–89 years.

Abbreviations: AD, Alzheimer's disease; BEC 96, battery of cognitive efficacy; CERAD, consortium to establish a registry for Alzheimer's disease; COT, crossing-off test; DO30, denomination of 30 images; FCSRT, free and cued selective reminding test; GRECO, group of research and cognitive assessments; IST, Isaacs set test; LLD, late-life depression; MIS, memory impairment screen; MMSE, mini-mental state examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association for probable AD; RAPID, regional network for diagnostic aid and management of patients with cognitive impairment; TMTA, trail making test, part A; TMTB, trail making test, part B.

The clinical groups were convenience samples of patients with LLD or with AD. All patients had been referred to one of the nine inpatient or outpatient local memory consultations centers in the Franche-Comté Region (France) between 2008 and 2016. Cognitive data on all patients were retrospectively obtained from the database Rapid-Fr network (Bereau et al., 2015). The aim of this health network, financed by the French government, is to coordinate memory consultations in the geographical area of Franche-Comté (France). All patients were between 60 and 89 years old. Exclusion criteria were determined by reviewing the medical records.

Patients with LLD met the diagnostic criteria of major depression disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DMS-IV) (American Psychiatric Association, 1994) and after a comprehensive clinical interview by a psychiatrist. All patients were or had been recently hospitalized and all were on medication. Exclusion criteria were: psychotic features, schizophrenia, bipolar disorder, current, or past history of neurological disease (e.g. dementia, head trauma, Parkinson's disease, epilepsy) substance abuse or a history of electroconvulsive treatment within the past 12 weeks. The final LLD sample included 390 patients.

The AD patients met National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association for probable AD (NINCDS-ADRDA criteria) (McKhann et al., 1984) after full workup including neurologic, cognitive, imaging, and laboratory tests. Exclusion criteria were: concurrent neurological disorder, an acute stroke and a Fazekas score > 2 to avoid mixtures of vascular and neurodegenerative processes (Fazekas et al., 1993). Given that depressive symptoms are commonly reported in patients with AD (20–30%) (Lyketsos et al., 2002; Zubenko et al., 2003) we did not exclude them from this study (Foldi et al., 2003). Because the differentiation between of depression from AD in older age is more difficult in the earliest stages of AD (Rotomskis et al., 2015), only mild AD patients (i.e., MMSE $\geq$ 20) were included in the current study. The final AD sample included 234 patients.

Neuropsychological Assessment

The RAPID battery was developed by a clinical research consortium in the Franche-Comté region (France) using the same standardized evaluation. The purpose of this consortium was to facilitate patient care management throughout the Franche-Comté region using a common neuropsychological battery of tests and software database (Bereau et al., 2015). All the tests of this battery were initially normed based on the same normative sample for a broad range of ages and educational levels (Ferreira et al., 2010).

All participants were administered the RAPID battery by trained neuropsychologists. The full test battery takes approximately 60 min to complete and includes nine tests that yield 13 primary independent scores measuring five cognitive domains: verbal episodic memory, executive skills, mental processing speed, constructional praxis, and language/semantic memory. The tests administered for each domain are described below.

Assessment of Verbal Episodic Memory

The Free and Cued Selective Reminding Test (FCSRT, Grober and Buschke, 1987). We used a french adaptation by Van der Linden et al. (2004). This test assesses the ability to learn a 16 written word list that refers to 16 semantic categories. After an encoding phase, participants have to perform three successive recall trials separated by an interfering task. Each trial includes two parts. First, each participant had to freely recall as many items as possible. Next, an orally presented semantic category (e.g., what was the name of the fish?) was provided for the words that were not spontaneously retrieved by the participants. The total free recall score (from 0 to 48) (i.e., participants are asked to retrieve the words spontaneously) and the total cued recall score (i.e., participants are asked to retrieve the words with the help of a semantic cue) were considered.

The Memory Impairment Screen (MIS, Buschke et al., 1999): a French version of the MIS was used (Chopard et al., 2007). The MIS is a 4-min, four-item delayed free- and cued-recall memory test. After an interfering task lasting at least 2 min, the subjects are invited to reproduce the words learned in any order over 20 s (free recall). A cued recall is proposed for any words not mentioned using free recall. For each word, the score for a correct answer is two points for free recall and one point for cued recall. The total MIS score ranged from 0 to 8 was considered.

The word delayed recall of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975): the MMSE is a global cognitive efficiency evaluation through use of 30 items to assess orientation, calculation, memory, language, and visio-constructional abilities. In this study, a consensual French version developed by GRECO (Group of Research and Cognitive Assessments) was used (Kalafat et al., 2003). The delayed recall of the three words (from 0 to 3) was considered.

Assessment of Executive Functions

The Trail Making Test, part B (TMTB, Reitan, 1958): participants are required to connect numbers and letters alternatively as quickly as possible. The total time to complete the TMT part B was considered as well as the total number of errors (i.e., sequential errors and/or perseverative errors).

The Isaacs Set Test (IST, Isaacs and Kennie, 1973): the IST is a 1-min verbal category fluency task. The subject has to orally produce as many words as possible in 15 s for each of the following categories: colors, animals, fruit, and cities. The total number of items named was considered (any repeated words or intrusions are not included).

Assessment of Processing Speed

The Trail Making Test part A (TMTA, Reitan, 1958): participants are required to connect with lines 25 circles numbered from 1 to 25 as quickly as possible. The total time to complete the TMTA was considered.

The Crossing-Off Test (COT, Botwinick and Storandt, 1973): the COT is a psychomotor task in which the participants have to make a slash mark through a set of 96 horizontal lines, as quickly as possible. There are eight lines per row, and individuals cross out the lines from left to right, one row after another. This test

is scored as the number of lines (96) crossed out per second (t) times 100 (Index of rapidity = $96/t \times 100$).

Assessment of Constructional Praxis

Copy of triangles from the Battery of Cognitive Efficacy (BEC 96): the copy of the triangles of the cognitive assessment battery test in 96 items (Signoret et al., 1998) is a test in which the subject must copy a geometric figure according to a model that is presented. This figure is made up of a set of three intersecting triangles. The total final score, which varies from 0 to 6, was considered.

The pentagon copy of MMSE (Folstein et al., 1975): copying the overlapping pentagons is a standard sub-item of the MMSE. It was scored dichotomously as either correct (1) or incorrect (0).

Assessment of Language/Semantic Memory

Oral name of images: oral denomination of 30 images (D030, Ferreira et al., 2010) is a test in which the subject must name 10 animals, 10 objects, and 10 actions. These images are from the BEC 96 (Signoret et al., 1998), the test D080 (Metz-Lutz et al., 1991), and the Montreal-Toulouse test of aphasia review protocol (Nespoulous et al., 1992). The overall score, made up of the total number of correct answers (from 0 to 30), was retained.

Categorical Matching: the Categorical Matching Test (Ferreira et al., 2010) assesses the subject's ability to perform semantic associations in the presence of distractors. The subject must designate one of three visual items, the one that is semantically connected to the target item. The total score of correct answers, which ranges from 0 to 10, was considered.

It should be noted that in our study sample the diagnosis of AD was not entirely blind to cognitive performance and therefore raises the question of a partial circularity. However, the construct of base rates of low scores was only conceived after the RAPID data were collected. Moreover, other tests such as the California Verbal Learning Test (Delis et al., 1987), the Wechsler Memory Scale (Wechsler, 2001, 2012), the Delayed Matching-to-sample Task (Barbeau et al., 2004; Rullier et al., 2014), the copy, immediate recall, and delayed recall conditions of the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1959; Meyers and Meyers, 1994), the Stroop test (Stroop, 1935), the GRECO neuropsychological semantic battery (Merck et al., 2011), the phonemic and semantic verbal fluency tests (Cardebat et al., 1995), or the oral denomination of 80 images (Metz-Lutz et al., 1991) in addition to the neuropsychological RAPID test Battery, have also been used to further assess the cognitive functioning contributing to limit the risk of circularity.

DATA ANALYSIS

Given that most of the primary measures of the RAPID test battery did not meet the normal distribution criteria (Ferreira et al., 2010), a low score was defined as less than or equal to the 5th percentile, which is a common psychometric criterion used in clinical practice to determine "cognitive impairment" (Lezak et al., 2004). This cut-off score was also included in previous multivariate base rate analyses (Brooks et al., 2009a,b; Iverson et al., 2011; Ivins et al., 2015; Holdnack et al., 2017; Karr et al., 2017; Rivera et al., 2019).

TABLE 1 | Demographic characteristics of the samples.

	HC	LLD	Mild AD
Sample size	352	390	234
Mean age (SD)	72.9 (7.7)	73.1 (7.7)	78.9 (6.1)
Age range	60–89	60–89	60–89
Education level			
High (%)	16.1	13.4	23.5
Middle (%)	32.5	32	28.2
Low (%)	51.4	54.6	48.3
Male/Female (%)	37/63	29/71	36/64

HC, healthy controls; LLD, late life depression; AD, Alzheimer's disease; SD, standard deviation. High (i.e., >11 years of education), Middle (i.e., 8–11 years of education), Low (<8 years of education).

The 5th percentile cut-off values for the 13 primary measures of the RAPID test battery were calculated in a previous study (Sylvestre et al., 2017) from the normative sample of older adults (Ferreira et al., 2010) based on three age categories (ranges 60–69, 70–79, and 80–89 years) and three educational levels: high level (i.e., >11 years of education), middle level (i.e., 8–11 years of education), or the lowest educational level (i.e., <8 years of education).

As a reminder, to estimate the variability of the number of low scores in each of the RAPID primary measures, 1,000 bootstrap replicates were computed (Efron, 1992). Rather than limiting ourselves to an observed value for a small number of subjects, we wanted to add an uncertainty factor to our estimation. With the "bootstrapping" technique, we were able to calculate the variability of an estimation as the probability laws of this was unknown.

The multivariate base rates of low scores on the RAPID battery for the healthy older people controls, LLD, and AD group were determined by simultaneously examining the performance of 13 primary measures. For each subject, the total number of low scores (i.e., at or below the 5th percentile) was calculated across all primary measures. The multivariate base rates of low scores were further calculated as cumulative percentages for each of the three groups within different cognitive domains: verbal episodic memory, executive skills, mental processing speed, constructional praxis, and language/semantic memory. A Chi-square test was used to compare relevant group frequencies generated by cross tabulation.

RESULTS

The demographic characteristics for each of the three groups are shown in **Table 1**.

The base rates of low scores within specific cognitive domains are presented in **Table 2**. As seen in **Table 2**, it is common (between 9.4 and 17.6%) for healthy older people to obtain at least one low score (i.e., ≥1). For example, they were 17.6 and

TABLE 2 | Base rates of low scores within specific cognitive domains of healthy controls and patients with late life depression and mild Alzheimer's Disease.

	Number of low scores				
	0	**≥1**	**≥2**	**≥3**	**4**
Verbal memory (HC)	82.4	17.6	4	1.7	0.6
Verbal memory (LLD)	48.8	51.2	21	5.9	1
Verbal memory (AD)	4.3	95.7	87.3	76.1	48.3
Executive skills (HC)	83.5	16.5	4.6	0.3	n/a
Executive skills (LLD)	35.9	64.1	48.1	17.9	n/a
Executive skills (AD)	26.1	73.9	50	18.4	n/a
Mental proc. speed (HC)	90.5	9.5	1.1	n/a	n/a
Mental proc. speed (LLD)	63.7	36.3	16.1	n/a	n/a
Mental proc. speed (AD)	75.2	24.8	6	n/a	n/a
Constr. praxis (HC)	90.3	9.4	0.3	n/a	n/a
Constr. praxis (LLD)	87.2	12.8	3.1	n/a	n/a
Constr. praxis (AD)	88	11.2	0.8	n/a	n/a
Language/Semantic (HC)	88.1	11.9	1.4	n/a	n/a
Language/Semantic (LLD)	85.4	14.6	1.8	n/a	n/a
Language/Semantic (AD)	66.3	33.7	3.8	n/a	n/a

HC, healthy older people controls; LLD, late life depression; AD: Alzheimer's disease; Cognitive domains defined as follows: verbal memory: MIS, memory impairment screen; MMSE-word recall, mini-mental state examination; FCSRT, Free and cued selective reminding test; free recall and cued recall; executive skills: TMT B, trail making test; time and number of errors; IST, Isaacs set test; processing speed: COT, crossing-off test; TMT, trail making test; A-time; constructional praxis: MMSE-copy, BEC 96 figures-copy; language and semantic memory: categorical matching, naming test, n/a: not applicable.

16.5% for verbal memory and executive function, respectively. The prevalence of having at least two low scores (i.e., ≥2) dramatically decreased and varied from 0.3 to 4.6%. For example, they were 4 and 4.6% for verbal memory and executive function, respectively. A great percentage of patients obtained at least one low score: between 12.8 and 64.1% for LLD, between 11.2 and 95.7% for mild AD. The prevalence of having at least two low scores varied from 1.8 to 48.1% for LLD and from 0.8 to 87.3% for mild AD.

When comparing the cumulative percentages of participants in LLD and healthy older people control group, a larger percentage of patients with LLD had two or more low verbal memory scores than healthy controls (21 vs. 4%) [$\chi^2_{(1)} = 47.74$, $p < 0.001$; Odds Ratio = 6.4, 95% CI = 3.8–10.9]. In the executive domain, a much higher percentage was found in patients with LLD (48.1%) than in healthy older people controls (4.6%) [$\chi^2_{(1)} = 175.38$, $p < 0.001$; Odds Ratio = 19.4, 95% CI = 12.5–30]. Patients with LLD are more likely to obtain two or more low processing speed scores (16.1%) than healthy older people controls (1.1%) [$\chi^2_{(1)} = 50.80$, $p < 0.001$; Odds Ratio = 16.8, 95% CI = 7.7–36.4]. For the constructional praxis, having two low scores occurred in 3.1% of the LLD patients and 0.3% of the healthy controls [$\chi^2_{(1)} = 8.4$, $p < 0.01$; Odds Ratio = 11.1, 95% CI = 2.2–57]. For the language/semantic memory domain the percentages look very similar (1.8 vs. 1.4%) in both groups ($\chi^2 = 0.16$, $p = 0.68$; Odds Ratio = 1.3, 95% CI = 0.4–4).

When comparing the cumulative percentages of participants in LLD and mild AD group (mean MMSE = 23.1 ± 2.2), a larger percentage of patients with mild AD had two or more low verbal memory scores than LLD (87.3 vs. 21%) [$\chi^2_{(1)} = 257.81$, $p < 0.001$; Odds Ratio = 25.5, 95% CI = 1.7–37.5]. In the executive domain, the percentages look very similar in both groups (48.1 vs. 50%) [$\chi^2_{(1)} = 0.24$, $p = 0.62$; Odds Ratio = 1.1, 95% CI = 0.8–1.5]. Patients with LLD are more likely to obtain two low processing speed scores than those with mild AD (16.1 vs. 6%) [$\chi^2_{(1)} = 13.44$, $p < 0.001$; Odds Ratio = 3.0, 95% CI = 1.7–5.3]. For the constructional praxis [$\chi^2_{(1)} = 3.29$, $p = 0.07$; Odds Ratio = 0.27, 95% CI = 0.06–1.2] and language/sematic memory domain [$\chi^2_{(1)} = 2.46$, $p = 0.11$; Odds Ratio = 2.19, 95% CI = 0.8–5.8], there was no significant statistical difference.

Having three low scores in the executive domain, was found in the same proportion for both LLD (17.9%) and AD (18.4%) group ($\chi^2 = 0.02$, $p = 0.89$; Odds Ratio = 1.03, 95% CI = 0.7–1.5). A larger proportion of patients with mild AD (76.1%) than patients with LLD (5.9%) had three or more low scores (i.e., ≥3) in the verbal memory domain [$\chi^2_{(1)} = 329.8$, $p < 0.001$; Odds Ratio = 50.7, 95% CI = 38.2–77.5].

DISCUSSION

The results of the present study reiterate that a substantial proportion of healthy older individuals obtained one or more low scores on the RAPID battery even at a stringent cut-off value (i.e., at or below the 5th percentile). They are consistent with previously reported studies on other neuropsychological test batteries (Heaton, 1991; Palmer et al., 1998; Brooks et al., 2009a, 2011; Karr et al., 2017) and confirmed that low scores are common in healthy older people when multiple test scores are simultaneously analyzed across a battery. This implies that isolated low scores obtained by an individual across multiple tests are not necessarily pathological or indicative of truly impaired

functioning (Schretlen et al., 2008; Binder et al., 2009; Sylvestre et al., 2017). Thus, our data showed that from 9.4 to 17.6% of healthy older people obtained at least one low score on either measure in each cognitive domain. These findings suggest that an isolated low score may result in a large number of false positives and may have little relevance in clinical evaluation (Palmer et al., 1998; Lezak et al., 2004). Indeed, if one or more low scores at or below the 5th percentile is used as a criterion for identifying memory, executive or speed processing impairment on the RAPID battery, it can be noted that, respectively, 17.6, 16.5, and 9.5% of healthy controls obtained such a result (i.e., a potential false positive). It is also important to emphasize that these percentages are much higher than the theoretical base rate of ≤5% when interpreting a single score in isolation (Brooks et al., 2013; Karr et al., 2017; Rivera et al., 2019). By contrast, having two or more low scores could be used as a more confident criterion since this pattern of results was uncommon in healthy older people controls (from 0.3 to 4.6%). This information on the base rate of low scores among healthy older adults is important since it may help clinicians to reduce the likelihood of misdiagnosing cognitive impairment among older depressed patients.

Indeed, many studies have already shown poor performance in verbal memory, executive function and processing speed in LLD (Baudic et al., 2004; Elderkin-Thompson et al., 2006; Dybedal et al., 2013). However, the majority of them reported results derived from comparisons of mean groups (i.e., average performance) in a case-control design, which may obscure the importance of cognitive impairment in patients with LLD (Gualtieri and Morgan, 2008; Iverson et al., 2011). It should be emphasized that a significant group difference does not inform about the proportion of patients who have cognitive impairment and those who have no cognitive impairment (Gualtieri and Morgan, 2008). This suggests that the average-to-average method is not sufficiently reliable to characterize the level of cognitive functioning in different samples of individuals (Ivins et al., 2015). From this perspective, presenting data in terms of frequency of low scores could be more informative and useful in clinical practice (Chelune, 2010; Iverson and Brooks, 2011; Ivins et al., 2015).

To the best of our knowledge, very few studies provided information about the prevalence of low scores for different cognitive domains in patients with LLD. One study (Dybedal et al., 2013) found that up to 50% of patients with LLD aged 60–85 years obtained a low score in at least one cognitive domain compared to 20% of the controls. Another study (Butters et al., 2004) showed that 61% of depressed patients aged 60 years and older had a low score in at least one domain compared to 32.5% of the controls. A recent research (Lanza et al., 2020b) found about one-third of depressed patients aged 54–81 years were below normal in executive function and about two out of three patients were below normal in memory function. However, in these researches, a low score was defined using the less stringent cut-off values (i.e., below the 10^{th} percentile or mean minus 1.5 standard deviation) of a very small control group ($n = 18$, $n = 40$, and $n = 40$, respectively) and not from large normative data stratified by age and education.

The comparison of the base rates of low scores in the LLD patients with that of mild AD showed a great overlap in the executive function. This result is in accordance with previous works and confirmed that tests of executive functions do not allow distinguish these two disorders (Swainson et al., 2001; Rushing et al., 2014). Executive dysfunction is common in LLD (Lockwood et al., 2002; Alexopoulos, 2003; Baudic et al., 2004; Herrmann et al., 2007; Dybedal et al., 2013) and may be broadly related to a slowed information processing speed (Butters et al., 2004) and frontostriatal circuit disorders caused by vascular lesions (Alexopoulos, 2006, Butters et al., 2008). In addition, executive dysfunction may also be secondary to a lack of motivation (Scheurich et al., 2008) or a decrease in effortful attention capacity (Elliot, 1998; Royall et al., 2012). The presence of executive impairment has also been demonstrated in the mild stages of AD in inhibition, task-switching, planning, flexibility, and concurrent manipulation of information (Colette et al., 1998; Perry et al., 2000; Stokholm et al., 2006; Godefroy et al., 2014).

This study also shows that a great percentage (51.2%) of individuals with LLD obtained at least one low memory score (see **Table 2**). Episodic verbal memory has been found to be impaired in older people with depression (Butters et al., 2004; Sheline et al., 2006; Lamar et al., 2012). It has been argued that memory impairment in LLD may be related to executive dysfunction (Fossati et al., 2002; Herrmann et al., 2007; Lamar et al., 2012). In addition, depressed patients may show a lack of effortful attention that may contribute to reduced memory performance (Hasher and Zacks, 1979). This view is consistent with the fact that depressed patients have more difficulty with tasks that require effortful information processing than those requiring automatic information processing (Hasher and Zacks, 1979; Hammar, 2003; Hammar et al., 2003). Our results are consistent with this and showed that in our LLD patient sample, the frequency of having a low score on the free recall of the FCSRT (25%) and of the MMSE (34%) (high-demanding tasks) was higher than on the cued recall of the FCSRT (12%) or the MIS (10%) that require much fewer attention resources. This result may reflect difficulty in retrieving information during effortful memory tasks in LLD (Alexopoulos, 2001).

It is also worth noting that a great proportion (76.1%) of individuals with mild AD obtained 3 or 4 low memory scores whereas this pattern of performance was uncommon (5.9%) in LLD patients. This result may be explained by the fact that AD patients are impaired on all memory tasks including effortful or automatic process (Leyhe et al., 2017). Thus, it has been suggested that cued recall could allow to differentiate between poor memory due to depression and those related to AD since it was expected to minimize the decreased attention resources or lack of strategies found most often in the patients with depression (Ivaniou et al., 2005; Dierckx et al., 2007). However, in the present study, if only 12% of LLD had a low performance on the cued recall of the FCSRT, 66% of mild AD obtained such a pattern showing that this index of measure is moderately sensitive to minimal impairment at a mild stage of the disease. Conversely, a greater percentage of mild AD obtained a low free recall at the FCSRT (84%) but this measure lacks of specificity since 25% of LLD patients (i.e., false positive) obtained such a score,

demonstrating a great overlap of this measure for differentiating these two conditions. Our findings thus suggest that using a pattern of low scores on multiple memory measures seems to be able to distinguish patients with LLD from patients with mild AD. They are not surprising and consistent with previous studies reported that memory tasks have relatively high power to discriminate AD and older depressed patients. However, these studies have focused on a single or overall cognitive composite score and were carried out in small samples size which could result in a probable lack of statistical power (Swainson et al., 2001; Foldi et al., 2003; Künig et al., 2006; Dierckx et al., 2007, 2011; Federico et al., 2008; Contador et al., 2010; Para et al., 2010; Croisile et al., 2011; Mazur-Mosiewicz et al., 2011; Rotomskis et al., 2015).

The present study has several limitations. First, as in some previous works (Gualtieri and Morgan, 2008; Iverson et al., 2011), our LLD group was a convenience sample: the intensity of depression, age of onset or number of prior episodes had not been recorded in the RAPID database. Nevertheless, the great majority of LLD patients were or had been hospitalized for major depression, and all were in regular contact with their psychiatrist, meaning that they had probably moderate or severe depression rather than a mild form of depression. Furthermore, it has been shown (Purcel, 1997) that in-patients performed worse on cognitive tests than the out-patients, and thereby may limit the generalizability of our study results. In the future, it would be interesting to collect this information in order to better characterize the pattern of cognitive impairment of this condition. Second, our study did not take into account pharmacological treatment that could affect cognitive performance in LLD patients. Indeed, all depressed patients were being treated with antidepressants at the time of neuropsychological testing, which could affect the cognitive performance of LLD patients. Non-tricyclic antidepressants are known to improve memory performance (Haynes et al., 2004; McIntyre et al., 2014), whereas those with anticholinergic properties have been found to impair memory performance (Thompson and Trimble, 1982). Third, no information were recorded in the RAPID database about vascular factors in patients with LLD. Many studies have revealed a strong association between LLD, cognitive impairment, cerebrovascular disease, and poor cognitive outcomes, including progressive dementia, especially AD (Butters et al., 2008). Further assessment of the impact on the possible role of vascular comorbidity in the prevalence of low cognitive scores in LLD will be needed. In addition, as for LLD patients, we also used a convenience sample of patients with AD that may not be representative of community-dwelling adults. Thus, the findings of this paper should be validated using a randomly recruited, nationally, representative samples. Lastly, the ecological validity of the RAPID battery has never been examined in community-dwelling older adults. However, it is worth noting that norms of the RAPID battery tests for older adults were obtained from the same sample, in testing conditions as close as possible as those of a patient referred to a neuropsychologist, i.e., with the same tests, in the same order and time of administration.

However, this study has the advantage of showing results from a large sample (742 participants), thereby making it possible to present the data in terms of frequency of low scores (Gualtieri and Morgan, 2008). Furthermore, the 5th percentile cut-off values used in this study to define a low score were determined from age-and education-adjusted normative data (Sylvestre et al., 2017) that help to minimize over-or underestimation of impairment due to these two potential confounding variables (Potter and Steffens, 2007).

Furthermore, it is also important to remember that the base rates of low scores are expected to increase both as the number of tests increases and with a more lenient cut-off (Schretlen et al., 2008; Binder et al., 2009; Iverson and Brooks, 2011). This means that higher rates of false-positive low scores would have been reported in our healthy older people group if we had used a less stringent cut-off value (such as the 16th percentile) or a battery including a higher number of tests for each cognitive domain (Oltra-Cucarella et al., 2019). This implies that a higher number of low test-scores should be used as a reliable criterion for identifying (Mistridis et al., 2015) or predicting (Bradfield et al., 2020) cognitive impairment. This emphasizes the need for clinicians to interpret isolated low scores with even greater caution when using a large number of tests with a less conservative cut-off.

The findings of the present study may have potential implications for clinical practice: for each cognitive domain, having at least one low score on the RAPID battery was common among our healthy older adult sample and cannot therefore be used to support the presence of cognitive impairment in patients with LLD (i.e., high risk of false positive). However, having at least two low scores seems to be a more valuable criterion for identifying cognitive impairment in LLD, given its low positive rates in healthy older people. The base rate of low scores could thus provide adjunctive information in the clinical assessment of patients with LLD. It could for instance help to target patients with LLD who exhibit more extensive executive dysfunction and maybe at higher risk of poor outcomes (Koening et al., 2014) since this is known to be associated with poor antidepressant response (Potter et al., 2004; Alexopoulos et al., 2005; Story et al., 2008) and lower remission rates (Potter et al., 2004; Sheline et al., 2006). More studies are needed to explain the relationship between executive dysfunction and poor antidepressant response in LLD (Pimontel et al., 2016). Moreover, it could be interesting to combine many factors (clinical, cognitive, imaging, genetic, and so on) in order to better determine the risk of non-remission to antidepressants (Masse-Sibille et al., 2018).

In the verbal memory domain, the presence of three or more low memory scores may help establish whether the memory impairment is secondary to geriatric depression or to neurodegenerative process such as AD. This pattern of low scores could also be used as a red flag for memory impairment and should encourage the practitioner to target the LLD patient's follow-up. This point is relevant since LLD patients with poor memory performance have an increased risk of developing AD (Diniz et al., 2013; Kaup et al., 2016). It is an important

challenge in psychiatry and neurology (Künig et al., 2006; Leyhe et al., 2017; Liguori et al., 2018) from a prognostic and therapeutic point of view (Birrer and Verumi, 2004; Mazur-Mosiewicz et al., 2011; Rotomskis et al., 2015; Gasser et al., 2018). However, future longitudinal research should consider estimating whether the base rates analyzing low memory scores by using different cut-offs, could have a useful predictive value for people with LLD.

In conclusion, the present study highlights the importance of knowing the base rates of low scores across a battery of tests in healthy older adults and mild AD for detecting the presence of cognitive impairment in older adults with depression. This base rate information may help reduce the likelihood of misdiagnosing cognitive impairments, improve the clinical decision-making and target LLD patients who require careful and regular cognitive follow up.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of Besançon university hospital. The patients/participants provided their written informed consent to participate in this study. The RAPID database was validated by an ethics committee: CNIL (French CNIL: 892143). All patients in the memory consultation center receive oral and written information on the possible use of their data for research purposes.

AUTHOR CONTRIBUTIONS

CM: analysis and interpretation of data, preparation of manuscript, and revising the manuscript. PV, DB, FM, MP, JGa, EM, JGi, JD, NN, YB, MB, and EH: revising the manuscript. GS: acquisition of subjects and data and revising the manuscript. AM, ML, MB, and IR: acquisition of subjects and data. GC: study concept and design, acquisition of subjects and data, analysis and interpretation of data, preparation of manuscript, and revising the manuscript. All authors contributed to the article and approved the submitted version.

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Plasma Total Tau and Neurobehavioral Symptoms of Cognitive Decline in Cognitively Normal Older Adults

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Depression and related neurobehavioral symptoms are common features of Alzheimer's disease and other dementias. The presence of these potentially modifiable neurobehavioral symptoms in cognitively intact older adults may represent an early indication of pathophysiological processes in the brain. Tau pathology is a key feature of a number of dementias. A number of studies have found an association between tau and neurobehavioral symptoms. The current study investigated the relationship of a blood-based biomarker of tau and symptoms of depression, anxiety, worry, and sleep disturbances in 538 community based, cognitively normal older adults. Logistic regression revealed no significant relationship between plasma total tau and any measures of neurobehavioral symptoms. To assess the impact of level of tau on these relationships, participants were divided into those in the highest quintile of tau and those in the lower four quintiles. Regression analyses showed a significant relationship between level of plasma total tau and measures of depression, apathy, anxiety, worry and sleep. The presence of higher levels of plasma tau and elevated neurobehavioral symptoms may be an early indicator of cognitive decline and prodromal Alzheimer's disease. Longitudinal research is needed to evaluate the impact of these factors on the development of dementia and may suggest areas for early intervention.

Keywords: plasma tau, depression, apathy, anxiety, worry, daytime sleepiness, cognitively normal, older adults

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INTRODUCTION

A number of neurobehavioral symptoms including depression, apathy, anxiety (Ma, 2020), worry (Bower et al., 2019), and sleep disturbances (Ju et al., 2014) have been shown to be risk factors for the development of cognitive decline. A history of depression (Geda et al., 2014) as well as the occurrence of late life depression (Linnemann and Lang, 2020) have been linked to the development of Alzheimer's disease (AD). Depression has been found to be both a risk factor for cognitive decline (Diniz et al., 2013) as well as a preclinical symptom of AD (Donovan et al., 2014; Kuo et al., 2020). Depression is among the most frequent neuropsychiatric disorders accompanying

AD and related dementias (Lyketsos et al., 2011; Zhao et al., 2016). Burke et al. (2018) using the National Alzheimer's Coordinating Center data from 12,083 cognitively normal participants found that depression, anxiety and sleep disturbances were associated with the risk of AD.

Symptoms of apathy have been associated with increased dementia risk in a community dwelling cohort and suggested to be prodromal to the development of dementia (van Dalen et al., 2018). Apathy was found to be a prodromal symptom of dementia in small vessel disease (Tay et al., 2020). Anxiety has been shown to be a predictor of cognitive decline and dementia (Gulpers et al., 2016). Santabárbara et al. (2020) in a meta-analysis of prospective cohorts with 29,608 participants concluded that anxiety was significantly associated with all-cause dementia. Worry has been shown to be a predictor of decline in learning and memory in cognitively normal older adults (Pietrzak et al., 2012). Worry is considered a modifiable predictor of cognitive decline and dementia (Bower et al., 2019). In a study of the association of worry, anxiety and depression to cognitive performance in a sample of older adults, worry was found to have a significantly greater negative impact than either anxiety or depression (de Vito et al., 2019). Sleep disturbances have been related to AD as either a marker of or a mechanism mediating the risk for AD (Lucey, 2020). Short sleep duration (Spira et al., 2013), increased napping (Owusu et al., 2019) and excessive daytime sleepiness have all been found to be predictive of cognitive decline (Keage et al., 2012; Carvalho et al., 2018). A recent meta-analysis found that depression and sleep duration (long or short) were the symptoms most consistently associated with cognitive decline (Hudon et al., 2020).

The presence of these potentially modifiable neurobehavioral symptoms in cognitively intact older adults may represent an early indication of pathophysiological processes in the brain. The Amyloid, Tau and Neurodegeneration [AT(N)] biologically based framework for understanding AD (Jack et al., 2018) emphasizes the role of markers of amyloid accumulation, tau and neurodegeneration. Although there have been inconsistent results relating affective symptoms to AD biomarkers (Banning et al., 2019) there is suggestive evidence that supports this line of inquiry.

