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Authors

Adamowicz, David
Wu, Tsung-Chin
Daly, Rebecca
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Publication Date

2024-01-10

DOI

10.1016/j.pnpbp.2023.110866

Peer reviewed

HHS Public Access

Author manuscript

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2025 January 10.

Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2024 January 10; 128: 110866. doi:10.1016/j.pnpbp.2023.110866.

Executive Functioning Trajectories and their Prospective Association with Inflammatory Biomarkers in Schizophrenia and Non-psychiatric Comparison Participants

David H. Adamowicz[a], **Tsung-Chin Wu**[b], **Rebecca Daly**[a,c], **Michael R. Irwin**[d], **Dilip V. Jeste**[a,c], **Xin M. Tu**[b], **Lisa T. Eyler**[a,c,e], **Ellen E. Lee**[a,c,e]

[a]Department of Psychiatry, University of California San Diego, La Jolla, CA, 92093, USA

[b]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, 92093, USA

[c]Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla, CA 92093, USA

[d]Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience, University of California, Los Angeles, CA, USA

[e]Desert-Pacific Mental Illness Research Education and Clinical Center, Veterans Affairs San Diego Healthcare System, San Diego, CA, 92161, USA

Abstract

Background and Hypothesis: Cognitive change in people with schizophrenia (PwS) is challenging to assess, but important to understand. Previous studies with limited age ranges and follow-up were subject to practice effects. Controlling for practice effects in a well-established cohort, we examined executive functioning trajectories and their association with inflammatory biomarkers, hypothesizing that PwS will have worsening executive functioning over time compared to non-psychiatric comparison participants (NCs), predicted by higher baseline inflammation with a stronger relationship in PwS than NCs.

Study Design: Executive functioning was assessed in 350 participants (n=186 PwS, 164 NCs) at 12–16-month intervals (0 to 7 follow-up visits). Inflammatory biomarkers at baseline included high sensitivity C-Reactive Protein (hs-CRP), Interferon-gamma, Tumor Necrosis Factor (TNF)-alpha, and Interleukin(IL) −6, −8, and −10. Executive functioning trajectories across diagnostic

Corresponding author: Ellen E. Lee MD, Assistant Professor in Residence, Department of Psychiatry, University of California San Diego, 9500 Gilman Drive #0664, La Jolla, CA 92023-0664, Fax: (858) 534-5475, Telephone: (858) 534-5525, eel013@health.ucsd.edu.

Author Statement

David Adamowicz: writing – original draft, Writing -Review & Editing, Visualization; **Tsung-Chin Wu**: Formal Analysis, Visualization, Methodology; **Rebecca Daly** – Data Curation; **Michael Irwin**: Conceptualization, Writing – Review & Editing; **Dilip Jeste**: Funding acquisition; **Xin Tu**: Methodology, Writing-Review & Editing; **Lisa Eyler**: Supervision, Writing-Review & Editing, Methodology, Conceptualization; **Ellen Lee**: Writing – Review & Editing, Conceptualizaton, Methodology.

Declarations of interest: none

Ethical Statement

The study protocol was reviewed and approved by the University of California San Diego (UCSD) Human Research Protection Program. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and signed informed consent of the participants was obtained after full explanation of the study procedures.

groups were estimated using a linear mixed-effects model controlling for age, sex, race/ethnicity, and education level, with additional models to assess prediction by baseline inflammation.

Study Results: Over 4.4 years average follow-up, improvements in executive functioning were attenuated in PwS and older participants. Controlling for practice effects negated improvements, revealing declines among highly educated participants regardless of diagnosis. Higher baseline hs-CRP predicted worse executive functioning only among NCs, while TNF-alpha was predictive of change in all participants only after controlling for practice effects. Only the main effect of hs-CRP on executive function was significant after adjusting for multiple comparisons. None of the other inflammatory biomarkers predicted executive functioning or trajectories of performance among study participants.

Conclusions: Systemic inflammation as reflected by baseline inflammatory biomarker levels did not predict longitudinal declines in executive functioning. Additional studies examining the temporal dynamics of inflammation and cognition in PwS will help further clarify their relationship and associated mechanisms.

