Title

Cognitive outcomes are differentially associated with depression severity trajectories during psychotherapy treatment for late life major depressive disorder.

Journal

International Journal of Geriatric Psychiatry, 37(8)

Authors

Kassel, Michelle
Rhodes, Emma
Insel, Philip
et al.

Publication Date

2022-08-01

DOI

10.1002/gps.5779

Peer reviewed

HHS Public Access

Author manuscript

Int J Geriatr Psychiatry. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Int J Geriatr Psychiatry. 2022 August ; 37(8): . doi:10.1002/gps.5779.

Cognitive outcomes are differentially associated with depression severity trajectories during psychotherapy treatment for late life major depressive disorder

Michelle T. Kassel, Ph.D.[1,2], **Emma Rhodes, Ph.D.**[1,2], **Philip S. Insel, Ph.D.**[2], **Kai Woodworth, B.A.**[2], **Christina Garrison-Diehn, Ph.D.**[2], **Derek D. Satre, Ph.D.**[2,3], **J. Craig Nelson, M.D.**[2], **Duygu Tosun, Ph.D.**[4], **R. Scott Mackin, Ph.D.**[2]

[1]Mental Illness Research, Education, and Clinical Centers, San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA

[2]Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, CA, USA

[3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[4]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA

Abstract

Objectives: Late Life Depression (LLD) is associated with persistent cognitive dysfunction even after depression symptoms improve. The present study was designed to examine cognitive outcomes associated with the pattern of depression severity change during psychotherapy intervention for LLD.

Methods: 96 community-dwelling adults ages 65–91 with major depressive disorder completed 12 sessions of Problem-Solving Therapy at the University of California, San Francisco. Nonlinear trajectories of depression severity ratings using the Hamilton Depression Rating Scale were computed from multiple time points collected throughout the weekly psychotherapy intervention. Performance on measures of cognition (information processing speed, executive functioning, verbal learning, memory) was assessed at baseline and post-treatment. Linear mixed-effects models examined associations between nonlinear depression severity trajectories and post-treatment change in cognitive performance.

Corresponding Author: Michelle T. Kassel, Ph.D., Mental Illness Research Education and Clinical Centers, San Francisco VA Health Care System, San Francisco, CA 94121, michelle.kassel@ucsf.edu, (415) 221-4810 x24525.

Author Contributions: *MTK*: Conceptualization, Methodology, Software, Formal Analysis, Data Curation, Writing-Original Draft, Writing-Review & Editing, Visualization; *ER*: Conceptualization, Data Curation, Writing-Review & Editing; *PSI*: Conceptualization, Methodology, Software, Writing-Review & Editing; *CW*: Investigation, Data Curation, Writing-Review & Editing, Project Administration; *CGD*: Investigation, Writing-Review & Editing; *DDS*: Conceptualization, Methodology, Writing-Review & Editing; *JCN*: Conceptualization, Methodology, Writing-Review & Editing; *DT*: Conceptualization, Methodology, Writing-Review & Editing; *RSM*: Conceptualization, Methodology, Resources, Supervision, Project Administration, Funding Acquisition, Writing-Review & Editing. All authors declare that they have reviewed and approved the manuscript prior to its submission.

Ethics Approval Statement: The study was conducted in compliance with the Code of Ethics of the Declaration of Helsinki. The study was approved by the University of California, San Francisco institutional review board.

Patient Consent Statement: Written informed consent was obtained from all individual participants included in the study.

Results: Broadly, different patterns of depression change during treatment were associated with improved cognition post-treatment. Greater and more consistent interval improvements in depression ratings were differentially associated with improvements in aspects of verbal learning, memory, and executive function post-treatment, while no associations were found with information processing speed.

Conclusions: The heterogeneity of depression trajectories associated with improved cognitive outcomes suggests that the temporal pattern of depression response may impact specific cognitive processes distinctly. Results suggest that use of nonlinear depression severity trajectories may help to elucidate complex associations between the time course of depression response and cognitive outcomes of psychotherapy in LLD. These findings have important implications for identifying treatment targets to enhance clinical and cognitive outcomes of psychotherapy in LLD.

Keywords

late life depression; cognition; psychotherapy; treatment response; longitudinal; memory; executive function; processing speed

1. Introduction

Late Life Depression (LLD) affects 15–20% of older adults[1], is associated with cognitive dysfunction[2,3], and significantly contributes to disability worldwide[4]. While multiple treatment modalities are effective in treating LLD mood symptoms, cognitive dysfunction may persist despite positive response to intervention[5]. Prior studies of cognitive outcomes typically have assumed linear change in depression with widespread use of two-timepoint pre- to post-intervention analyses that overlook variability in depression severity over the course of treatment[6,7]. Indeed, the temporal pattern of depression response can vary throughout treatment with evidence for distinct trajectories commonly showing gradual, stepwise, or rapid initial symptom improvement, among other possibilities[8,9]. These depression trajectories have shown differential associations with acute treatment response status and with long-term mood symptom outcomes[6,10]. Nonetheless, current work has yet to investigate the association of depression treatment trajectories with cognitive outcomes. Nonlinear examination of the temporal pattern of change in depression severity over the course of treatment can help to clarify associations between depression severity and cognitive outcomes of psychotherapy in LLD.

