1 Executive Functioning and Anxiety/Depressive Symptoms as Mediators Between ADHD and Quality of Life: A 10-year Longitudinal Study

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Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with impaired executive functioning and anxiety/depressive symptoms, which may contribute to reduced quality of life. We tested the hypotheses that (1) a childhood diagnosis of ADHD is related to reduced quality of life in emerging adulthood and that (2) this relationship is mediated by impaired executive functioning and anxiety/depressive symptoms.

Participants and Methods: We assessed 85 children and adolescents with ADHD and 50 typically developing peers at baseline (Mean age = 11.6 years, 58% males), two-year follow-up, and 10-year follow-up with neuropsychological tests of executive functioning, the Behavioral Rating Inventory of Executive Function (BRIEF), the Short Moods and Feelings Questionnaire (SMFQ), and the Revised Children's Manifest Anxiety Scale, second edition (RCMAS-2), as well as the Perceived Quality of Life scale (PQoL) at the 10-year follow-up. Four neuropsychological tests of executive functioning, the Letter-Number Sequencing test (working memory), the Color-Word Interference test condition 3 (response inhibition), the Color-Word Interference test condition 4 (shifting), and the trail making test condition 4 (cognitive flexibility) were combined into a neuropsychological executive functioning composite score based on high factor loadings (≥ .73). the parent-reported BRIEF indexes, the behavioral regulation index, and the metacognition index were used as measures of everyday executive functioning. We conducted independent samples t-tests to compare the groups and simple and parallel mediation analyses with full information maximum likelihood estimation to examine whether the different executive functioning measures and anxiety/depressive symptoms at two-year follow-up mediated the relationship between baseline ADHD and self-reported quality of life at 10-year follow-up.

Results: Baseline ADHD was associated with more difficulties with executive functioning on a composite measure of neuropsychological tests ($p < .001$, Hedges $g = .79$) and parent-reported everyday metacognitive ($p < .001$, Hedges $g = 2.37$) and behavioral regulation executive functioning ($p < .001$, Hedges $g = 1.55$), as well as self-reported anxiety ($p < .001$, Hedges $g = 1.05$) and depressive symptoms ($p < .001$, Hedges $g = 1.00$) at two-year follow-up. Baseline ADHD was associated with lower self-reported quality of life ($p = .001$, Hedges $g = -.67$) at 10-year follow-up. The mediation analysis showed that everyday metacognitive executive functioning ($p = .011$, $\beta = -.497$) and an anxiety/depressive symptoms composite ($p < .001$, $\beta = -.404$) parallelly mediated the relationship between ADHD and quality of life.

Conclusions: Impaired everyday executive functioning and anxiety/depressive symptoms may represent two distinct pathways to reduced quality of life in emerging adults with a childhood diagnosis of ADHD. These findings stress the importance of targeting both cognitive and emotional aspects in interventions for children and adolescents with ADHD to improve later quality of life.

2 Neuropsychological Predictors of Posttraumatic Stress Disorder and Depressive Symptom Improvement in Compensatory Cognitive Training for Veterans with a History of Mild Traumatic Brain Injury

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Objective: Mild traumatic brain injury (mTBI), depression, and posttraumatic stress disorder (PTSD) are a notable triad in Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans. With the comorbidity of depression and PTSD in Veterans with mTBI histories, and their role in exacerbating cognitive and emotional dysfunction, interventions addressing cognitive and psychiatric functioning are critical. Compensatory Cognitive Training (CCT) is associated with improvements in areas such as prospective memory, attention, and executive functioning and has also yielded small-to-medium treatment effects on PTSD and depressive symptom severity. Identifying predictors of psychiatric symptom change following CCT would further inform the interventional approach. We sought to examine neuropsychological predictors of PTSD and depressive symptom improvement in Veterans with a history of mTBI who received CCT.

Participants and Methods: 37 OEF/OIF/OND Veterans with mTBI history and cognitive complaints received 10-weekly 120-minute CCT group sessions as part of a clinical trial. Participants completed a baseline neuropsychological assessment including tests of premorbid functioning, attention/working memory, processing speed, verbal learning/memory, and executive functioning, and completed psychiatric symptom measures (PTSD Checklist-Military Version; Beck Depression Inventory-II) at baseline, post-treatment, and 5-week follow-up. Paired samples t-tests were used to examine statistically significant change in PTSD (total and symptom cluster scores) and depressive symptom scores over time. Pearson correlations were calculated between neuropsychological scores and PTSD and depressive symptom change scores at post-treatment and follow-up. Neuropsychological measures identified as significantly correlated with psychiatric symptom change scores (p≤.05) were entered as independent variables in separate multiple linear regression analyses to predict symptom change at post-treatment and follow-up.