Keywords

longitudinal; cognition; cytokines; psychosis; aging

Introduction

While schizophrenia is most associated with positive symptoms, cognitive deficits contribute more to the high functional and economic burden of the illness (Cloutier et al., 2016). Cognitive deficits among people with schizophrenia (PwS) are usually premorbid and are accentuated after the first psychotic break (Aas et al., 2014). While not all first-episode patients have significant cognitive decline 3 years afterward, the subset with decline has worse daily functioning and negative symptomatology (Rodríguez-Sánchez et al., 2013). Longitudinal studies of PwS with 10-year follow-up reported declines in verbal knowledge, visuospatial and verbal memory after the first psychotic episode (Wannan et al., 2018; Zanelli et al., 2019). While these deficits tend to stabilize over time, certain domains continue to decline with age, notably executive functioning, verbal knowledge, and verbal fluency (Fett et al., 2020; Fucetola et al., 2000). One 20-year longitudinal study found performance differences between PwS and NCs increased until age 50 years and then plateaued (Fett et al., 2020). These previously established cognitive trajectories in PwS did not consider practice effects, and they likely involve both neurodevelopmental and neurodegenerative processes that are mediated by inflammatory mechanisms (Möller et al., 2015; Na et al., 2014). Impaired acquisition of function in early development and continued cognitive decline with a suspected acceleration of aging in PwS have been attributed, in part, to neuroinflammation and systemic inflammation that contribute to neuronal damage (Monji et al., 2013).

Pro-inflammatory cytokines are thought to have a direct effect on neurotransmission and are associated with severity of psychopathology in PwS (Barron et al., 2017). It is well established that many cytokines, chemokines, and vascular inflammatory markers are increased in PwS, relative to non-psychiatric comparison (NC) groups (Hong et al., 2017;

Joseph et al., 2015; Lee et al., 2017; Nguyen et al., 2018). Cross-sectional studies have shown associations between inflammatory biomarkers and cognitive functioning in PwS, but these studies lack the ability to make causal inferences, have mixed findings and limited age range, and do not consider the long-term effects of aging (Adamowicz et al., 2022; Johnsen et al., 2016; Ospina et al., 2021). Some have found C-Reactive Protein (CRP) levels to be associated with the severity of cognitive impairment (Dickerson et al., 2007; Joseph et al., 2015), with a recent meta-analysis identifying a negative correlation between CRP and multiple cognitive domains in PwS based on 11 studies (Patlola et al., 2023). One recent study has shown that increased Interleukin (IL)-6 levels in 82 PwS at baseline predicted smaller hippocampal volumes, but not verbal learning and memory, at 3 years follow-up (Miller et al., 2021). While this study included a large set of additional inflammatory biomarkers and PwS identified from a national registry, the data were limited to two timepoints and the analyses did not examine age-specific or sex-specific relationships with inflammation and brain changes. Even fewer studies have examined the impacts of education and race/ethnicity on cognitive trajectories in PwS. There has been greater emphasis on the impact of inflammation on aging and cognition in neurodegenerative conditions like Alzheimer's disease, where increased inflammation is thought to contribute to disease progression, possibly predating any premorbid neuropathology (Holmes, 2013). However, among psychotic disorders like schizophrenia, longitudinal studies of cognition that examine inflammation as a predictor of change are lacking.

The current study addresses the limitations of previous cross-sectional studies and sparse longitudinal studies by examining trajectories of executive functioning (a cognitive domain specifically thought to decline over time in PwS) over a broad age range (26-68 years at baseline) and across longer follow-up periods (>4 years on average). We also considered the effects of practice on cognitive performance, which some studies have found to be minimal in PwS after 8 weeks follow-up (Harvey et al., 2005), while others have found to be significant over longer intervals (mean = 18.1 months) and of similar magnitude of improvement as in NC participants (Heaton et al., 2001). We also examined the association of longitudinal cognitive assessments with inflammatory biomarker levels at baseline in both PwS and NCs to gain a better understanding of how inflammation and cognition are linked in the disorder. While inflammatory biomarker values were available at multiple time points, we focused on baseline values as those may be more useful for prognosis. Furthermore, we found inflammatory biomarker values to be highly correlated over time (r=0.33 to 0.70 between baseline and second follow-up visit). With the present study, we hypothesized that: 1) PwS will have greater declines in cognitive functioning over time compared to NCs, reflecting accelerated cognitive aging, and 2) baseline levels of inflammatory biomarkers will predict worsening cognition over time, more so in PwS than NCs. We also explored the impact of sex, baseline age, race/ethnicity, and education on these trajectories and relationships, as their effects as potential covariates have not been thoroughly investigated in PwS.