Nearly 60% of individuals with LLD exhibit impairment in cognition[3], commonly in information processing speed, executive functioning, and verbal learning and memory[2,3,11–13]. Multiple psychotherapies adapted to account for cognitive dysfunction common in LLD have demonstrated efficacy in reducing depressive symptoms[14–16]. However, cognitive recovery may remain limited despite successful mood treatment, though mild focal improvements in information processing speed, executive functioning, and verbal learning and memory have been described, with similar findings among behavioral[12,17,18] and pharmacological[19–22] interventions. To date, these studies have evaluated cognitive outcomes with two-timepoint (baseline and post-treatment) linear models of change in depression severity and lack nuanced assessment of cognitive associations that account for variability in mood response throughout the treatment course.

Reliance on traditional two-timepoint pre- to post-intervention analyses of depression severity is problematic due to improper assumption of linear change over time and inference of change based on minimal data points. As such, conventional two-timepoint linear percent change scores do not appropriately model the degree of variability in the development of mood symptom response[6,23,24]. In contrast, use of multiple time points provides greater statistical power[25] and nonlinear modelling of the depression severity time course allows for more granular assessment of complex cognitive associations pertaining to depression symptom response patterns during treatment. Further, the temporal pattern of depression severity change may provide meaningful information about the development of mood symptom response[6,26,27], which is useful in understanding intervention effects such as cognitive change. Other typical methods for reporting depression treatment outcomes include a specified cut score or ≥50% reduction in depression severity[28] on a given endpoint measure to classify responder or remitter status, though each definition is somewhat arbitrary and based on limited data[29–31]. The proposed method to examine cognitive outcomes with nonlinear trajectories of change in depression during treatment can decrease reliance on assumptions of linear change in depression severity, inappropriate reduction of dynamic data over time, dichotomization of continuous variables, and arbitrary cut points assigned clinical utility. Clarifying the relationship of depression severity change throughout treatment with cognitive outcomes can inform treatment targets for cognitive decline in LLD.

The purpose of the present study was to evaluate potential associations between nonlinear depression severity trajectories over the course of psychotherapy treatment and cognitive outcomes across domains typically impacted in LLD. In a sample of older adults with LLD, we assessed depression severity at multiple timepoints over 12 weeks of psychotherapy. Neuropsychological assessments were completed at baseline and post-treatment. We hypothesized that distinct patterns of nonlinear trajectories of depression severity would be differentially related to cognitive outcomes. Specifically, we expected that greater magnitude and consistency of interval improvement in depressive symptom severity throughout the course of treatment would be associated with improved performance on measures of information processing speed, executive functioning, and verbal learning and memory at post-treatment.

2. Materials and Methods

2.1. Participants

Primary English-speaking adults aged 65 and older were recruited from the community via print advertisements. Participants were assessed at the University of California, San Francisco (UCSF) using the Structured Clinical Interview for the Diagnostic and Statistical Manual-4th edition (SCID-IV) and were required to meet diagnostic criteria for unipolar Major Depressive Disorder (MDD) without psychotic features, current depressive episode duration ≥6 weeks, and moderate to severe depression (≥19 on the 24-item Hamilton Depression Rating Scale (HDRS)[32,33]). Exclusion criteria included antidepressant use or psychotherapy within the past 6 weeks; electroconvulsive therapy within the past 6 months; use of cognitive enhancing medication; comorbid psychiatric diagnoses aside from

Generalized Anxiety Disorder or Specific Phobia; neurological or major medical conditions; history of substance use disorder within the past 6 months; traumatic brain injury or loss of consciousness ≥30 minutes; and history of diagnosis or current evidence of dementia (Mini Mental Status Exam score <26). Participant eligibility was confirmed by a multidisciplinary consensus panel.

2.2. Procedure

The study was approved by the UCSF institutional review board and conducted in accordance with the Declaration of Helsinki. All eligible participants provided written informed consent. Participants engaged in 12 weekly 50-minute sessions of Problem-Solving Therapy (PST)[34], a brief evidence-based psychotherapy with demonstrated treatment efficacy for LLD[14,35,36], with a Ph.D. level licensed clinical psychologist trained in the PST protocol. Separate research personnel trained and supervised by a licensed neuropsychologist administered neuropsychological assessments with each participant at baseline and upon completion of the psychotherapy intervention. Participants completed the 24-item GRID-HDRS[32,33] at baseline (week 0) and at weeks 1–6, 8, 10, and 12, administered by trained research personnel not involved in provision of psychotherapy. Demographic information (participant age, sex, years of education) and depression history characteristics (e.g., onset age, current episode length) were collected for each participant. Given the previously reported efficacy of PST for MDD in older adults[14,35,36], the present study was designed to examine predictors of response to PST and assessed cognition at baseline and post-treatment and no control group was employed.