Tau is a brain specific microtubule associated protein. The intracellular aggregation of tau produces neurofibrillary tangles, which are a primary feature of AD neuropathology (Iqbal et al., 2010). Tau abnormalities related to hyperphosphorylation have been found in over 20 neurodegenerative brain disorders including Parkinson's dementia, Lewy Body Dementia and Corticobasal Degeneration (Kovacs, 2017). Although the exact nature of the role of tau in affective symptoms is unclear, a number of studies have found an association between tau and neurobehavioral symptoms. A study of memory clinic patients found a significant correlation between level of tau and behavioral and psychological symptoms of dementia (Cotta Ramusino et al., 2021). Research on tau levels in cognitively normal older adults has shown that those with elevated tau were twice as likely to be depressed (Babulal et al., 2020). In a study of the trajectory of depression and apathy over time in prodromal Alzheimer's, lower $A\beta_{42}$ and higher tau were related to an increased likelihood of depression and apathy (Banning et al., 2021). Apathy has been associated with the accumulation of tau in the right frontal regions of the brain (Marshall et al., 2019). Anxiety has been related to the level of total tau (t-tau) in individuals with mild cognitive impairment (Ramakers et al., 2013). Disturbances in the sleep cycle has been found to be effected by tau accumulation in cognitively normal and those with very mild cognitive impairment (Lucey et al., 2019; Benedict et al., 2020).

The vast majority of studies on the role of tau have used CSF markers of tau or with the availability of tau radiotracers, positron emission tomography (PET) tau biomarkers. The addition of plasma tau to CSF tau has been shown to improve diagnostic accuracy (Fossati et al., 2019). Although the association between plasma t-tau and CSF tau has been found to be relatively weak, (Mattsson et al., 2016; Pase et al., 2019) a number of studies have supported the use of plasma in investigating Alzheimer's risk (Chiu et al., 2014; Mielke et al., 2017). Compared to other methods of assessing tau, blood based biomarkers have the added benefit of not requiring the invasiveness of a spinal tap nor the expense and lack of availability of tau PET. The current study utilizes blood-based biomarkers of t-tau to investigate the relationship between plasma total tau and symptoms of depression, apathy, anxiety, worry and sleep disturbances in a cohort of community based cognitively normal older adults.

MATERIALS AND METHODS

Participants

Participants were drawn from the HABLE cohort a community-based, longitudinal study of cognitive aging in Mexican-Americans. A 409 cognitively normal Mexican Americans (323 females, 86 males) and 129 cognitively normal non-Hispanic whites (91 females, 38 males) made up the sample. A full description of the HABLE protocol has been published elsewhere (O'Bryant et al., 2021). Briefly, the HABLE study protocol includes a functional exam, blood draw, neuroimaging, clinical labs, interview (medical history, family medical history, and sociocultural factors), neuropsychological testing and the assessment of neuropsychiatric symptoms. Study material is administered in either English or Spanish per the participants reported language preference. The HABLE protocol is conducted under IRB protocols 2016-128 and 2017-165 and all participants and/or caregivers sign written informed consent. All participants are evaluated at a single site within the Institute of Translational Research at the University of North Texas Health Science Center, Fort Worth, Texas.

Affective Measures

Depressive symptomology was assessed using the Geriatric Depression Scale 30-item (GDS) (Yesavage et al., 1982) a scale designed to be used for screening depression in the elderly. A factor analytic study (Hall and Davis, 2010; Hall et al., 2011) revealed four factors and based on that analysis, the GDS was divided into four symptom subscales. Dysphoria (11 items) – related to sad mood; Meaninglessness (7 items) – evaluating the meaning or lack of meaning in one's life; Apathy

(6 items) – associated with absence of motivation and Cognitive Impairment (6 items) – having awareness and concern of one's cognitive decline.

The level of anxiety was assessed using the Beck Anxiety Inventory (BAI) (Beck et al., 1988). The BAI is a 21-item state anxiety scale measuring the intensity of cognitive, affective, and somatic anxiety symptoms experienced during the last 7 days. The scale is composed of two factors: physical symptoms and cognitive symptoms of anxiety (Beck et al., 1988).

The Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990) is a 16-item questionnaire that assesses the trait of worry, using a Likert rating from 1 (not at all typical of me) to 5 (very typical of me) and measures the tendency of an individual to engage in excessive, generalized, and uncontrollable worry.

The Epworth Sleepiness Scale (ESS) (Johns, 1991) is an eight-item measure aiming to assess daytime sleepiness and is an indirect assessment of sleep difficulties that may be associated with depression and cognitive decline.

Diagnostic Classification

Using a classification decision tree, normal cognition was assigned based on the following: (1) no complaints of cognitive change (self or other) and (2) Clinical Dementia Rating scale sum of boxes score = 0 and (3) all cognitive test scores when converted to z scores fell broadly within normal testing limits which was defined as being no greater than −1 z score.

Blood Processing

Fasting blood collection and processing were completed based on the international guidelines for AD biomarker studies (O'Bryant et al., 2015) and processed within 2 h (stick-to-freezer). Samples were assayed in the University of North Texas Health Science Center Institute for Translational Research (ITR) Laboratory by the ITR Biomarker Core. The ITR Biomarker Core utilizes the Hamilton Robotics EasyBlood for blood processing, aliquoting and re-aliquoting. A total of 500 μl of plasma was utilized to measure biomarker levels using the Single Molecule Array (Simoa) technology (Simoa; Quanterix, Lexington, MA, United States). Tests were performed to optimize dilution factors and centrifugation and the suggested dilution factor of 4× was suitable for our samples. After thawing, the samples were vortexed and spun at 10,000 g for 5 min; the supernatant was directly transferred to a 96 well plate.

Assaying Tau

Utilizing Simoa technology, multiplexed detection of t-tau was accomplished by labeling beads with dyes of various wavelengths and concentrations creating distinct subpopulations of beads. Antibodies for each specific protein were immobilized to these color-encoded beads. Mixture of these beads were incubated with each sample generating detection of multiple proteins. From the materials provided, a recombinant 3-Plex calibration curve was constructed and transferred to the 96 well plate. Calibration range for plasma t-tau was 0–100 pg/mL and dynamic range of 0–400 pg/mL. The t-tau control samples (analog 2.24 pg/mL) and inter-assay control (pooled normal plasma) were all transferred to the 96 well plate. The sample and control concentrations were calculated from 4 PL curve fit. CV for t-tau was reported at 0.061. LLODs for t-tau were reported at 0.019 pg/mL. Interplate CVs were derived for high and low pooled controls from the Quanterix automated system and for t-tau, High control CV = 0.040, Low control CV = 0.047.

Statistical Analyses

Data were analyzed using SPSS-25 (IBM). Independent *t*-tests were conducted to examine differences in demographic characteristics and differences between quintile groups. Chi squared analysis was applied to categorical data. Regression models were created to examine the link between t-tau and symptoms of depression, anxiety worry and sleepiness with t-tau, age, sex and education as predictors. Regression models were created to examine the impact of level of t-tau (quintiles), age, sex and education on each of the affective measures. Statistical significant was set at $p < 0.05$.

RESULTS

Table 1 presents the characteristics of the sample. The two ethnic groups did not differ on plasma tau nor on any of the affective measures, hence the two groups were combined for analysis. Regression analyses (**Table 2**) were conducted to assess the ability of plasma total tau to predict symptoms of depression, anxiety, worry and sleep disturbances in a sample of cognitively normal older adults. Age, sex, and education along with plasma total tau were entered as predictors. Total tau was not a significant predictor of any of the affective measures.

To assess the possible impact of level of t-tau, the sample was divided into those in the highest quintile of plasma tau ($N = 110$) and those in the lower 4 quintiles of t-tau ($N = 428$). The characteristics of the sample are shown in **Table 1**. The quintile groups did not differ in age ($t = -0.744$, df = 536, $p = 0.457$) education ($t = 0.467$, df = 536, $p = 0.476$) nor distribution of the sexes ($X^2 = 0.1984$, $p = 0.656$). **Table 3** presents the scores on each of the affective measures comparing the two group. Those in the highest quintile scored significantly higher on GDS total score, GDS Apathy subscale, BAI total score, BAI Physical Symptoms, BAI Cognitive Symptoms, PSWQ and the ESS.

To evaluate the possible clinical significance of these differences, the two groups were compared using accepted clinical cutoff scores. Applying the clinical cutoff of 9 (Laudisio et al., 2018) to the GDS, 42% of the highest quintile group scored higher than the cutoff while 32% of those in the

TABLE 1 | Characteristics of the sample.

	Total sample *N* = 538	Lower quintiles *N* = 428	Highest quintile *N* = 110
Age	*M* = 59.941	*M* = 59.815	*M* = 60.429
	SD = 7.792	SD = 7.813	SD = 7.628
Education	*M* = 9.719	*M* = 9.644	*M* = 10.001
	SD = 4.795	SD = 4.895	SD = 4.594
Gender % Female	77%	77%	79%
Plasma total tau	*M* = −6069.746	*M* = 1.569	*M* = 3.208
	SD = 71411.513	SD = 0.441	SD = 1.347

TABLE 2 | Linear regression for plasma total tau and tau quintiles and affective measures.

	Plasma total tau			Plasma tau quintiles		
Affective measures	**β**	***t***	***p***	**β**	***t***	***p***
Geriatric depression scale (GDS) total	0.052	1.251	0.211	0.088	2.088	0.037*
GDS dysphoria	0.036	0.868	0.386	0.067	1.585	0.114
GDS meaninglessness	0.032	0.750	0.454	0.049	1.152	0.250
GDS apathy	0.062	1.456	0.146	0.113	2.680	0.008*
GDS cognitive impairment	0.058	1.394	0.164	0.068	1.620	0.106
Beck anxiety inventory (BAI)	−0.015	−0.344	0.731	0.090	2.128	0.034*
BAI physical symptoms	−0.003	−0.066	0.947	0.110	2.594	0.010*
BAI cognitive symptoms	−0.024	−0.550	0.583	0.098	2.289	0.022*
Penn state worry questionnaire	0.007	0.155	0.877	0.118	2.792	0.005*
Epworth sleepiness scale	−0.029	−0.684	0.494	0.100	2.326	0.020*

*≤ 0.05.

lower quintiles scored above the cutoff ($X^2 = 3.805$, $p = 0.049$). On the BAI 35% of those in the highest quintile scored above the clinical cutoff of 14 (Diefenbach et al., 2009) and 24% of those in the lower quintiles scored above the cutoff ($X^2 = 5.032$, $p = 0.025$). When the clinical cutoff of 50 was applied to the PSWQ (Wuthrich et al., 2014), 38% of those in the highest quintile scored above 50 compared to 27% of those in the lower quintiles ($X^2 = 4.666$, $p = 0.031$). Comparing the groups on the ESS using a cutoff of 10 (Johns, 1991), 21% of those in the highest group scored above 10 and 9.7% of those in the lower quintiles were above the cutoff ($X^2 = 10.459$, $p = 0.001$).

Regression analyses were conducted to assess the effect of level of total tau on each of the affective measures. Level of t-tau (quintile groups), age, sex and education were entered as predictors. **Table 2** presents the results of the regression analyses showing that level of plasma t-tau was a significant predictor of total depression and symptoms of apathy. The scores on measures of anxiety and worry were significantly predicted by the level of t-tau, as was the score on a measure of sleep difficulty.

TABLE 3 | Scores on affective measures X quintile group.

Affective measures	**Lower quintiles** ***N* = 428**	**Highest quintile** ***N* = 110**	***p***
Geriatric depression scale (GDS) total	*M* = 7.89 SD = 6.702	*M* = 9.33 SD = 7.240	*t* = −1.977 df = 536 *p* = 0.049*
GDS dysphoria	*M* = 2.65 SD = 2.981	*M* = 3.08 SD = 3.160	*t* = −1.333 df = 536 *p* = 0.183
GDS meaninglessness	*M* = 1.12 SD = 1.576	*M* = 1.30 SD = 1.733	*t* = −1.029 df = 536 *p* = 0.304
GDS apathy	*M* = 1.64 SD = 1.512	*M* = 2.11 SD = 1.586	*t* = −2.879 df = 536 *p* = 0.004*
GDS cognitive impairment	*M* = 2.49 SD = 1.752	*M* = 2.76 SD = 1.733	*t* = −1.445 df = 536 *p* = 0.149
Beck anxiety inventory (BAI)	*M* = 5.20 SD = 7.551	*M* = 7.55 SD = 8.858	*t* = −2.5835 df = 536 *p* = 0.010*
BAI physical symptoms	*M* = 2.82 SD = 4.231	*M* = 3.84 SD = 4.881	*p* = 0.030* *p* = 0.030*
BAI cognitive symptoms	*M* = 2.35 SD = 3.743	*M* = 3.36 SD = 4.455	*t* = −2.434 df = 536 *p* = 0.015*
Penn state worry questionnaire	*M* = 39.48 SD = 15.809	*M* = 44.205 SD = 16.301	*t* = −2.779 df = 536 *p* = 0.006*
Epworth sleepiness scale	*M* = 4.52 SD = 4.030	*M* = 5.564 SD = 4.465	*t* = −2.411 df = 536 *p* = 0.016*

*$p \leq 0.05$.

DISCUSSION

This study is one of the first to show the association of plasma t-tau levels with levels of symptoms of depression, anxiety, worry and daytime sleepiness in cognitively normal older adults. The current findings are consistent with earlier findings using CSF and PET data that t-tau is related to the presence of a range of neurobehavioral symptoms in cognitively normal older adults but only at the highest level. Our findings suggest that the association between depression and other neurobehavioral disorders and tau related AD pathology may vary depending on the type and severity of the affective symptoms and the level of peripheral tau.

There are a number of strengths and limitations to the study. The participants were community-based and a robust diagnostic algorithm was applied to determine cognitive status. The study assessed a range of neurobehavioral symptoms. The current research investigated plasma tau, a more accessible biomarker of cognitive decline than CSF tau or tau imaging. The limitations are related to the sample and methodological approach used in the study. The sample was drawn from a study of cognitive aging in Mexican-Americans and was composed predominately of Mexican-Americans, which limits the generalizability of the findings. The current study utilized cross-sectional data and the nature of changes over time and the impact of the progression of cognitive decline on the tau – affective symptom relationship could not be assessed. The analysis utilized scores on measures that are frequently used in research settings but much less so in primary care settings (Olariu et al., 2015; Bhattacharjee et al., 2018) limiting the applicability of the findings. Other factors that may mediate the tau-affective symptom relationship such as apolipoprotein-ε4 status need to be investigated. Longitudinal research with a larger sample size and more representative of the overall population would be useful.

A number of questions arise from the results of this study that can only be answered by longitudinal data. The most salient is determining if elevated plasma tau is a risk for cognitive decline when associated with symptoms of affective disorders. Specifically, which of these symptoms or combination of symptoms when paired with elevated plasma t-tau are the best predictors of the risk for Alzheimer's and other dementias. For example, is elevated plasma t-tau combined with subsyndromal depressive symptoms in cognitively normal older adults a better predictor of cognitive decline than either separately. Or is apathy, which has been related to neurofibrillary tangles in AD (Skogseth et al., 2008) when combined with elevated plasma t-tau a better predictor? To what extend do other neurobehavioral symptoms such as anxiety and worry along with elevated plasma t-tau predict the development of dementia? It would be useful to assess the relationship of the combination of elevated plasma t-tau and specific affective symptoms to different types of dementing disorders as it has been shown that different neuropsychiatric symptoms predict different subtypes of dementia (Liew, 2020). It may well be that any of these affective symptoms when combined with elevated plasma t-tau may be useful indicators of future cognitive decline due to the fact that the scores on the measures of affective symptoms used in this study are highly correlated. Additionally, all of these neurobehavioral symptoms can be viewed as stressors and chronic stress has been shown to exacerbate tau burden (Arenaza-Urquijo et al., 2020).

If future longitudinal research supports the utility of the combination of plasma t-tau and these potentially modifiable neurobehavioral syndromes in predicting the development of dementia, the assessment of plasma t-tau when patients present with complaints of depression, apathy, anxiety, worry or daytime sleepiness may be clinically relevant. Treating these affective symptoms of these patients may forestall later tau related cognitive decline.

AUTHOR'S NOTE

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of North Texas Health Science Center IRB (IRB protocols 2016-128 and 2017-165) and is in accordance with Code of Ethics of the World Medical Association Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH was involved in designing the project, writing, and revising the manuscript. MP reviewed and made substantial edits to the manuscript. LJ was involved in reviewing and editing the manuscript. SO'B was involved designing the project and writing the manuscript. All authors made substantial contributions to the creation and writing of this manuscript, agree with the findings and have given consent to include their names on this manuscript.

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Conflict of Interest: SO'B has multiple patents on precision medicine for neurodegenerative diseases.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Post-traumatic Stress Disorder and Risk Factors in Patients With Acute Myocardial Infarction After Emergency Percutaneous Coronary Intervention: A Longitudinal Study

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This study aimed to investigate the status and risk factors of post-traumatic stress disorder (PTSD) in patients with acute myocardial infarction (AMI) after emergency percutaneous coronary intervention (PCI) in acute and convalescence phases. A longitudinal study design was used. Two questionnaire surveys were conducted in the acute stage of hospitalization, and 3 months after onset in patients. Logistic regression was used to analyze the risk factors for PTSD in AMI patients. The incidence of PTSD was 33.1 and 20.4% in acute and convalescent patients, respectively. The risk factors related to PTSD were door-to-balloon time (DTB) (≥92.6 min), left ventricular ejection fraction (LVEF) (<50%), smoking, anxiety, and depression. AMI patients after PCI had PTSD in the acute and convalescent stage. The findings indicate that tailored measures should be developed and carried out to prevent PTSD and improve the mental health of patients with AMI after undergoing PCI.

Keywords: acute myocardial infarction, anxiety, depression, percutaneous coronary intervention, post-traumatic stress disorder

INTRODUCTION

Acute myocardial infarction (AMI) is a common and serious heart disease with rapid onset, extremely high morbidity, and mortality (Reed et al., 2017). Approximately 50% of AMI patients have multivessel coronary artery disease (Saito and Kobayashi, 2019). The key to successful AMI treatment is to open the infarct-related artery as soon as possible, and emergency percutaneous coronary intervention (PCI) is the mainstay of treatment for AMI patients (Levine et al., 2016). Post-traumatic stress disorder (PTSD) is defined as a stress-related disorder with a subsequent autoimmune disease that might arise after exposure to a serious traumatic event or injury (Liang et al., 2020). Previous studies have shown that approximately 12% of AMI patients developed PTSD (Edmondson et al., 2012), and 66.7% of patients had PTSD symptoms 2 years after AMI (Castilla and Vázquez, 2011). The abruptness of the event, the risk of death, and the patient's intense sense of loss of control and helplessness during the event as well as the intrusive experience of the treatments, such as PCI, could lead to the development of PTSD (Ledermann et al., 2020).

In addition, the occurrence of PTSD after emergency PCI is associated with poor therapeutic efficacy, such as repeated rehospitalization, multiple complications, and increased mortality (Guler et al., 2009; Edmondson et al., 2012; Sumner et al., 2015; Burg and Soufer, 2016). Therefore, approximately 18–23% of patients with AMI, who perceived the event as life-threatening and distressing, showed clinically relevant acute stress symptoms (Ledermann et al., 2020). AMI is a stressful traumatic event, and AMI patients usually have a severe psychologically traumatic experience that endangers their lives. Recently, an increasing number of studies have explored AMI-related PTSD (Edmondson et al., 2011; Perkins-Porras et al., 2015; Singh et al., 2017; Birk et al., 2019). Previous study (Meli et al., 2019) showed that invasive treatment was a risk factor for PTSD in AMI patients, and AMI patients that received invasive surgery were more prone to develop PTSD symptoms than those that received conservative treatment. PTSD after AMI could cause prolonged psychological pain and increase the risk of major adverse cardiac events, which results in impaired quality of life (Känel et al., 2011; Edmondson and von Känel, 2017).

Some studies found that the occurrence of PTSD in AMI patients might be related to the patient's social demographic factors (e.g., age, gender, and race), disease factors, socioeconomic factors, psychological factors (e.g., anxiety and depression), and personality (e.g., introversion and impulsive personality traits) (Wikman et al., 2008; Hari et al., 2010; Roberge et al., 2010; Dinenberg et al., 2014; Oflaz et al., 2014; Stevanović et al., 2016). Previous studies found that depression was strongly associated with the development of PTSD and comorbidity and that depression (hospitalization or before onset) was predictive of PTSD (Whitehead et al., 2006; Roberge et al., 2010). Konrad et al. (2017) reported that several environmental factors in emergency departments influenced a patient's perception of threat to life, and increased risk for subsequent PTSD in AMI patients. Many patients showed a strong fear of dying after the onset of acute symptoms, and emotional distress is common in approximately one-third of patients that reported mild-to-moderate depressive symptoms post-hospitalization for AMI (Wikman et al., 2008).

Currently, the number of AMI patients after discharge that have PSTD symptoms is difficult to assess, and the diversity of symptoms means that it is difficult to determine the progression of PSTD and evaluate the effectiveness of treatment. Therefore, this study adopted a longitudinal study design to investigate PTSD and the risk factors in AMI patients following emergency PCI during the in-hospital acute stage and at-home convalescent stage. The results could mean that is it possible to identify patients at risk and help to improve postoperative nursing.

MATERIALS AND METHODS

Study Design and Procedures

A longitudinal design was used in this study. AMI patients that were admitted to the University Hospital, Guangzhou, Southern China, between September 1, 2019, and March 31, 2020, and were successfully implanted with coronary stents by emergency PCI were enrolled in this study.

Patients that had all the following were included in this study: (1) AMI and emergency PCI; (2) aged $\geq$ 18 years; (3) no other major traumatic events in the previous 6 months, such as car accidents and family changes; (4) willingness to participate in the survey; and (5) clear consciousness, no cognitive impairment, capacity to communicate using language or text. The following patients were excluded from this study: (1) patients that needed to be transferred to ICU for treatment due to serious illness after PCI; (2) patients that had severe hepatic and renal insufficiency and malignant tumors; (3) patients that had a previous mental illness, such as dementia, anxiety, depression, or a family history of mental illness; (4) patients that had a respiratory infection, urinary tract infection, and other serious infectious diseases, and (5) patients that received coronary artery bypass graft surgery.

The sample size of this study was estimated based on the previous study (Xiao, 2008). The PTSD scale consisted of 17 items, each item for five cases at least, considering 15% non-response, a minimum of sample size was 98. 113 AMI patients completed two times survey, which achieved the requirements of sample size.

Instruments

Demographic and Baseline Clinical Data

Demographic and baseline clinical data for patients included gender, age, level of education, marital status, smoking history, body mass index (BMI), baseline clinical characteristics (e.g., history of hypertension, diabetes, and hyperlipidemia), chest pain center time index and door-to-balloon (DTB), infarction area, number of coronary artery stenoses, and left ventricular ejection fraction (LVEF).

PTSD Checklist-Civilian Version

The scale (Känel et al., 2011) to evaluate PTSD was developed by the PTSD research center in the United States, which includes three characteristic syndromes: (1) re-experience (5 items); (2) avoidance (7 items); and (3) hypervigilance (5 items), with 17 items in total (Li et al., 2010). Each item was used with a five-point Likert scale, with a total score from 17 to 85. The higher the score, the more probable the patient was to develop PTSD. Cronbach's regression coefficient for the scale was 0.87. According to a previous study, a total score $\geq$ 44 suggested the presence of the symptoms of PTSD (Li et al., 2010).

Hospital Anxiety and Depression Scale

The hospital anxiety and depression scale (HADS) was used to assess the mental state of patients. The HADS scale has good predictive accuracy for anxiety and depression patients and can be used for patients without the participation of psychologists or psychiatrists (Reed et al., 2017). The HADS consists of two subscales (1) anxiety (A); and (2) depression (D), each has seven items, and each item is divided into four grades from 0 to 3. A score from 0 to 7 indicated no depression or anxiety, from 8 to 10 indicated depression or anxiety, from 11 to 14 indicated possible moderate depression or anxiety, and from 15 to 21 indicated severe depression or anxiety. Cronbach's regression coefficient for the scale was 0.83.

Procedure

Acute myocardial infarction patients that underwent emergency PCI were screened by two trained research assistants based on electronic medical records and clinical recommendations. Researchers conducted unified training for investigators before data collection. Patients that had a lower educational level, older age, or visual impairment had each item explained in detail to ensure that they understood the meaning of each item clearly.

The first survey was conducted between days 1 and 3 after patients were stabilized during the acute hospitalization stage after emergency PCI. Face-to-face PCL-C and HADS questionnaires were conducted and the participants' medical record number and telephone number were recorded to track the patient's condition. The second survey was conducted during at-home convalescence (3 months after the onset of the disease). PCL-C and HADS questionnaires were conducted again by telephone. Each survey lasted approximately 5–10 min, and the investigators only asked questions and explained the meaning of the questions; however, they did not help the patients to make the choices.

Statistical Analyses

SPSS 20.0 statistical software was used for data analysis. Data processing included the elimination of questionnaires that had an information missing rate of $> 10\%$ or that had the same answers but with obvious problems. Continuous variables were described by mean and standard deviation, and classified variables were described by frequency and percentage. Continuous variables and categorical variables were compared using a *t*-test and a Chi-squared test, respectively. Associated risk factors for PTSD were analyzed using a logistic regression model. All hypothesis tests were bilateral tests. A *p*-value < 0.05 indicated that the difference was statistically significant.

RESULTS

General Demographic Characteristics

After application of the inclusion and exclusion criteria, a total of 129 AMI patients were enrolled in this study. In this study, at stage T1, 129 questionnaires were issued, and 121 valid questionnaires were collected, eight questionnaires had missing information, which included three patients that had missing HADS data, three patients that had missing PCL-C data, and two patients that had experienced deteriorating conditions and had been transferred to ICU for treatment. Therefore, 121 patients presented valid questionnaires at this stage. At stage T2, 113 valid questionnaires were followed up by telephone, eight patients were lost during follow-up. Among eight lost participants, one patient died in the ICU because of illness deterioration, four patients did not answer the telephone, and three patients could not complete the questionnaire by telephone.

At stage T1, the 121 patients included 103 (85.1%) males and 18 (14.9%) females with an average age of 61.2 ± 10.7 years (age range: 36–85 years). Among these 121 patients, 115 patients (95.0%) had ST segment elevation myocardial infarction (STEMI) and six patients (5.0%) had non-ST segment elevation myocardial infarction (NSTEMI). At stage T2, the 113 patients included 95 (84.0%) males and 18 (26.0%) females with an average age of 63.7 ± 10.0 years (age range: 38–84 years). Among these 113 patients, 107 patients (94.7%) had STMEI and six patients (5.3%) had NSTEMI (**Table 1**).

Acute and Convalescent Stages of Post-traumatic Stress Disorder

Out of 121 patients in the acute stage, 40 had PTSD, with an incidence rate of 33.1% and a PTSD average score of 35.71 ± 7.52. Out of 113 patients during the convalescent stage, 23 had PTSD, with an incidence rate of 20.4% and a PTSD average score of 28.95 ± 8.4.

Analysis of Anxiety and Depression in Acute and Convalescent Stages

During the acute stage, 121 patients had average scores of anxiety and depression of 7.62 ± 3.56 and 8.64 ± 3.54, respectively, with rates of anxiety and depression of 46.3 and 46.3%, respectively. During the convalescent stage, 113 patients had average scores of anxiety and depression of 6.09 ± 2.77 and 7.03 ± 3.33, respectively, with rates of anxiety and depression of 41.6 and 45.1%, respectively (**Figure 1**).

Risk Factors for Post-traumatic Stress Disorder During Acute and Convalescent Stages

As listed in **Table 2**, during the acute stage, univariate analysis of PTSD revealed that the risk factors for PTSD included young age [OR = 0.18, 95% CI: 0.08–0.41, $p < 0.001$], higher education level [OR = 5.93, 95% CI: 2.59–13.57, $p < 0.001$], smoking [OR = 4.42, 95% CI: 1.95–10.00, $p < 0.001$], DTB $\geq$ 92.6 min [OR = 11.94, 95% CI: 4.85–29.43, $p < 0.001$], and LVEF $< 50\%$ [OR = 0.25, 95% CI: 0.11–0.58, $p = 0.001$]. Binary logistic analysis suggested that DTB $\geq$ 92.6 min [OR = 34.83, 95% CI: 8.61–141.00, $p < 0.001$] and LVEF <50% [OR = 0.08, 95% CI: 0.02–0.30), $p < 0.001$] were independent risk factors for PTSD in AMI patients.

During the convalescent stage, univariate analysis revealed that the risk factors for PTSD included young age [OR = 0.20, 95% CI: 0.07–0.60, $p = 0.004$], higher education level [OR = 4.57,95% CI: 1.7–12.31, $p = 0.003$], smoking [OR = 8.21, 95% CI: 2.57–26.18, $p < 0.001$], and LVEF $< 50\%$ [OR = 0.12, 95% CI: 0.05–0.34, $p < 0.001$]. Multiple factor logistic regression analysis suggested that smoking [OR = 5.12, 95% CI: 1.30–20.16, $p = 0.019$] and LVEF<50% [OR = 0.08, 95% CI: 0.02–0.28), $p < 0.001$] were the independent risk factors for PTSD in AMI patients (**Tables 2**, **3**).

Relationship Between Anxiety, Depression, and Post-traumatic Stress Disorder

The probability of PTSD symptoms in patients with anxiety and depression symptoms were compared and patients with anxiety and depression symptoms were more probable to have PTSD symptoms (**Figure 2** and **Table 4**).

TABLE 1 | Demographic and baseline clinical data of patients during acute and convalescent stages.

Variables	AMI patients (*n* = 121)	PTSD during acute stage (*n* = 121)			PTSD during convalescent stage (*n* = 113)		
		No (*n* = 81)	Yes (*n* = 40)	*p**	No (*n* = 90)	Yes (*n* = 23)	*p**
Age	61.2 ± 10.7	64.3 ± 9.5	54.8 ± 10.3	<0.001	62.8 ± 10.2	52.9 ± 8.9	<0.001
Gender (age)				0.109			0.043
Male	103 (85.1)	66 (81.5)	37 (92.5)		72 (80.0)	23 (100)	
Female	18 (14.9)	15 (18.5)	3 (7.5)		18 (18.5)	0 (0)	
BMI (kg/m^2)	24.1 ± 1.9	24.0 ± 2.0	24.3 ± 1.8	0.414	24.0 ± 1.9	24.3 ± 2.0	0.629
Degree of education				<0.001			0.002
Junior high school or below	73 (60.3)	60 (74.1)	13 (32.5)		60 (66.7)	7 (30.4)	
High school or technical secondary school	48 (39.7)	21 (25.9)	27 (67.5)		30 (33.3)	16 (69.6)	
Marital status				0.631			0.287
Married	100 (82.6)	66 (81.5)	34 (85.0)		71 (78.9)	21 (91.3)	
Divorced or widowed	21 (17.4)	15 (18.5)	6 (15.0)		19 (21.1)	2 (8.7)	
Smoking				<0.001			<0.001
No	65 (53.7)	53 (65.4)	12 (30.0)		57 (63.3)	4 (17.4)	
Yes	56 (46.3)	28 (34.6)	28 (70.0)		33 (36.7)	19 (82.6)	
Disease diagnosis				0.177			0.452
STEMI	115 (95)	79 (97.5)	36 (90.0)		84 (93.3)	23 (100)	
NSTEMI	6 (5)	2 (2.5)	4 (10.0)		6 (6.7)	0 (0)	
FMC (min)	545.2 ± 918.9	407.6 ± 677.7	823.8 ± 1,239.7	0.053	595.4 ± 994.3	379.2 ± 573.6	0.320
DTB (min)	92.6 ± 56.12	69.3 ± 23.4	139.6 ± 72.0	<0.001	89.2 ± 49.8	112.8 ± 79.2	0.185
Number of coronary artery stenoses				0.159			0.815
Single branch	41 (33.9)	24 (29.6)	17 (42.5)		29 (32.2)	8 (34.8)	
Multiple branches	80 (66.1)	57 (70.4)	23 (57.5)		61 (67.8)	15 (65.2)	
Area of infarction				0.202			0.969
Anterior wall	38 (31.4)	22 (27.2)	16 (40.0)		28 (31.1)	8 (34.8)	
Inferior wall	46 (38.0)	36 (44.4)	10 (25.0)		34 (37.8)	8 (34.8)	
Multiple sites	25 (20.7)	15 (18.5)	10 (25.0)		18 (20.0)	5 (21.7)	
Other sites	12 (9.9)	8 (9.9)	4 (10.0)		10 (11.1)	2 (8.7)	
LVEF				0.001			<0.001
<50%	34 (28.1)	15 (18.5)	19 (47.5)		17 (18.9)	15 (65.2)	
≥50%	87 (71.9)	66 (81.5)	21 (52.5)		73 (81.1)	8 (34.8)	
Hypertension				0.404			0.112
No	67 (55.4)	47 (58.0)	20 (50.0)		46 (51.1)	16 (69.6)	
Yes	54 (44.6)	34 (42.0)	20 (50.0)		44 (48.9)	7 (30.4)	
Diabetes mellitus				0.390			0.675
No	79 (63.2)	55 (67.9)	24 (60.0)		59 (65.6)	14 (60.9)	
Yes	42 (34.7)	26 (32.1)	16 (40.0)		31 (34.4)	9 (39.1)	
Hyperlipidemia				0.653			0.076
No	76 (62.8)	52 (64.2)	24 (60.0)		61 (67.8)	11 (47.8)	
Yes	45 (37.2)	29 (35.8)	16 (40.0)		29 (32.2)	12 (52.2)	

*$p < 0.001$, paired t-tests.