Methods

Participants

The full cohort for the present study was recruited from an ongoing longitudinal study of aging biomarkers and included 350 participants (186 PwS and 164 NCs), 298 of whom had at least one follow-up visit, up to a maximum of 7 follow-up visits for a total of 8 distinct visits (Table 1).

Participants were residents of the greater San Diego area, aged 26-68 at baseline, and fluent in English. For PwS, the schizophrenia diagnosis was made on the basis of the Structured Clinical Interview for the DSM-IV-TR (SCID) (First, 2002), with DSM-5 criteria (American Psychiatric Association, 2013) not yet available at the start of recruitment. Participants recruited since the DSM-5's availability have met criteria for a diagnosis of schizophrenia or schizoaffective disorder under both definitions. NCs were recruited from an ongoing survey study of aging among community-dwelling healthy adults, directly from the community, online advertisements, or by word of mouth. NCs were excluded from the study if they had a past or present diagnosis of a major neuropsychiatric illness based on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Additional exclusion criteria for both PwS and NCs were as follows: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other non-tobacco substance use disorder within 3 prior months; 3) diagnosis of dementia, intellectual disability disorder, or a major neurological disorder; and 4) medical disability affecting a participant's ability to complete study procedures. Sociodemographic characteristics (age, sex, race/ethnicity, education) were gathered through participant interviews and review of their records. The study protocol was reviewed and approved by the University of California San Diego (UCSD) Human Research Protection Program. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Trained study staff reviewed the consent form with all prospective participants and administered the UCSD Brief Assessment of Capacity to Consent (UBACC)[117] to evaluate each potential participant's understanding of the purpose, procedures, risks, benefits [or lack thereof], and voluntary nature of participation. If, and only if, the potential participant demonstrated comprehension of all the above aspects of the project and expressed willingness to participate in the study, then the participant was invited to enroll in the study and to sign the IRB-approved consent form.

Clinical Outcomes

Previous research from our group demonstrated that deficits in individual component skills may underlie executive deficits in PwS (Savla et al., 2011), therefore incorporating several subtests into a composite was thought to be more reflective of executive dysfunction per se than any individual test on its own. Executive functioning measures included a composite score of subtests from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001): Trail Making (time to complete letter-number sequencing task), Color-Word Inhibition (time to complete switching condition), and the Letter Fluency task (total words across F, A, and S trials). Z-scores were derived from each participant's raw score minus the mean score across participants, divided by the standard deviation for each respective test. These Z-scores, where higher scores equate to better performance, were averaged into

an executive functioning composite score, as a more reliable measure than any individual subtest score. Psychopathology measures included the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS).

Cytokine Assays

Fasting blood samples were drawn at baseline and follow-up visits every 18-24 months. Briefly, 65 mL of blood was collected in ethylenediaminetetraacetic acid (EDTA)-treated vacutainers between 7:00 am and 12:00 pm, then centrifuged at 3000 rpm. Plasma was then stored at −80°C until assays were performed. Plasma biomarker levels were quantified using Meso Scale Discovery MULTI-SPOT® Assay System and analyzed on a SECTOR Imager 2400 instrument (Rockville, MD, USA). Standard curves were formed by fitting ECL signal from calibrators to a 4-parameter logistic model with a 1/y2 weighting, using MSD Discovery Workbench® analysis software. Samples were run in duplicates, using V-PLEX Human Biomarker panels (Catalog # K151A0H-2) to measure the biomarkers. V-PLEX kits are fully validated according to fit-for-purpose principles and the FDA's analytical validation guidelines according to the manufacturer (MSD). Plasma high sensitivity CRP (hs-CRP) levels were measured using a commercially available (MSD, Rockville, MD) enzyme-linked immunosorbent assay (ELISA) at the UCSD Clinical & Translational Research Institute. Interferon (IFN)-gamma, IL-10, IL-6, IL-8, and Tumor Necrosis Factor (TNF)-alpha were assayed at UCLA. The laboratory technician performing the assays was blinded to the participant's diagnosis. Intra-and inter-assay variability was <20% for all assays. The lowest detected levels for specific biomarkers were as follows: 0.04 pg/mL (IL-6), 0.05 pg/mL (IL-10), 0.10 pg/mL (hs-CRP), 0.30 pg/mL (TNF-alpha), 0.82 pg/mL (IL-8), and 0.85 ng/mL (IFN-gamma). No sample showed levels below the detection limits.