2.3. Measures

Measures of information processing speed, executive functioning, and verbal learning and memory were administered as part of a comprehensive neuropsychological battery. The Hopkins Verbal Learning Test-Revised (HVLT-R)[37] and the Wechsler Memory Scale-III[38] Logical Memory (LM) subtest assess auditory verbal learning and memory either for a word list (HVLT-R) or a contextualized narrative (LM). Primary outcome measures included *Immediate Recall* of total words (HVLT-R) or narrative elements (LM) and *Delayed Recall* of list (HVLT-R) or narrative (LM) items after a 20–30-minute delay. The Wechsler Adult Intelligence Scale-III[39] Digit Symbol-Coding examines information processing speed for visual material, with total items correct as the primary outcome variable. The Trail Making Test Parts A (TMT-A) and B (TMT-B) were employed to evaluate basic visual information processing speed and rapid shifting of mental set (an aspect of executive function), respectively[40]. Total completion time in seconds was the primary outcome measure for TMT-A and TMT-B. Finally, the Stroop Color Word Interference Test was used to assess inhibition of a prepotent response, a component of executive functioning[41]. The American National Adult Reading Test[42] was also completed at baseline to estimate premorbid intellectual functioning.

2.4. Statistical Analyses

All statistical analyses were conducted using R version 4.0.3 (www.R-project.org). Changes in cognitive performance were computed by subtracting baseline from post-treatment scores for each variable of interest. Longitudinal changes in depression severity and cognition were

modeled using a series of linear mixed-effects regressions with a random intercept and slope and an independent covariance structure, conditional on the random effects. All models included time relative to baseline visit and the interaction between time and the cognitive variable of interest. Departures from linearity in the depression severity trajectory were captured via continuous time parameterized using a 3-knot restricted cubic spline[43] selected for best model fit via Akaike's Information Criterion (AIC)[44], with knot placement at the initial eligibility screen, median time point, and post-treatment assessment. Associations between trajectories of depression severity and predictors were tested using interactions between the two resultant spline parameters for time and the cognitive variable of interest, [predictor*(β_{time1}+β_{time2})]. Corresponding additive models that did not allow for depression to vary nonlinearly over time were also computed for comparison with the nonlinear spline models of depression severity and cognitive change over time. Likelihood ratio tests evaluated the significance of the nonlinear spline interactions to test whether longitudinal change in depression severity was associated with change in the cognitive variable of interest. Model fit was evaluated via AIC to determine whether nonlinear modeling of time improved model fit over the additive model. Participant age, sex, years of education, MDD onset age, and current episode length were entered as covariates in each model.

Sensitivity analyses were subsequently conducted to examine cognitive outcomes employing conventional methods for qualitative comparison and used only pre- and post-treatment depression ratings to compute a two-timepoint linear percent change score in HDRS at post-treatment. Linear mixed-effects models evaluated the interaction between time and linear percent change in HDRS on predicting change in the cognitive variable of interest. Participant age, sex, years of education, MDD onset age, and current episode length were also entered as covariates in each model. Results are described for qualitative comparison of methods and multiple comparisons correction was not performed.

3. Results

One-hundred-five participants enrolled in the study. Ninety-six older adults (59.38% women) ages 65–91 (M=71.40, SD=5.69) with 9–20 years of education (M=16.40, SD=2.21) and verbal IQ estimates in the broad average range (M=105.00, SD=4.27, range=90–110) completed both baseline and post-treatment cognitive assessments and comprised the study sample. Participant self-report indicated average MDD onset age of 28.20 years (SD=22.20, range=7–82) with 82.29% of participants classified as having early onset MDD (defined as onset age <65). Consistent with symptom chronicity reported in LLD[45], average length of current major depressive episode was 180.00 months (SD=258.00, median=48, mode=24, range=5–852) with participant estimates of 2.68 (SD=1.70, range=1–10) lifetime major depressive episodes.

3.1. Cognitive associations with nonlinear depression trajectories

Likelihood ratio test results revealed significant interactions indicating that nonlinear depression trajectories were differentially associated with cognitive change after treatment (Table 1; Figure 1). Specifically, longitudinal reductions in depression severity were associated with improved performance at post-treatment on measures of verbal learning

and memory, including for HVLT-R immediate (X^2(2, N=96)=12.03, p=.002) and delayed recall (X^2(2, N=96)=7.61, p=.022), and LM immediate recall (X^2(2, N=96)=12.45, p=.002). Associations with depression severity trajectories were also evident on a task of executive functioning, TMT-B, (X^2(2, N=96)=7.96, p=.019).

Although analyzed on a continuous basis, to visualize the associations of nonlinear depression trajectories with cognitive change, participants were binned into 3 groups based on cognitive change scores indicating improvement (+1 SD), decline (−1 SD), or no change (0 SD) in performance relative to the entire sample (Figure 1). Visual inspection of the plots revealed that both greater magnitude and consistency of interval decline in depression severity were associated with improved verbal learning and memory for a word list (HVLT-R immediate and delayed recall). Qualitative visual inspection indicated improved learning of contextualized narrative information (LM immediate recall) showed associations with a pattern of steady interval declines in depression severity throughout the duration of treatment. Improved performance on rapid set-shifting (TMT-B) appeared most associated with trajectories demonstrating a greater magnitude of decline in depression severity over the initial half of the psychotherapy trial, although depression severity in the final weeks of psychotherapy did not remain different from those whose performance declined on TMT-B at post-treatment. No significant associations with depression severity trajectories were found on measures of delayed story recall, information processing speed, or inhibition (Table 1). Across analyses, participant age, years of education, sex, MDD onset age, and current episode length did not significantly predict longitudinal change in depression severity.