DISCUSSION

In this study, the incidence of PTSD in AMI patients following PCI was 33.1% during the acute stage and 20.4% during the at-home recovery stage 3 months after discharge. Compared with the recovery period, the incidence of PTSD in the acute phase was higher in AMI patients after emergency PCI. A systematic review and meta-analysis showed that the incidence of PTSD after acute coronary syndromes was approximately 12%, with a prevalence rate from 0 to 32% in each study (Edmondson et al., 2012). The differences between these observations and data available in the literature could be attributed to the differences in the methods used to evaluate PTSD and the sample size. In this study, the AMI patients that had emergency PCI during the acute and convalescent stages had a higher incidence of PTSD, which was probably affected by the COVID-19 pandemic (i.e., increased isolation) during the assessment period. Because of COVID-19, AMI patients following PCI worried that they, their family members, and friends might be infected. Therefore, they experienced more psychological pressure and were more

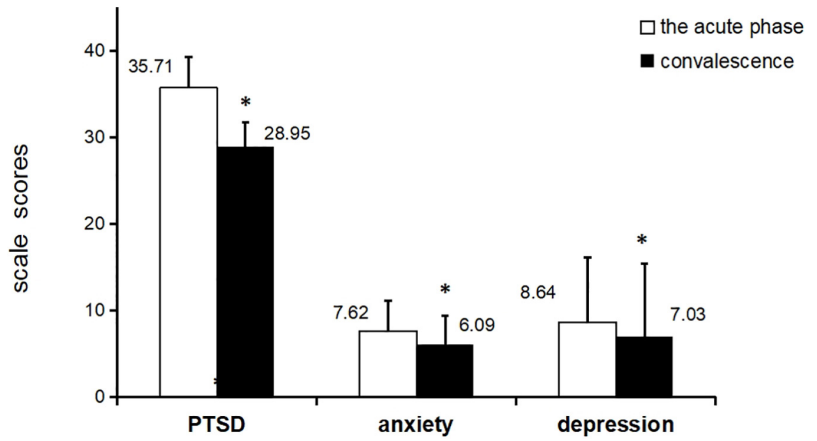

FIGURE 1 | The average scores of PTSD, anxiety, and depression in acute and convalescent phase *p<0.001, paired t-test, PTSD=post traumatic stress disorder.

probable to develop PTSD (Edmondson et al., 2012; Vindegaard and Benros, 2020). Although the proportion of patients with PTSD decreased slightly during the recovery period, patients were not fully disengaged from the traumatic event. Therefore, AMI is a persistent potential threat, and patients might experience AMI-related symptoms after onset, which might last for many years (Wikman et al., 2008). These observations suggest that medical staff should pay more attention to the early mental and psychological health of AMI patients after emergency PCI and if they have PTSD symptoms. If required, psychological and other medical treatments should be administered to patients that have obvious PTSD symptoms to promote early recovery.

Multivariate analysis of PTSD during the acute stage showed that the longer the DTB time, the increased risk of PTSD. In 2013, The guidelines emphasized that DTB duration for STEMI patients that received PCI should be < 90 min (O'gara et al., 2013). The guidelines for myocardial revascularization published in 2014 suggested that the appropriate DTB time was < 60 min (Kolh and Windecker, 2014). Therefore, DTB time is the most critical time index during the treatment procedure (O'gara et al., 2013; Kolh and Windecker, 2014), and reopening the blood supply in the shortest time to achieve myocardial level reperfusion could save more functional myocardium. The

TABLE 2 | Determination of risk factors for PTSD during acute stages.

Variables	Univariate analysis		Multifactor analysis	
	OR (95% CI)	*P**	OR (95% CI)	*P**
Age				
< 61.2	1.00 (Ref.)		1.00 (Ref.)	
≥ 61.2	0.18 (0.08–0.41)	< 0.001	0.23 (0.05–1.15)	0.073
Degree of education				
Junior high school and below	1.00 (Ref.)		1.00 (Ref.)	
Senior high school and above	5.93 (2.59–13.57)	< 0.001	3.06 (0.62–15.01)	0.169
Smoking				
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	4.42 (1.95–10.00)	< 0.001	2.77 (0.75–10.22)	0.125
DTB (min)				
< 92.6	1.00 (Ref.)		1.00 (Ref.)	
≥ 92.6	11.94 (4.85–29.43)	< 0.001	34.83 (8.61–141.00)	< 0.001
LVEF				
< 50%	1.00 (Ref.)		1.00 (Ref.)	
≥ 50%	0.25 (0.11–0.58)	0.001	0.08 (0.02–0.30)	< 0.001

*p < 0.001, paired t-tests.
DTB, door-to-balloon; LVEF, left ventricular ejection fraction.

TABLE 3 | Determination of risk factors for PTSD during convalescent stages.

Variables	Univariate analysis		Multifactor analysis	
	OR (95% CI)	*P**	OR (95% CI)	*P**
Age				
< 61.2	1.00 (Ref.)		1.00 (Ref.)	
≥ 61.2	0.20 (0.07–0.60)	0.004	0.40 (0.07–2.23)	0.297
Degree of education				
Junior high school and below	1.00 (Ref.)		1.00 (Ref.)	
Senior high school and above	4.57 (1.70–12.31)	0.003	2.35 (0.46–12.07)	0.307
Smoking				
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	8.21 (2.57–26.18)	< 0.001	5.12 (1.30–20.16)	0.019
LVEF				
< 50%	1.00 (Ref.)		1.00 (Ref.)	
≥ 50%	0.12 (0.05–0.34)	< 0.001	0.08 (0.02–0.28)	< 0.001

*p < 0.001, paired t-tests.
DTB, door-to-balloon; LVEF, left ventricular ejection fraction.

TABLE 4 | Comparison of the positive rates of PTSD between anxiety and depression subgroups during the acute stage.

Index	PTSD during acute stage (*n* = 121)		*P**
	No (*n* = 81)	Yes (*n* = 40)	
Anxiety			< 0.001
Yes (*n* = 65)	59 (90.8)	6 (9.2)	
No (*n* = 56)	22 (39.3)	34 (60.7)	
Depression			< 0.001
No (*n* = 65)	60 (92.3)	5 (7.7)	
Yes (*n* = 56)	21 (37.5)	35 (62.5)	

**Chi-square tests.*

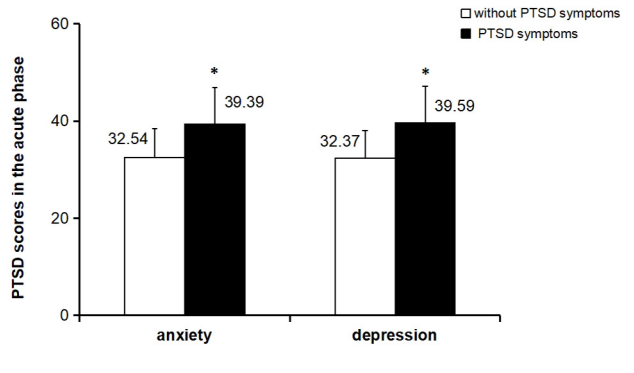

FIGURE 2 | Comparison of PTSD scores between anxiety and depression subgroups in the acute phase *p<0.001 paired t-test.

severity of AMI is a risk factor for PTSD (Xia Liu et al., 2019). A shorter DTB might remove the patient from danger more quickly; therefore, reducing the psychological burden as well as the probability of PTSD, anxiety, and depression. Therefore, rapid revascularization and reduction of DTB time during the treatment of AMI patients is critical to reduce the incidence of PTSD.

The results of this study indicated that LVEF < 50% was a risk factor for PTSD. LVEF is an important indicator for the evaluation of cardiac function (Jia et al., 2011). The degree of myocardial ischemia in STEMI patients depends on the time of vascular opening and delayed vascular opening results in massive cardiac cell death, myocardial infarction, left ventricular remodeling, and a continuous decrease in LVEF. A larger scope for myocardial necrosis has an increased negative impact on cardiac function and blood circulation dynamics, and therefore, generates more somatic symptoms, and places increased psychological stress on AMI patients. Newman et al. (2011) surveyed 241 patients with acute coronary syndromes and reported that those with PTSD symptoms (18%) were higher than those without PTSD symptoms (82%) (LVEF: 53.0 vs. 46.1%). In addition, (Sawatari et al., 2016) found that LVEF level was a useful to predict of PTSD severity. Therefore, early active treatment should be carried out to improve the cardiac function of severe AMI patients to promote the early recovery, reduce psychological stress, and prevent, or reduce PTSD, or both.

In this study, patients that were smokers were more probable to develop PTSD, which agreed with previous research (Calhoun et al., 2008). AMI patients were admitted to the Coronary Care Unit after emergency PCI and were not allowed to smoke, and eventually had to stop smoking. Because nicotine enhances cognition and attention, giving up smoking might increase the cognitive and attention deficit associated with PTSD. Compared with smokers without PTSD, smokers with PTSD had a higher rate of relapse aspiration and withdrawal syndrome during cessation, and their tolerance for pain associated with the withdrawal threshold was low, and the trauma of withdrawal was more sensitive (Dedert et al., 2012; Ashare et al., 2014; Tidey and Miller, 2015). Therefore, smoking cessation guidance for AMI patients should be strictly implemented during the acute hospitalization stage, and the possibility of PTSD should be assessed during the convalescent stage. In addition, during the convalescent stage, more support and intervention should be administered to AMI patients to help them stop smoking.

The development of PTSD in AMI patients was closely related to anxiety and depression during the acute and convalescent stages. AMI patients had increased anxiety and depression with different degrees before and after PCI surgery, probably because they were excessively worried about the risks of PCI itself and the potential complications and other uncertain factors (Langvik and Hjemdal, 2015). Previous studies concluded that depression and PTSD were reciprocal risk factors (Whitehead et al., 2006; Roberge et al., 2010). Therefore, when AMI patients display any signs of anxiety and depression after emergency PCI, nursing staff should closely monitor and evaluate if the patients develop PTSD during the acute and convalescent stages. When symptoms of anxiety, depression, and PTSD coexist, nursing staff should assess if symptoms of serious complications occur and offer early psychological intervention to prevent PTSD and to improve the prognosis of AMI patients.

Although age and education was not significant risk factors of PTSD in the multivariable model, young age or higher education level was associated with PTSD risk during the acute stage and the convalescent stage in the univariate analysis. Consistent with the previous research, patients with cancer who were younger reported to be a greater risk of PTSD (Abbey et al., 2015). Lin et al. (2017) showed the highly educated participants were likely to have PTSD. Therefore, AMI patients with young age or high education levels should be provided with health care to prevent PTSD after emergency percutaneous coronary intervention.

This study has some limitations. First, this study was a single-center study with a small sample size, therefore, caution should be employed when generalizing from the findings, and further research with a larger sample is needed to validate them. Second, the convalescent stage analyzed in this study was 3 months after discharge, which was relatively short. Therefore, future studies should have a follow-up for a longer recovery period to evaluate the occurrence of PTSD in AMI patients following PCI more accurately. In addition, the measurement methods used in this study were questionnaires that were completed by the patients or obtained by phone. Therefore, the possibility that the patients were subjective when answering questions could not be ruled out, which might not reflect their real psychological state.

CONCLUSION

In this study, a higher incidence of PTSD was reported in AMI patients during the acute and convalescent stages after emergency PCI. The occurrence of PTSD was closely related to a long DTB time, LVEF < 50%, and smoking, and the AMI patients with PTSD had a higher comorbidity rate with anxiety and depression than those without PTSD. Therefore, attention should be paid to the mental health problems of AMI patients during the acute and convalescent stages after emergency PCI. During the acute stage, emergency care should be strengthened for AMI patients with early emergency PCI, DTB time should be shortened to reduce the incidence of PTSD, and smoking, poor heart function, and anxiety and depression symptoms should be closely monitored. During the convalescent stage, follow-up should be improved to closely monitor if AMI patients have PTSD symptoms after discharge, and suitable interventions should be conducted to reduce the adverse health outcomes associated with PTSD.

Future research should focus on the development of tools to screen and assess PTSD in AMI patients to determine the incidence and severity of PTSD more accurately. The follow-up time should be extended to assess PTSD at different time points after AMI to determine whether patients have PTSD after 6 months, 1 year, or a longer period after discharge from hospital. In addition, qualitative research should be designed to explore the causes of PTSD from the patients perspective to adopt more personalized interventions to prevent or reduce the occurrence of PTSD, reduce the adverse outcomes caused by PTSD, and improve the quality of life of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XC, JW, YG, XL, YD, and CM: conceptualization. XC and JW: methodology and writing—original draft preparation. YD and XL: formal analysis and investigation. JW and CM: writing—review and editing. XC and CM: funding acquisition and supervision. YG and XL: resources. XC and JW equally contributed to the writing of this article. All authors contributed to the article and approved the submitted version.

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The Mental Health of Caregivers and Their Patients With Dementia During the COVID-19 Pandemic: A Systematic Review

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Background: Coronavirus Disease 2019 (COVID-19) is a worldwide public health concern. It continues to spread rapidly throughout the world causing multiple physical and psychological consequences in the population. Especially, people affected by severe psychiatric or neurological diseases are highly susceptible to serious health complications not only due to the direct effect of the infection but also to the indirect effect of COVID-19 following social distancing during lockdowns and its general social consequences. Indeed, lockdown and difficulties in using the care services produced psychological consequences in caregivers such as depression, anxiety, and worsening of the quality of life which in turn affected the ability to manage patients. Our aim was to systematically review the psychological consequences of the COVID-19 lockdown in caregivers of patients with cognitive impairment and dementia and the impact on the health of their patients.

Methods: A systematic literature search was conducted by searching in MEDLINE/PubMed, Scopus, and Web of Science by two independent researchers following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. Data extraction and quality assessment were also performed. Papers were screened for eligibility by abstract and then those which met inclusion criteria were included in this review.

Results: The initial search returned 410 records. After the abstract screening and the inclusion/exclusion criteria were applied, 315 were excluded because they were irrelevant, 30 because they were reviews, meta-analyses, letters to editors, editorials, guidelines, or case reports, and 10 because they were duplicates. Then, 38 out of 55 abstracts/full-text articles were excluded because they did not simultaneously assess mental health of patients and caregivers. In the end, 17 papers were deemed eligible and included in the present review.

Conclusion: Based on current literature, the COVID-19 pandemic and the ensuing lockdown caused severe psychological consequences for caregivers of patients with

dementia, worsening their mental health, and increasing the psychological and physical burden, independently from the severity of the disease of their relatives, which resulted also independently globally worsened.

Keywords: caregivers, cognitive dysfunction, COVID-19, dementia, pandemic, psychological symptoms, SARS-CoV-2, systematic review

BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in Coronavirus Disease 2019 (COVID-19) has caused the most severe health crisis since the 1918 influenza pandemic (Osuchowski et al., 2021). After the cluster of COVID-19 cases reported in China at the end of 2019, the virus has spread rapidly throughout the world, with over 200 million cases and 4 million deaths, with an unprecedented impact on healthcare systems, national economies, and society (Coronavirus Resource Center, 2021).

To contain the COVID-19 diffusion and avoid the overload of their medical systems, world government authorities have introduced restrictive measures based on lockdowns, travel limiting, social distancing, self-protection measures (e.g., wearing a face mask), and quarantine, which have caused negative psychological consequences in the population (Brooks et al., 2020; Clemente-Suárez et al., 2020).

The isolation that limits both individual movements and social contacts, the fear of contagion, the financial worries, and the loss of relatives or friends for COVID-19 has severely affected mental health wellbeing, increasing the risk of anxiety, depression, irritability, insomnia, and post-traumatic stress symptoms (Clemente-Suárez et al., 2020; Fofana et al., 2020).

On the other hand, it has been hypothesized that COVID-19 may induce a neuro-inflammatory state, triggering or accelerating neurodegeneration processes and related symptoms, such as neuropsychiatric manifestations (Iodice et al., 2021; Solomon, 2021), which in turn may further decline as a consequence of psychological symptoms due to stressor events (Song et al., 2020).

Taken together, this evidence suggests a greater vulnerability to COVID-19 sequelae for people already suffering from cognitive impairment (e.g., dementia, Parkinson's) who need a support network, such as caregivers and social and health services (Aamir et al., 2021). The changes in routine living conditions, such as the lockdown-related difficulties to access the care services, can deteriorate their mental and physical health. As a result, stress-related symptoms, depression, anxiety, and worsening quality of life may also occur in caregivers, impairing in turn, the ability to manage patients (Cagnin et al., 2020). Indeed, during the COVID-19 lockdown, caregivers of patients with severe neuropsychiatric diseases experienced an increased burden related to changes in neuropsychiatric symptoms of patients (Boutoleau-Bretonnière et al., 2020), and they also reported heightened feelings of responsibility as caretakers (Rising et al., 2021). In particular, it was demonstrated that female caregivers of patients suffering from neurocognitive disorders were affected by anxiety and depressive symptoms (Li et al., 2021). However, while dementia patients are often evaluated from both clinical and behavioral points of view, their caregivers are frequently neglected. Indeed, caregivers experience a double burden of both their loved one's care and their personal living with lockdown measures (Iodice et al., 2021; Numbers and Brodaty, 2021; Suárez-González et al., 2021). Finally, the impact of changes in the mental health status of caregivers on their patients adds to this already novel complicated situation; therefore, a systematic review focusing on the perspective of caregivers has long been needed.

Considering that this pandemic could be long-lasting and that the mental health of caregivers of patients with cognitive decline/dementia has been demonstrated to be at risk regardless of the COVID-19 emergency (De Fazio et al., 2015; Corrêa et al., 2019; Lloyd et al., 2019), there is a need to investigate the real effects of the current emergency on caregivers of patients with dementia to identify and address adequate interventions (Liu et al., 2021).

Our aim was to systematically review the psychological consequences of the COVID-19 lockdown in caregivers of patients with cognitive impairment and dementia and the impact on the health of their patients.

METHODS

Literature Search

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009), a systematic search of the electronic databases MEDLINE/PubMed, Scopus, and Web of Science was performed from inception to August 1, 2021 by entering the following search string: ("COVID-19" OR "coronavirus disease" OR "coronavirus" OR "SARS-CoV-2" OR "novel coronavirus") AND ("caregiver*" OR "relative" OR "Spouse*" OR "Adult Children" OR "Family" OR "Home Nursing" OR "career*" OR "caring" OR "caretaker" OR "home") AND ("dement*" OR "Alzheimer's*" OR "mild cognitive impairment" OR "cognitive impairment" OR "cognitive

Abbreviations: BAI, beck anxiety inventory; BDI, beck depression inventory; COVID-19, coronavirus disease 2019; GAD-7, generalized anxiety disorder 7; HADS, hospital anxiety and depression scale; MCS, mental component summary; MoCA, montreal cognitive assessment; NMSS, non-motor symptoms scale; NPI-Q, neuropsychiatric inventory questionnaire; PCS, physical component summary; PDQ-8, parkinson's disease questionnaire-8; PHQ-9, personal health questionnaire 9; PSS, perceived stress scale; QoL, quality of life; QoL-AD, quality of life in alzheimer's disease; QUIP-RS, questionnaire for impulsive-compulsive disorders in parkinson's disease–rating scale; RMBPC, revised memory and behavior problem checklist; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, zung's self-rating anxiety scale; SDS, zung's self-rating depression scale; SF-8, short form health survey; SWEMWBS, short warwick-edinburgh mental well-being scale; ZBI, zarit burden interview.

dysfunction" OR "neurocognitive impairment" OR "MCI" OR "Mild dementia" OR "Parkinson's").

Two blinded investigators (EC and RF) independently conducted a literature search, title/abstract screening, and full-text review. They also hand-screened the reference list of selected articles in order to search for additional literature. In case of disagreements, a final decision was achieved consulting a third investigator (RR).

Study Selection

Original studies investigating psychological consequences of the COVID-19 lockdown in caregivers of patients with cognitive impairment and dementia and the impact on health of patients were deemed eligible for inclusion, according to the population, intervention, control, and outcomes (PICO) methodology. No time and language limits were used. Articles presenting only an opinion, reviews, letters to the editor, and commentaries were excluded. Studies evaluating only the point of view of patient or caregiver were not deemed eligible for the present review.

Quality Assessment

The two reviewers (EC and RF) used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the quality of the evidence (Guyatt et al., 2011). The quality of evidence was rated as "high," "moderate," "low," or "very low" based on GRADE rating standards. A "high-quality" rating indicates that future research is very unlikely to change existing evidence and that the true effect is similar to the estimated effect; a "moderate-quality" and a "low-quality" rating indicates that future research may change/is likely to change the evaluation results, respectively; a "very low-quality" rating indicates that there is high uncertain about the existing evidence and that the true effect is likely to be substantially different from the estimated effect.

Data Extraction

Two blind researchers (EC and RF) performed data extraction from included papers: first the name of the author, year of publication, study design, study sample, study measures, outcome, comments (limitations), timeline, and level of Grade. The reviewers independently extracted data from each relevant study and all reviewers checked the data for disagreement.

RESULTS

Search Results

The initial search returned 410 records. Among these, 10 were identified as duplicates and were subsequently excluded. The title and abstract screening, based on the assessment of the inclusion/exclusion criteria, was performed for the remaining 400 papers; 315 were excluded because they were irrelevant and 30 because they were reviews, meta-analyses, letters to the editors, editorials, guidelines, or case reports. Then, 55 abstracts/full-text articles were assessed for eligibility: 38 were excluded because they did not simultaneously assess mental health of patients and caregivers. In the end, 17 papers were deemed eligible and included in the present review. The flow chart shows the search strategy (**Figure 1**).

Content Results

The majority of the studies presented a cross-sectional observational qualitative study design. One was a multicentric study (Rainero et al., 2021), and only one study was a controlled non-randomized interventional prospective study (Lai et al., 2020). A great heterogeneity was reported among studies included and there was wide variability in the sample number from $N = 5{,}321$ caregivers and 4,913 patients (Rainero et al., 2021) to 11 carers and four patients (West et al., 2021). Online self-report questionnaires or interviews were conducted remotely by telephone or video call in almost all studies included and applied both to patients and family caregivers. The assessment of participants was performed using Montreal Cognitive Assessment (MoCA), the Revised Memory and Behavior Problem Checklist (RMBPC), and the Quality of Life in Alzheimer's Disease (QoL-AD) (Lai et al., 2020). Zung's depression (SDS) and anxiety (SAS) assessment scales and the Perceived Stress Scale (PSS) (Carpinelli Mazzi et al., 2020), the Short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS), the Generalized Anxiety Disorder 7 (GAD-7), the Personal Health Questionnaire 9 (PHQ-9) (Giebel et al., 2020b), Unified Parkinson's Disease Rating Scale Part II, Non-Motor Symptoms Scale (NMSS), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS), and Parkinson's Disease Questionnaire-8 (PDQ-8). Hospital Anxiety and Depression Scale (HADS) scores were retrieved in patients and caregivers, who also underwent the Zarit Burden Interview (ZBI) (Oppo et al., 2020). HADS was used to assess anxiety and depression. The physical component summary (PCS) and mental component summary (MCS) scores of the short form (SF)-8 were used to evaluate health-related quality of life (QoL) (Suzuki et al., 2021), Neuropsychiatric Inventory Questionnaire (NPI-Q), ZBI, Beck Depression (BDI), and Anxiety (BAI) Inventories (Borelli et al., 2021). All the studies were conducted during the first lockdown, in different countries.

According to the GRADE approach, only one study presented high quality (Rainero et al., 2021) and three a moderate quality (Lai et al., 2020; Giebel et al., 2020b; Macchi et al., 2021), whereas most of the included research showed very low-to-low quality. Cross-sectional study design, not validated scales, self-report measures, and video or telephone interviews were the encountered limitations.

Four studies reported an increased level of anxiety, depression, and insomnia among caregivers, due to mandatory confinement and increased stress but also independently by the dementia stage, but globally those caring for severe cases had more stress compared to milder forms of the disease (Cohen et al., 2020; Rainero et al., 2021; Tsapanou et al., 2021).

Carpinelli Mazzi et al. found that education was a protective factor against anxiety and depression for caregivers, whereas women reported higher anxiety and depression levels (Carpinelli Mazzi et al., 2020). Moreover, Sukuzi et al. evaluated a negative impact of the COVID-19 pandemic on health-related QoL and its

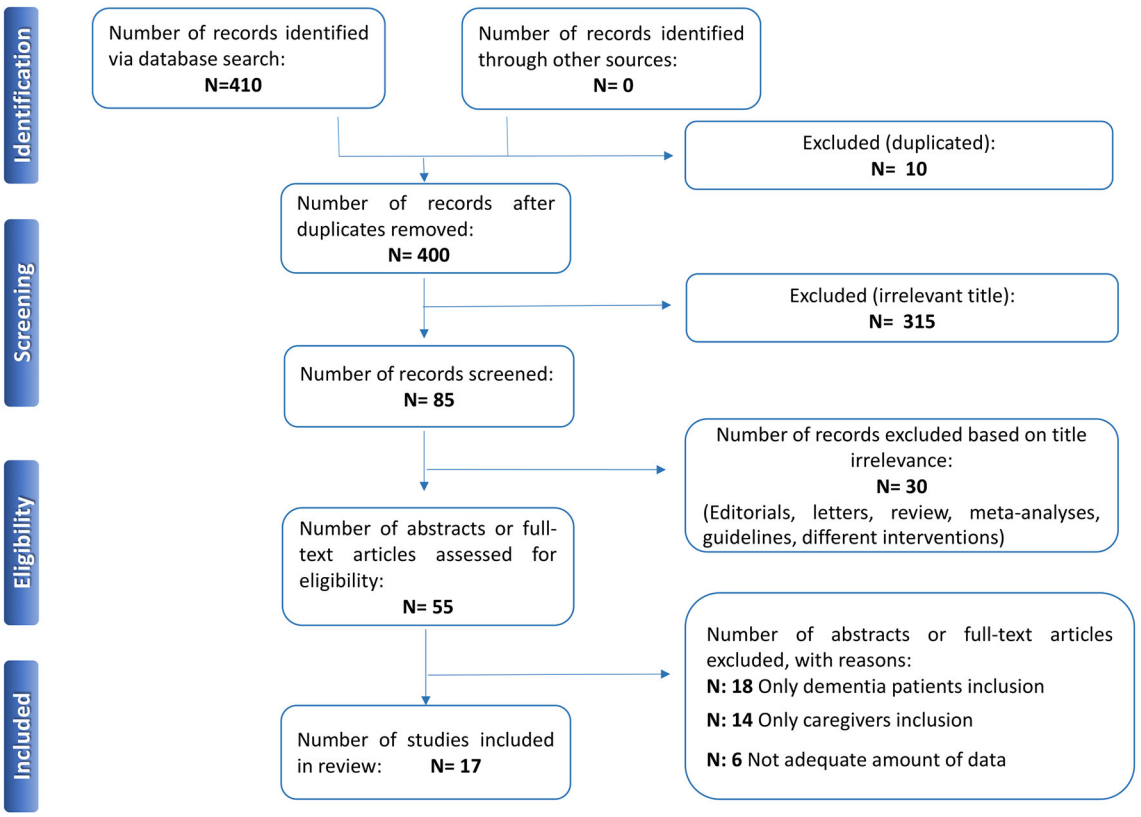

FIGURE 1 | PRISMA flow-chart. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

determinants in Parkinson's patients and their caregivers (Suzuki et al., 2021).

Overall, during COVID-19 confinement, caregivers reported a great increase in their psychological and physical burden, and patients with dementia experienced increased anxiety and an overall decline. The outbreak period led to a marked reduction of access to health services and social support services (Tam et al., 2021). The only positive feature was recorded thanks to the use of technology: telemedicine by videoconference was associated with improved resilience and wellbeing to both people with neurocognitive diseases and their caregivers at home compared to the telephone-only group (Lai et al., 2020) (**Table 1**).

DISCUSSION

This systematic review identified 17 studies that provided dyadic information on psychological symptoms of family caregivers of patients with cognitive impairment or dementia due to different causes and in various stages of dementia living in the community and the effects in these subjects and on the health of patients during the first COVID-19 lockdown.

The United Kingdom (UK) and Italy contributed with the greatest number of studies and patients, respectively. Therefore, despite remaining studies also representing Asian and American populations, and a small UK study aimed to specifically investigate the impact of the COVID-19 pandemic on black, Asian, and minority ethnic populations (West et al., 2021), results are hardly generalizable.

Indeed, data on all minority groups are not available, and socio-economic, cultural, educational, and setting factors should be considered also in studies with a larger sample size. As an example, in the largest study included in this review (Rainero et al., 2021), caregivers of patients with dementia reported a significant increase in anxiety, depression, irritability, distress, and an overall clinical worsening of their loved ones, although these results cannot be referred to caregivers of institutionalized patients.

Moreover, as in most studies included, no validated scales were used to measure psychological symptoms. In other studies, although they were used, the scales administered had not been previously validated either in the translated version or to be used as telephone interviews (Carpinelli Mazzi et al., 2020). Suzuki et al. used stepwise linear regression analysis to identify key predictors of health-related QoL after having administered validated scales for anxiety, depression, and QoL (Suzuki et al., 2021). This study, limited by the retrospective nature, showed a negative impact of depression, stress, and worsening patient mood on mental aspects of the health-related QoL in caregivers/spouses of patients with Parkinson's disease (Suzuki et al., 2021). Validated outcome measures were also used to describe an association between the worsening of cognition in patients with dementia and the increasing burden and distress

TABLE 1 | The main characteristics of included studies in the review.