Statistical Analyses

Raw biomarker values were log-transformed to reduce heteroscedasticity and improve the model fit by spreading the data more evenly. Sociodemographic, biomarker, and clinical outcome variables were summarized, with group differences examined using independent sample t-tests, chi-square tests, Analysis of Variance (ANOVA), or linear regression. Trajectories of cognitive outcomes over time (days since baseline visit) across diagnostic groups (PwS vs. NCs) were estimated using linear mixed-effects models (LMM) with random intercept and slope for each participant, controlling for age group at baseline (by decade), sex, race/ethnicity, and education level. Age group was binned by decades to increase power given the few numbers of participants at certain ages, while race was binarized into white versus other races, given the low number of participants of other races. We selected LMMs for these analyses in order to include all available data.

We tested a model that included main effects only; then the interactions between time and diagnostic group; interactions between time and all covariates; interactions between diagnostic group and all covariates; and interactions of time, diagnostic group, and all covariates. Three-way interactions were removed from the model if not significant. LMM with random intercept and slope was also used to analyze the association of cognitive performance over time with baseline inflammatory biomarker level as well as with diagnostic group, controlling for baseline age, sex, race/ethnicity, and education level.

Interaction between time and baseline inflammatory biomarker level and interaction between diagnostic group and baseline inflammatory biomarker level were included in the model in addition to the interaction terms in the final LMM without baseline inflammatory biomarker level. A pseudo-replacement approach was used to control for practice effects on cognitive variables, as described below. The LMM results include t-statistics. Statistical significance was set at $p < .05$ (two-tailed). In the models using inflammatory biomarker outcomes (hs-CRP, TNF-alpha, IFN-gamma, IL-10, IL-8, IL-6), we corrected for multiple comparisons by adjusting p-values for false discovery rate (Benjamini and Hochberg, 1995) over the six dependent variables tested.

To model changes in cognitive performance over time and association of such changes with other variables of interest, it is necessary to account for practice—or learning—effects, due to repeated assessments. Although a well-recognized and important issue, there is not much published literature addressing this important topic (Elman et al., 2018; Kremen et al., 2013; Goldberg et al., 2010). As practice effects are confounded by normal age-related cognitive declines, it is difficult to tease out the two sources of variability in most studies. In this study, we are able to model, estimate, and control for practice effects, due to the unique accelerated longitudinal design using multiple cohorts with participants' age at entry in the study ranging from 26 to 68 years (see below for further methodological detail). In addition, the study employed a fixed assessment schedule with a 12-month interval between any two consecutive assessments. Although there is some deviation for some participants, we considered 12 months as the time lag between two consecutive visits for our analysis purposes so that we can estimate practice effects for each reassessment. The interaction between practice effect and diagnostic group and the interactions between practice effect and all covariates were included in the LMM controlling for practice effects. The other interaction terms that were included in the LMM without controlling for practice effects were also included. Again, all three-way interactions were removed from the model if not significant.

Estimating and Controlling for Practice Effects

Since age is the primary confounder of practice effect, we matched participants with the same age to model and estimate practice effects. Since the repeated assessments occur every 12 months, we modeled practice effects at each reassessment after 12 months by the difference in mean of the cognitive outcome of interest between the first and each reassessment based on the subgroup of participants with their age differences less than 12 months. Since the magnitude of the 12-month practice effect may also vary across different ages, we also included an age by practice effect interaction to account for such variability.

To illustrate the idea of the model, assume there are a total of 3 assessments (two reassessments after the first assessment at study entry). The youngest subpopulation is 26 years of age at study entry and the study includes participants of age 26, 27, 28 and so on. Shown in Figure 1 are the different age subgroups (determined by age at baseline) with 1^{st}, 2^{nd} (red for 1^{st} reassessment) and 3^{rd} (blue for 2^{nd} reassessment). Shown in Figure 2 are age-matched subgroups for modeling practice effects due to the 1^{st} (difference between

red and black) and 2nd (difference between blue and black) reassessment. The difference between blue and red is the practice effect between the 1st and 2nd reassessments.