3.2. Sensitivity analyses using conventional two-timepoint linear change methods

To contextualize the potential advantages of nonlinear depression severity trajectories to investigate change with cognition after psychotherapy, sensitivity analyses using conventional two-timepoint pre- to post-treatment linear change metrics were performed on the same dataset. Linear mixed-effects models evaluated the interaction between time and linear percent change in HDRS, calculated exclusively from the baseline and post-treatment depression severity assessments, on predicting change in the cognitive variable of interest. Results revealed associations with HVLT-R immediate (X^2(2, N=96)=5.92, p=.015) and delayed (X^2(2, N=96)=7.35, p=.007) recall such that greater percent improvement in depression related to improved word list performance. No associations with linear percent change in depression were found for measures of story learning or memory, information processing speed, or executive functioning (Table 2). Exploratory linear mixed-effects analyses dichotomizing response status yielded no cognitive change associations (Supplemental Table 1).

4. Discussion

The present study is the first to our knowledge to evaluate the impact of nonlinear depression severity trajectories during psychotherapy on change in cognitive performance following treatment for LLD. Overall, our hypothesis that the temporal pattern of change in depression severity during treatment would differentially relate to cognitive

outcomes was supported for aspects of learning, memory, and executive functioning, with distinct associated depression patterns by cognitive domain assessed. Broadly, either greater magnitude or more consistent interval improvements in depression severity were differentially related to improved performance post-treatment on measures of verbal learning, word list memory, and rapid set-shifting. The heterogeneity of depression severity trajectories associated with improved cognitive outcomes suggests that the time course of mood symptom response may impact specific cognitive processes distinctly. Critically, sensitivity analyses of identical participant data using traditional two-timepoint pre- to post-treatment linear change in depression severity only partially replicated results, finding only list learning and memory improvements and no associations with other cognitive measures. Together, these results suggest that use of nonlinear depression severity trajectories offers greater sensitivity to elucidate complex associations of the development of mood response with cognitive outcomes of psychotherapy in LLD.

Individuals with larger and more consistent improvements in depression severity throughout treatment showed improvement on immediate and delayed recall of a list-learning task. By comparison, only consistent interval improvements in depression severity over the 12-weeks were associated with improved story learning, and story memory outcomes did not relate to depression severity trajectories. While our results are consistent with select studies showing verbal learning and memory improvements with successful treatment of LLD[17,18], the distinct depression severity trajectories associated with improvements suggest different relative contributions of depression severity change patterns for word lists and stories. Others have similarly shown discrepancies between word list and story recall, with LLD exhibiting lower word list yet comparable story recall relative to healthy comparisons[13]. Together, these findings highlight the potential influence of executive function underlying the discrepancies observed between type of verbal learning and memory. Encoding of a word list appears more reliant on individual variability in executive functioning to monitor, organize, and update information streams[46–48], whereas story learning reduces the burden on executive functioning by providing narrative details within a broader contextual framework[49]. As such, poorer semantic organization in LLD has been shown to mediate performance on list-learning tasks[50] but not narrated stories[51]. Interestingly, in our sample, improved list-learning performance was associated with a depression severity trajectory that resembles the confluence of the two depression trajectories related to improved story learning and rapid set-shifting. This converging pattern of depression response further underscores the likely higher contribution of executive functioning to list-learning performance. Overall, our results indicate that distinct patterns of emerging clinical response differentially influence encoding of a word list with greater executive demand relative to contextualized narrative information.

Depression trajectories associated with improved rapid set-shifting exhibited initial early improvements in depression severity, regardless of steady interval declines throughout treatment. Prior work using conventional endpoint metrics has similarly demonstrated mild focal improvements in speeded measures of executive functioning[12], though specific associations with the temporal pattern of depression response have not been previously described. Precedent literature has established that depression trajectories of early symptomatic improvements relate to higher rates of response and remission[52,53]. As such,

it is conceivable that existing studies examining dichotomous clinical outcomes (e.g., remission or response status), or those based solely on pre-to post-treatment measurements may overrepresent individuals with early symptomatic change trajectories in the responder and remitter groups. Thus, it is possible that these studies have largely captured trajectories of early treatment response associated with improved speeded executive functioning. No associations with inhibition were evident in our sample. Depression symptom profiles vary widely[54] and may differentially relate to specific cognitive processes. Examination of multiple constructs of executive functioning in a separate sample will help to illuminate the impact of patterns of depression severity change on distinct cognitive processes.

Notably, no associations between depression severity and information processing speed were observed in our sample. While mild improvements in information processing speed with successful treatment have been periodically reported in LLD[55], results of these traditional two-timepoint linear analyses may be more susceptible to the influence of practice effects as a contributing factor since the time course of depression change throughout treatment remains unexplored, and thus improvements may relate, in part, to the impact of repeat testing within a short time frame[56]. Further, despite repeated investigation with traditional methods, mixed findings documented in extant literature[5,12,17] along with the present results suggest that improved processing speed with treatment response may be less consistent than previously reported. Examination of cognitive associations with longitudinal depression severity trajectories reduces the likelihood of identifying false positive improvements due to repeat testing.