Author, year	Study design	Study sample	Measures	Outcome	Comments	Timeline	Grade

Cohen et al. (2020)	Cross-sectional non-interventional study	80 family caregivers of AD or related dementia patients	Online questionnaire based on a visual analog scale to test burden	- Family was the primary provider of care in 65%
				- COVID-19 confinement increased caregiver's stress independently of the dementia stage, but those caring for severe cases had more stress compared to milder forms of the disease
				- 50% patients with dementia experienced increased anxiety
				- Most family members discontinued all sort of cognitive and physical therapies
				- Family members' main concerns:
				  - Severe dementia case: fear of absence of the paid caregiver during the epidemic
				  - Mild dementia cases: fear of spreading the disease while assisting patients
					Limitations:
					- Small sample size
					- *p*-values not adjusted for multiple comparisons
					- Possible high rates of type I error
					- No validated instruments to measure burden of care or anxiety
						Argentine—April 2020—first lockdown	*

Tsapanou et al. (2021)	Cross-sectional non-interventional study	204 caregivers of people with MCI or dementia	Self-reported questionnaire for caregivers regarding the status of patients and their own. Domains: changes in physical, psychological and routine activities with possible answers: "not at all," "some" and "a lot"	- Significant overall decline of the people with MCI/dementia - Main decline in: communication, mood, movement, and compliance with the new measures - Caregivers reported a great increase in their psychological and physical burden	Limitations: - Self-reported measure, small sample size - Short period of time for the results reported - Results might be affected by the caregiver's increased workload Strengths: - First study regarding elder Mediterranean population including specific questions about the patients with mci/dementia and their caregivers	Greece, Feb-June 2020—first lockdown	**
Lai et al. (2020)	Controlled not randomized interventional prospective study	60 dyads of elderly NCD patient-caregiver recruited through an activity center	Neurocognitive functioning, behavioral and psychological problems, and QoL were assessed in the care-recipient with NCD by MoCA, RMBPC, and QoL-AD	- Telemedicine by video conference was associated with improved resilience and wellbeing to both people with NCD and their caregivers at home compared to the telephone-only group	Limitations: - No head-to-head comparison between video conferences and phone calls with matching contact time - The switch from phone calls to video conference likely had affected the content, style, and manner of the delivery by the health care providers, and these should have been recorded and subjected to analysis to isolate potential mediator variables	Hong-Kong—March-May 2020—first lockdown	***

(Continued)

TABLE 1 | Continued

Author, year	Study design	Study sample	Measures	Outcome	Comments	Timeline	Grade
Carpinelli Mazzi et al. (2020)	Cross-sectional observational study	239 caregivers of patients with dementia	SDS, SAS, and PSS by telephone interview or online self-compilation	- Education was a protective factor against anxiety and depression for caregivers - Length of isolation was associated with the higher SAS and SDS scores. - Women reported higher SAS and SDS mean scores than men - A marked reduction of health services was observed in all patients	Limitations: - SAS not validated in Italian language - No validation of any of the measures for telephone interviews	Italy, first lockdown	**
Giebel et al. (2020a)	Cross-sectional observational qualitative study	Unpaid carers ($n = 42$) and PLWD ($n = 8$)	The semi-structured interviews were conducted using a topic guide, containing questions about the participant's service use before and after the COVID-19 outbreak and governmental restrictions	- A significant reduction in social support service usage since the outbreak emerged - Thematic analysis identified three overarching themes: loss of control, uncertainty, and adapting and having to adapt to the new normal - Carers and PLWD were greatly affected by the sudden removal of social support services, and concerned about when services would re-open - Carers worried about whether the person they cared for would still be able to re-join social support services	Limitations: - Sample size heterogeneity and number; not validated assessment	UK—April 2020—first lockdown	*
Giebel et al. (2020b)	Cross-sectional observational qualitative study	569 participants completed the survey (61 people with dementia, 285 unpaid carers, and 223 older adults)	SWEMWBS, GAD-7, PHQ-9	- Higher variations in social support service hours significantly predicted increased levels of anxiety in people with dementia and older adults, and lower levels of mental well-being in unpaid carers and older adults	Limitations: - Sample size heterogeneity and number - Patient enrollment procedure	UK—April-May 2020—first lockdown	***
Oppo et al. (2020)	Cross-sectional observational qualitative study	32 patients with PD/caregiver dyads	- Patients: UPDRS, NMSS QUIP-RS, and pDQ-8 - Carers: ZBI - Patients and carers: HADS and verbal rating scale (0–6) to measure changes in stress levels	- Patients experiencing increased stress level during lockdown had worse NMSS and HADS scores - Worse NMSS in patients associated to higher stress among carers - UPDRS-II score not associated with higher stress levels in patients/carers - Patients with increased stress had significant worse mood/cognition score of NMSS	Limitation: - Small sample size and the use of telephone interviews - Use of a non-validated outcome measure (verbal rating scale)	Italy—not provided 2020—first lockdown	**

(Continued)

TABLE 1 | Continued

Author, year	Study design	Study sample	Measures	Outcome	Comments	Timeline	Grade
Rainero et al. (2021)	Cross-sectional observational qualitative multicentric study	- 5,321 caregivers of patients regularly followed - 4,913 patients with dementia (3372 AD; 360 DLB; 415 FTD; 766 VD)	- Semi-structured, self-made interview gathering demographic and clinical data from patient and caregiver - CDR	- According to family caregivers, social isolation, and physical restraint caused a worsening in cognitive function (55% of patients, mainly DLB and AD), an aggravation of several behavioral symptoms (52% patients), and a worsening in motor function (37% patients) and onset of new symptoms (26% patients) - Caregivers reported a high increase in anxiety, depression, distress, and burden	Limitation: - Data only regard patients with dementia living at home (data cannot be generalized to institutionalized patients) - Cross-sectional study - Not possible to administer face-to-face standardized neuropsychological - Tests	Italy—April 2020—first lockdown	****
West et al. (2021)	Cross-sectional observational qualitative study	15 participants: 11 family carers and four persons living with dementia	Semistructured qualitative interviews conducted remotely over telephone or via secure video technologies	- Eight key themes, with subthemes: fear and anxiety, food and eating (encompassing food shopping and eating patterns), isolation and identity, community and social relationships, adapting to COVID-19, social isolation and support structures, and medical interactions - Fear and anxiety formed an overarching theme that encompassed all others	Limitation: - Study focused on south Asian and afro-Caribbean groups and views may not be generalizable to other minority groups. Strengths: - Study of BAME communities, including persons with dementia and their carers - Analysis performed by a different group - Analysis with an iterative constructivist approach and thematically codification	UK—May 2020—first lockdown	*
Tuijt et al. (2021)	Cross-sectional observational qualitative study	30 people with dementia living in their own homes and 31 family carers	Interviewed via video or telephone call	- Five main themes: awareness of restrictions, restructuring caring relationships to manage COVID-19 risk, protective factors, the psychological and cognitive impact of restrictions, and the importance of social engagement - People living with dementia often had a basic understanding of COVID-19 restrictions but could have difficulty translating this into personalized risk-appraisal of their own actions - Patients reported negative psychological and cognitive effects due to the imposed restrictions (e.g., increased apathy, irritability, or anxiety) fuelled by lack of social engagement	Limitation: - Difficulty communicating through telephone or video calls	UK—March-July-2020—first lockdown	**

(Continued)

TABLE 1 | Continued

Author, year	Study design	Study sample	Measures	Outcome	Comments	Timeline	Grade
Suzuki et al. (2021)	Cross-sectional observational qualitative study	100 patients with PD and their caregivers/spouses	HADS and SF-8	The study reveals the negative Impact of the COVID-19 pandemic on health-related QoL and its determinants in PD patients and their caregivers	Limitation: - Retrospective questionnaire-based - Changes in motor symptoms after the outbreak of COVID-19 were not assessed by means of clinical examination by neurologists	Japan, June and December 2020—first lockdown	**
Azevedo et al. (2021)	Cross-sectional observational qualitative study	321 dyadic interviews were conducted to patients and caregivers	Two semi-structured questionnaires via telephone to family caregivers of people diagnosed with dementia	- Significant decline in memory function among 53% of people with dementia - 31% of individuals with dementia felt sadder and 37% increased anxiety symptoms. Symptoms of anxiety were greater in individuals with mild to moderate dementia; symptoms of agitation were greater in individuals with severe dementia - Compulsive-obsessive behavior, hallucinations, increased forgetfulness, altered appetite, and increased difficulty in activities of daily living were reported more frequently among individuals with moderate to severe dementia - Caregivers reported feeling more tired and overwhelmed and these symptoms were also influenced by the severity of dementia	Limitation: - Interviews carried out by telephone - Countries experiencing different moments of the pandemic	Argentine, Brazil, Chile—May to July 2020—first lockdown	**

Tuijt et al. (2021)	Cross-sectional observational qualitative study	30 patients living with dementia and 31 carers	Semi-structured interviews with a background in psychology and dementia conducted remotely by telephone or video call	- The following three themes were identified:
				  - Proactive care at the onset of COVID-19 restrictions
				  - Avoidance of healthcare settings and services
				- Difficulties with encounters
				- People living with dementia and their carers felt check-up calls were reassuring but limited in scope and content. Some avoided healthcare services, wishing to minimize COVID-19 risk or reduce NHS burden, or encountering technological barriers
				- Difficulties in remote consultations included lack of prompts to remember problems, dealing with new emerging difficulties, rescheduling/missed calls, and inclusion of the voice of the person with dementia
					Limitations:
					- Sample size
					- The median year of diagnosis (2019) was relatively recent
						UK, May-August 2020—first lockdown	*

(Continued)

TABLE 1 | Continued

Author, year	Study design	Study sample	Measures	Outcome	Comments	Timeline	Grade
Macchi et al. (2021)	Multicenter, clinical trial of community-based	108 patients with PD, AD or related disorders and 90 caregivers	Semi-structured interviews, open-ended survey responses, medical record documentation, and participant-researcher communications	- Four main themes emerged: disruptions to delivery of healthcare and other supportive services; increased symptomatic and psychosocial needs; increased caregiver burden; and limitations of telecommunications when compared to in-person contact These themes interacted and intersected	Limitation: - Cohort lacks diversity regarding race, ethnicity, and was highly educateds	USA, March-August 2020—first lockdown	***
Hanna et al. (2021)	Cross-sectional observational qualitative study	4 PLWD and 16 unpaid carers	Semi-structured, follow-up telephone interviews	- Three primary themes emerged: impact on mental health during lockdown; changes to mental health following easing of public health; and the long-term effect of public health measures - The loss of social support services was key in impacting this cohort mentally and emotionally, displaying a need for better psychological support, for both carers and PLWD	Limitation: - Sample size and few people from BAME background - Interviews could not be conducted face-to-face	UK, June-July 2020—first lockdown	*
Borelli et al. (2021)	Cross-sectional observational qualitative study	58 patients and caregivers	A structured telephone interview with NPI-Q, ZBI, BDI and BAI	- Frequent patients' neuropsychiatric worsening and caregiver burden - Worsening of cognition was associated with increased caregivers' psychological distress	Limitations: - Cross sectional design of the study - Lack of previous caregiver scores in the scales may overestimate the pandemic's impact	Brazil, May-July 2020—first lockdown	**
Tam et al. (2021)	Cross-sectional observational qualitative study	395 care partners and 22 individuals with lived experiences of dementia	Survey	- Care partners reported a number of serious concerns, including the inability to visit the person that they care for in long-term or palliative care - The pandemic increased their levels of stress overall and felt lonelier and more isolated than they did before the pandemic - The use of technology was reported as a way to connect socially with their loved ones, with the majority of participants connecting with others at least twice per week	Limitations: - Cross sectional study design	Canada, June-August 2020—first lockdown	**

AD, Alzheimer's disease; BAME, Black, asian and minority ethnic; BPSD, Behavioral and psychological symptoms of dementia; CDR, Clinical dementia rating; DLB, Dementia with lewy bodies; FTD, Frontotemporal dementia; MCI, Mild cognitive impairment; MoCA, Montreal cognitive assessment; NCD, Neurocognitive decline; NMSS, Non-motor symptoms scale; PD, Parkinson's disease; PDQ-8, Parkinson's disease questionnaire-8, PLWD, Person living with dementia; PSS, Perceived stress scale; QoL, Quality of life; qol-ad, Quality of life in alzheimer's disease; QUIPRS, Questionnaire for impulsive-compulsive disorders in parkinson's disease–rating scale; RMBPC, Revised memory and behavior problem checklist; SAS, Zung's self-rating anxiety scale; SDS, Zung's self-rating depression scale; SWEMWBS, Short warwick-edinburgh mental well-being scale; UPDRS, Unified parkinson's disease rating scale; VD, Vascular dementia; ZBI, Zarit burden interview.

*Grade score: *Very low quality, **Low quality, ***Moderate quality, ****High quality.*

in their caregivers (Borelli et al., 2021), as well as anxiety and worsened QoL associated with the inability to access social support services (Giebel et al., 2020b).

On the other hand, additional information emerged from semi-structured qualitative interviews and open-ended surveys, showing the perspective of caregivers, their feelings, and main concerns, which might suggest potential areas of intervention to address unmet social and healthcare needs.

During this social distancing period, approximately half of the family caregivers felt more tired, overwhelmed, and nervous, and more than a third felt sadder and more irritable (Azevedo et al., 2021). Furthermore, the dementia severity affected the burden experience that was perceived as greater in carers of people with severe dementia (Cohen et al., 2020; Azevedo et al., 2021). In these patients, agitation, cognitive, and behavioral symptoms were greater or more common compared with individuals with mild-to-moderate dementia (Azevedo et al., 2021). Moreover, caregivers of patients with mild cognitive impairment or dementia referred to an increase of their own burden together with a significant decline of overall patients, although a self-reported questionnaire was used and statistical association measures were not performed between these two variables (Tsapanou et al., 2021).

Feelings of stress attempting to take care of their loved ones and the negative impact on the mental and emotional wellbeing of the loss of social support services were also reported in small sample size studies, suggesting the need for better psychological support (Hanna et al., 2021). Care partners felt less able to manage their own wellbeing and reported burnout and worries about both their increasing workload and the infection risk of patients with dementia (Tam et al., 2021). They were also concerned about the faster deterioration of their relatives, which is partly real (social isolation and physical restraint worsen cognitive and motor function), partly biased by the overload, and a heightened awareness assessing health needs (Canevelli et al., 2020; Tuijt et al., 2021).

Additionally, the negative impact of restrictive measures on the autonomy of patients with dementia and on all aspects of caregivers' lives increased pressure on caring relationships (Tuijt et al., 2021).

One of the few moderate quality studies according to the GRADE approach provided a person-centered description of the impact of the COVID-19 pandemic, whose results can be considered an exhaustive overview of the main themes that also emerged from other semi-structured interviews and open-ended surveys (Macchi et al., 2021). Besides the increased caregiver strain, disruption to the delivery of healthcare and supportive services was deeply perceived. This latter included cancellations of routine appointments and elective procedures, loss of ambulatory services and home health aides, and avoidance of assisted living facilities to avoid contagion. Moreover, increased symptomatic and psychosocial needs, as well as the indispensable role of in-person contact and support emerged (Macchi et al., 2021). Routinely used social support services and facilities are known to improve wellbeing and quality of life of dementia patients (Greenberg et al., 2020). The limited access/suspension of essential services due to COVID-19 contributed to worsening psychological symptoms and quality of life, especially for patients with more routine social activity outside the home before the pandemic (Tuijt et al., 2021).

Along with dementia severity, type of symptoms (especially neuropsychiatric and autonomic, such as sleep disturbances) and prolonged time of isolation may have impacted stress level, anxiety, and depression of caregivers (Carpinelli Mazzi et al., 2020; Oppo et al., 2020). These were higher in female caregivers compared with males (Carpinelli Mazzi et al., 2020). Women represented the majority of caregivers (up to 80% of the carers population) (Azevedo et al., 2021), as confirmed in epidemiological data (Alzheimer's Society, 2020); socio-economic, health, and psychosocial factors contribute to gender differences in psychological wellbeing (Kiely et al., 2019). As an example, the educational level of carers seemed to represent a protective factor (Carpinelli Mazzi et al., 2020).

In addition to potential protective factors, literature evidenced many strategies to relieve stress of caregivers, such as avoiding isolation, sharing the burden of care with other family members, and support networks (Hughes et al., 2014). Indeed, in ethnic minorities in which more established familial care structures existed, changes to living arrangements due to COVID-19 did not increase the pressure of carers, although a likely greater difficulty in accessing support services emerged (Tuijt et al., 2021).

However, these findings should be interpreted bearing in mind the very low to low quality of evidence of the majority of the studies included and a large number of limitations.

Although the studies' selection ensured a specific dyadic evaluation of patients and caregivers, which allowed, on the one hand, a deeper comprehension of both settings and mutuality of the care relationship and on the other a reduction of heterogeneity of studies, this latter still remains, as well as a wide variability in the sample number. Contrariwise, the lack of variability of the sample in terms of represented populations negatively affects generalization of the findings.

Besides these issues and no validated outcome measures, qualitative research and self-reported data through video or telephone interviews affected the quality of the results. Indeed, the interviews may have been influenced by the emotional state of the caregivers on the day of the survey, and by the role and position of the researcher who conducted the interviews, communication, and connection difficulties (Bauhoff, 2011). Furthermore, video or telephone interviews are clearly compromised by a selection bias, under-representing people with difficulties accessing technologies. Finally, almost all the papers included in this review had a cross-sectional design, which does not allow for comparison with baseline data (i.e., before the COVID-19 period). Therefore, it is impossible to quantify the overall increase in psychological and physical burden of caregivers emerging from studies. Independently from the pandemic, caring for patients with dementia is a complex task associated with significant burden and distress, which increase as the disease progresses and cognitive, behavioral, and motor symptoms worsen (Chiao et al., 2015; Sutcliffe et al., 2017; Black et al., 2018). Thus, it would be useful to compare results at different time points and observe the effects of isolation and social distancing over time. The only prospective study included showed the positive impact of supplementary telehealth delivered via video-conferencing apps compared with phone calls alone

(Lai et al., 2020). Remote support to examine patients has been validated in several studies (Roy et al., 2021) although a general reluctance among practitioners to implement alternatives to face-to-face consultations was reported (Brant et al., 2016), and patients and caregivers did not perceive it as a substitute for in-person services (Macchi et al., 2021; Tam et al., 2021). Video conferences may overcome these limitations capturing some typical aspects of the face-to-face interaction, suggesting that improving remote support and using communication technologies could represent a new way through which health and social support services can aid. To date, telemedicine is not widely applicable yet: a large number of people do not have access to this resource or the ability to use them.

CONCLUSIONS

Despite the very low-to-low quality of evidence and several methodological limitations of some studies included in this review (not allowing a sound estimation of our aim), results suggest a great increase in psychological and physical burden of caregivers during COVID-19 confinement and an overall worsening of clinical conditions of patients. This analysis indicates that the perceived burden in caregivers increased independently from the severity of their relatives' disease, albeit it was apparently higher for those caring for severe cases compared with milder. Furthermore, gender represents a risk factor and supporting strategies, such as telemedicine, likely improve outcomes of caregivers and patients.

Restrictive measures led to a marked reduction of health and social support services, which added new burdens and/or intensified pre-existing ones. Better psychological support and new healthcare strategies, such as the implementation of telemedicine and digital communications (addressing technological barriers), are needed to provide assistance, ensure a supportive network, and relieve the stress of caregivers.

Further high-quality studies are necessary, and prospective data will help to monitor any change in social and health needs in patients and carers. Moreover, data on heterogeneous samples for ethnicity, cultural and socio-economic conditions, and kind of care relationships should be encouraged to meet specific needs and direct healthcare resources throughout the pandemic.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

PDF ideated the manuscript. EAC and RdF conducted the literature search and data analysis. EAC, RdF, RR, MR, LD, ER, GDS, CS-G, and PDF contributed to writing the original draft and to its reviewing and editing. All authors contributed to the article and approved the submitted version.

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The Impact of Dementia's Affiliate Stigma on the Mental Health of Relatives: A Cross Section Survey

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Objective: To determine the impact of the affiliate stigma on mental well-being of relatives caring for a person with dementia.

Design: The study was conducted in a cross sectional design.

Setting: The study was conducted in a public setting, addressing relatives caring for a person with dementia.

Participants: Participants were relatives of patients with a formal diagnosis of dementia. Relatives were defined as caring or living closely to a patient. Participants were recruited with the help of care and welfare organizations.

Outcome Measures: The main outcome measure was the impact of the affiliate stigma on mental well-being of caring relatives.

Results: 228 participants fully completed the survey. Women, relatives with a higher education and partners experienced more impact of the affiliate stigma on mental well-being than man, relatives with a lower education and relatives with another relationship to the person with dementia (resp. F-ratio = 15.67; $p = 0.0001$; F-ratio = 2.5865; $p = 0.0381$; F-ratio = 3.1131; $p = 0.0099$). The duration of dementia and the age of the caregiver had a clear significant effect on affiliate stigma (F-ratio = 4.9104; $p = 0.0083$) (F-ratio = 6.5515, $p = 0.0112$).

Conclusion: This study revealed that caregiver related features are predicting the presence of an affiliate stigma. Interventions to prevent or reduce the impact of this stigma might focus on these groups. Education about dementia and the impact on patients, relatives and the broader social context might alter the affiliate stigma surrounding dementia.

Keywords: dementia, family care, mental health, primary care, taboo

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INTRODUCTION

Dementia is the collective name given to a group of symptoms that indicates a significant decline in a person's level of cognitive functioning. This syndrome has a global prevalence of about 7% in the population aged 65 years or older (Prince et al., 2013). Currently, more than 48 million people suffer from dementia worldwide. Without effective treatment, the World Health Organization estimates that this prevalence will continue to rise to 131 million people by 2050 (Alzheimer, 2016; Gale et al., 2018; Wolters and Ikram, 2018).

In addition to the decline in cognitive functioning, persons with dementia also experience a significant loss in social, occupational and/or domestic functioning. This makes them dependent on persons in their environment to carry out daily activities. This dependence puts a great physical, emotional and financial burden on the relatives of persons with dementia (Schoenmakers et al., 2010a; Chow et al., 2018). The assumptions made in our society about persons with dementia are often based on stereotypes. This stereotypical presentation is influenced by the later stages of the syndrome, where the person with dementia is fully care dependent (Van Gorp and Vercruysse, 2012). The result of these negative assumptions is that self-stigmatization occurs in both persons with dementia and their relatives, which can cause them feeling insecure in their dealing with the person with dementia (Greenwood et al., 2018; Jeong et al., 2020; Rewerska-Juśko and Rejdak, 2020). In certain cases, stigma negatively influences the opportunities of a timely diagnosis of dementia (Dubois et al., 2016). The affiliation stigma appears relatively independently of the type of dementia and seems rather related to other features and characteristics of patients, caregivers and community (Greenwood et al., 2018; Rewerska-Juśko and Rejdak, 2020).

In 2008, the WHO released a report defining the concept of stigma. With stigma, a distinction is made between the person who is stigmatized and others who attribute negative characteristics to the stigmatized person. In the event that stigma is present in the context of mental illness, it often results in social exclusion and discrimination, which in turn creates an additional emotional burden (Europe WHOROF, 2008). In addition to the emotional burden present in the stigmatized individual, several studies report that the family caregivers and relatives of individuals with mental illness also often experience stigma. This form of stigma present among family caregivers and relatives has been described as "courtesy stigma" or "associative stigma" (Goffman, 1963; Mehta and Farina, 1988). These terms point to the discrimination and prejudice that people may experience because they are associated with individuals who belong to a stigmatized group. In addition to "courtesy stigma," other studies focused on the internalization of stigma that lives among family caregivers and relatives of individuals with mental illness. This internalization was described as "affiliate stigma." The term "affiliate stigma" refers to the negative feelings that relatives of stigmatized individuals develop toward themselves, because they perceive the associative stigma that prevails in society. These negative feelings can cause attitude changes toward the person with dementia. Making less contact with the person with dementia, concealing the association with them from the public or generally less engaging in social contact are some examples (Mak and Cheung, 2008).

To date, only a limited number of studies have investigated the affiliate stigma associated with dementia. The purpose of this study is to identify the affiliate stigma present among the relatives of individuals with dementia and its effect on their mental well-being.

METHODS

Design

This study examined the relationship between the affiliate stigma experienced by relatives of persons with dementia and the impact on their mental health well-being.

Data for this study were collected cross-sectionally over a 4-month period from August 2020 to November 2020. All participants were informed of the anonymity of the data handling and the purpose of the study prior to starting the survey.

Setting and Participants

Survey participants were relatives of patients with a formal diagnosis of dementia (diagnosed by a physician). No further specification of type or stage of dementia was required since caregiver and contextual characteristics are single predictors of care burden and affiliate stigma (Schoenmakers et al., 2010a; Rewerska-Juśko and Rejdak, 2020). Relatives were defined as caring or living closely to a patient without restriction in time spent caring or relationship with the care receiver (self-appointed carer). Participants were recruited with the help of care and welfare organizations. Participants who did not have a close relative with dementia, formal or professional caregivers and participants who did not complete the survey were excluded from the study or from further data analysis.

To calculate the sample size we started from a convenience sample of 500 participants to achieve a confidence interval between 1.5 and 2.5 for the score on mental well-being. The desired sample consisted of 217 participants.

Collection of Data

The survey was presented on a secured platform (server of the university KU Leuven) using Qualtrics Software. Study data were collected anonymously *via* a survey distributed through social media with a special focus on communities of family caregivers, relatives, and acquaintances of persons with dementia. The Expertise Centre Dementia Flanders was involved in the recruitment process. In addition, the survey was also shared through the site of a home nursing group that cares for patients with dementia and their relatives. Before starting the survey, the purpose of the study was explained. Surveys that were not completed in full were excluded from further processing.

The survey consisted of three parts: the first part contained questions about the background features of the participants (age, gender, and highest education degree), their relationship with the person with dementia, and how long ago the patient was diagnosed with dementia.

The questions in the second part of the survey were taken from the Affiliate Stigma Scale (ASS) (Mak and Cheung, 2008). The Affiliate Stigma Scale was originally developed to gauge the self-stigmatization that occurs among family caregivers, relatives, or acquaintances of patients with mental illness. The term "mental illness" was replaced with "dementia" in the Affiliate Stigma Scale. The scale consists of 22 questions that test for the internalization of stigma present in relatives. The scale addresses the cognitive, affective, and behavioral domain. The cognitive and the affective

component contain 7 items and the behavioral component contains eight items. Participants answered all 22 items using a 4-point Likert scale ranging from "1 = Totally disagree" to "4 = Totally agree." From these 22 items, the mean affiliate stigma score was calculated, which was a measure of reported stigma. The higher the mean score on the Affiliate Stigma Scale, the higher the internalized stigma. There is no cut off score.

The third section of the survey mapped the mental well-being of the participating relatives. This survey was composed based upon items from the Patient Health Questionnaire-9 and the 20-item Center for Epidemiologic Studies Depression Screening (Williams et al., 1999; Siu et al., 2016). Ten indicators of perceived mental well-being were included in the survey: helpless, failed, ashamed, concentration troubles, sleeping troubles, tiredness (little energy), less appetite, sadness, anxiety, anger. Answer options were distributed on a 4-point Likert scale ranging from "1 = Never" to "4 = Always." A mean score was calculated from the values reported on these ten items and named the "mood score" in further analysis. The higher this mean score, the lower the mental well-being. There was no cut off score.

Data Analysis

The collected data were processed via Excel for descriptive analyses and from there imported into SAS9.4 for multivariate analyses using the General Linear Model procedure (GLM) with estimated effects.

The hypothesis assumed a significant effect of the affiliate stigma reported by the relatives of persons with dementia on their mental well-being (mood-score). The GLM-procedure was used to calculate the effect (by the estimated effect measure) of the affiliate stigma on mental well-being including all background features (independent variables). Second, the impact of the background features on affiliate stigma was analyzed, also by GLM-procedure (F-distribution).

Ethical Consideration

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 (Puri et al., 2009). All procedures involving human subjects/patients were approved by the Medical Ethical Board of the University Hospitals of Leuven under the number MP015226 (May 2019) prior to data collection. Participants were comprehensively informed about the study and explicitly agreed to participate. By a simple opting out button, participants could withdraw from further participation.

Patient and Public Involvement

There was no patient or public involvement in the conception or dissemination of this study.

RESULTS

Over a 4-month period, 504 relatives started the survey. During data processing, 40 participants were excluded because they did not have a relative with dementia. In addition, another 236 participants were excluded due to early termination of the survey. 228 participants were included in the final data analysis.

TABLE 1 | Background features of the participants.

Feature	Number	%
Demographic features *n* = 228		
Age in years	42.92 (average)	Stand dev (15.75)
Sex		
Male	35	15.35%
Female	193	84.65%
Education degree		
No degree	5	2.19%
Highschool	70	30.70%
Bachelor	114	50.00%
Master	35	15.35%
PhD	4	1.75%
Relation to the patient		
Partner	14	6.14%
Sibling	7	3.07%
Parent	97	42.54%
Grandparent	73	32.02%
Aunt/uncle	8	3.51%
Friend/neighbor	24	10.53%
No data	5	2.19%
Time since diagnosis		
< 6 months	8	3.51%
6 months to 1 year	19	8.33%
> 1 year	199	87.28%
No data	2	0.88%

The mean age of the participants was 42.92 years, with a standard deviation (SD) of 15.75 years (**Table 1**). Most of the participants were women (193, 84.65%). Half of the participants earned a bachelor's degree (114, 50.00%) and about one-third earned a high school diploma (70, 30.70%). For the majority of those who completed the survey, the nearest person with dementia was a parent (97, 42.54%) or grandparent (73, 32.02%). Dementia was diagnosed more than 1 year ago in the majority of cases (199, 87.28%) (**Table 1**).

The mean affiliate stigma score of the participants was 1.63 [95% CI (1.57, 1.70)]. The mean mood-score of participants was 1.83 [95% CI (1.76, 1.89)]. The estimated effect of the affiliate stigma score on mental well-being, considering account age, gender, degree, relationship with the patient and duration of dementia was 0.66 [95% CI (0.55, 0.76), $p < 0.001$] (**Table 2**).

There was a significantly different impact of affiliate stigma on mental well-being between men and women (F-ratio = 15.67; $p < 0.001$) where women experienced a higher impact [0.26, 95% CI (0.13, 0.39), $p < 0.001$]. Education also predicted the impact of affiliate stigma on mental well-being (F-ratio = 2.58; $p = 0.038$). There was a significant difference between individuals who did not obtain a DIPLOMA and those with a high school diploma

TABLE 2 | Impact of affiliate stigma score on mental well-being, adjusted for age, gender, diploma, relationship with the person with dementia and time since diagnosis.

Term	Estimate	Std error	t ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	0.8655918	0.262209	3.30	0.0011*	0.3485889	1.3825947
Affiliate Stigma Score mean	0.65527	0.051272	12.78	<0.0001*	0.5541761	0.756364
Age	0.0007379	0.002343	0.31	0.7531	−0.003882	0.0053576
Sex (M)	−0.261222	0.065981	−3.96	0.0001*	−0.391318	−0.131126
Degree (Bachelor diploma)	0.1786387	0.164229	1.09	0.2780	−0.145175	0.5024525
Degree (PhD)	0.2081076	0.239022	0.87	0.3850	−0.263176	0.679391
Degree (Master diploma)	0.20349	0.172063	1.18	0.2383	−0.135769	0.542749
Degree (highschool)	0.3304696	0.164059	2.01	0.0453	0.0069919	0.6539474
Relation (sibling)	−0.341489	0.164282	−2.08	0.0389	−0.665407	−0.01757
Relation (grandparents)	−0.357473	0.130205	−2.75	0.0066	−0.614201	−0.100745
Relation (parent)	−0.318028	0.104772	−3.04	0.0027	−0.524608	−0.111447
Relation (aunt/uncle)	−0.600482	0.159235	−3.77	0.0002*	−0.914449	−0.286515
Relation (Friend/neighbor)	−0.346818	0.128372	−2.70	0.0075	−0.599932	−0.093704
Time since diagnosis (<6 months)	−0.037392	0.128639	−0.29	0.7716	−0.291032	0.2162485
Time since diagnosis (1 year−6 months)	0.0206053	0.088116	0.23	0.8153	−0.153134	0.1943451

N = 228.
$^{*}p < 0.01$.
Estimated effect as contrast with: Sex: female.
Education degree: no degree.
Relationship: partners.
Time since diagnosis: > 1 year.

TABLE 3 | Distribution of background features for affiliate stigma.

Source	Nparm	DF	Sum of squares	F ratio	Prob > F
Age	1	1	1.4436932	6.5515	0.0112
Sex	1	1	0.0535956	0.2432	0.6224
Degree	4	4	1.6324794	1.8521	0.1203
Relation	5	5	2.4800308	2.2509	0.0507
Time since diagnosis	2	2	2.1641102	4.9104	0.0083*

N = 228.
$^{*}p < 0.01$.
Nparm, non-parametric test for multivariate data; DF, degrees of freedom.

experiencing less impact of [0.33, 95% CI (0.001, 0.65)] ($p = 0.045$) (**Table 2**).

The relationship between participants and the person with dementia affected the impact of affiliate stigma on mental well-being (F-ratio = 3.1131; $p = 0.01$). The partners experienced the largest impact of affiliate stigma on mental well-being as compared to all other relationships {mean mood score of 2.01 [95% CI (1.77, 2.25)]}. This impact significantly differs from the children's mean mood score of 1.69 [95% CI (1.54, 1.84), $p = 0.00$]. The aunts and uncles of persons with dementia experienced the lowest impact of affiliate stigma on their mental well-being and presented with a mean mood score of 1.41 [95% CI (1.14, 1.68)], with an estimated difference of 0.60 [95% CI (0.29, 0.91)] as compared to the partners ($p = 0.0002$) (**Tables 2**, **3**).

The impact of the demographic factors on the affiliate stigma score was analyzed secondarily. The relationship with the patient was a nearly significant predictor of the affiliate stigma (F-ratio = 2.251; $p = 0.051$) (**Table 3**). This analysis showed that the duration of dementia and the age of the care had a significant effect on affiliate stigma (F-ratio = 4.910; $p = 0.008$) (F-ratio = 6.5515, $p = 0.011$). Relatives of patients who had received the formal diagnosis of dementia for more than 1 year, presented with a mean affiliate stigma score of 1.65 [95% CI (1.48,1.82)], which was significantly higher {0.51 [95% CI (0.17, 0.85)]} than in relatives of patients who received the diagnosis less than 6 months ago ($p = 0.0033$). Older caregivers seemed also suffering more form affiliate stigma than their younger colleagues do [−0.08, 95%CI (−0.001 to 0.014)] (**Table 4**).

DISCUSSION

Literature investigating affiliate stigma in the context of dementia is limited to date. This research shows that the affiliate stigma surrounding dementia negatively affects the mental well-being of close relatives. Female caregivers and partners are particularly affected. Furthermore, from this study, it appears that the longer the diagnosis of dementia exists and the older the caregiver, the higher the experience of the affiliate stigma.

Prior studies to date focused on the affiliate stigma in family caregivers of persons with dementia, whereas this study has also included other relatives. Caregivers who appoint themselves as a caregiver are considered as formal caregivers independently of their relationship with the care receiver or the time spent caring (Schoenmakers et al., 2010a, 2011).

This study shows that the impact of the affiliate stigma on mental well-being is higher in female relatives, which is in line with the findings in previous research (Kahn et al., 2016). More women than men take up the role of family

TABLE 4 | Impact of the demographic factors on the affiliate stigma score.

Term	Estimate	Std error	t ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	1.350816	0.239517	5.64	<0.0001*	0.8785706	1.8230614
Age	−0.008061	0.003149	−2.56	0.0112*	−0.01427	−0.001852
Sex (M)	−0.044408	0.090046	−0.49	0.6224	−0.221949	0.1331326
Degree (Bachelor diploma)	−0.004354	0.074761	−0.06	0.9536	−0.151757	0.1430488
Degree (PhD)	−0.105318	0.247695	−0.43	0.6711	−0.593688	0.3830525
Degree (Master diploma)	−0.290234	0.223106	−1.30	0.1948	−0.730122	0.1496545
Degree (highschool)	0.2014181	0.102802	1.96	0.0514	−0.001273	0.4041095
Relation (sibling)	0.2289657	0.220934	1.04	0.3013	−0.206641	0.6645726
Relation (grandparents)	−0.016039	0.126772	−0.13	0.8994	−0.265992	0.2339129
Relation (parent)	0.1901151	0.114073	1.67	0.0971	−0.034797	0.4150277
Relation (aunt/uncle)	0.4922047	0.171877	2.86	0.0046*	0.1533216	0.8310877
Relation (Friend/neighbor)	0.2829005	0.195482	1.45	0.1494	−0.102523	0.6683242
Time since diagnosis (<6 months)	0.3700052	0.2028	1.82	0.0695	−0.029849	0.7698589
Time since diagnosis (1 year−6 months)	0.5118241	0.171968	2.98	0.0033*	0.1727613	0.8508869

*$p < 0.01$.
Estimated effect as contrast with: Sex: female.
Education degree: no degree.
Relationship: partners.
Time since diagnosis: >1 year.

caregiver and women often adopt different coping strategies than men (Schoenmakers et al., 2009; Werner et al., 2012). Coping strategies are more determined by caregivers characteristics than by care characteristics; female caregivers generally use a more emotional coping strategy while male caregivers tend to cope in a more problem solving way (Schoenmakers et al., 2009, 2010a). This might explain why woman suffer more form the affiliate stigma. Above, being a family caregiver implies a physical and emotional burden, which has an additional negative effect on mental well-being (Schulz and Martire, 2004; Papastavrou et al., 2007; Ask et al., 2014).