For each cognitive outcome, we use longitudinal models to model the change of the outcome and its association with independent variables. Let y_{it} denote the cognitive outcome and x_{it} a vector of independent variables from the i^{th} participant at time t ($1 \le i \le n$, $1 \le t \le m$), with n denoting the sample size and m denoting the total assessments. Let $u_{it} = (u_{it1}, u_{it2}, \ldots, u_{it(m-1)})^\top$ denote a vector of binary indicators, where u_{itj} is a binary indicator of the j^{th} reassessment with $u_{itj} = 1$ if the i^{th} participant has the j^{th} reassessment at time t and $u_{itj} = 0$ otherwise. Also let v_{it} denote a time-varying variable indicating the age of the i^{th} participant at time t. We model the longitudinal relationship of y_{it} with x_{it} controlling for practice effects using the generalized estimating equations (GEE):

$$E(y_{it}|x_{it}) = x_{it}^\top \beta_0 + u_{it}^\top \beta_1 + v_{it}^\top \beta_2 + v_{it} u_{it}^\top \beta_3, \ 1 \le i \le n, \ 1 \le t \le m+1 .$$

Inference about $\beta = (\beta_0^\top, \beta_1^\top, \beta_2^\top, \beta_3^\top)^\top$ is based on the GEE (Tang et al., 2012). Since no mathematical distribution model is imposed on y_{it}, GEE provides valid inference for a broad class of data distributions.

Results

Demographic variables

There was no significant difference in age or sex between diagnostic groups, but PwS had a larger proportion of non-white participants than NCs ($X^2(1, N = 350) = 6.98$, p=.008). The groups also differed in terms of years of education, with PwS having significantly less education than NCs ($t(348) = 10.23$, $p < .001$). PwS had worse executive functioning than NCs, as measured by the executive function composite of three D-KEFS scores (Table 2). Study participants had, on average, 4.4 years of longitudinal follow-up (mean=1608 days, S.D.= 904 days, range 221-3290 days). The 52 participants with only a single visit (33 PwS and 19 NCs) had no demographic differences compared to those with follow-up data. Among PwS, those lost to follow-up had similar demographic and psychopathology measures compared to those with follow-up.

Executive Functioning and Trajectories

The results of our linear mixed effects model, which excluded all three-way interactions since none were significant, showed as suggested by the above univariate analysis, that executive function composite score was lower in PwS compared to NCs across all timepoints ($t(334) = -3.42$, $p < .001$) (Supplemental Table 1). Executive functioning scores increased over time ($t(928)=4.26$, $p<.001$). People with more education performed better on the executive function composite across all timepoints ($t(334) = 4.08$, $p < .001$), as did white participants compared to those from other races ($t(334) = 3.17$, $p = .002$). Men and women performed similarly across all timepoints ($t(334) = -0.40$, $p = 0.69$).

These main effects must be interpreted in the context of observed interactions. Namely, the diagnostic group difference in performance across all time points was observed mainly

in women with schizophrenia, who had worse performance than men with schizophrenia (Figure 3A; t(334) = 2.19, p = .029). There was also a significant diagnostic group by education interaction (t(334) = 2.00, p = .046), such that diagnostic group differences were greater at lower education levels (Figure 4A).

In testing our hypothesis on trajectories of change, we found a significant main effect of time such executive functioning improved over time (t(928) = 4.26, p < .001) (Figure 4A, Supplemental Table 1). This improvement in executive functioning was attenuated among PwS compared to NCs (t(928) = −2.14, p = .032). Executive function performance improvement was more pronounced in participants with fewer years of education (t(928) = −2.60, p = .010) and was attenuated in participants >35 years old ($X^2(3, N = 350) = 13.0$, p = .005). The degree of improvement did not differ based on sex (t(928) = −0.96, p = 0.34). Although no 3-way interactions were significant, exploratory examination of the plots suggests that, among participants with more education, there was a tendency for improved performance only in NCs and not PwS below the age of 36, while above the age of 45, PwS appeared to have worsening performance over time (Supplemental Figure 1A). Among PwS, executive function composite performance was higher in men than in women, in particular during the first year of the follow-up period, but there was no sex difference among NCs (Figure 3A).

Consideration of practice effects

After controlling for practice effects, there was no significant improvement in executive function composite scores over time (Supplemental Table 2). This improvement was previously seen among those with lower levels of education and in participants younger than 36 with higher levels of education, for both PwS and NCs. There was no longer a differential trajectory of executive functioning in PwS compared to NCs (Figure 4B). There was no significant interaction of the practice effect with baseline age, diagnostic group, sex, education level, or race/ethnicity. In participants with higher education, a decline in executive functioning over time was revealed regardless of sex or diagnostic group (t(888) = −2.02, p = .044; Figure 4B), with a tendency for this to be the case particularly among older participants (Supplemental Figure 1B).