Results: Over 50% of CCT participants had clinically meaningful improvement in depressive symptoms (≥17.5% score reduction) and over 20% had clinically meaningful improvement in PTSD symptoms (≥10-point improvement) at post-treatment and follow-up. Examination of PTSD symptom cluster scores (re-experiencing, avoidance/numbing, and arousal) revealed a statistically significant improvement in avoidance/numbing at follow-up. Bivariate correlations indicated that worse baseline performance on D-KEFS Category Fluency was moderately associated with PTSD symptom improvement at post-treatment. Worse performance on both D-KEFS Category Fluency and Category Switching Accuracy was associated with improvement in depressive symptoms at post-treatment and follow-up. Worse performance on D-KEFS Trail Making Test Switching was associated with improvement in depressive symptoms at follow-up. Subsequent regression analyses revealed worse processing speed and worse aspects of executive functioning at baseline significantly predicted depressive symptom improvement at post-treatment and follow-up.

Conclusions: Worse baseline performances on tests of processing speed and aspects of executive functioning were significantly associated with improvements in PTSD and depressive symptoms during the trial. Our results suggest that cognitive training may bolster skills that are helpful for PTSD and depressive symptom reduction and that those with worse baseline functioning may benefit more from treatment because they have more room to improve. Although CCT is not a primary treatment for PTSD or depressive symptoms, our results support consideration of including CCT in hybrid treatment approaches. Further

research should examine these relationships in larger samples.

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3 Network Analysis of Neuropsychiatric Symptoms in Alzheimer's Disease

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Objective: Neuropsychiatric symptoms due to Alzheimer's disease (AD) and mild cognitive impairment (MCI) can decrease quality of life for patients and increase caregiver burden. Better characterization of neuropsychiatric symptoms is needed to identify effective treatment targets. The current investigation leveraged the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to examine the network structure of neuropsychiatric symptoms among symptomatic older adults with cognitive impairment.

Participants and Methods: The identified sample includes those from the NACC UDS (all versions) with complete data on the Neuropsychiatric Inventory Questionnaire (NPI-Q) at initial visit. The NPI-Q is an informant-based estimation of the presence and severity of neuropsychiatric symptoms (delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, motor disturbance, nighttime behaviors, appetite and eating problems). The following inclusionary criteria were applied for sample identification: age 50+; cognitive status of MCI or dementia; AD was the primary or contributing cause of observed impairment; and at least one symptom on the NPI-Q was endorsed. Participants were excluded if they endorsed "unknown" or "not available" on any NPI-Q items. The final sample (n = 12,507) consisted of older adults (M_{age}=73.94, SD_{age}=9.41; 46.2% male, 53.8% female) who predominantly identified as non-Hispanic white (NHW) (74.5% NHW, 10.9% non-Hispanic Black, 8.5% other, 5.8% Hispanic white, .3% Hispanic Black). The majority of the sample met criteria for dementia (77.6% dementia, 22.4% MCI) and AD was the presumed primary etiology in 93.9%.

The *eLasso* method was used to estimate the binary network, wherein nodes represent NPI-Q variables and edges represent their pairwise dependency after controlling for all other symptom variables in the network. In other words, the network represents the conditional probability of an observed binary variable (e.g., presence/absence of delusions) given all other measured variables (e.g., presence/absence of all other NPI-Q symptoms) (Finnemann et al., 2021; van Borkulo et al., 2014). Strength centrality and expected influence were calculated to determine relative importance of each symptom variable in the network. Network accuracy was examined with methods recommended by Epskamp et al. (2018), including edge-weight accuracy, centrality stability, and difference tests.

Results: Edge weights and node centrality (CS(cor=.7)=.75) were stable and interpretable. The network (M=.28) consisted of mostly positive edges and some negative edges. The strongest edges linked nodes within symptom domain (e.g., strong positive associations among externalizing symptoms). Disinhibition and agitation/aggression were the most central and influential symptoms in the network, respectively. Depression or dysphoria was the most frequently endorsed symptom, followed by anxiety, apathy or indifference, and irritability or lability.

Conclusions: Endorsed disinhibition and agitation yielded a higher probability of additional neuropsychiatric symptoms and influenced the activation, persistence, and remission of other neuropsychiatric symptoms within the network. Thus, interventions targeting these symptoms may lead to greater neuropsychiatric symptom improvement overall. Depression or dysphoria, while highly endorsed, was least influential in the network. This may suggest that depression and dysphoria are common, but not central neuropsychiatric features of AD pathology. Future work will compare neuropsychiatric symptom networks