When considering the relationships with the person with dementia, it appears that partners and children report the highest impact of affiliate stigma on mental well-being, which was confirmed in previous research (Werner et al., 2012; Kahn et al., 2016). Partners generally are permanently on care duty and therefore more burdened (Schoenmakers et al., 2010a). Second, the intra-relation and intra-familial role switch is a source of stress for the caring partner and children (Schoenmakers et al., 2010a).

While previous research suggests that lower educational attainment is associated with a higher effect of stigma on mental well-being, this study reveals the opposite (Krajewski et al., 2013; Werner and AboJabel, 2020). In our study, the small number of participants without an education degree might affect the findings. On the other hand, being highly educated might also reduce the impact of feelings of shame as "it (dementia) appears to happen in the best families" (Schoenmakers et al., 2010a).

The results from this study indicate that if the formal diagnosis of dementia exists for a longer period, relatives report a higher affiliate stigma. An explanation for this might be that these relatives already experience a high burden, reinforcing the impact of negative feelings and in this case of the affiliate stigma (Schoenmakers et al., 2009). The relationship between reported affiliate stigma and duration since the formal diagnosis of dementia needs further investigation in the future.

This study has several limitations. First, this study included relatives of patients with all different types of dementia. Since dementia is defined as a syndrome with a broad range of etiologies, the presentation of behavioral changes of persons with dementia also differs. These different presentations might influence the onset of affiliate stigma in relatives. Second, this study was conducted in a selected population (recruited through care and welfare organizations), whereby the different groups were not equally represented. Above, participating relatives were already supported by professionals or at least "help seeking," since they were recruited through organizations. Therefore, the resilience of these participants might differ from relatives caring without support (Schoenmakers et al., 2010b). Third, the items used to survey mental well-being were selected from existing surveys. We included items explicitly referring to mental well-being: sleep, cognitive functioning, social functioning, appetite, mood status. This selection was drawn by consensus among the researcher and we did not perform a validation of this survey. We thereby only focussed on the negative of mental well-being.

The strength of the study is the relatively large study population as compared to other studies. The use of the self-rating Affiliate Stigma Scale for this population is relatively unique. The affiliate stigma on dementia is well known but poorly studied. The use of the self-rating Affiliate Stigma Scale is therefore a strength. This scale has been reported in previous studies to have a broad scope, as it can be efficiently applied to both family caregivers and other family members of different levels of education (Saffari et al., 2019). We particularly opted not to use the Family Stigma in Alzheimer's Disease Scale (FS-ADS) as this is instrument focusses on Alzheimer's Disease while our

premise is that the type of dementia does not play a major role in the presentation of affiliate stigma.

CONCLUSION

Only few studies are available that investigate affiliate stigma and its effect on mental well-being. From this study, we have learned that some groups are more prone to impact of the affiliate stigma on well-being. Women, partners and relatives with a higher education need particular attention and support to lower the impact of the affiliate stigma on mental well-being. In addition, the longer the diagnosis of dementia exists, the higher the affiliate stigma. Education about dementia and the impact on patients, relatives and the broader social context might alter the affiliate stigma surrounding dementia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Board of the University Hospitals of Leuven under the number MP015226. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PV and BS: conception and design of the research, analysis of data, and revision the article. PV: acquisition of data and drafting the article. All authors read and approved the final manuscript.

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REVIEW
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Cognitive Impairment and Neurocognitive Profiles in Major Depression—A Clinical Perspective

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Increasingly, studies have investigated cognitive functioning from the perspective of acute *state*- to remitted phases of Major Depressive Disorder (MDD). Some cognitive deficits observed in the symptomatic phase persist in remission as *traits* or *scars*. The etiological origin and clinical consequences of the neurocognitive profiles reported in the literature are still unclear and may vary across populations. Deficits are suspected to influence the association between MDD and neurodegenerative disorders and could thus be of particular clinical consequence. The aim of this review is to describe the clinical neuropsychological profile in MDD and how it is related to research during the past decade on cognitive deficits in MDD from a state, trait, and scar perspective. This review, with a clinical perspective, investigates research from the past decade regarding cognitive functioning in MDD in a long-term perspective. We focus on the clinical manifestation of deficits, and the potential neurodegenerative consequences of the neurocognitive profile in MDD. Searches in Medline, PsycINFO and Embase were conducted targeting articles published between 2010 and 2020. Examination of the evidence for long-lasting neurocognitive deficits in major depression within the cognitive domains of Memory, Executive Functions, Attention, and Processing Speed was conducted and was interpreted in the context of the State, Scar and Trait hypotheses. Defining the neurocognitive profiles in MDD will have consequences for personalized evaluation and treatment of residual cognitive symptoms, and etiological understanding of mood disorders, and treatments could potentially reduce or delay the development of neurodegenerative disorders.

Keywords: MDD, cognitive functioning, scar, trait, state, remission, relapse, residual cognitive symptoms

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INTRODUCTION

Cognitive deficits are a central component in Major Depressive Disorder (MDD) (1–3). It is estimated that 25–70% of the patients will suffer from cognitive deficits (4, 5), however these numbers vary depending on clinical factors such as symptom severity, duration, onset, treatment factors as well as methodological approaches for measuring cognitive functions (4, 6, 7). Thus, there is considerable complexity when it comes to understanding cognitive deficits in MDD in the current literature.

It is clear that cognitive impairment in depression is a substantial problem associated with severe difficulties in occupational, social, and interpersonal functioning (8–10). In addition, deficits are also associated with significantly lower quality of life (11), even in phases of recovery (12, 13). A growing pool of literature during the past decade shows that impairment in cognitive functioning persists in remission and worsens over time with repeated episodes (14), and age (15). Given the wealth of studies showing cognitive deficits in MDD, in addition to important clinical consequences of this disorder, it is important to draw on the literature for potential novel etiological and clinical implications, to prevent and remediate cognitive decline.

The causes and consequences of neurocognitive impairment in depression is still debated. Several authors have explored this issue through the state, trait and scar hypotheses (2, 16–19). These hypotheses are essential to understanding the neurocognitive profile in mood disorders because they entail specific hypotheses regarding the etiological development and clinical consequences of cognitive deficits in MDD. The state hypothesis explains the cognitive deficits as caused by the depressive symptom state. This perspective predicts that cognitive impairment will normalize in parallel with affective symptom reduction. The scar hypothesis suggests that depression is neurotoxic and causes irreversible cognitive impairment over time (20, 21). Finally, the trait hypothesis suggests a neurocognitive vulnerability existing prior to the depressive symptoms and claims that cognitive impairment contributes to an increased risk of developing depression, in addition to persistence in remission, representing a risk of relapse. See **Figure 1** for further description/discussion.

Among other things, the severity of symptom load in depression will be associated with severity in cognitive impairment, according to the state hypothesis. Following this, neurocognitive impairment is a consequence of clinical symptoms of depression, such as dysphoric mood, reduced motivation, indecisiveness, sleeping problems, loss of energy and a feeling of hopelessness and attentional burden due to worry and rumination. The origin/cause of cognitive impairment is temporary and is caused either by the depression having a transient neurobiological impact, or indirectly, by the depressive symptoms leading to lack of motivation and effort affecting cognitive performance, and/or attentional taxing *via* symptoms such as rumination. Most likely, these three explanations together contribute toward the understanding of the origin of cognitive impairment during depression. However, traditionally the cognitive profile was expected to normalize during symptom improvement, and consequently patients were expected to function on a pre-morbid level in recovery, and not differently than a demographically comparable, non-depressed population. The past decade of research casts doubt over these expectations (14).

The scar hypothesis indicates a progressive decline in cognitive impairment related to duration and number of episodes. In this context, depressions is understood as neurotoxic, causing cognitive impairment (23). Dysregulation of the HPA-axis has been suggested as one of several neurobiological origins interfering with neurogenesis (24–26). Due to the neurogenesis in the absence of depressive episodes, one might expect a possible normalization of cognitive functioning over time. See II in **Figure 1**. Importantly, this perspective could have implications for the development of neurodegenerative disorders like Alzheimer's disease (23).

The trait hypothesis suggests that a neurocognitive vulnerability (traits) contributes to an increased risk of developing depression. In this perspective, the origin is found in predispositions, prior to illness and independent of clinical state. The origin may be biological, either inheritable and/or caused by environmental mechanisms such as prenatal or early childhood life stress. With this perspective, the cognitive profile is stable over time; thus, the cognitive impairment will not fluctuate with clinical state and persist in remission.

One aspect underlining the importance of understanding neurocognitive impairment is the substantial risk of relapse and recurrence in depression. Even with effective treatments for reducing symptoms of depression, most patients will experience relapse or recurrent episodes (27, 28). While only a few studies have explored the role of residual cognitive symptoms in relapse and recurrence risk, an association has been indicated between cognitive functioning and relapse risk (29, 30). In addition, many patients report substantial cognitive difficulties in everyday life, and it has been shown that subjective cognitive dysfunction is related to functional disability (31), persistence in remission (32), and even predictive of new episodes of MDD (33).

Over the past decade, substantial parts of the research have changed focus from the acute/symptomatic- to the remitted state, and a growing body of literature has focused on the long-term course of this impairment, resulting in heterogenous findings and conclusions [for reviews and meta studies see (10, 14, 18, 21, 34)], with regard to how cognitive deficits are understood.

The aim of this paper is to review the literature from the past decade regarding cognitive functioning in depression, to clarify the role and origin of the long-term neurocognitive profile in depression through the clinical-, and the state, trait, and scar perspective. Furthermore, clinical implications of cognitive residual symptoms, potential increased risk for neurodegenerative disorders, and potential preventive interventions for cognitive enhancement, and suggestions for future studies are discussed.

METHODS

This review is based on computerized searches in Medline, PsycINFO and Embase, exclusively for articles published during the decade between 2010 and 2020 using the terms DEPRESSIVE/ MAJOR DEPRESSION, COGNITIVE DYSFUNCTION, NEUROCOGNITIVE, LONGLASTING, PREVAILED, RESIDUAL, EUTHYMIC, REMISSION in combination. In addition, reference lists were examined for further relevant studies. Every unique abstract, a total of 414, was examined to determine if it is relevant for the topic. Seventy papers were finally included in the summary. Both longitudinal- and cross-sectional original studies were considered relevant, and both reviews and meta-studies were included.

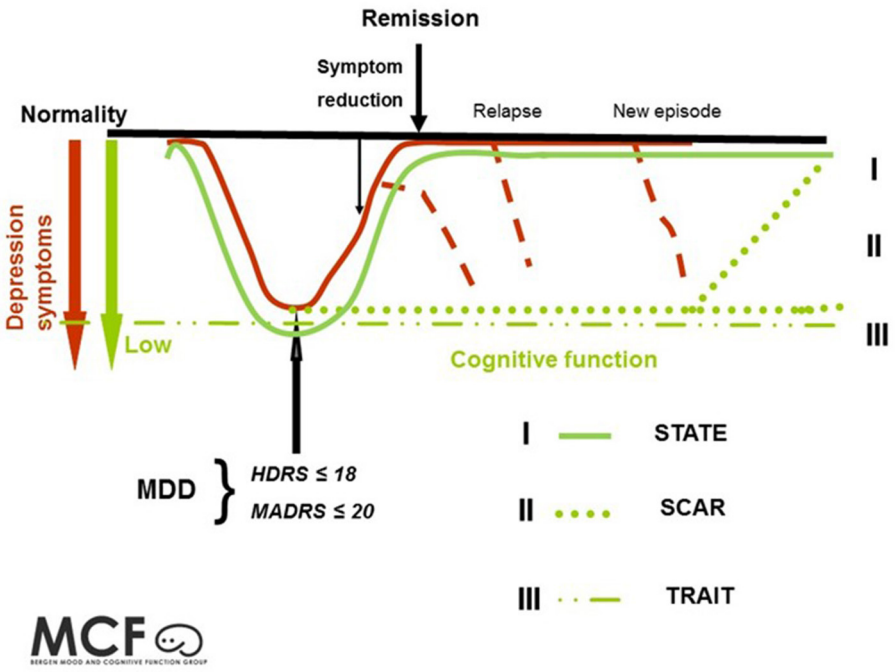

FIGURE 1 | Illustrates three hypotheses regarding the neurocognitive profile in depression. **(I)** The state hypothesis: cognitive impairment is state dependent and follows mood symptoms. See "I". **(II)** The scar hypothesis: cognitive impairment is a result of a scarring effect from the neurotoxic effects of depression. See "II". **(III)** The trait hypothesis: cognitive impairment is related to stable persistent features. See "III". This figure is adapted from Hammar and Årdal (2) and Frank et al. (22).

Cognitive Functioning as a Theoretical Concept

Cognitive functioning is a complex theoretical concept, and there is a lack of consensus concerning the definition and use of the term in the literature (7, 34, 35). One consequence of this is the variety of interpretations and conclusions regarding cognitive functioning in depression.

This complexity is sometimes hard to grasp for clinicians and patients outside the field of clinical neuropsychology. As shown in **Figure 2**, cognitive functioning is a concept consisting of several interrelated sub-concepts defined as domains. Furthermore, within each domain there are several specific aspects. In a traditional neuropsychological assessment, each specific aspect is measured by standardized tests or experimental paradigms. These findings will normally be interpreted and explained on an aspect level in a clinical setting (see **Figure 2**); however, the literature traditionally describes findings on a domain level, with the risk that important findings on an aspect level will be ignored. When studies report results as composite scores, summarized by scores of different aspects within a specific domain (36, 37), it may lead to a wrong conclusion regarding lack of differences between groups (type 2 error) with the risk that specific impairments will disappear in the composite score. This is of particular importance in clinical neuropsychological work in which the whole ideographical profile is of importance for the individual patient. Consequently, an incorrect portrayal of patients' cognitive profile could be reported, failing to mirror actual challenges in daily life functioning. In addition, using population norms to explain test results (38) may ignore the important ideographic interpretation of how the different cognitive tests are related to the individual patient. In addition, some norms are not standardized for regional conditions and could thus underestimate deficits (39). In addition, a recent meta study by Parkinson et al. (40) argued that results in one domain may not reflect the effects on one test, thus precluding results from single tests.

Composite scores, however, are important in research to identify latent variables representing different cognitive domains, avoiding task impurity problems, and useful for structural equation models investigating cognitive functions above and beyond the clinical setting (7).

With this in mind, the literature from the past decade will be summarized with a focus on cognitive functioning over time, in a long-term perspective, investigating the three previously mentioned hypotheses in particular, in the cognitive domains of memory, executive functioning, attention, and psychomotor processing speed. The concept long-term perspective is used to describe the cognitive profile over time in non-symptomatic phases, which can be reflected in both cross- sectional and longitudinal studies.

RESULTS

The Domain of Memory

Patients with a history of depression often report that they experience memory problems, both in an acute phase (41) and

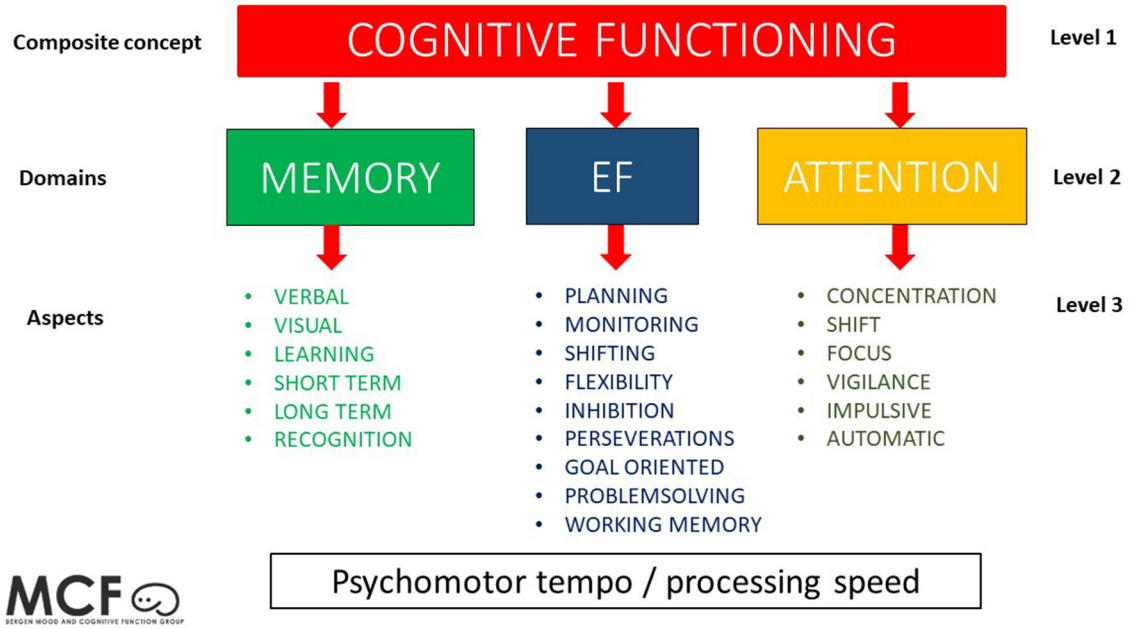

FIGURE 2 | This figure shows a conceptual model of the levels of cognitive functioning, with cognitive functioning as a composite concept (level 1) having three major sub-concepts as domains (level 2) and several specific aspects within each domain (level 3). In this model, psychomotor tempo/processing speed is illustrated as interrelated with all the other domains.

in a recovery phase (42). Based on clinical practice, patients not only describe this problem evidenced in themselves, but also in family members and others. This could lead to increased stress, frustration, relational problems, and negative self-representation (43). Many former patients relate these memory problems to possible brain damage or dementia, leading to a negative impact on self-representation, rumination and coping. Such an interpretation combined with the lack of correct knowledge regarding the role and origin of residual cognitive impairment might lead to an increased risk of relapse and new episodes.

Numerous studies have investigated aspects of memory during the past decade and findings so far appear divergent and non-conclusive. Lee et al. (44) concluded in their meta-study that memory represented a state marker being associated with clinical state in first episode patients. This was also evident in the meta-study by Ahern and Semkovska (45), concluding that first-episode patients showed normalized learning, memory, and autobiographic memory in remission. Pu et al. (46) found deficits in verbal memory but only for a subgroup of patients with MDD. This group also showed deficits in information processing that could influence memory consolidation. This was also the case in Lee et al. (44), where patients with mild depressive symptoms showed second largest impairments in verbal memory, only superseded by processing speed. An older MDD group showed deficits in visual and verbal, learning and memory, but also in most cognitive functions. Xu et al. (47) reported immediate visual memory impairment (WMS-R Immediate Visual Reproduction; copying figure after 10 s exposure) in patients in the depressed state and in remission compared to healthy controls, suggesting visual memory deficits may be a trait for mood disorders. This finding, however, was not supported in a study conducted by Hammar and Schmid (48), whose findings indicate that visual memory performance in patients with major depression normalizes during a 9-month period, thus indicating a state-related relationship. This study had a small sample, suggested a deficit in copying at follow up, and lacked the immediate condition that could be most analogous to Xu et al. (47). Thus, a trait/scar deficit in visual construction is indicated. Hammar et al. (49) suggested that MDD patients showed intact verbal memory performance, a deficit in immediate verbal learning, and deficits in visual memory in the symptomatic phase. Immediate verbal learning deficits were still evident during partial remission (50). Shimizu et al. (51) reported that remitted MDD patients had poorer verbal memory, both immediate and delayed (as well as deficits in most other cognitive areas), compared to healthy controls. This was in line with findings showing that despite significant improvement in memory from the symptomatic phase to remission, patients were still significantly impaired compared to healthy controls (52). Wekking et al. (53) found impairment in several measures of memory in remitted patients but could not establish that the impairment predicted future relapse within in a 24-month period. Vasavada et al. (54) found deficits in verbal learning before ECT treatment, but also following symptom reduction, suggestive of trait or scar effects. A study of remitted patients and their high-risk twins (55) did not find any verbal memory impairments in either group, contrary to what would be expected from a trait perspective. However, a recent meta-study found small impairments in most cognitive functions in

first-degree relatives of patients with MDD, including in memory, supporting this hypothesis (56). Finally, studies investigating first-episode patients and patients with recurrent depression with biological correlates have supported a scar hypothesis: Hansson et al. (25) reported no relationship between an abnormal HPA axis and cognitive dysfunction in verbal memory in first-episode patients. However, abnormal HPA-axis and cognitive impairment was evident in patients with a history of recurrent depression, indicating that the episodes might have a scarring effect on verbal memory functioning (24). Tully (57) also finds potential scarring effects, with depressive symptoms and high blood pressure associated with decline in visual memory. This view is also supported by a review by Mcintyre et al. (58), that posits that a subgroup of individuals with MDD show progressive decline in memory. A study on late-life depression suggested that depressive symptoms were a prodrome for Alzheimer (59), that could suggest a dementia state effect on reduced memory in late life MDD (see **Table 1**).

In conclusion, the literature supports evidence of a long-term memory impairment in depression. This is not independent of attentional and learning deficits, as evidenced by the sustained difficulties with immediate memory, and it could therefore be influenced by impaired informational encoding more than a long-term memory deficit. In addition, all three hypotheses concerning role and origin have partial support. Hence, the neurocognitive memory profile in depression is neither specific nor conclusive and requires a multidimensional approach. This domain is of particular interest with regard to development of neurodegenerative disorders and is often affected first in the development of Alzheimer's disease. Studies seem to find increased deficits in memory related to depression with increasing age (14, 60).

The Domain of Executive Functioning (EF)

Patients who have experienced or are experiencing depression frequently report that they often have difficulty performing tasks that require initiating or finishing activities, problem solving or getting an overview of situations, multitasking, or emotional regulation; inhibiting negative or troubling thoughts (41–43). We clinically relate these tasks to a higher order of functioning for regulation of behavior, thoughts and emotions –defined as Executive Functions.

Aspects of EF have been investigated in several studies, and findings tend to highlight inhibition, defined as suppressing an automatic response in order to make a less automatic but task-relevant response (61). The concept of inhibition has been operationalized differently in different studies depending on the neuropsychological task used (7). Lee et al. (44) suggested in his review that inhibition could be a trait marker in first-episode patients. This conclusion was supported in findings from several studies conducted by Schmid and Hammar (62), who stated that impaired inhibition on the stroop test, in addition to semantic fluency, is present early in the course of MDD, indicating that EF represents a trait in MDD, irrespective of symptom severity and number of previous episodes. Moreover, the authors showed that impairment in inhibition and switching and semantic fluency in first-episode MDD persisted in long-term follow up (63), with the former associated with relapse during the first year after the first episode (30), and with deficits in inhibition in a subgroup with relapse 5 years later (64), suggesting a relationship between impaired ability in EF of inhibition and switching and relapse in MDD. These findings were also evidenced in patients with recurrent depression and showed that impaired inhibition in the acute phase persisting in phases of symptom reduction (65). Another study on the same patient group showed that impaired inhibition in the symptomatic phase was strongly correlated with impaired inhibition in long-term follow up, indicating that this may represent stable a trait marker in recurrent MDD (66). Moreover, one of the longest follow-ups investigating the same recurrent MDD patients and controls over a 10-year period showed that patients were still impaired with regard to inhibition (13). A twin study did found no EF deficits, neither affected- nor high-risk twins (55). However, a meta study of cognition in first-degree family members did find small effects for deficits in EF (56). This strengthens the hypothesis of at least some trait relation. In addition, findings regarding neural correlates and impaired inhibition were reported in partially remitted and remitted-recurrent MDD patients showing hypoactivation in striatal areas (67). These findings could be interpreted as results of scars or being trait-related. This is in line with findings from Peters et al. (19), who concluded that impaired inhibition as cognitive control in acute and remitted states may represent a trait vulnerability or an early course scar of MDD viable target for secondary prevention or cognitive remediation. Also, Bora et al. (60) concluded in their meta-analysis that response inhibition seems to be a persistent feature in adult-onset MDD, thus supporting the trait hypothesis. They reported that among all cognitive functions, inhibitory control showed the largest magnitude of observed deficits in euthymic MDD patients compared to controls. However, in contrast to all previous findings, Aker et al. (68) reported no deficits in cognitive inhibition in remitted patients, only in response inhibition. Wekking et al. (53) also found persisting deficits in most cognitive measures, except inhibition. Both studies used a contrast score that only approached statistical significance and results similar to other studies (30, 63).

Other studies have focused on different aspects of EF. Contrary to several conclusions regarding trait-related explanations, Roca et al. (69) showed normalization in several cognitive measures such as problem-solving in first-episode and recurrent-episode remitted patients; however, they did not find improved inhibition in the sample. Still, they conclude that remission, rather than numbers of previous episodes, has a high impact on cognitive performance in MDD patients, thereby supporting a state model. Other studies consistently find EF impaired in the depressed state (70, 71), with some inconsistencies with regards to improvements with symptom reduction (54, 72, 73). Pu et al. (46) found small correlations between an EF composite and depressive symptoms; however, this could vary by specific EF tasks measured (63). Age could also influence EF deficits, Boedeker et al. (74) found impairments in switching, but no statistically significant differences in inhibition, in an aging MDD sample. Maalouf et al. (75) using a planning

TABLE 1 | Findings within the domain of memory regarding origin of impairment.

Study	*N*	Age (SD)	Sex	Education (SD)	Depression severity (SD)	Number of episodes	Study design	Neuropsychological tests	Key outcomes
The state hypothesis									
Lee et al. (44)	15 samples with 644 patients	39(10)	Not reported	Not reported	Not reported	First episode patients	Meta-analysis	Logical Memory 1 and 2, Rey Auditory Verbal Learning Test (RAVLT), California Verbal Learning Test (CVLT-II), Hopkins Verbal Learning Test (HVLT), Buschke's Selective Reminding Test (SRT). Visual Reproduction 1 and 2, Rey Complex Figure Test (RCFT), Weschler Memory Scale (WMS)	Memory functioning was associated with clinical state
Hammar and Schmid (48)	Baseline: 24 MDD patients (PG) 24 individually matched healthy controls (HC)	PG: 38(11) HC: 38(11)	18 females	PG:12(2) HC: 13(2)	T1: HDRS 23(5) T2: HDRS 11(5)	Recurrent depression minimum 2 episodes	Longitudinal with baseline (T1) and 9 months follow up (T2)	Rey Complex Figure Test	Significant improvement in depressions symptoms and in visual memory impairment
Ahern and Semkovska (45)	31 studies with 994 patients	Weighted mean age: Patient 27 Control 30	patients: 586 females Control: 761 females	Not reported	Not reported	First Episode patients	Review and meta-analysis	Several test in domains of: Autobiographical memory Visual learning and memory Learning Delayed memory Verbal learning and memory Recognition Learning Delayed memory	Remission was associated with a normalization of function in, learning and memory, autobiographical memory
Pu et al. (46)	170 patients with non-psychotic MDD	38(12)	79 females	Duration of education 15(2)	HAMD: 8(4)	Not reported Duration of illness 8(6) years	Cross-sectional	Brief Assessment of Cognition in Schizophrenia (BACS) Verbal memory: List Learning Test	Impaired memory was associated with the clinical state of MDD
Javaherian et al. (59)	Depressive symptoms (DS) $n = 54$ No Depressive symptoms (NoDS) $n = 300$	DS = 71(5) No DS 72 (5)	DS = 38 females No DS = 151 female,	DS = 15(3) No NoDS = 16 (3)	GDS: 3(2) NPI-Q item 5a (=yes)	Not reported	Cross-sectional	Free and Cued Selective Reminding Test, the Associate Learning subtest from the Weschler Memory scale (WMS), WMS-Revised Logical Memory	Depressive symptoms was associated with reduced episodic memory in later stage preclinical Alzheimer's
The scar hypothesis									
Hansson et al. (24)	24 MDD patients (PG) 24 individually matched healthy controls (HC)	PG: 38(11) HC: 37(11)	18 females	PG:12(2) HC: 13 (2)	MADRS 27(5)	Recurrent depression minimum 2 episodes	Cross sectional	California Verbal Learning Test (CVLT-II) Rey Complex Figure Test	Findings indicate that dysregulation of the HPA-axis is related to poor verbal memory functioning

(Continued)

TABLE 1 | Continued

Study	*N*	Age (SD)	Sex	Education (SD)	Depression severity (SD)	Number of episodes	Study design	Neuropsychological tests	Key outcomes
Hansson et al. (25)	21 MDD patients (PG) 21 individually matched healthy controls (HC)	PG: 26(6) HC: 25(6)	12 females	PG: 14(2) HC: 14 (1)	MADRS: 24(4)	First episode MDD patients (FE).	Cross sectional	California Verbal Learning Test (CVLT-II) Rey Complex Figure Test	No associations between cortisol levels and cognitive functioning, indicating that FE patients are not as affected as recurrent MDD patients.
Vasavada et al. (54)	44 MDD 33 demographically similar controls (CG)	MDD: 41 (13) CG: 39 (12)	MDD: 26 females CG: 19 females	MDD: 16 (3) CG: 17 (2)	M ADRS T1 = 37 (8) T4 = 17 (12)	>1 Episode, 16 years mean duration	Longitudenal	Hopkins Verbal Learning Test—Revised, Brief Visuo-spatial Memory Test—Revised	Verbal learning deficits initially, and no significant improvement in symptom remission
Semkovska et al. (14)	11 882 major depressive episode remitters 8,533 healthy controls	Not reported specifically	Not reported specifically	Not reported specifically	Not reported specifically	Not reported specifically	Systematic review and meta-analysis	Several tests in domain measures of Verbal memory and visuo or spatial memory	Deficits in long-term memory persist in remission from a major depressive episode and worsen with repeated episodes
The trait hypothesis									
Xu et al. (47)	293 Unipolar depression patients (UP) 202 Healthy Controls (HC)	UP: 35(13) HC:34(10)	162 females	UP: 11 (4) HC: 13 (4)	HDRS: 27(6)	2(2)	Longitudinal Baseline and 6 weeks follow up	Immediate Visual Reproduction of Wechsler Memory Scale-Revised in China (WMS-RC)	Remitted unipolar patients showed cognitive impairment in executive function in addition to processing speed and visual memory
Mackenzie et al. (56)	3,246 First-degree relatives MDD (fdrMDD) 5,222 controls	fdrMDD 15(14) controls 15(12)	1,872 femalesfdrMDD 2,921 female controls	Not reported	Not reported	Not reported	Systematic review and Meta analysis	CVLT, RAVLT, Verbal Paired Associates Initial and Delay Recall RCFT Self-Referential Encoding and Incidental Recall Task, Autobiographical Memory Test, Computerized Autobiographical Memory Test	Globally impaired cognition in fdrMDD, including for the domain of memory

(Continued)

TABLE 1 | Continued

Study	*N*	Age (SD)	Sex	Education (SD)	Depression severity (SD)	Number of episodes	Study design	Neuropsychological tests	Key outcomes
Tully et al. (57)	2,812 Older participants divided by: late onset symptomatic ($n = 105$) asymptomatic ($n = 200$) early onset smptomatic ($n = 51$) asymptomatic ($n = 74$)	Median age 72	1,788 females	Not reported	Not reported	Not repored	Prospective cohort study	Visual memory (BVRT)	Late onset MDD showed global decline, and in visual memory with interactions between MDD and white matter intensities
McIntyre et al. (58)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Review	Not reported	A subset of adults MDD patients show progressive decline in memory

MADRS, Montgomery-Asberg Depression Rating Scale.

task in adolescents with acute and remitted MDD and they stated that planning and impulsivity appear to be state-specific markers of MDD in adolescents, and are related to depression severity and are not persistent in remission, but a relatively small- and poorly matched sample as well as tasks used could explain this. Early experiences could influence cognition, and Saleh et al. (76) found worse EF in a MDD group with early life stress. Chakrabarty et al. (77) found that only a MDD population with trauma showed persisting deficits in WM in remission. Albert et al. (36) found a relationship between longer duration of depression age, and EF with no effects of current depression severity on performance. The authors concluded that cognitive performance worsens with recurrence over the life span. These findings can be interpreted as support for the scarring hypothesis. Bhardwaj et al. (78) drew the same conclusion, demonstrating an impairment in a planning and problem-solving task in recovered MDD patients and found that performance was correlated with number of previous episodes of depression. They concluded that impairments of EF are present in recovery and are thus not simply state markers, but instead scars caused by previous episodes (see **Table 2**).

In sum, existing research supports the assumption of a long-term impairment within the EF domain in general, evident in inhibition in particular, with evidence indicating a trait-related profile. However, all three hypotheses regarding role and origin in EF were supported. Similarly to findings within the memory domain, the neurocognitive profile of EF in depression is neither specific nor conclusive.

The Domain of Attention

Depressed patients and formerly depressed patients often report problems maintaining attention during conversations or when reading a book or watching TV, etc. These problems have an impact on daily life functioning and may frequently be interpreted as ignorance rather than the result of a cognitive impairment related to the depression or as a residual cognitive symptom (41, 42). This is clinically related to the domain of attention.