Baseline Inflammatory Biomarkers and Cognition

Over the mean 4.4-year follow-up period, linear mixed models controlling for sex, age, diagnostic group, education, race/ethnicity, and including baseline inflammationindicated that there were no significant main effects of any inflammatory biomarkers nor predictive effects of baseline biomarkers on change in executive functioning over time. However, when practice effects were added to the models, we found that participants with higher levels of hs-CRP at baseline had worse performance in executive functioningacross all timepoints (t(315) = −2.58, p = .010, FDR-p = 0.049) (Supplemental Table 3). An interaction with diagnostic group demonstrated this was only the case in NCs and was not observed among PwS (t(315) = 2.14, p = .033, FDR-p = 0.150), as opposed to ourprediction that the relationship would be stronger for PwS than NCs. This interaction was not significant after FDR correction, however. In practice effect-corrected models, participants from both diagnostic groups with higher TNF-alpha at baseline had less improvement of executive

functioning performance over time (t(808) = −2.16, p = .031, FDR-p= 0.134) (Supplemental Table 4), but this was not significant after FDR correction. No main effects or interactions with time were observed for IFN-gamma, IL-10, IL-8, or IL-6. Thus, we found no reliable evidence for a relationship between inflammation and executive functioning trajectories in PwS and NCs.

Discussion

Overall, these findings only partially supported our hypotheses. Examining a cognitive domain that is thought to selectively decline over time in PwS, we did not find evidence of accelerated cognitive aging in PwS after controlling for practice effects. Only higher baseline hs-CRP levels predicted worse executive functioning over time in all participants.

The lack of accelerated cognitive aging among PwS in the current study is consistent with two prior studies with short term (mean 1.6 years) and longer term (5-6 years) follow-up of PwS and NCs (Friedman et al., 2001; Heaton et al., 2001). Heaton and colleagues reported on a cohort similar to the current study, 142 community-dwelling PwS with mean age of 47.6 (SD = 15.7) years, and found improvements over time in a cognitive composite score (3). However, the Heaton et al. study did not account for practice effects. In contrast, Harvey and colleagues found age-related changes in 30-month cognitive trajectories among chronically hospitalized PwS, though this study lacked an NC group (Harvey et al., 1999). Lower levels of education were also a predictor of decline in the Harvey et al. cohort, in contrast to the education effect in our study. The current study findings appear attributable to the controlling for practice effects and possibly reflected regression to the mean, i.e., the more highly educated individuals at higher baseline cognitive functioning could only decline. The discrepancies in findings may be related to the setting, severity, baseline age of the PwS cohorts as well as lack of consideration of practice effects in previous work.

We found that high baseline hs-CRP levels predicted poorer executive functioning across time; evidence that this primarily was true among NC but not PwS did not hold up after adjusting for multiple comparisons. Cross-sectional results from an earlier iteration of the same cohort as the one from this study also showed that hs-CRP levels were negatively correlated with executive functioning, but only among NCs (Joseph et al., 2015). We did not see a significant relationship of hs-CRP to trajectories of executive functioning in any model, however other studies have found that decreased CRP in the acute phase of psychosis was associated with improved cognitive performance at 6 months follow-up (Fathian et al., 2019). The lack of an inverse relationship between hs-CRP levels and cognitive trajectories among PwS with more extended longitudinal follow-up is a powerful negative result that suggests a lack of predictive value for baseline inflammatory biomarkers, despite cross-sectional associations with cognition. To this point, other studies that noted a relationship between increased CRP levels and worse cognition in PwS were largely cross-sectional and lacked an NC group (Bulzacka et al., 2016; Micoulaud-Franchi et al., 2015), while another study was conducted in the setting of acute psychosis with the relationship not persisting after limited (6 weeks) follow-up (Johnsen et al., 2016).

The finding that elevated baseline TNF-alpha levels predicted worse cognition over time did not withstand testing for multiple comparisons. There are data suggesting that TNF-alpha levels are decreased among PwS compared to NCs chronically; but while some report an inverse relationship of TNF-alpha levels with cognition (Lv et al., 2015), others report a positive correlation (Zhang et al., 2016), demonstrating inconsistency even among cross-sectional studies.