Qualitative comparison of nonlinear depression time course analyses to conventional methods suggests that potential effects of depression severity on cognitive outcomes may be obscured by traditional analytic methods in previous studies. While nonlinear depression trajectories revealed differential associations of the pattern of depression response with verbal learning, word list memory, and set-shifting, conventional methods employed in the same sample evidenced only significant effects for list-learning performance and no associations with dichotomized response status. Traditional analysis methods may overlook important variability in the pattern and time course of mood response to treatment, leading to an incomplete picture and unclear expectations of cognitive change with adequate treatment. The current nonlinear method also provides a more nuanced approach to examining depression and associated cognitive change since individual participants are not assigned to fixed clinical outcome groups. Instead, intra-individual variability in cognitive outcomes as a function of depression response trajectories can be explored among different cognitive processes without rigid endpoint classifications. Our results demonstrate that heterogeneous patterns of depression response differentially relate to cognitive outcomes in LLD and highlight the need to examine the spectrum of change in depression severity during treatment when assessing cognitive change. Further appraisal of the impact of depression severity trajectories on cognitive change in additional samples holds promise to help determine when to shift to adjunctive or alternative treatments to optimize clinical and cognitive outcomes.

While there are several advantages to the present study in a well-characterized treatment sample of older adults with LLD, the study is not without limitation. First, our sample

was comprised primarily of individuals who identified as White, limiting generalizability of findings to a more diverse sample. Although age, education, sex, MDD onset age, and current episode length were used as covariates, analyses did not explicitly account for baseline cognitive performance or other demographic or depression history characteristics that may influence patterns of depression change and cognitive outcomes. While multiple measurements of depression severity throughout treatment is a notable strength of the present study, cognition measured only at baseline and post-treatment limits our ability to evaluate how acute changes in depression severity may correspond to subtle variations in cognition during treatment. Additionally, the majority of our sample reported early onset MDD, thus results may not generalize to late onset MDD, warranting separate examination in future work. Further, as the present study was not intended to evaluate efficacy of PST, a control condition was not included and results therefore cannot be compared with potential effects of other treatments or waitlist conditions. Consistent with our results, PST and psychotherapies focused on improving practical skills in executive function may be particularly well suited to enhance executive functioning abilities routinely employed in everyday life including implicit monitoring and organization of verbal information and shifting mental set between tasks. Future research in additional psychotherapy modalities and pharmacological interventions will be critical to extend the present work to scrutinize reproducibility of results. Moreover, greater fractionation of cognitive processes, use of more ecologically valid measures, and evaluating the degree to which pre-treatment cognitive performance influences outcomes will be useful in further clarifying these relationships.

The present study found that heterogeneity in the time course of depression response was differentially related to cognitive outcomes of psychotherapy in LLD. More consistent and greater interval improvements in depression severity were associated with better cognitive outcomes on tests of verbal learning, memory, and executive function. These findings underscore the importance of thorough examination of depression severity trajectories when evaluating the complexities of cognitive change with treatment in LLD. While dichotomizing treatment response outcomes is useful for rapid clinical decision-making, its simplicity is not well-suited to examine the apparent dynamic temporal patterns of depression change that can illuminate understanding of associated cognitive outcomes. Replication of depression severity trajectory analyses in separate samples and across intervention modalities will be important to disentangle mechanisms associated with cognitive change. Moreover, given the recurrent nature of MDD, additional longitudinal follow-up beyond time-limited treatment trials is important to examine long-term associations between variation in depression trajectories and cognitive outcomes. The novel finding that patterns of depression severity trajectories differentially relate to cognitive outcomes of psychotherapy has the potential to inform future work to advance treatment targets for cognitive decline in LLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This research is supported by the National Institute of Mental Health (R-01 MH101472, R.S.M.). Writing of this manuscript was supported by the Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs (M.T.K.).

Conflict of Interest Disclosure:

The authors declare the following financial interests/personal relationships: Dr. Insel has served as a consultant for Roche; Dr. Nelson has been an advisor or consultant to Astellas, Axsome, Biohaven, Janssen, Johnson and Johnson, Novartis, Otsuka, Sunovion; Dr. Mackin has received research support from The National Institute of Mental Health and Johnson and Johnson. Drs. Kassel, Rhodes, Garrison-Diehn, Satre, and Tosun, and Ms. Woodworth report no conflicts to declare for this work. This manuscript is based on work supported, in part, by the Department of Veterans Affairs, but does not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Geriatric Mental Health Foundation. Depression in late life: not a natural part of aging. 2008.
2. Alexopoulos GS. Mechanisms and treatment of late-life depression. Translational Psychiatry. 2019;9(1):188. [PubMed: 31383842]
3. Rhodes E, Insel PS, Butters MA, et al. The Impact of Amyloid Burden and APOE on Rates of Cognitive Impairment in Late Life Depression. J Alzheimers Dis. 2021;80(3):991–1002. [PubMed: 33682706]
4. World Health Organization. The global burden of disease : 2004 update. Geneva: World Health Organization;2008.
5. Riddle M, Potter GG, McQuoid DR, Steffens DC, Beyer JL, Taylor WD. Longitudinal Cognitive Outcomes of Clinical Phenotypes of Late-Life Depression. Am J Geriatr Psychiatry. 2017;25(10):1123–1134. [PubMed: 28479153]
6. Uher R, Muthén B, Souery D, et al. Trajectories of change in depression severity during treatment with antidepressants. Psychological Medicine. 2010;40(8):1367–1377. [PubMed: 19863842]
7. Hayes AM, Laurenceau J-P, Feldman G, Strauss JL, Cardaciotto L. Change is not always linear: The study of nonlinear and discontinuous patterns of change in psychotherapy. Clinical Psychology Review. 2007;27(6):715–723. [PubMed: 17316941]
8. Dew MA, Reynolds CF 3rd, Houck PR, et al. Temporal profiles of the course of depression during treatment. Predictors of pathways toward recovery in the elderly. Arch Gen Psychiatry. 1997;54(11):1016–1024. [PubMed: 9366658]
9. Vittengl JR, Clark LA, Thase ME, Jarrett RB. Nomothetic and idiographic symptom change trajectories in acute-phase cognitive therapy for recurrent depression. J Consult Clin Psychol. 2013;81(4):615–626. [PubMed: 23627652]
10. Vittengl JR, Clark LA, Thase ME, Jarrett RB. Defined symptom-change trajectories during acute-phase cognitive therapy for depression predict better longitudinal outcomes. Behav Res Ther. 2016;87:48–57. [PubMed: 27591917]
11. Koenig AM, DeLozier IJ, Zmuda MD, et al. Neuropsychological functioning in the acute and remitted States of late-life depression. J Alzheimers Dis. 2015;45(1):175–185. [PubMed: 25471193]
12. Mackin RS, Nelson JC, Delucchi K, et al. Cognitive Outcomes After Psychotherapeutic Interventions for Major Depression in Older Adults with Executive Dysfunction. The American Journal of Geriatric Psychiatry. 2014;22(12):1496–1503. [PubMed: 24378255]

13. Lamar M, Charlton R, Zhang A, Kumar A. Differential associations between types of verbal memory and prefrontal brain structure in healthy aging and late life depression. Neuropsychologia. 2012;50(8):1823–1829. [PubMed: 22564447]
14. Areán PA, Raue P, Mackin RS, Kanellopoulos D, McCulloch C, Alexopoulos GS. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. The American journal of psychiatry. 2010;167(11):1391–1398. [PubMed: 20516155]
15. Alexopoulos GS, Raue PJ, Kanellopoulos D, Mackin S, Arean PA. Problem solving therapy for the depression-executive dysfunction syndrome of late life. International Journal of Geriatric Psychiatry. 2008;23(8):782–788. [PubMed: 18213605]
16. Miller MD, Reynolds CF 3rd. Expanding the usefulness of Interpersonal Psychotherapy (IPT) for depressed elders with co-morbid cognitive impairment. Int J Geriatr Psychiatry. 2007;22(2):101–105. [PubMed: 17096459]
17. Wetherell JL, Hershey T, Hickman S, et al. Mindfulness-Based Stress Reduction for Older Adults With Stress Disorders and Neurocognitive Difficulties: A Randomized Controlled Trial. J Clin Psychiatry. 2017;78(7):e734–e743. [PubMed: 28686822]
18. Naismith SL, Diamond K, Carter PE, et al. Enhancing Memory in Late-Life Depression: The Effects of a Combined Psychoeducation and Cognitive Training Program. The American Journal of Geriatric Psychiatry. 2011;19(3):240–248. [PubMed: 20808114]
19. Bondareff W, Alpert M, Friedhoff AJ, Richter EM, Clary CM, Batzar E. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry. 2000;157(5):729–736. [PubMed: 10784465]
20. Newhouse PA, Krishnan KR, Doraiswamy PM, Richter EM, Batzar ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry. 2000;61(8):559–568. [PubMed: 10982198]
21. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry. 2007;164(6):900–909. [PubMed: 17541049]
22. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol. 2012;27(4):215–223. [PubMed: 22572889]
23. van Eeden WA, van Hemert AM, Carlier IVE, Penninx BW, Giltay EJ. Severity, course trajectory, and within-person variability of individual symptoms in patients with major depressive disorder. Acta Psychiatr Scand. 2019;139(2):194–205. [PubMed: 30447008]
24. Fried EI, Nesse RM. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. BMC Medicine. 2015;13(1):72. [PubMed: 25879936]
25. Norton BJ, Strube MJ. Understanding statistical power. J Orthop Sports Phys Ther. 2001;31(6):307–315. [PubMed: 11411625]
26. Petersen JJ, Hartig J, Paulitsch MA, et al. Classes of depression symptom trajectories in patients with major depression receiving a collaborative care intervention. PLOS ONE. 2018;13(9):e0202245. [PubMed: 30192786]
27. Sakurai H, Uchida H, Abe T, et al. Trajectories of individual symptoms in remitters versus non-remitters with depression. Journal of Affective Disorders. 2013;151(2):506–513. [PubMed: 23886402]
28. Montgomery SA. Clinically relevant effect sizes in depression. European Neuropsychopharmacology. 1994;4(3):283–284.
29. Fähndrich E. The arbitrariness of response definition in clinical trials with antidepressants. Pharmacopsychiatry. 1984;17(4):107–108. [PubMed: 6382360]
30. Prien RF, Carpenter LL, Kupfer DJ. The definition and operational criteria for treatment outcome of major depressive disorder. A review of the current research literature. Arch Gen Psychiatry. 1991;48(9):796–800. [PubMed: 1929769]
31. Mulder RT, Joyce PR, Frampton C. Relationships among measures of treatment outcome in depressed patients. J Affect Disord. 2003;76(1–3):127–135. [PubMed: 12943942]

32. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62. [PubMed: 14399272]
33. Williams JB, Kobak KA, Bech P, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. Int Clin Psychopharmacol. 2008;23(3):120–129. [PubMed: 18408526]
34. Nezu AM, Maguth Nezu C, D'Zurilla TJ. Problem-solving therapy: A treatment manual. New York, NY, US: Springer Publishing Co; 2013.
35. Kirkham JG, Choi N, Seitz DP. Meta-analysis of problem solving therapy for the treatment of major depressive disorder in older adults. Int J Geriatr Psychiatry. 2016;31(5):526–535. [PubMed: 26437368]
36. Alexopoulos GS, Raue PJ, Kiosses DN, et al. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. Arch Gen Psychiatry. 2011;68(1):33–41. [PubMed: 21199963]
37. Brandt JBR. Hopkins Verbal Learning Test—Revised. Lutz, FL: Psychological Assessment Resources, Inc.; 2001.
38. Wechsler D. Wechsler memory scale - Third Edition (WMS-III). San Antonio, TX: Psychological Corporation; 1997.
39. Wechsler D. Wechsler Adult Intelligence Scale-Third Edition. London: The Psychological Corporation Limited; 1997.
40. Reitan R. Trail Making Test: Manual for Administration and Scoring. Mesa, AZ, USA: Reitan Neuropsychology Laboratory; 1992.
41. Golden C. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Chicago, IL, USA: Stoelting Co; 1978.
42. Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. J Clin Exp Neuropsychol. 1991;13(6):933–949. [PubMed: 1779032]
43. Hastie TJ, and Tibshirani RJ. Generalized additive models. Routledge; 2017.
44. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716–723.
45. Beekman AT, Geerlings SW, Deeg DJ, et al. The natural history of late-life depression: a 6-year prospective study in the community. Arch Gen Psychiatry. 2002;59(7):605–611. [PubMed: 12090813]
46. Kassel MT, Rao JA, Walker SJ, et al. Decreased Fronto-Limbic Activation and Disrupted Semantic-Cued List Learning in Major Depressive Disorder. Journal of the International Neuropsychological Society : JINS. 2016;22(4):412–425. [PubMed: 26831638]
47. Schallmo MP, Kassel MT, Weisenbach SL, et al. A new semantic list learning task to probe functioning of the Papez circuit. J Clin Exp Neuropsychol. 2015;37(8):816–833. [PubMed: 26313512]
48. Moscovitch M, Winocur G. The frontal cortex and working with memory. In: Principles of frontal lobe function. New York, NY, US: Oxford University Press; 2002:188–209.
49. Rabin LA, Paré N, Saykin AJ, et al. Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2009;16(3):357–376. [PubMed: 19353345]
50. Elderkin-Thompson V, Mintz J, Haroon E, Lavretsky H, Kumar A. Executive dysfunction and memory in older patients with major and minor depression. Arch Clin Neuropsychol. 2007;22(2):261–270. [PubMed: 17443924]
51. Keiski MA, Shore DL, Hamilton JM. The role of depression in verbal memory following traumatic brain injury. The Clinical Neuropsychologist. 2007;21(5):744–761. [PubMed: 17676541]
52. Targum SD. Early symptomatic improvement affects treatment outcome in a study of major depressive disorder. J Psychiatr Res. 2017;95:276–281. [PubMed: 28926793]
53. Targum SD, Catania CJ. Early treatment response affects signal detection in a placebo-controlled depression study. Personalized Medicine in Psychiatry. 2017;4–6:19–24.
54. Fried EI, Nesse RM. Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. Journal of Affective Disorders. 2015;172:96–102. [PubMed: 25451401]

55. Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. Aust N Z J Psychiatry. 2009;43(12):1105–1117. [PubMed: 20001409]

56. Duff K. One-week practice effects in older adults: tools for assessing cognitive change. Clin Neuropsychol. 2014;28(5):714–725. [PubMed: 24882553]

Key points:

- The present study investigated novel associations between the temporal pattern of change in depression severity during psychotherapy with cognitive outcomes in Late Life Depression
- Distinct patterns of depression change characterized by large or consistent improvements during psychotherapy were differentially related to improved verbal learning, memory, and set-shifting, but not inhibition or information processing speed
- The time course of depression response during treatment may impact specific cognitive processes distinctly
- Evaluating the time course of depression treatment trajectories can refine examination of concomitant cognitive outcomes of psychotherapy in LLD