Several studies confirm that attention deficits are related to depression both in the acute phase of the illness (2, 44) and in remission (51, 79, 80). Ji et al. (72) found improvements in digit span in remission, that could indicate a relationship between MDD and attention. In addition, another study found an association between attention and inflammatory markers, which could partly explain state effects in attentional deficits. Findings are divergent, however, some studies report no attentional deficits measured by digit span in MDD in patients both in the acute depressive state and in remission (47). Consistent with this, Boedeker et al. (74) did not find deficits in digit span in an aging MDD sample. This could reflect heterogeneity in the neurocognitive profile. Studies that separate subgroups of MDD in first-episode and recurrent-episode showed that first-episode patients differed in neurocognitive profile: While first-episode patients demonstrated no impairment in attention in effortful information processing in the symptomatic phase of depression (81), the group suffering from recurrent episodes showed an impairment in symptomatic and symptom reduction phases, which *normalizes* over a 10-year period (82). Such findings might

TABLE 2 | Findings within the domain of executive functions regarding origin of impairment.

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
The state hypothesis									
Maalouf et al. (75)	20 adolescents with MDD in acute episode (MDDa) 20 previously depressed adolescents in remission (MDDr) 17 healthy control participants (HC)	MDDa: 15 (2) MDDr: 15(1) HC: 15 (2)	MDDa: 17 females MDDr: 15 females HC: 9 females	Not reported	CDRS-R MDDa: 59 (11) MDDr: 2 (3) HC:19 (2)	MDDa: 1.4 (0.6) MDDr: 1.2 (0.5)	Cross-sectional	The Cambridge Neuropsychological Tests Automated Battery (CANTAB): (a) Stockings of Cambridge (SOC) task, as a measure of executive function; (b) Rapid Visual Processing (RVP) task, as a measure of sustained attention; and (c) the Delayed matching to Sample task (DMS), a measure of visual short-term memory	Executive dysfunction and impulsivity appear to be state-specific markers of MDD in adolescents that are related to depression severity and not present in remission
Roca et al. (69)	26 First episode (FE) 53 recurrent episode (RE) depressive patients	FE: 44 (9) RE: 47 (8)	FE: 21 females RE: 41 females	University degree FE: 19% RE: 13%	HDRS FE: 22 (3) RE:24 (5)	RE: 4 (3)	Observational longitudinal cohort study	TMT AoB Digit Span Stroop Tower of London Verbal Fluency task (FAS) Semantic Verbal fluency (animals)	Show normalization in several cognitive processes, such as problem solving, however not in inhibition
Pu et al. (46)	170 patients with non-psychotic MDD	38(12)	79 females	Duration of education 15(2)	HAMD: 8 (4)	Not reported Duration of illness 8 (6) years	Cross-sectional	BACS	Three MDD subgroups, one with global impairments including executive dysfunction
Mak et al. (71)	35 MDD, 35 Healthy matched controls (hMC)	MDD: 25 (4) hMC: 22(3.)	20 females MDD 23 females hMC	MDD: 14 (2) hMC: 15.4 (1.22)	MADRS MDD: 23 (5)	1 (1)	Cross sectional case-control	WCST, TMT, VFT	MDD scored worse than hMC on excecutive functions (WCST) and TMT B (n.s. medium e.s.)
Koo et al. (70)	20 MDD, 20 Healthy controls (HC)	MDD: 51 (11) HC: 76 (6)	11 females MDD 13 females HC	Not reported	BDI MDD: 28 (8) HC: 3 (3)	3 (2)	Cross sectional case-control	TMT B, Stroop	MDD showed poorer performance than HC across all cognitive tests, including TMT B and Stroop interference
Boedeker et al. (74)	30 MDD, 90 Healthy controls (HC)	MDD: 74 (4) HC: 47 (13)	22 females MDD 47 females HC	MDD: 9 (2) HC: 9 (1)	Not reported	Not reported	Cross-sectional	Verbal fluency, TMT, Stroop	MDD showed poorer performance than HC on TMT B, Verbal fluency, and Stroop (n.s.)

(Continued)

TABLE 2 | Continued

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
The scar hypothesis									
Bhardwaj et al. (78)	20 patients in recovery from recurrent unipolar (PG) depression 20 healthy controls (HC)	PG: 34 (8) HC: 33 (8)	PG: 2 females HC: 3 females	PG: 13 (3) HC: 13 (3)	HDRS: 4 (2)	4 (2)	Cross-sectional	WCST	Cognitive impairment correlated with numbers of previous episodes
Xu et al. (47)	293 Unipolar depression patients (UP) 202 Healthy Controls (HC)	UP: 35 (13) HC:34 (10)	131 males and 162 females	UP: 11 (4) HC: 13 (4)	HDRS: 27 (6)	2 (2)	Longitudinal Baseline and 6 weeks follow up	Modified WCST-M Tower of Hanoi (TOH) Trail Making Test-part B (TMT-B)	Remitted unipolar patients showed cognitive impairment in executive function
Hammar et al. (67)	17 partially remitted and remitted MDD patients (PG) 17 Healthy Controls (HC)	PG: 41(11) HC: 40(13)	PG: 3 males and 13 females HC: 3 males and 14 females	Not reported	HDRS: 7 (7)	At least 2 previous episodes	Cross-sectional	Experimental paradigm with a combination of a Stroop task and a n-back task	Striatal hypoactivation and impaired cognitive performance in a sample of partially remitted MDD patients compared to never-depressed controls, indicating neuronal scarring from the disorder
Albert et al. (36)	91 depressed (PG) 105 non-depressed (HC)	PG: 36 (9) HC:30 (9)	PG: 30 males 61 females HC: 37 males and 68 females	PG: 15 (2) HC: 16 (2)	MADRS: 24(4)	Mean Duration in days: 2116 (1800)	Cross-sectional	Executive function: COWAT, Trail Making B time semantic fluency Stroop Color-Word interference condition	A relationship between longer duration of depression age, and EF with no effects of current depression severity on performance
Saleh et al. (76)	64 antidepressant free depressed (PG) 65 non depressed (CG)	PG: 35 (9) CG: 29 (9)	39 females PG 43 females CG	PG: 35.1 (8.9) CG:29 (9.2)	MADRS PG: 25 (5)	Episodes not reported, duration in years 6 (5)	Cross sectional case-control	WM composite consisting of digit span	Found worse WM (but not EF composite) in a MDD group with early life stress
Vasavada et al. (54)	44 MDD 33 demographically similar controls (CG)	MDD: 41 (13) CG: 39 (12)	MDD: 26 females CG: 19 females	MDD: 16 (3) CG: 17 (2)	M ADRS T1 = 37 (8) T4 = 17 (12)	>1 Episode, 16 years mean duration	Longitudinal	Trail Making B, Stroop	Trail Making B poorer in MDD and did not improve following remission

(Continued)

TABLE 2 | Continued

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
Chakrabarty et al. (77)	MDD without maltreatment (DM+): 93 MDD with maltreatment (DM-): 90 Healthy controls with maltreatment (HM+): 22 Healthy controls without maltreatment (HM-): 80	DM+: 37 (12) DM-: 34 (13) HM+: 34 (10) HM-: 33 (11)	DM+: 63 females DM-: 51 females HM+: 12 females HM-: 54 females	DM+: 14 (2) DM-: 14 (2) HM+: 16 (2) HM-: 16 (2)	MADRS DM+: 31 (6) DM-: 29 (6)	DM+: 4 (4) DM-:3 (3)	Longitudinal with baseline, 8 weeks and 16 weeks follow-up	Central Nervous System Vital Signs (CNS-VS) computerized battery with a global composite score	Maltreatment may be a risk factor for more severe and persistent cognitive deficits in adult MDD
The trait hypothesis									
Lee et al. (44)	15 samples with 644 patients	39 (10)	Not reported	Not reported	Not reported	First episode patients	Meta-analysis	WCST, Modified Card Sorting Test (MCST); CANTAB Intradimensional/Extradimensional-Shift (ID/ED)	Executive Functioning seems to be a trait-marker
Peters et al. (19)	Remitted MDD (rMDD): 62 Healthy controls (HC): 43	rMDD: 21 (2) HC: 21 (2)	47 females rMDD 23 females HC	rMDD: 14 (1) HC: 15 (1)	HAMD-D rMDD: 3 (3)	Not reported	Cross-sectional	Stroop, TMT, COWAT, Go/no-Go	Impaired inhibition as cognitive control in acute and remitted states may represent a trait vulnerability or an early course scar of MDD
Schmid et al. (66)	20 recurrent MDD patients (PG) 19 healthy controls (HC)	PG: 38 (11) HC: 38 (11)	PG: 18 females HC: 18 females	PG: 12 (2) HC:13 (2)	MADRS: 15 (6)	At least 2 previous episodes	Longitudinal with baseline and 9 months follow up	D-KEFS Color–Word Interference Test (CWIT) The D-KEFS Verbal Fluency Test (VFT)	Recurrent MDD patients show a prolonged impairment in inhibition and semantic fluency
Årdal and Hammar (13)	19 recurrent unipolar MDD patients (PG) 19 healthy controls (HC)	Baseline PG: 43(10) HC: 42 (10)	PG: 10 females HC: 10 females	Baseline PG: 14(4) HC: 14 (4)	HDRS: 5	Total numbers of episodes: 10	Longitudinal with Baseline, 6 months and 10 years follow ups	The Stroop test	Long-lasting impairment in cognitive inhibition at the 10-year follow-up study
Schmid and Hammar (62)	30 MDD patients (PG) 30 individually matched healthy controls (HC)	PG: 26(6) HC: 26 (6)	16 males and 14 females	PG: 14 (2) HC: 14 (2)	MADRS: 25(4)	First episode patients	Cross-sectional	D-KEFS Color–Word Interference Test (CWIT) The D-KEFS Verbal Fluency Test (VFT)	Impaired inhibition on the stroop test, in addition to semantic fluency are present early in the course of MDD
Schmid and Hammar (30)	28 First episode MDD patients (PG) 28 healthy controls (HC)	PG: 27(5) HC: 27(5)	PG: 14 females HC: 14 females	PG. 14(2) HC: 15(2)	MADRS: 10(6)	First episode patients	Longitudinal with baseline and 1-year follow up	D-KEFS Color–Word Interference Test (CWIT)	Impaired ability in the EF of inhibition/switching was related to vulnerability for relapse

(Continued)

TABLE 2 | Continued

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
Bora et al. (60)	27 studies with 895 patients with MDD 993 healthy controls	Specified for each study included	61% females	Specified for each study included	Specified for each study included	Specified for each study included	Meta-analysis	Global composite score by averaging effects sizes.	Poor response inhibition seems to be persistent in adult-onset MDD
Mackenzie et al. (56)	3,246 First-degree relatives MDD (fdrMDD) 5,222 controls	fdrMDD 15 (14) controls 15 (12)	1,872 fe male fdrMDD 2,921 female controls	Not reported	Not reported	Not reported	Systematic review and Meta analysis	WCST, Intra/Extra dimensional Set Shifting, Stroop, TMT B, Digit span, letter number substitution, letter n-back, hot executive functions (various tasks).	Small ($p = 0.10$) e.s. for poorer EF in first degree relatives of patients with MDD suggestive of genetic defecits in EF
Ji et al. (72)	67 patients with MDD (MDD) 56 Healthy controls (CG)	MDD: 31 (10) CG: 34 (13)	MDD: 37 females CG: 31 females	MDD: 14 (3) CG: 13 (5)	HAMD-17: MDD 21 (3) CG: 2(2)	4 (2)	Longitudinal with a 6 month follow up	Digital symbol substitution, and digit span forwards- and backwards test	Persisting deficits in WM in remission
Ronold et al. (63)	23 MDD patients (PG) 20 matched healthy controls (HC)	MDD: 31 (6) HC: 30 (6)	MDD: 12 females CG: 11 females	MDD: 15 (2) HC: 17 (2)	MADRS: 9 (8)	Not reported	Longitudinal five year follow up of first episode MDD	D-KEFS: CWIT, VFT, TMT	Persisting deficits in inhibition unrelated to depressive symptoms

COWAT, Controlled Oral Word Association Test; BDI, Becks Depression Inventory; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; CDRS-R, Children's Depression rating Scale-revised; MADRS, Montgomery-Åsberg Depression Rating Scale.

support the Scar hypothesis, showing that duration could be a critical cue to the attentional deficit. These findings were done with a novel paradigm measuring visual attention and might not be generalizable to all other aspects of attention, however. Differences in age between FE and recurrently depressed could perhaps explain this (83). Pu et al. (46) also found subgroups with differing deficits, with one showing among other cognitive deficits, impaired attention. Clery-Melin and Gorwood (84) found differing outcomes supporting the Trait hypothesis; they showed that attention measured by omission mistakes was an unchanged marker before and after treatment and could predict clinical and functional outcome. They interpreted their findings as reflecting a specific ability to control attention and thereby regulate emotional stimuli, thus representing a trait resilience marker, meaning that patients with enhanced ability in attention are more likely to achieve full clinical and functional remission. Attentional control could arguably be considered an EF, however. In addition, this could illustrate the differences in attentional tasks between error scores and RT. The trait perspective was also supported in a meta-analysis conducted by Lee et al. (44), in which they concluded that attention is more likely a trait-marker in first-episode patients. Attention is a complex cognitive domain and is highly interrelated with the other cognitive domains such as memory, EF and psychomotor tempo and could thus influence all other domains (35) (see **Table 3**).

In sum, an update from the past decade on attentional deficits in depression shows that several aspects of attention are affected, both during the depressive episode and as a residual symptom. The role of attention deficits in relapse and development of new episodes is still unclear and impairments in this domain probably influence results in the other domains (35).

The Domain of Processing Speed

Sometimes patients with previous episodes of depression state that they need more time to complete tasks compared to earlier, this is something we often define as processing speed, psychomotor tempo or information processing. In the clinical setting, it could be labeled latency time and can be quite severe in some severely depressed in-patients (42). Processing speed is consistently impaired in the acute phases of MDD (33; 54) thus supporting a state perspective. Pu et al. (46) however, found only minor relationships between motor-speed and depressive symptoms. Zhang et al. (86) also found slower improvements in processing speed rather than depressive symptoms, suggesting persisting deficits. Albert et al. (36) found a composite measure of processing speed to be the most impaired in MDD. Similarly to EF above, the authors find an interaction between age, duration of depression, reduced processing speed, although current symptoms of depression did not influence this processing speed (when controlling for age, race, sex, educational level and medical comorbidity), thus supporting the trait and scar hypothesis. Meluken et al. (55) did not find deficits in processing speed in relatively young MDD population and related twins, in contrast to state and trait perspectives. The study from Saleh et al. (76) suggest that early traumatic experiences could influence processing speed in MDD, and Chakrabarty et al. (77) found that a MDD population with trauma showed persisting deficits in processing speed following remission. In addition, Jaeger (87), in a review of the digit symbol substitution test, i.e., a measure of processing speed, cites research that finds consistent impairments in processing speed and effect sizes that increase in elderly MDD populations. This is supported in Boedeker et al. (74), who found deficits in an elderly MDD population. Other studies have shown that patients in remission of recurrent depression also suffer from impairment in processing speed (47, 51, 53). Xu et al. (47) did, however, find the most substantial improvements on measures of processing speed. This is in line with Schmid (30, 62). Egerhazi et al. (52) also observed an improvement in psychomotor speed during remission. Vasavada et al. (54) found improvements only in processing speed. Meta studies support this: Patients with first-episode MDD showed an impairment in psychomotor speed in the depressive state and the authors concluded that this deficit was associated with clinical state (44). Ahern and Semkovska (45) also reported in their review and meta-analysis of first-episode depressed patients that remission was associated with normalization of function in processing speed. However, different subgroups could show different impairments (46) (See **Table 4**).

In sum, processing speed seems to be the most impaired aspect of cognition in depression, but is also most influenced by state trait (and scar) effects. Subgroups in MDD could show more impairment. Results regarding processing speed in MDD deviate in several instances; however, altogether, it seems that recurrent patients show a prevalent slowing in processing speed, whereas first-episode patients show normalization of speed in remission. This pattern might indicate a scaring effect on speed, but also effects of increased aging.

DISCUSSION

The recent literature regarding cognitive impairment and neurocognitive profiles in MDD shows various and divergent results. There are findings of impaired cognitive functioning across domains in a long-term perspective. All three hypotheses regarding neuropsychological profiles; state, scar and trait receive various degrees of support. More specifically, while the neurocognitive profile in the attention and memory domains is more unclear, particular aspects in the EF domain, such as inhibition (and switching?), seem to show a trait-related neurocognitive profile and could contribute to the vulnerability toward relapse and recurrent episode. Further, processing speed seems to be best explained as a result of a scarring effect. Another conclusion, drawn from the current review is that it seems that the state related neurocognitive profile is more evident in patients with their first episode in MDD; such a conclusion will support a scar profile over time related to duration and number of episodes.

Most studies show cognitive impairment in most domains [(2); Snyder, Semkovska]; however, some studies report non-findings, where the patient group shows intact functioning across domains (38, 81). These reports are fewer in number, probably because science has a tradition of publishing group differences rather than null finings. Semkovska et al. (14) did not find evidence for bias in most of their included variables.

TABLE 3 | Findings within the domain of attention regarding Origin of Impairment.

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
The state hypothesis									
Ye et al. (85)	30 patients with MDD (MDD) 30 Healthy controls (HC)	MDD: 42(11) HC: 42(10)	MDD 18 females HC 17 females	MDD 11(4) HC 12(4)	PHQ-9 ≥ 7	Not reported	Case control	Rapid Visual Information Processing (RVP) from CANTAB	Poorer attention in MDD relative HC, IL-6 levels associated with impaired sustained attention
Pu et al. (46)	170 patients with non-psychotic MDD	38 (12)	79 females	Duration of education 15 (2)	HAMD: 8 (4)	Not reported Duration of illness 8 (6) years	Cross-sectional	BACS	Three MDD subgroups, one with attention impairments
Ji et al. (72)	67 patients with MDD (MDD) 56 Healthy controls (CG)	MDD: 31 (10) CG: 34 (13)	MDD: 37 females CG: 31 females	MDD: 14 (3) CG: 13 (5)	HAMD-17: MDD 21 (3) CG: 2 (2)	4 (2)	Longitudinal with a 6 month follow up	Digital symbol substitution, and digit span forwards- and backwards test	Poorer cognitive functioning in MDD group, remission associated with improved attention
The scar hypothesis									
Hammar et al. (81)	31 patients with First Episode (PG) 31 individually matched Healthy controls (HC)	26 (6)	15 females	14(2)	MADRS: 24 (4)	First Episode	Cross-sectional	Experimental Paradigm based on visual attention	First Episode patients show no impairment on an effortful visual attention task
Hammar and Årdal (82)	T1: 21 patients diagnosed with MDD	T1: 43 (10)	11 females	14 (4)	T1 HDRS: 22 (4) T2 HDRS: 6 (5)	10 (13)	Longitudinal with a 10 year follow up (T2)	Experimental Paradigm based on visual attention	Patients with recurrent MDD showed impairment at baseline, however normalized performance in a 10-year follow up
The trait hypothesis									
Lee et al. (44)	15 samples with 644 patients	39 (10)	Not reported	Not reported	Not reported	First episode patients	Meta-analysis	Digit span forwards; spatial span forwards Digit span backwards; spatial span backwards Trail Making Test B	Attention seems to be a trait-marker
Clery-Melin and Gorwood (84)	508 depressed patients	44 (13)	60% females	31% below high school	QIDS-SR: 16 (5)	First Episode: 62% 1 episode: 15% 2 and more episodes: 23%	Cross-sectional	d2 TMT	Findings indicated a stable marker of attentional deficit

BACS, The brief assessment of cognition in schizophrenia (BACS); IL-6 = CANTAB, Cambridge Neuropsychological Tests Automated Battery; PHQ-9, Patient health questionnaire; QIDS-SR, The Self-Report Quick Inventory of Depressive Symptomatology; HDRS, Hamilton Depression Rating Scale.

TABLE 4 | Findings within the domain of processing speed regarding origin of impairment.

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
The state hypothesis									
Lee et al. (44)	15 samples with 644 patients	39 (10)	Not reported	Not reported	Not reported	First episode patients	Meta-analysis	Trail Making Test A; Digit Symbol-Coding; Symbol Digit Modalities Test	Psychomotor speed was associated with clinical state
Egerhazi et al. (52)	25 patients in acute phase (AP) 11 patients re-tested in remitted phase (RP)	AP: 57 (8) RP: 55 (6)	AP: 14 females RP: 9 females	Not reported	AP HDRS: 23 (5) RP: HDRS: 8(4)	Not reported	Longitudinal Baseline and 6 months follow up	CANTAB	Cognitive impairment is mood related with an improvement in psychomotor speed during remission
Vasavada et al. (54)	44 MDD 33 demographically similar controls (CG)	MDD: 41 (13) CG: 39 (12)	MDD: 26 females CG: 19 females	MDD: 16 (3) CG: 17 (2)	MADRS T1 = 37 (8) T4 = 17 (12)	>1 Episode, 16 years mean duration	Longitudenal	Trail A, Digit span	Processing speed only domain improving
Ahern and Semkovska (45)	31 studies with 994 patients	Weighted mean age: Patient 27 Control 30	patients: 586 females Control: 761 females	Not reported	Not reported	First Episode patients	Review and meta-analysis	TMTA, number-coding, symbol digit-modalities, substitution test, Stroop I/II,	Remission was associated with a normalization of function in processing speed
Jaeger (87)	Review of specific studies using the digit symbol substitution task	Not reported	Not reported	Not reported	Not reported	Not reported	Review	digit symbol substitution task	Consistently impaired performance on the digit symbol substitution task
Mak et al. (71)	35 MDD 35 Healthy matched controls (hMC)	MDD: 25 (4) hMC: 22 (3)	20 MDD 23 females hMC	MDD: 14 (2) hMC: 15 (1)	MADRS MDD: 23 (5)	1 (1)	Cross sectional case-control	TMT	MDD scored worse than hMC on processing speed
Pu et al. (46)	170 patients with non-psychotic MDD	38 (12)	79 females	Duration of education: 15 (2)	HAMD: 8 (4)	Not reported Duration of illness 8 (6) years	Cross-sectional	Brief Assessment of Cognition in Schizophrenia (BACS) Verbal memory: List Learning Test	A subgroup with MDD showed processing speed deficits
The scar hypothesis									
Saleh et al. (76)	64 antidepressant free depressed (PG) 65 non depressed (CG)	PG: 35(9) CG: 29(9)	39 females PG 43 females CG	PG: 35.1(8.9) CG:29(9.2)	MADRS PG: 25(5)	Episodes not reported, duration in years 6 (5)	Cross sectional case-control	Composite consisiting of TMTA, Stroop 1, symbol digit modalities	Early traumatic experiences could influence processing speed in MDD

(Continued)

TABLE 4 | Continued

Study	*N*	Age (SD)	Sex	Education	Depression severity	Number of episodes	Study design	Neuropsychological tests	Key outcomes
Chakrabarty et al. (77)	MDD without maltreatment (DM+): 93 MDD with maltreatment (DM-): 90 Healthy controls with maltreatment (HM+): 22 Healthy controls without maltreatment (HM-): 80	DM+: 37 (12) DM-:34 (13) HM+: 34 (10) HM-: 33 (11)	DM+: 63 females DM-: 51 females HM+: 12 females HM-:54 females	DM+: 14 (2) DM-: 14(2) HM+: 16 (2) HM-: 16 (2)	MADRS DM+: 31 (6) DM-: 29 (6)	DM+: 4 (4) DM-:3 (3)	Longitudinal with baseline, 8 weeks and 16 weeks follow-up	Central Nervous System Vital Signs (CNS-VS) computerized battery with a global composite score	Maltreatment may be a risk factor for more severe and persistent cognitive deficits in adult MDD
Semkovska et al. (14)	11 882 major depressive episode remitters 8,533 healthy controls	Not reported specifically	Not reported specifically	Not reported specifically	Not reported specifically	Not reported specifically	Systematic review and meta-analysis	TMT A, Digit symbol Test	Number of episodes showed significant relationship to digits symbol (largest) and TMT A
The trait hypothesis									
Wekking et al. (53)	137 remitted MDD patients	45 (9)	102 females	14 (2)	HDRS: 4 (23)	6 (9)	Cross-sectional	Stroop I (Color) Stroop II (Word)	Persisting PS deficits unrelated to prior course of illness (except age of onset)
Xu et al. (47)	293 Unipolar depression patients (UP) 202 Healthy Controls (HC)	UP: 35 (13) HC:34 (10)	162 females	UP: 11 (4) HC: 13 (4)	HDRS: 27 (6)	2 (2)	Longitudinal Baseline and 6 weeks follow up	Processing speed: Trail Marking Test-part A (TMT-A) Digit symbol of Wechsler Adult Intelligence Scale	Remitted unipolar patients showed cognitive impairment in processing speed
Shimizu et al. (51)	43 remitted MDD patients (PG) 43 healthy Controls (HC)	PG: 38 (9) HC: 39 (11)	PG: 10 females HC 18 females	PG: 15 (2) HC: 15 (1)	HAM-D: 3 (2)	2 (1)	Cross-sectional	Continuous performance test (CPT) Trail Marking Test (TMT)	Patients in remission of recurrent depression show impairment I processing speed
Albert et al. (36)	91 depressed (PG) 105 non-depressed (HC)	PG: 36(9) HC:30(9)	PG: 61 females HC: 68 females	PG: 15 (2) HC: 16 (2)	MADRS: 24 (4)	Mean Duration in days: 2,116 (1,800)	Cross-sectional	Processing speed: Symbol–Digit Modality Trail Making A Stroop Color Naming condition	Found a composite measure of processing speed to be the most impaired in MDD

MADRS, Montgomery-Åsberg Depression Rating Scale.

Still, many patients with a prior history of depression report that they struggle with everyday cognition, such as organizing activities, maintaining attention during a conversation and being more vulnerable to distractions in crowded spaces. They indicate that these challenges lead to stress and feelings of being unable to satisfy their own, or others' expectations. This may create an interpersonal vulnerability. Self-report measures reveal these subjective cognitive problems to a much larger degree than measures with objective standardized tests or experimental paradigms (31, 33). Although the patients have many of their cognitive skills intact, one might wonder why they still struggle to use them optimally in everyday life and thereby underestimate their actual cognitive potential due to negative bias and depressive residual symptoms. If the cognitive capacity is limited in one area, this will have an impact on other areas, since daily life functioning requires multiple simultaneous cognitive skills to enable a person to function optimally. In addition, depressive biases could influence self-report and contribute to negative self-ratings, which could explain why symptoms and self-reported cognition and depressive symptoms show greater relationships than self-report and neuropsychological results (88, 89). Reduced cognitive functioning in phases of recovery and being unable to achieve at a premorbid level may lead to negative self-representation and ruminative tendencies (7, 90, 91), and thus increase the risk of relapse and recurrence of the illness (29, 38, 92). Self-reported cognitive deficits are related to both functional disability outcome and are predictors of relapse and recurrent episodes (31, 33).

Targeted Treatment for Cognitive Residual Symptoms

Because of the association between cognitive residual symptoms and the risk of relapse and new episodes, we have to invent treatment programmes (93) targeting these symptoms both acutely (94), and in remission (42, 95). By targeting the cognitive residual symptoms with interventions that remediate or enhance the cognitive capacity one might prevent the negative loop as consequence of failing to function optimally in everyday life (96, 97).

Cognitive enhancement therapy (CET) comprises three important elements; (1) psychoeducation of cognitive residual symptoms, (2) strategies and training of cognitive residual symptoms, (3) transfer the skills to everyday life functioning (96). There are however, several major challenges that must be addressed before such interventions can be standardized treatments of cognitive residual symptoms. First, knowledge regarding cognitive residual symptoms has been acknowledge and understood among healthcare personal and has to be incorporated both in education and in therapist training. Secondly, the frontiers of such interventions have to be explored in open and full trials with specified outcome measures, with a clear goal of enhancing the cognitive capacity in this patient group with a transfer to everyday life functioning. Thirdly, such interventions must be available to the patient group, which is normally outside primary care, since end of treatment for depression is often set at remission of mood symptoms. One way to achieve this is to make CET available in e-health care. Conclusions from a recent open pilot study of an internet-delivered CET intervention showed high compliance and feasibility in such an approach, besides the fact that the remitted MDD patients reported significantly less cognitive residual symptoms after the intervention and that this improvement prevailed at 6 months' follow-up (98). Through in-depth knowledge regarding neurocognitive profiles of depression, it will be possible to target specific aspects in CET treatment to prevent chronic course, disability, and potentially reduce the incidence of dementia. Recent and high-quality evidence on the effectiveness of cognitive-oriented psychosocial interventions has been provided in the treatment of other mental disorders characterized by cognitive impairment, e.g., schizophrenia (99) and one might expect that these promising findings may also be applicable for remitted MDD patients with cognitive residual symptoms.

Limitations

It is important to note that the present study is not a systematic review. It is based on a comprehensive literature search and is intended to present a narrative review to identify research gaps in the field and highlight methodological concerns. This, however, comes with the risk of not being able to clarify issues such as the future research questions that are not needed (100). Moreover, this summary has not found any cohort studies measuring cognitive functioning prior to first episode of depression, which is the ideal design for support of the trait hypothesis. Following this, the presented literature supporting the trait hypothesis should be interpreted as tentative.

CONCLUSIONS AND FUTURE STUDIES

MDD is characterized by residual cognitive symptoms. The origin of these residual symptoms can be explained by three major neurocognitive profiles: the scar profile, the state profile and the trait profile. However, the understanding of the origin and role in the neurocognitive profile is still oversimplified, and further knowledge is needed in order to enhance our understanding of the complexity of cognitive impairment in depression.

We therefore suggest a shift of focus in two main areas when studying the neurocognitive profile in depression: (1) A shift in focus from domain level to aspect level in cognitive functioning (see **Figure 2**). As an example, studying EF at the domain level might provide general and unspecific knowledge, with the risk of concluding intact EF functions in people with a history of depression. In contrast, when focusing at an aspect level, such as inhibition in EF, it is evident that this provides a more nuanced knowledge regarding the role and origin of neurocognitive profiles in depression. (2) A shift in focus from considering that depression labels one unitary group with little or no differentiation with regard to age, onset, duration, number of episodes, etc., to a much more nuanced diagnostic approach. In addition, we suggest a focus on possible origins to the onset of depression (such as inheritance or life events), when including patients in future studies. We expect

that an in-depth, careful analysis of patients prior to inclusion, as opposed to the understanding of depression as a unitary group, will contribute toward discovering subgroups of patients with neurocognitive profiles more prone to lead to cognitive residual symptoms.

Defining the neurocognitive profiles in depression could have significant consequences when developing new treatments targeting cognitive residual symptoms so as to prevent relapse, new episodes and increased the risk of neurodegenerative disorders later in life.

AUTHOR CONTRIBUTIONS

All authors have contributed to the writing of the Introduction, Methodological, Result and Discussion Sections. ÅH and EHR have been responsible for the tables and ÅH for the figures. All authors have approved the final manuscript.

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SYSTEMATIC REVIEW
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The Impact of Cognitive Behavioral Therapy on Peripheral Interleukin-6 Levels in Depression: A Systematic Review and Meta-Analysis

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There is interest in the role of peripheral interleukin-6 (IL-6) in depression and the effect of treatment (e. g., pharmacologic, psychosocial, neurostimulation). However, the relationship between cognitive behavioral therapy (CBT), IL-6 and depression has not yet been established. We conducted a meta-analysis to explore the association between CBT and change of peripheral IL-6 levels in depressive symptoms or major depressive disorder (MDD). A systematic search of online databases (i.e., PubMed, Web of Science, Google Scholar, PsycINFO, and Cochrane Library) was completed from inception to May 2021. In total, 10 eligible papers with 940 participants reporting peripheral IL-6 levels before and after CBT were included in the analysis. The main result indicates that peripheral levels of IL-6 were significantly lower after CBT intervention in individuals with depression, with a small effect (SMD = 0.38, 95% CI: 0.07, 0.69, $p = 0.02$). The results of subgroup analyses demonstrate that (1) there was a significant decrease in IL-6 for studies that were equal to or <8 weeks in duration vs. more than 8 weeks in duration, and (2) IL-6 was significantly reduced in the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis (i.e., DSM-IV, DSM-IV-TR, or DSM-V) of MDD, but not for the subgroup without DSM diagnosis. Publication year was identified as a potential contributor to heterogeneity of the results from our analysis. Taken together, our findings support the notion that CBT influences peripheral IL-6 in individuals with depression and represents a point of commonality with other antidepressant treatment modalities (e.g., antidepressants).

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Keywords: cognitive behavioral therapy, IL-6, depression, inflammation, cytokines, biomarkers

INTRODUCTION

Major depression is a major public health issue implicating significant economic and psychosocial burden (1). Current predictions reported by the World Health Organization (WHO) indicate that depression will be the leading cause of disease burden globally by 2030 (1). The pathophysiology of depression is unknown, but is known to be factorial involving neurobiological systems subserving

stress response, and their interaction with environmental, psychosocial, and spatial determinants of health (2). A study by (3) reported that major depression is associated with activation of the inflammatory response system (4). It is also reported that an activated inflammatory system is associated with abnormal hedonic and cognitive function in adults with depression (5–7).

It is separately reported that disparate antidepressant modalities influence peripheral cytokine concentrations in adults with depression (6). Moreover, it is separately reported that elevated inflammatory markers may be a predictor of non-response with selective serotonin reuptake inhibitor (SSRI) therapy (2, 8). However, previous studies have reported mixed results as it relates to the relationship between depression and inflammatory biomarkers (9–11). Due to the heterogeneity of inflammatory markers as a group, it has been suggested to explore the effect of a single inflammatory marker, such as IL-6, in depression (12–14). Excess or chronic inflammatory cytokine activity, on the other hand, disrupts various neural activities, including neurotransmitter signaling, neurotransmitter synthesis, reuptake, and release (15–17). Thus, neurocircuit function, especially that linked to mood and cognition, is affected (18).

Cognitive behavioral therapy (CBT) is a structured, short-term and targeted psychotherapy with replicated evidence of acute antidepressant and recurrence prevention effects in adults with MDD. Cognitive behavioral therapy is one of the most common psychosocial interventions for mental disorders (19, 20). Cognitive behavioral therapy targets cognitions (i.e., thoughts) that reinforce dysfunctional beliefs and behaviors relevant to clinical symptoms (20, 21).

The mechanism of action of CBT is unknown and its effect on neurobiological systems implicated in depression are not well-characterized. The latest meta-analysis paper revealed that psychosocial interventions including CBT were significantly associated with levels of proinflammatory cytokines or markers (22). However, the study only included two papers on the topic of association between CBT and immune system function in people with depression. Besides, depression was not precisely defined in the study. Preliminary evidence suggests that peripheral IL-6 levels in adults with depression are reduced after 7 weeks of CBT in responder analysis (23). Results are mixed, insofar as a 16-week study of CBT monotherapy in adults with a first-episode of depression was associated with reduced TLR-4 signaling, but the changes from baseline to endpoint in TLR-2 signaling, IL-6, and c-reactive protein (CRP) levels were not statistically significant. A systematic review by Lopresti et al. (24) evaluating the association between CBT and change of peripheral IL-6 levels was not able to identify a consistent effect. For more rigorous verification, a meta-analysis evaluating the impact of CBT on changes of peripheral IL-6 levels in individuals with depression is urgent needed.

Against a background of inconsistent findings in the extant literature, the aim of the study herein was to use a meta-analysis to comprehensively and systematically evaluate the impact of CBT on changes of peripheral IL-6 levels in individuals with depression. The results of this analysis are intended to guide further mechanistic research and inform conceptual frameworks.

METHODS

Search Strategy

Two investigators (HJM and JTX) independently conducted the literature search to identify studies reporting IL-6 levels of subjects with depression before and after CBT intervention. The information in this review was compiled by searching online databases: PubMed, Web of Science, Google Scholar, PsycINFO, Cochrane Library databases, and by searching the reference lists of relevant papers to locate additional studies that were not identified by the database searches. The databases were scanned from inception to May 2021. Systematic searches were completed using terms including "cognitive behavioral therapy," "CBT," "psychotherapy," "inflammation," "IL-6," "interleukin," and "immunity," "MDD," "major depressive disorder," "depressive."

Eligibility Criteria

The inclusion criteria were as follows: (1) The study subjects were adults (≥18 years old) with a diagnosis of major depressive disorder (MDD) based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (i.e., DSM-IV, DSM-IV-TR, or DSM-V), or MDD with other chronic diseases; Or had a verified scale to assess depressive symptoms (including subthreshold depression: clinically relevant depressive symptoms, without meeting criteria for a full-blown MDD); (2) Follow-up results after CBT intervention were reported (baseline assessment scores vs. post-treatment scores); (3) The peripheral IL-6 levels were evaluated before and after CBT; (4) identified random controlled trials (RCT), open-label studies, and longitudinal studies with pre-test-post-test design were included in our analysis.

Exclusion criteria included: (1) Non-original studies (e.g., review, meta-analysis, systematic review, standards, guidelines, teaching materials, books; (2) Non-research articles (e.g., descriptive introduction of disease progression, etiology, intervention, differential diagnosis, research protocol); (3) Conference abstracts and unpublished literature; (4) case reports, case studies, case series studies, case control studies; (5) Basic experimental research studies (e.g., animal, cell, tissue, etc.); (6) studies including subjects that did not have a DSM-defined diagnosis of MDD, and/or included case groups with comorbid mental disorder diagnoses (e.g., schizophrenia, bipolar disorder) without depressive symptoms; (7) studies without follow-up results (8) studies including healthy individuals or individuals with other diseases analyzed as the control group; (9) studies that did not report on peripheral IL-6 levels as part of the study outcome.

Outcome and Recorded Variables

The purpose for the meta-analysis was to examine the relationship between CBT and the change of peripheral IL-6 levels in individuals with depression from baseline to endpoint. First author, published year, country, sex (male/female), mean age (age range), total *N* at baseline, clinical diagnosis, comorbidity, IL-6 measure method, diagnostic criteria, study design and duration of intervention were recorded for each eligible study for analysis. All eligible studies were screened and evaluated by

two independent investigators. We also carefully verified data from each included article to ensure the accuracy of the extracted data. Any discrepancies were resolved by discussion among all of the authors.

Statistical Analysis

Statistical analysis was performed using Review Manager 5.4.1 and Stata 12.0. Forest plots were used to estimate the change of peripheral IL-6 levels in individuals with depression from baseline to end point, which was evaluated by the standardized mean difference (SMD) within a 95% confidence interval (CI). According to the statistical power analysis for the behavioral sciences (2nd edition), the effect size of SMD is judged using the following rules: trivial (SMD $<$ 0.20), small (0.20 $\leq$ SMD $<$ 0.50), medium (0.50 $\leq$ SMD $<$ 0.80), and a large effect (SMD $\geq$ 0.80). The chi-square and I-Squared (I^2) test was used to evaluate the heterogeneity across the studies. It has been suggested that the adjectives low, moderate, and high (heterogeneity) be assigned to I^2 values of 25, 50, and 75%. If $P < 0.10$ or $I^2 > 50\%$, there would be a high degree of heterogeneity with statistical differences (25), and a random effects model was applied to pool data. The fixed effects meta-analysis was used in the other cases. To identify probable causes of heterogeneity, subgroup analyses about the development levels of countries, publication years, whether DSM diagnosed and duration of CBT intervention were carried out.

Meta-regression analysis was also performed to examine whether IL-6 levels in subjects with depression could be influenced by pre-specified independent variables, which evaluated the effect of years of publication, mean ages, and sex ratios. Sensitivity analysis was performed to identify potential outliers by eliminating each study individually, which examined the impact of each study on the overall effect size. Publication bias was assessed by applying Egger's test and Begg's test for funnel plot asymmetry.

We used Grades of Recommendations Assessment, Development and Evaluation (GRADE) to assess the quality of included studies (26). The assessments were based on following aspects: study limitations, risk of bias, inconsistency of results, indirectness (i.e., different subjects, interventions and results from the aimed ones), random error and publication bias. The

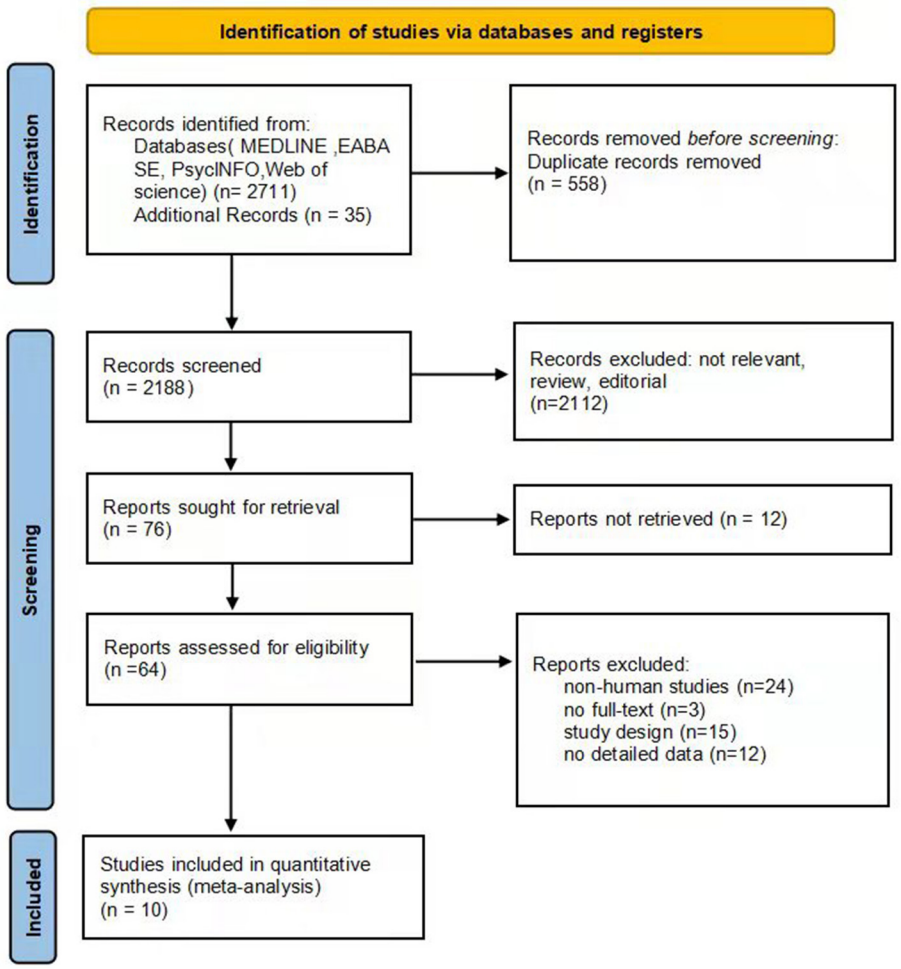

FIGURE 1 | Summary of the article extraction process, including the reasons for exclusion.

TABLE 1 | Characteristics of included studies.

References	Country	Sex (Male/Female)	Mean age (Age range)	Total *N* at baseline	Clinical diagnosis	Comorbidity	IL-6 measure method	Diagnostic criteria	Study design	Duration	Quality assessments
Moreira et al. (23)	Brazil	7/21	24.46 ± 3.61	97	MDD	No	Commercial mmunoassay kit	DSM-IV	Double-blind, Randomized trial	7 w*	Moderate
Euteneuer et al. (28)	German	18/16	36.9	101	MDD	Anxiety disorders Somatoform disorders	Flow cytometry using bead-based assays	DSM-IV	Double-blind, Randomized trial	16 w	High
Gazal et al. (29)	Brazil	0/11	25.18 ± 3.51	11	MDD	No	IL-6 immunoassay kit	DSM-IV	before-after study in the same patient	7w	Moderate
Kéri et al. (32)	Hungary	19/31	22.6	80	MDD	No	High-sensitivity enzyme-linked immunosorbent assay kits	DSM-IV and SCID-CV and HAM-D	Double-blind, Randomized trial	16 w	High
Zautra et al. (35)	USA	46/97	52.41	144	Depressed	Rheumatoid arthritis	Commercially available enzyme linked immunosorbent assay kits	DSM-IV	Randomized trial	8 w	High
Berk et al. (27)	USA	23/44	52.5	132	MDD	One or more chronic medical illnesses	Millipore's multiplexed high sensitivity cytokine magnetic bead-based immunoassay kits	DSM–IV and BDI-II	Double-blind, multi-site randomized clinical trial	12 w	High
Hsu et al. (31)	China		75.3 (±4.61)	20	Depressed	No	Not mentioned	CES-D	Randomized trial	8 w	Moderate
Hermanns et al. (30)	German	46/60	43.2 ± 14.9	214	Depressed	Diabetes	Quantikine HS (IL-6) ELISA kits	CES-D	Blind, Randomized Study		High
Moore et al. (34)	USA	9/40	70.86	100	Depressed	Dementia	ELISA	Positive and Negative Affect Schedule	Double-blind, Randomized trial	6 w	High
Lasselin et al. (33)	Sweden	9/32	40.9	41	Depressed	Longstanding pain	ELISA	HADS	Randomized trial	12 w	Moderate

**w, weeks.*

MDD, major depressive disorder; ELISA, high-sensitive enzyme-linked immunosorbent assays; DSM-IV, diagnostic and statistical manual of mental disorders IV; CES-D, center for epidemiological survey; HADS, Hospital anxiety and depression scale; BDI-II, beck depression inventory II; HAM-D, Hamilton depression scale; SCID-CV, structured clinical interview for DSM-IV axis I disorders -clinical version.

total grade scored ≥0 indicated high-grade evidence, that scored −1 indicated moderate-grade evidence, that scored −2 indicated low-grade evidence, that scored ≤-3 indicated very low-grade evidence. A two-tailed $P < 0.05$ were considered significant in all test.

RESULTS

Search Results

The summary of the article extraction process for this meta-analysis is shown in **Figure 1**. In total, 2,746 records were identified as potentially eligible through the initial systematic literature search. After removing duplicate studies, 2,188 studies remained, of which 2,112 were further excluded based on reviews of titles and abstracts. Afterwards we examined the full text of the remaining 76 relevant articles, and 12 of them were not retrieved. In the remaining 64 papers, 24 were non-human studies, 3 were not full-text, 15 did not meet a criterion for inclusion, and 12 did not provide detailed data. Finally, 10 studies were eligible for inclusion in our meta-analysis (23, 27–35).

Ten studies were identified comprising 940 participants were conducted in six countries: USA ($n = 3$); Germany ($n = 2$); Brazil ($n = 2$); and China ($n = 1$), Sweden ($n = 1$), Hungary ($n = 1$). Six studies used Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) as diagnostic criteria for depression; two implemented the Center for Epidemiological Survey (CES-D) and one study each used the Positive and Negative Affect Schedule, Hospital Anxiety, and Depression Scale (HADS), respectively. Eight studies had more females than males, among them, one had only female; one study had less females than males; and one did not include the sex. According to the GRADE system, four studies are rated moderate and six are rated HIGH. The main characteristics of the included studies and quality assessments are shown in **Table 1**.

Preliminary Meta-Analysis Analysis Results

Overall meta-analysis results are shown in **Figure 2**. Due to the high heterogeneity among included literatures ($p < 0.00001$; $I^2 = 79\%$), the random effects model was adopted for the analysis. Since the scales are consistent across studies, we used SMD for data processing. The results indicate that there was a statistically significant difference in the peripheral levels of IL-6 before and after CBT intervention, with a small effect (SMD = 0.38, 95% CI: 0.07, 0.69, $p = 0.02$). In order to explore the potential sources of heterogeneity, subgroup analysis, regression analysis, and sensitivity analysis were carried out in the following studies.

Subgroup Analysis

We performed the subgroup analyses to identify the sources of the literature heterogeneity. For the classification of developed and developing countries, we found that the overall combined change of peripheral IL-6 levels was statistically significant in developing countries (SMD = 0.70, 95% CI: 0.02, 1.38, $p = 0.04$), but the data heterogeneity remained medium ($p = 0.10$, $I^2 = 57\%$). In the subgroup of developed countries, IL-6 levels do not have a significant overall comprehensive effect ($p = 0.11$), and its heterogeneity is also large ($p < 0.0001$, $I^2 = 82\%$), indicating that subgroup analysis of the classification of developed and developing countries cannot explain the heterogeneity sources of IL-6 levels in all included studies.

According to the treatment duration of the studies included in our analysis, we used 8 weeks as a cut-off point to conduct subgroup analysis. Four original studies reported a treatment duration ≤8 weeks, five studies reported a treatment duration of more than 8 weeks, and one study did not report the treatment duration. As shown in **Figure 3**, there was significant difference in the subgroup ≤8 weeks (SMD = 0.86, 95%CI: 0.49, 1.23, $p < 0.00001$), whereas there was no significant difference in subgroup >8 weeks ($p > 0.05$). Moreover, the heterogeneity was lower in both of the two subgroups. There was strong heterogeneity and significant difference among subgroups ($p = 0.0003$, $I^2 = 87.6\%$).

According to the diagnosis method, we used diagnosis of depression as a cut-off point to conduct subgroup analysis. Six original studies reported depression diagnosed method is DSM, four reported others. As shown in **Figure 4**, there was significant difference in the subgroup DSM diagnosis (SMD = 0.41, 95%CI: 0.01, 0.80, $p = 0.05$), whereas there was no significant difference in subgroup without DSM diagnosis ($p > 0.05$). The heterogeneity was high in both of the two subgroups. There was low heterogeneity and significant difference among subgroups ($p = 0.83$, $I^2 = 0\%$).

Meta-Regression Analysis

We conducted univariate meta-regression analysis for the year of publication, average age and sex ratio (male/female) of the included studies (**Supplementary Table 1**). Among them, the analysis results of the year of paper publication were statistically significant [$\beta = -0.49$, 95% CI = (−0.88, −0.09), $t = -2.86$, $p = 0.02$], and the goodness-of-fit of the model was good ($Tau^2 = 1.423$). The estimation of variation among studies was relatively high (Adjusted R-squared = 52.91%).

Sensitivity Analysis and Publication Bias

In order to test the stability of the results, we conducted sensitivity analysis to test the stability of the combined effect sizes, and their 95% CI. As shown in **Supplementary Figure 4**, the point estimate after the deletion of Moore et al. (34) fell outside the 95% CI of the total effect size. After the deletion, the estimate value was 0.26, and 95% CI = (−0.003, 0.532); therefore, the study may have impact on the pooled effect size. The Egger's test and Begg's test were used to evaluate the possibility of publication bias. The results indicated there was no potential publication bias for all included studies according to Egger's 95% CI = (−1.91, 7.48), $t = 1.37$, $p = 0.208$. In addition, the results of Begg's test did not show publication bias with $z = 1.34$, $p = 0.180$.

DISCUSSION

The results of our analysis indicate that CBT is associated with significant decreases of peripheral IL-6 levels with small effect in persons with depressive symptoms or MDD. Due to the potential heterogeneity of main outcome, subgroup analysis and meta-regression analysis were used to identify probable sources of heterogeneity. Subgroup analysis revealed a significant decrease

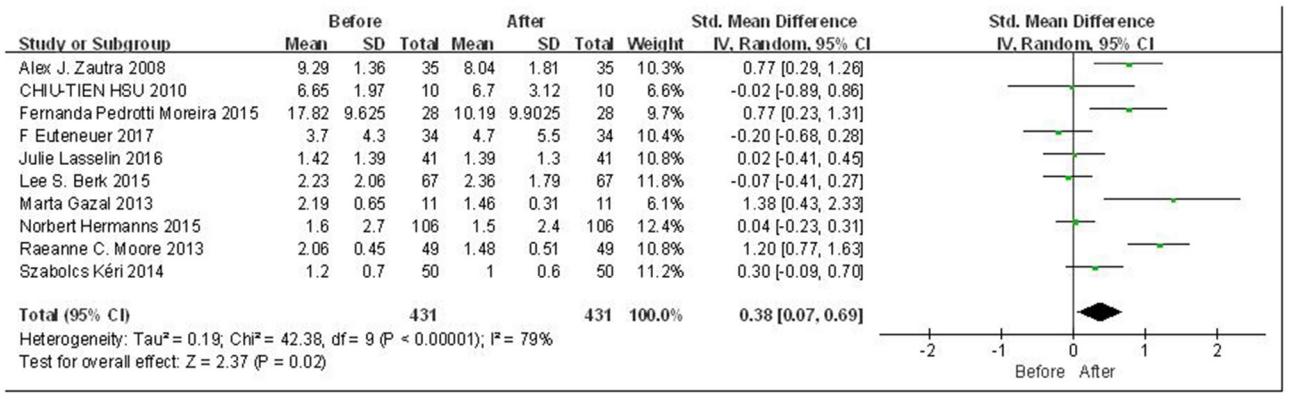

FIGURE 2 | Forest plot for change in IL-6 before and after CBT.

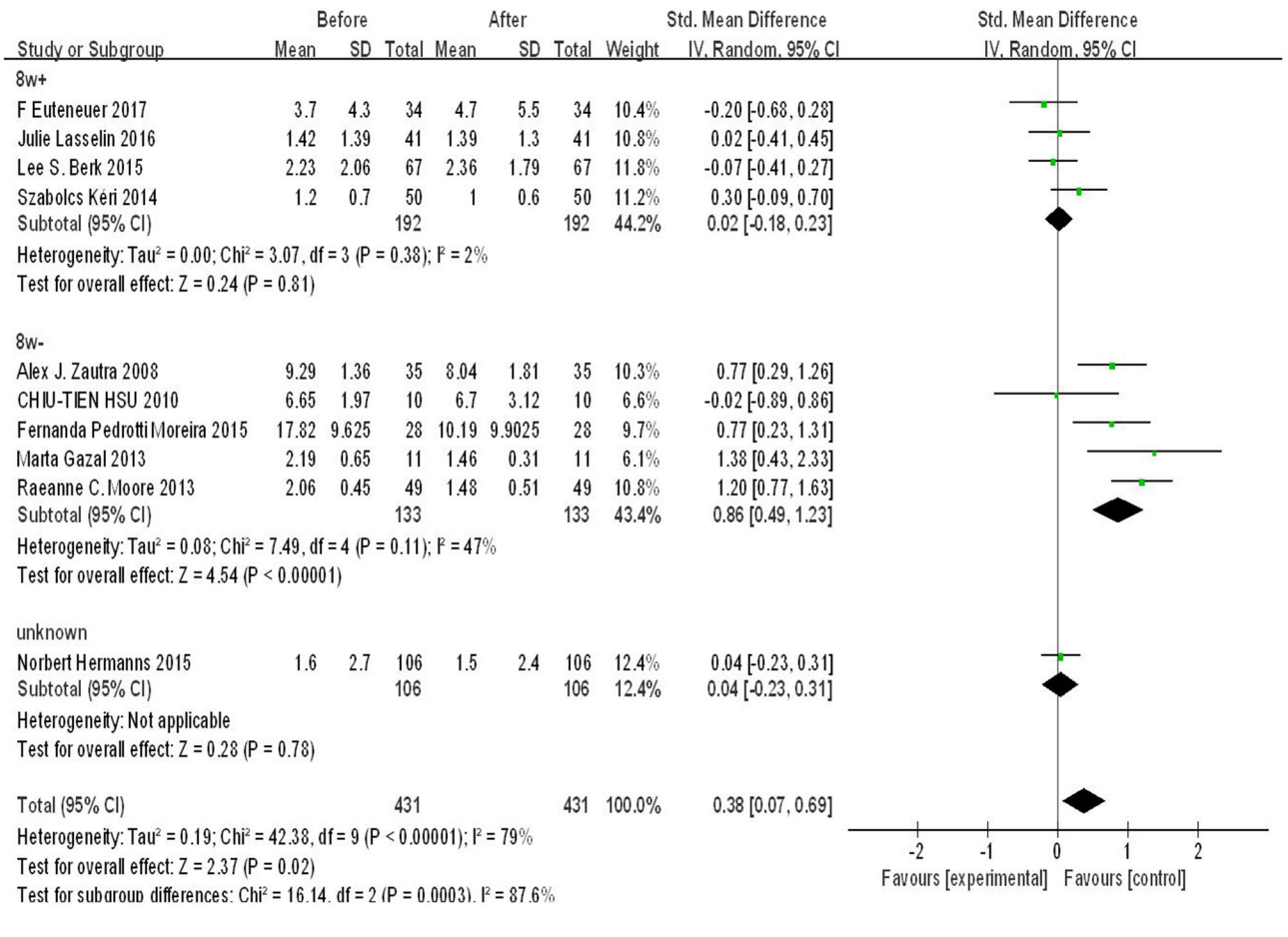

FIGURE 3 | Forest plot for change in IL-6 before and after CBT with CBT intervention duration of 8 weeks.

in peripheral IL-6 in studies of 8 weeks duration or less, with no effect noted in studies of >8 weeks duration. The association between CBT and change in peripheral IL-6 was delimited to those studies that codified the diagnosis of MDD using the DSM (i.e., DSM-IV, DSM-IV-TR, or DSM-V). It was also revealed that publication year might be a potential contributor to heterogeneity in the findings. Moreover, no potential publication bias was identified in the studies in our analysis.

In general, our meta-analysis identified the potential modulating effect of CBT on IL-6. Cognitive behavioral therapy

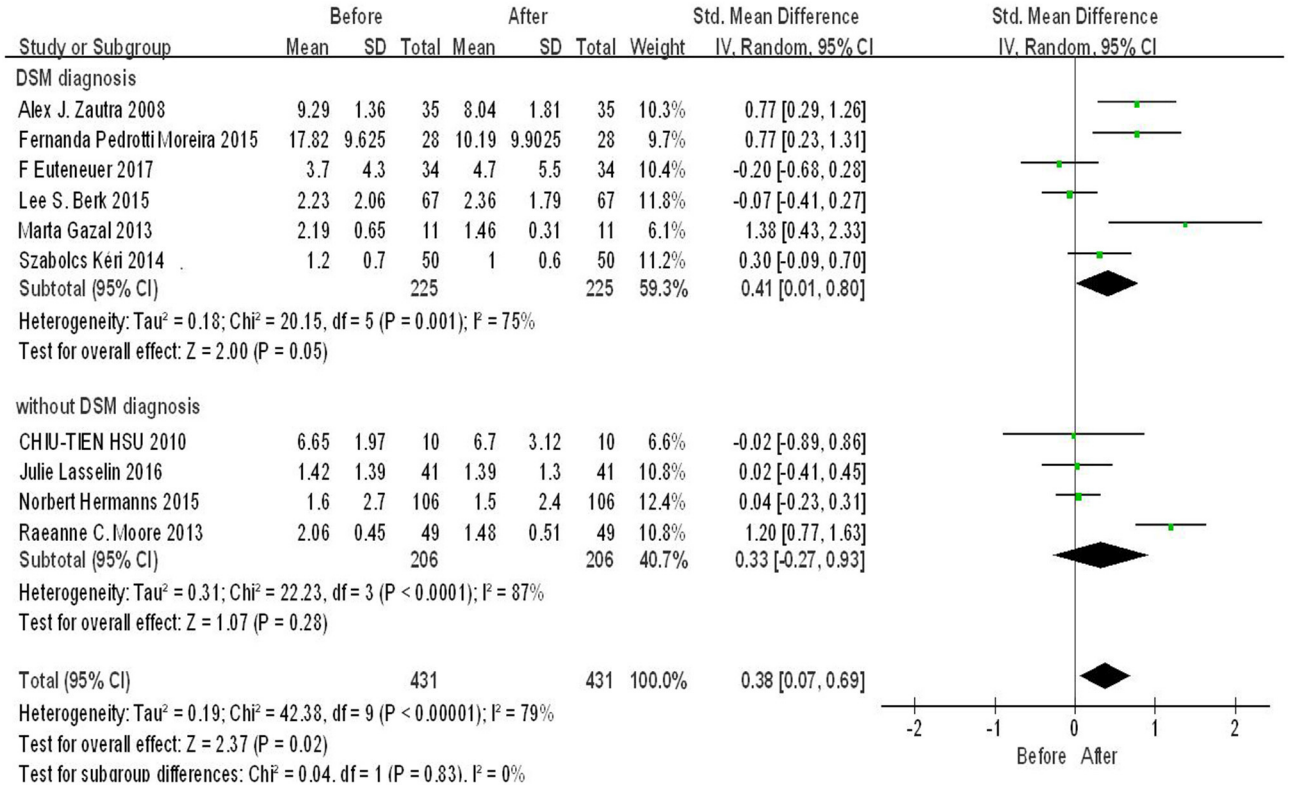

FIGURE 4 | Forest plot for change in IL-6 before and after CBT under different depression diagnosis method.

covers a range of strategies that could account for its potential anti-inflammatory effects. Cognitive behavioral therapy can trigger positive lifestyle changes that in turn reduce inflammation (36). Cognitive behavioral therapy also encourages the teaching of different relaxation techniques as well as participation in enjoyable activities (24). According to (37), research shows that in a dose-dependent manner, consistent relaxation practice may have favorable benefits on numerous immunological responses. An objective of CBT is to alter information processing. It has been reported that individuals who experience more frequent positive events show lower log IL-6 stimulation production, and that small positive events in daily life may result in reduced inflammatory responses to immune challenges (38). This study also reported that the effects were stronger for those in the lowest quartile of positive event frequency, implying that a lack of optimism in daily life may have a significant impact on inflammation. Furthermore, interpersonal happy events were more likely than non-interpersonal positive events to predict lower IL-6 overall and lower fibrinogen in women (38).

Our results only identified the changes of peripheral IL-6 in individuals with DSM diagnosed MDD, no statistical changes were reported in individuals with depressive symptoms assessed by other scales. Major depressive disorder is heterogenous in phenomenology, illness trajectory, and pathoetiology (39). According to (40), some individuals with depression may be more likely to exhibit an inflammatory biotype. For instance, it has been reported that individuals with depression who have melancholic traits have a distinct inflammatory profile compared to individuals without melancholic features (41). Moreover, distinct inflammatory profiles may also be linked to different depression subtypes (42–44). Whether it is diagnosed as MDD, Depression subtypes, and the effect of disease progression on inflammatory response deserve further attention. Therefore, whether the diagnosis of MDD, depression subtypes or the disease progression affects the inflammatory response after CBT deserves further attention.

According to Lanquillon (45), there were significant decreases in C-reactive protein in both responders and non-responders (i.e., with or without a 50% reduction in depression measurement, respectively) receiving either pharmacologic or psychosocial interventions. However, it has been separately reported that peripheral IL-6 is reduced in intervention responders but not for intervention non-responders; a finding also replicated by Yoshimura et al. (46). The latter study revealed that IL-6 could act as a proxy to treatment response, and may account for heterogeneity or response within the sample.

Our subgroup analysis showed that only the studies with intervention of less than 8w had a significant decrease in peripheral IL-6, but the changes of peripheral IL-6 in studies with more than 8w had no statistical difference. It has been proposed that IL-6 hyperproduction may play a pathogenetic role in the immunological pathophysiology of major depression

due to its critical involvement in the early phase of the immune response cascade. Increased IL-6 activity in severe depression may be linked to hypotransferrinemia, hyperhaptoglobinemia, and hyperactivity of the HPA axis, according to the findings (47). Thus, our results may present that the short-term CBT may have obvious effects on inflammatory response due to rapid improvement of depressive symptoms. However, we did not find the direct evidence to support why the long-term effects of CBT on peripheral IL-6 were not significant. It is worthy to explore the underlying mechanisms. The future researches should increase the time and frequency of follow-up to furtherly determine our findings.

It is also worth noting that we identified publication year as a source of heterogeneity in our analysis. It is a testable hypothesis that changes in diagnostic criteria and treatments over the past two decades accounts for this variability. It is also possible that refinement of the CBT model and its implementation over the past several decades may be contributing to the observed heterogeneity (48). Our current findings provide valuable evidence for exploring the role of IL-6 in individuals with MDD receiving CBT in the future researches.

Moreover, evidence indicated that women are 1.5 to two times more likely than males to develop depression, and the onset of depression increases during the childbearing years. This female preponderance has been observed to last into elderly life. Patients above the age of 75 had a lower prevalence of depression, which did not appear to be connected to their socioeconomic level. Comorbid diseases, serum IL-6, albumin, and age may all have a role in determining which patients are more likely to develop depression symptoms (49). Therefore, further validation of confounding factors is needed in future studies. In addition, CRP and its precursor, IL-6, are linked to an increased incidence of depression, according to research (49). Therefore, future studies need to analyze the role of CRP levels, taking into account its association with IL-6.

Limitations

There are several limitations that affect interpretations and inferences of our study. Firstly, the sample size of this meta-analysis was relatively small (i.e., only 10 eligible studies were included in the data analysis). Secondly, studies included in our analysis had varying definitions of depression and five studies included individuals with subthreshold depression. Moreover, the sensitivity analysis indicated that our results had insufficient stability. Additionally, limited information in the included studies betrayed a thorough analysis of the sources of heterogeneity. As with all studies, we could not control for residual confounding effects. Finally, previous antidepressant treatment may also affect the levels of inflammatory factors such as IL-6, but we could not distinguish participants with prescribed medications or medication-free in the original studies.

CONCLUSIONS

Our results indicate that individuals with MDD or depressive symptoms receiving CBT have lower peripheral IL-6 concentrations. It is unknown whether the change on peripheral IL-6 levels is simply an association or whether the relationship observed has predictive and/or moderational effects. We did not evaluate CBT-IL-6 association from the point of view of dimension-based outcomes. Future studies will need to determine whether elevated IL-6 levels identify a biotype more likely (or less likely) to respond to CBT treatment (50).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BC and FY conceived and designed the study. HM and JX performed the data extraction and statistical analysis. RM, BC, FY, and KT contributed to the discussion. HM, JX, and RL took the lead in writing the manuscript. All authors discussed the results and commented on the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.844176/full#supplementary-material

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The relationship between psychological resilience, neuroticism, attentional bias, and depressive symptoms in college Chinese students

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In recent years, the incidence of depressive symptoms among Chinese college students has been increasing. Studies have shown that depressive symptoms are related to a variety of psychosocial factors, among which neuroticism, resilience, and attention bias are most notably related, but the correlation among the three is not clear. This study aimed to investigate the influence mechanisms of different degrees of resilience, attentional bias, and neuroticism in the formation of depressive symptoms. The college freshmen of this study were selected through stratified multi-stage cluster sampling. Students provided informed consent and then completed a general situation questionnaire and four scales: the Chinese version of the Connor–Davidson Resilience Scale, the Attention to Positive and Negative Information Scale, the Eysenck Personality Questionnaire, and the Zung Self-Rating Depressive Symptoms Scale. In total, 1,493 freshmen participated in the research group. Our results showed that low resilience, negative attention bias, and high neuroticism jointly increased the risk of depressive symptoms. There is a significant correlation between these three factors and depressive symptoms. Additionally, strength, tenacity, and attention bias all had more significant effects on the occurrence of depressive symptoms. These findings indicate that there may be an important psychological mechanism for the occurrence, development, and poor prognosis of depressive symptoms.