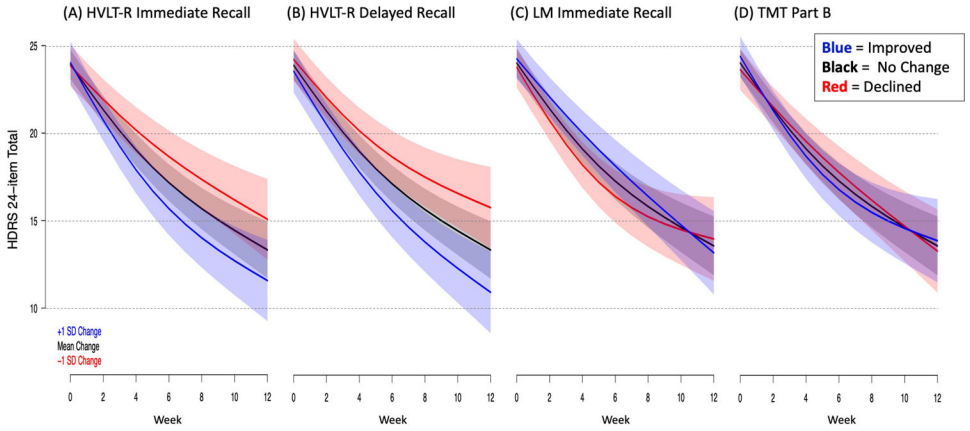

Figure 1.

Depression severity trajectories associated with cognitive change post-treatment. All variables were analyzed on a continuous basis; however, for illustration purposes only, participants are binned into 3 discrete groups representing depression severity trajectories of participants who demonstrated improvement (blue), no change (black), or decline (red) on the depicted cognitive measure at post-treatment. Panels A-C: Higher scores indicate better performance, with positive change signifying improvement at post-treatment. Panel D: Higher scores index poorer performance, with negative change denoting improvement (TMT Part B). HDRS = Hamilton Depression Rating Scale; HVLT-R = Hopkins Verbal Learning Test-Revised; LM = Wechsler Memory Scale-III Logical Memory; TMT = Trail Making Test.

Table 1.

Cognitive change associations with nonlinear depression severity trajectories

Measure	Baseline Raw *Mean (SD)*	Raw Change *Mean (SD)*	X^2 (2, *N*=96)	*p*	AIC Int	AIC Add
Verbal Learning and Memory						
HVLT-R Immediate Recall	23.5 (4.81)	0.61 (4.60)	12.03	.002	5051.58	5459.62
HVLT-R Delayed Recall	7.67 (2.70)	−1.08 (3.04)	7.61	.022	5217.53	5321.17
LM-I Immediate Recall	41.0 (10.8)	4.48 (6.52)	12.45	.002	5823.02	5831.46
LM-II Delayed Recall	24.6 (8.98)	4.00 (5.59)	4.78	.092	5829.69	5830.47
Information Processing Speed						
Trail Making Test-Part A †	40.9 (15.5)	−0.36 (17.00)	2.45	.294	5835.72	5834.16
Digit Symbol-Coding	57.9 (13.8)	2.08 (8.70)	3.48	.175	5775.32	5774.80
Executive Function						
Trail Making Test-Part B †	103.0 (53.9)	−7.61 (43.60)	7.96	.019	5830.02	5833.97
Stroop Interference	31.8 (9.3)	2.28 (4.59)	2.89	.236	5720.64	5719.53

Note. Results of likelihood ratio tests comparing the additive and interactive effects of nonlinear depression severity trajectories with cognitive change. AIC = Akaike's Information Criterion for model selection of best fit; AIC Int = AIC of Interaction model; AIC Add = AIC of Additive model. All cognitive values reported as raw scores for baseline assessment or raw score change (12-week – baseline) in primary outcome measures (total correct or time to complete in seconds for Trail Making Test-Parts A and B). HVLT-R = Hopkins Verbal Learning Test-Revised; LM = Wechsler Memory Scale-III Logical Memory.

† Higher raw scores reflect better performance on all measures except for Trail Making Test-Parts A and B in which lower scores indicate better performance.

Table 2.

Sensitivity analyses: Cognitive change associations with linear percent change in depression

Measure	X^2 (2, N=96)	p	AIC Int	AIC Add
Verbal Learning and Memory				
HVLT-R Immediate Recall	5.92	.015	1058.07	1061.98
HVLT-R Delayed Recall	7.35	.007	865.66	871.01
LM-I Immediate Recall	0.98	.323	1300.14	1299.11
LM-II Delayed Recall	1.70	.193	1241.75	1241.44
Information Processing Speed				
Trail Making Test-Part A	0.62	.430	1553.38	1552.00
Digit Symbol-Coding	1.32	.250	1364.37	1363.69
Executive Function				
Trail Making Test-Part B	0.16	.691	1919.30	1917.45
Stroop Interference	0.24	.624	1210.76	1209.00

Note. Cognitive associations with two-timepoint linear percent change in depression severity based solely on depression ratings at pre- and post-treatment visits. AIC = Akaike's Information Criterion for model selection of best fit; AIC Int = AIC of Interaction model; AIC Add = AIC of Additive model. HVLT-R = Hopkins Verbal Learning Test-Revised; LM = Wechsler Memory Scale-III Logical Memory.