KEYWORDS

college freshmen, resilience, attentional bias, depression, neuroticism

Introduction

Mental health problems among college students in recent years have been a significant concern for society. According to a meta-analysis of 84 studies involving 1,292,811 college students, the detection rate of depressive symptoms among college students in China was 26% (Luo et al., 2021). The main symptoms of depression are

depressed mood, decreased interest, and slow thinking (Fan, 1993), and they can have a serious negative impact on people's lives (Luo et al., 2021). Depression results from the interaction between individual genes and the environment (Garber and Rao, 2014). Specifically, depressive symptoms are related to negative life events (Chen et al., 2013), interpersonal relationships (Dunn et al., 2011; Yang and Chen, 2015), personality dimension, parenting style, and family environment (Assche et al., 2017). A previous study has shown an increased risk of depression among Chinese college students during the COVID-19 pandemic (Zhang et al., 2021). At the same time, some scholars believe that the high detection rate of depressive symptoms among Chinese college students is related to professional satisfaction, employment prospects, personality, family, ethnicity, physical, academic performance, and interpersonal relationships (Yang and Chen, 2015; Wang M. et al., 2020; Feng et al., 2022). These are the important factors that affect emotions; however, why do some people become depressed while others are not affected by the same factors? Some researchers believe that one crucial factor that determines depressive symptoms is resilience, also known as "mental elasticity" or "recovery power," which is the psychological characteristic that someone possesses to solve problems and adapt to new situations with a positive mindset (Luthar et al., 2000). Studies have shown that depressive symptoms are associated with poor psychological resilience (Wang C. X. et al., 2020). Resilience has a buffering effect on people when they are faced with unexpected incidents in life and can reduce the symptoms of depression and anxiety (Ye et al., 2016; Sheerin et al., 2018). According to recent research, people with high resilience and a positive attitude toward life have lower levels of anxious and depressive symptoms (Song et al., 2021). The resilience of college students has a negative correlation with the extent of depressive symptoms, and high resilience has a preventive effect on these symptoms (Wei, 2019; Xu et al., 2021). Resilience has both short-term and long-term protective effects on college students (Wu et al., 2020). Guo et al. (2020) found that teacher support enhances mental well-being by decreasing negative emotions and then increasing resilience, meaning that the mediating effect of resilience between teacher support and mental well-being was relatively larger. Cognitive bias is believed to be related to various emotional disorders in human relationships, such as anxiety and depression (Taylor and John, 2004). Cognitive bias can be divided into different categories, including attention bias, interpretation bias, memory bias, and executive control bias (Joormann and Gotlib, 2010; Koster et al., 2011; Murrough et al., 2011). Attention is the first step in the cognitive process and plays a very important role. Studies on attentional bias have shown that depressive symptoms can be alleviated if attentional bias on positivity is enhanced (Dai et al., 2019). Meanwhile, improving attentional control also promotes resilient traits (Schäfer et al., 2015).

Neuroticism is a pattern of negative emotional responses to setbacks, failures, and dangers (Lahey, 2009). One study found that neuroticism significantly predicted depressive mood (Pereira-Morales et al., 2019). Kendler et al. (2004) found that high neuroticism contributes to a high overall risk of an individual's severe depressive symptoms. Studies have shown that people with high neuroticism are more susceptible to negative stimuli (Qin and Hi, 2008). These studies suggest that resilience, attention bias, and neuroticism may be closely related to depressive symptoms.

However, it is not clear which of the three traits plays a more significant role in depression. Thus, in this study, we aimed to determine the influence of neuroticism, attentional bias, and different degrees of resilience on the occurrence of depressive symptoms, in the hopes that we may understand their different roles and the psychological mechanism of depressive symptoms. We hypothesized that neuroticism, attention bias, and resilience are related to the occurrence of depressive symptoms. We also predicted that neuroticism and negative attention bias may have a greater impact on depressive symptoms under the condition of low resilience. We investigated a large sample of college freshmen to verify our hypothesis and build a foundation for research on the psychological mechanism of the production of depressive symptoms and the prevention and treatment strategy for depression in college students.

Materials and methods

Participants and procedure

This study was conducted between February and March 2021. The research data were collected through the Questionnaire Star online system. Participants were selected through stratified multi-stage cluster sampling. First, five universities were randomly selected from a larger group, that is, four from 60 universities in Tianjin and one from 20 universities in Ningxia. In the second stage, we randomly selected a major in each school to recruit students from. A total of 1,698 college freshmen were selected. The school tutor sent the survey link to each student by WeChat. The students read the informed consent form on their cell phones and agreed to participate in the study by completing the form. A total of 1,493 valid questionnaires were collected, representing 87.9% of the total number. There were 568 men and 925 women representing 38 and 62% in the research group, respectively. The average age of the participants was 18.92 ± 0.984 years. The study was approved by the Ethical Committee of the Tianjin Anding Hospital.

Instruments

Demographic information

Participants first completed a demographic information survey form that included age, gender, residence, major, and grade point average.

Connor–Davidson resilience scale

The Chinese version of the Connor–Davidson Resilience Scale (CD-RISC) was revised by Nan Xiao and Jianxin Zhang in 2007. The scale has 25 items covering three factors: tenacity (11–23), strength (1, 5, 7–10, 24–25), and optimism (2–4, 6). The scale is scored on a 5-point scale, with 0 meaning "never," and 4 meaning "always." The higher a participant's score, the higher their level of resilience. The sum of the items corresponding to each factor is the factor score. The total scale score is the sum of all items. The original Chinese version of the CD-RISC has a high internal consistency, with Cronbach's $\alpha = 0.91$ (Yu and Zhang, 2007).

Attention to positive and negative information scale

The Attention to Positive and Negative Information Scale (APNI) was used to assess positive and negative information attentional biases. The APNI was first developed by Noguchi in 2006 and translated and revised into Chinese by Dai et al. (2015). The scale had 22 items, divided into two separate scales of attention to positive information (API; 1, 6, 7, 9, 11, 13–18, 20) and attention to negative information (ANI; 2–5, 8, 10, 12, 19, 21, 22), and was used to evaluate the individual's attention to positive and negative information in their life. Relative negative attention bias is expressed as ANI/API. The scale is scored on a 5-point scale, with 1 meaning "not at all" and 5 meaning "completely conform." The sum of the items corresponding to each factor is the factor score. The higher the API score, the greater the attentional bias to positive information, and the higher the score of ANI, the greater the attentional bias to negative information. The Cronbach's alpha for the API and ANI scales was 0.86 and 0.82, respectively. The test–retest reliability of API is 0.79, and ANI 0.62.

Eysenck personality questionnaire

The Eysenck Personality Questionnaire (EPQ) was compiled by Professor Eysenck and the revision committee was chaired by Professor Yaoxian Gong. Gong conducted the standardization of the Chinese version of the EPQ questionnaire in 1983. The revised EPQ for children measures four factors (introversion, neuroticism, psychoticism, and masking) across 88 items with yes-or-no answer choices. The Chinese version of the EPQ has good reliability and validity owing to working standardization. The correlation coefficient of EPQ scale ranges from 0.83 to 0.90, with a Cronbach's alpha ranging from 0.68 to 0.81. According to the formula in the EPQ scale, the division between neuroticism and non-neuroticism is calculated using the formula $M \pm 0.67$ *SD*, or $12.31 + 0.67 * 4 = 14.99$. People with scores higher than 14.99 points are considered to experience neuroticism (Gong, 1983).

Zung self-rating depressive symptoms scale

The Zung Self-Rating Depressive Symptoms Scale (SDS) was developed by William W. K. Zung in 1965 and translated into Chinese by Wang et al. (1999). Participants assessed their emotional state in the previous week. The SDS consists of 20 questions with each answered on a 4-point scale with 1 meaning "never or occasionally," and 4 meaning "always." The total points scored act as the raw score, and the statistical result is based on the standard score. The raw score needed to be multiplied by 1.25 and rounded up to an integer to be the standard score. A standard score above 52 indicates the presence of depressive symptoms, while a score below or equal to 52 indicates the absence of depressive symptoms. The Cronbach's alpha of SDS in this study was 0.861.

Statistical analyses

The collected data were analyzed using SPSS 21.0. The statistical data of measurement statistics were analyzed using *t*-tests, analysis of variance (ANOVA), and non-parametric tests. (Figures 1–3; Tables 1, 2). The statistical data of count statistics were analyzed using a Chi-square test (Figure 4). Cohen's d and effect size (*r*) were conducted to determine the effect size between the two groups (Table 1), and the between variables were correlated using Pearson's correlation analysis (Tables 3, 4). Additionally, multiple linear regression analysis was used to analyze the relationship between neuroticism, attentional bias, resilience, and depressive symptoms. Depressive symptoms (SDS) scores were used as dependent variables, while neuroticism, attentional bias, and resilience factors were used as independent variables. Variables were screened using the stepwise method, and factors affecting depressive symptoms were controlled as co-variables (Table 5). Significance levels were set at 0.05 and all tests were two-sided.

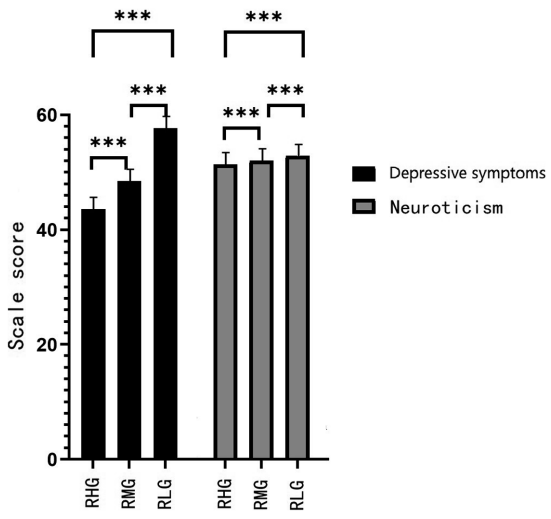

FIGURE 1
Comparison of scores on depressive symptoms and neuroticism in RHG, RMG and RLG. Data are expressed as means ± standard error of the mean (SEM). *** $p<0.001$.

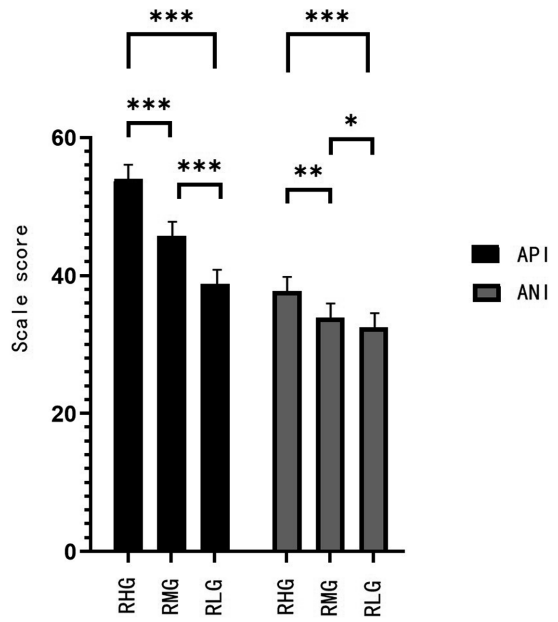

FIGURE 2
Comparison of scores on API and ANI factors in RHG, RMG and RLG. Data are expressed as means ± standard error of the mean (SEM). * p<0.05, ** p<0.01, *** p<0.001.

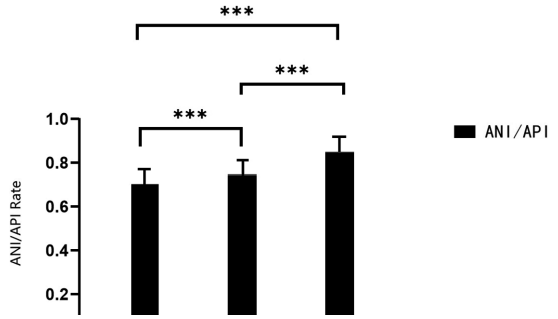

FIGURE 3
Comparison of ANI/API ratio in RHG, RMG, and RLG. Data are expressed as means ± standard error of the mean (SEM). *** p<0.001.

Results

Resilience subgroups

The average scores of resilience were calculated and categorized. Participants who scored higher than the average score plus 1 standard deviation were assigned to the resilience high-score group (RHG); those who scored between the average score plus or minus 1 standard deviation were assigned to the resilience medium-score group (RMG); and those who scored lower than the average score minus 1 standard deviation were assigned to the resilience low-score group (RLG). The average score on resilience and the standard deviation of the research group was 66.02 ± 16.621. The RLG, RMG, and RHG delimitation scores were 49.399 and 82.641. A total of 239 (16%) participants were in the RHG, 1,064 (71.3%) participants were in the RMG, and 190 (12.7%) participants were in the RLG. Non-parametric test showed a statistically significant difference in the resilience score of RLG, RMG, and RHG (K-W = 943.305, $p < 0.001$). Significant differences were also found between the RLG, RMG, and RHG groups in a two-way comparison: RLG and RMG (Cohen's d = −2.472, $r = -0.777$); RMG and RHG (Cohen's d = −3.757, $r = -0.883$); and RLG and RHG (Cohen's d = −6.179, $r = -0.951$). Table 1 illustrates these findings.

Comparison of depressive symptoms, neuroticism, attentional bias of RHG, RMG, and RLG

The depressive symptoms, neuroticism, API and ANI, and ANI/API ratio had significant statistical differences among the RHG, RMG, and RLG ($p < 0.05$; Figures 1–3; Table 2).

Comparison of the detection rate of depressive symptoms and neuroticism proclivity among RHG, RMG, and RLG

A total of 585 participants with depressive symptoms were detected, with a detection rate of 39.2%. Depressive symptoms accounted for only 32.2% in the RHG, 34.9% in the RMG, and 72.1% in the RLG ($\chi^2 = 99.597$, $p < 0.001$). Neuroticism accounted for 10.5% in the RHG, 16.3% in the RMG, and 35.8% in the RLG ($\chi^2 = 52.511$, $p < 0.001$). The detection rates of depressive symptoms and neuroticism in the Chi-square statistical analysis results are shown in Figure 4.

Comparison of average scores of depressive symptoms, neuroticism, attentional bias, and resilience between men and women in the research group

The survey showed that 252 (44.4%) of men had depressive symptoms and 333 (36%) of women had depressive symptoms. There was a significant difference between the men and women ($\chi^2 = 10.336$, $p < 0.01$), but no significant difference in the average scores of depressive symptoms and API between gender. The total and factor scores of resilience, ANI, and ANI/API were significantly higher in men than in women ($p < 0.01$), and the neuroticism score for women was significantly higher than that of men ($p < 0.01$) as shown in Table 3.

TABLE 1 Comparison of the resilience scores of RHG, RMG, and RLG (Mean±SD).

	RLG	RMG	RMG	RHG	RLG	RHG
Number	190(12.7%)	1,064(71.3%)	1,064(71.3%)	239(16%)	190(12.7%)	239(16%)
Mean ± SD	40.43 ± 10.522	64.57 ± 8.946	64.57 ± 8.946	92.82 ± 5.749	40.43 ± 10.522	92.82 ± 5.749
K-W	−627		−1278.5		−651.5	
P	0.000		0.000		0.000	
Cohen's d	−2.472		−3.757		−6.179	
Effect Size(r)	−0.777		−0.883		−0.951	

TABLE 2 Comparison of the Depressive symptoms, Neuroticism, API, ANI, and ANI/API scores of RHG, RMG, and RLG (Mean±SD).

Groups	Depressive symptoms	Neuroticism	API	ANI	ANI/API
RLG	57.638 ± 8.481	52.586 ± 1.280	38.811 ± 7.520	32.516 ± 6.295	0.848 ± 0.141
RMG	48.435 ± 10.226	52.036 ± 1.107	45.746 ± 5.726	33.927 ± 5.301	0.747 ± 0.113
RHG	43.572 ± 13.477	51.408 ± 1.228	53.962 ± 6.885	37.766 ± 9.383	0.702 ± 0.155
RLG/RMG	10.887***	6.334***	12.209***	2.499*	9.725***
RMG/RHG	5.763***	7.720***	15.851***	3.482**	5.706***
RLG/RHG	9.972***	9.329***	15.458***	6.820***	9.424***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

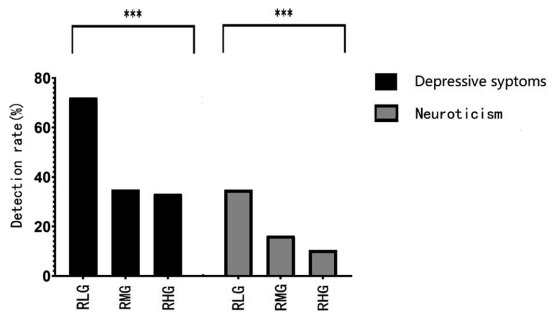

FIGURE 4
Comparison of the detection rate of depressive symptoms and neuroticism in RHG, RMG, and RLG. Data are expressed as percentage. *** p<0.001.

Correlation analysis of depressive symptoms, neuroticism, attentional bias, and resilience in the research group

Depressive symptoms had a very significant positive correlation with neuroticism and ANI/API ratio ($r = 0.175–0.543$, $p < 0.01$), with resilience and its 3 dimensions had a significant negative correlation ($r = 0.327–0.432$, $p < 0.001$). Neuroticism had a very significant positive correlation with the ANI/API ratio ($r = 0.199$, $p < 0.01$), and a very significant negative correlation with resilience and its 3 dimensions ($r = 0.227–0.295$, $p < 0.01$). Resilience had a very significant positive correlation with its 3 dimensions ($r = 0.821–0.975$, $p < 0.001$). Table 4 further illustrates these results.

Correlation analysis of depressive symptoms and neuroticism, attentional bias, and resilience in RHG, RMG, RLG, male, and female

According to the Pearson's correlation analysis, the depressive symptoms of the RHG had a significant positive correlation with ANI, ANI/API ratio, and tenacity ($p < 0.01$). Depressive symptoms in the RMG had a significant positive correlation with neuroticism, ANI, and ANI/API ratio ($p < 0.01$), and a significant negative correlation with API, resilience, and its three factors tenacity, strength, and optimism ($p < 0.01$). The depressive symptoms of the RLG had a very significant positive correlation with neuroticism and ANI/API ratio ($p < 0.01$) and a very significant negative correlation with API, and resilience across its three factors of tenacity, strength, and optimism ($p < 0.01$). Male and female depressive symptoms were significantly positively correlated with neuroticism and ANI ($p < 0.05$), and negatively correlated with resilience, its three dimensions, and API ($p < 0.001$; Table 5).

Multiple linear regression analysis between neuroticism, attentional bias, resilience, and depressive symptoms in the research group

Depressive symptoms (SDS) scores were used as dependent variables, while neuroticism, attentional bias, and resilience factors were used as independent variables. We included gender, age,

TABLE 3 Comparison of depressive symptoms, neuroticism, attentional bias and resilience scores in men and women (Mean±SD).

	Depressive symptoms	Neuroticism	API	ANI	ANI/API	Tenacity	Optimism	Strength	Resilience
Total									
Male	49.278±11.830	51.892±1.275	46.306±8.050	35.062±6.910	0.766±0.129	35.89±10.000	10.46±3.090	23.31±6.001	69.66±18.233
Female	48.551±10.908	52.075±1.134	46.100±6.982	33.932±6.103	0.745±1.131	32.53±8.705	9.43±2.567	21.82±5.001	63.78±15.131
t	1.187	−2.792	0.504	3.204	3.040	6.621	6.621	4.944	6.437
P	0.236	0.005	0.614	0.001	0.002	0.000	0.000	0.000	0.000

TABLE 4 Correlation analysis of depressive symptoms and resilience, neuroticism, and attentional bias in research group.

Correlation	1	2	3	4	5	6	7
1.Depressive symptoms	1						
2.Neuroticism	0.175**	1					
3.ANI/API	0.543***	0.199**	1				
4.Tenacity	−0.358***	−0.295***	−0.306***	1			
5.Strength	−0.432***	−0.286***	−0.349***	0.881***	1		
6.Optimism	−0.327***	−0.227**	−0.299**	0.723***	0.746***	1	
7.Resilience	−0.399***	−0.298***	−0.338***	0.975***	0.951***	0.821***	1

**$p < 0.01$; ***$p < 0.001$.

TABLE 5 Correlation analysis of depressive symptoms, neuroticism, attentional bias, and resilience in RHG, RMG, RLG, male, and female.

Depressive symptoms	Neuroticism	API	ANI	ANI/API	Tenacity	Optimism	Strength	Resilience
RHG	−0.115	−0.042	0.469**	0.534***	0.201**	0.001	−0.017	0.119
RMG	0.148*	−0.382***	0.184**	0.502***	−0.259***	−0.176**	−0.386***	−0.337***
RLG	0.228**	−0.376***	−0.081	0.369***	−0.227**	−0.318***	−0.272**	−0.239**
Male	0.083*	−0.378***	0.122*	0.533***	−0.354***	−0.291***	−0.413***	−0.379***
Female	0.248**	−0.438***	0.175**	0.549***	−0.381***	−0.376***	−0.463***	−0.436***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

ethnicity, neuroticism, attentional bias, and psychological resilience as independent variables in the linear regression analysis and entered the equation by stepwise method. The results showed that gender, age, ethnicity, neuroticism, and optimism did not enter the equation and had no significant effect on depressive symptoms in Chinese college students. API ($B = -0.752$, standardized $\beta = -0.046$, $p < 0.001$), A NI ($B = 0.796$, standardized $\beta = -0.042$, $p < 0.001$), tenacity ($B = 0.139$, standardized $\beta = -0.053$, $p < 0.01$), and strength ($B = -0.691$, standardized $\beta = -0.093$, $p < 0.001$) entered the equation and these variables had a more significant effect on depressive symptoms in Chinese college students (Table 6).

Discussion

In this study, we aimed to determine the influence of neuroticism, attentional bias, and varying degrees of resilience on the occurrence of depressive symptoms in a sample of Chinese freshman students. The detection rate of depressive symptoms in this study was 39.2%. Online surveys may not require as much disclosure of respondents' information and may therefore better reflect the actual situation of the respondents. Our findings indicate a high depressive symptom rate among college freshmen, and that depressive symptoms have become a problem requiring urgent attention. This is similar to the results of studies during the COVID-19 pandemic (e.g., Luo et al., 2021). The impact of the COVID-19 pandemic on Chinese college students is multifaceted. For example, 67.65% of college students felt the negative effect of the COVID-19 pandemic on their studies, 51.47% thought that the COVID-19 pandemic would bring employment pressure. Furthermore, 32.35% of college students thought that their families expected too much of them, and the impact of the epidemic on the employment environment at home and abroad made them unable to fulfill their parents' wishes (Feng and Feng, 2021). In East Asian countries, parents have higher expectations for their children's academic performance. This cultural emphasis on academic achievement drives students to place great importance on learning knowledge at the expense of developing various competencies, resulting in poor coping skills and a tendency to develop mental health problems (Sun et al., 2013; Yoon et al., 2017). Additional

TABLE 6 Multiple linear regression analysis between attentional bias, resilience, and depressive symptoms in the research group.

	B	Standardized β	t-value	P	95%CL	
API	−0.752	0.046	−16.360	0.000	−0.842	−0.662
ANI	0.796	0.042	19.147	0.000	0.714	0.877
Tenacity	0.139	0.053	2.627	0.009	0.035	0.243
Strength	−0.691	0.093	−7.419	0.000	−0.873	−0.508

studies have shown that the depressive symptoms of college students are more likely to be affected by factors such as poverty in graduation year, family poverty, dissatisfaction with their major, poor employment prospects, single-parent families, and national minority (Wang M. et al., 2020; Feng et al., 2022). Regarding college students' personality traits, studies have shown that extroversion, agreeableness, conscientiousness, and openness are negatively correlated with depression, while neuroticism is positively correlated with depression (Han, 2017). This suggests that the personality traits of the college students who participated in this study are one of the factors that cannot be ignored in the formation of their depressive symptoms. During the COVID-19 pandemic, the above factors may have been more pronounced in the development of depressive symptoms in college students.

Why do some people develop depressive symptoms whereas others do not when confronted with similar stress? Resilience is defined as the capacity of an individual to respond to stress and trauma (Martinez et al., 2021). Studies have shown that college students' resilience is negatively correlated with the degree of depressive symptoms. High resilience can prevent college students from becoming depressed (Wei, 2019) and the preventive effect of resilience has been shown to improve mental health (Akeman et al., 2020). Neuroticism and attentional bias are closely related to depressive symptoms (Kendler et al., 2004; Dai et al., 2019). What are the effects of neuroticism, attention bias, and different degrees of resilience on depressive symptoms?

The rates of depressive symptoms and neuroticism in groups with different degrees of resilience are especially interesting. Depressive symptoms only accounted for 32.2% in the RHG and 34.9% in the RMG, versus 72.1% in the RLG. Neuroticism accounted for 10.5% in RHG, 16.3% in RMG, and 35.8% in RLG. The lower the resilience, the lower the average scores of attention to positive and negative information, and the higher the ANI/API ratio. That is, the lower the resilience, the more likely the attentional bias is to shift to negative information attention. This may be the reason for the higher average scores of depressive symptoms and neuroticism and a higher detection rate of both. The detection rate of depressive symptoms in the RLG was 2.2 times of the RHG, and 2.1 times of the RMG, and the detection rate of neuroticism was 3.4 times of RHG and 2.2 times of the RMG. This implies that low resilience, high neuroticism, and relative attentional bias to negative information are risk factors for the occurrence of depressive symptoms. This result is consistent with previous studies (Kendler et al., 2004; Dai et al., 2019; Wilson and Howard, 2020).

However, are these three factors independent influencing factors in the occurrence of depressive symptoms, or are they interrelated? How relevant are they? The pathological mechanism is not yet clear. Relevant analysis of this research group showed that resilience was significantly negatively correlated with depressive symptoms, neuroticism, and ANI/API; neuroticism was significantly positively correlated with ANI/API and depressive symptoms; and ANI/API was significantly positively correlated with depressive symptoms. The lower the resilience, the higher the relatively negative information attention bias and neuroticism depressive symptoms. Their interaction with depressive symptoms forms a circular effect. Such a vicious cycle may be one of the psychological mechanisms by which depressive symptoms occur (Wang et al., 2019; Sheng et al., 2022).

What are the differences in the correlation of depressive symptoms and neuroticism and attention bias among different resilience groups? According to the results of this study, there were significant differences in depressive symptoms, neuroticism, and attentional bias in the resilience groups, which means the higher the average score on attentional bias to negative information, neuroticism, ANI/API ratio, and tenacity, the more severe the depressive symptoms. Meanwhile, the total score on neuroticism, attention to positive information, and depressive symptoms did not have a significant correlation in the RHG. This indicates that the enhanced attentional bias to negative information and increased ANI/API ratio are the factors susceptible to depressive symptoms in the RHG. In the RHG, that is not the tenacity factor of resilience the higher the better, because each thing has two sides. Over-tenacity and the relatively negative information attention bias may increase the risk of depressive symptoms in the RHG. In the RMG and RLG, higher neuroticism, relative attentional bias to negative information, and a lower degree of resilience and attentional bias to positive information will increase depressive symptom scores. When grouping according to different degrees of resilience, we found varied correlations between depressive symptoms and neuroticism. For the RHG, neuroticism may not have a big impact on depressive symptoms, while for the RMG and RLG, the higher the propensity for neuroticism, the easier it is to fall into depressive symptoms, which is in accordance with previous studies (Kendler et al., 2004) and indicates a close relationship between the degree of neuroticism and resilience. According to the gender grouping in RESEARCH GROUP, men accounted for 38%, while women accounted for 62%, and the detection rate of depressive symptoms in men accounted for 44.4%, which was significantly higher than that in women (36.0%). However, there was no difference in depressive symptoms and API

scores between men and women. Men had significantly higher ANI, ANI/API ratio, and resilience than women, and women had significantly higher neuroticism scores than men, indicating that the high detection rate of male depressive symptoms may be due to the greater impact of negative information attention bias, while female neuroticism and psychological elasticity may have a greater impact on depressive symptoms. The correlation analysis between male and female neuroticism, resilience, attention bias, and depressive symptoms shows that the correlation mechanism between these factors and depressive symptoms is almost the same between men and women.

However, which of these factors has a more direct impact on the occurrence of depressive symptoms? The results of multiple regression analysis show that both high ANI and the decrease of API had a significant impact on the occurrence of depressive symptoms. Under normal circumstances, there may be a balance between API and ANI. The decrease of API and the increase of ANI may break that balance, lead to the relative or absolute increase of ANI, and further lead to an increase in depressive symptoms or symptom severity. This proves our previous assumption of using ANI/API to represent the relative degree of ANI. To our surprise, high tenacity and low strength have a significant impact on the occurrence of depressive symptoms, rather than low tenacity and low strength. Low strength may reduce resilience and lead to depressive symptoms. Why high tenacity promotes depressive symptoms should be further investigated in future research. Neuroticism, a relatively high attentional bias to negative information (high ANI/API ratio), and low resilience may increase the risk of depressive symptoms. Neuroticism, resilience, and attentional bias seem to be sensitive psychological indicators for predicting the risk of depressive symptoms. Once stress factors are encountered, low resilience, high neuroticism, and negative attentional bias make it more difficult to recover from depressive symptoms. This explains why some people recover from a stressful situation quickly, while others experience lasting depressive symptoms. This study confirmed that low resilience, neuroticism, and negative attentional bias were not only independent influence factors on depressive symptoms, but also significantly correlated with each other to promote the degree of depressive symptoms. These results confirmed our hypothesis. If we can intervene in these factors and improve their function, it may be an effective way to alleviate depressive symptoms. Increasing resilience and reducing the proclivity of neurotic behavior and attentional bias to positive information are some of the most important measures to improve strategies against stress and prevent and treat depressive symptoms. Studies show that focusing on working out solutions and paying more attention to positive aspects after a traumatic incident may alleviate post-traumatic stress disorder symptoms and increase overall mental health (Alamdar et al., 2020). Our regression analysis showed that tenacity, strength, and positive–negative attentional information bias played the most prominent roles in depressive symptoms, while neuroticism did not play a significant role in the regression analysis. This shows that interventions for depressive symptoms should focus more on attentional bias and psychological resilience. One way is to increase attentional bias to positive information through training, which may lower the relative attention bias to negative information, ANI/API ratio, and degree of neuroticism, thus increasing resilience and lowering the degree of depressive symptoms. This may be more important for male college freshmen, however, since female college freshmen had lower resilience and higher neuroticism in this study. Targeted training and improving resilience may be more effective in preventing and treating depressive symptoms in female freshmen. Future interventions should place great importance on the issues of resilience, attention bias, and neuroticism. Future research should investigate how to improve countermeasures to these problems and implement them for university students of all genders.

Limitations

Our results may be of great significance for the prevention and treatment of depressive symptoms in college students; however, during the COVID-19 pandemic, Chinese college students' resilience, neuroticism, and attentional bias may differ according to their personality, family, ethnicity, and academic performance, thus influencing the onset of depressive symptoms. This has not been discussed in depth in this paper due to space limitation. Our research group was limited to college freshmen in Chinese universities and did not cover all grades. Therefore, the findings do not represent the entire college student population, which future research should address in multiple regions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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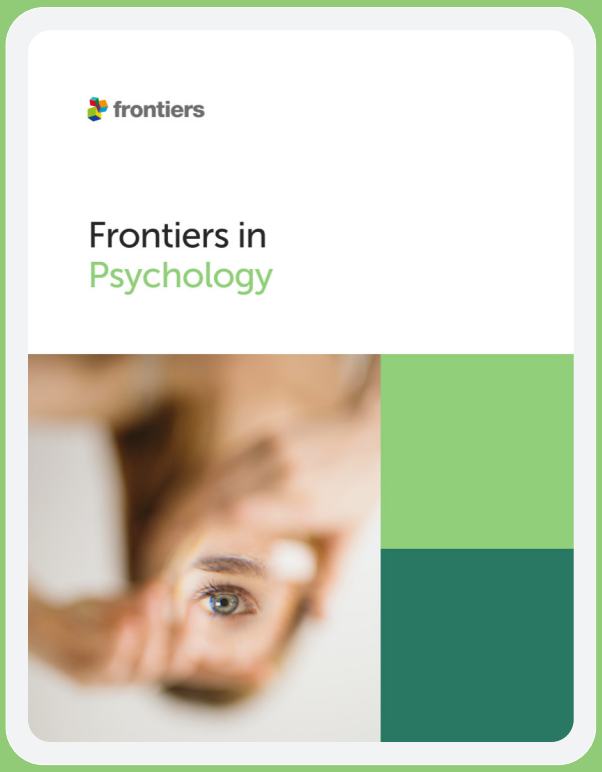

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