We did identify education level as a key moderator of executive functioning trajectories among PwS and NCs. The improvements over time that were more pronounced in the less educated participants were nullified once practice effects were controlled for, validating the pseudo-replacement approach comparing participants at a subsequent visit with those entering the study at the same baseline age. In more highly educated participants, this approach also mitigated the initial group differences observed.

The finding that executive functioning deficits among PwS, compared to NCs, were most apparent at lower levels of education may indicate that higher levels of education may partly compensate for the cognitive deficits observed long term among PwS. These findings are supported by studies showing that cognitive remediation may have similar amelioration effects in PwS (Vita et al., 2021), and the premise that cognitive reserve mediated in part by higher educational attainment is a protective factor against cognitive decline. The current study findings that white participants had higher executive functioning composite scores than other races may be explained by the lack of race-specific norms used in the cognitive outcomes of this study. The use of these race-based norms has recently been questioned as downplaying the impact of social determinants of health on cognition, with a call to directly measure and adjust for social determinants of brain health, such as education quality rather than just the number of years (Possin et al., 2021). While NCs showed no sex differences in executive functioning trajectories, women with schizophrenia performed worse than men, which may be an unexpected finding on its own, but is consistent with cross-sectional data showing low estrogen levels being associated with cognitive deficits in female PwS of reproductive age (Ko et al., 2006). Postmenopausal PwS have also shown improvements in executive functioning following treatment using a selective estrogen receptor modulator in a small (n=33) 12-week, double-blind, randomized, placebo- controlled study, illustrating the possible interplay between hormone levels and cognition in this population (4).

Cognitive decline is challenging to prevent among PwS and predicts disability and functioning. A 2021 study reported that PwS have 10 to 20-fold higher prevalence of dementia, compared to the general population (Stroup et al. 2021). Anti-inflammatory treatments for PwS have shown early promise for improving cognition, though the benefits are not universal (Cho et al, 2019). Better understanding of inflammatory biomarker changes over time in PwS and how they relate to age-related cognitive decline will be essential in identifying those who might benefit the most from anti-inflammatory treatments during the early stages of illness (Müller et al., 2010, 2002; Sommer et al., 2012). For instance, the CATIE study reported that PwS who had higher baseline IL-6 levels prior to receiving the study antipsychotic had greater improvements in positive and negative symptoms at 3 and 6 months. There were larger symptom gains among PwS who were treated with antipsychotics that are thought to have anti-inflammatory effects (Feng et al., 2020). Along

these lines, inflammatory composites may have greater predictive capability that individual markers, though the combination of inflammatory biomarkers warrants further data-driven examination. Similar findings relating to cognitive symptoms may help with prognosis (with the goal of slowing or preventing cognitive decline in PwS), offering interventions targeted towards inflammation to those whose cognitive changes are most tightly linked with certain biomarkers. Some have suggested that cognitive improvements reported from starting certain antipsychotics in PwS are the result of practice effects, once again emphasizing the importance of taking them into account when repeating cognitive assessments over time in this population (Goldberg et al., 2007).

While this study has several strengths, there are several limitations to consider. One limitation is the use of a single time point at baseline for inflammatory biomarker levels. We used the current approach as baseline inflammatory biomarker levels were highly correlated with subsequent follow-up, indicative of an inflammatory trait rather than a state. While we were able to examine the influence of age, education level, and diagnostic group on cognitive trajectories; the analytic approach did not enable us to identify other moderating factors or subgroups based on trajectories alone. One limitation of the present study is the focus on executive functioning rather than other cognitive domains, which may show differing patterns. Similarly, we did not assess for personality disorders or other persistent features that may be linked to cognitive trajectories. Another limitation is the inability to estimate the anticholinergic effects of medications, which have an outsized burden in PwS and have been shown to be associated with cognitive impairment in this population (Joshi et al., 2021), due to the limitations of the current dataset. Furthermore, peripheral cytokines and chemokines are used as a proxy for neuroinflammation, due to easier accessibility compared to cerebrospinal fluid. Based on the stable outpatient characteristics of the present cohort, as previously mentioned, this study's findings may not be generalizable to different populations of PwS.

Conclusion

Over the average 4.4 years of follow-up in this cohort of stable outpatient PwS, cognitive impairment trajectories varied by education level and were affected by age and practice effects. Controlling for these factors abolished improvements seen in the less educated group, while a decline among the older and more educated PwS was no different from the decline observed among NCs. Sex differences in PwS were subtle,with women worsening to a greater degree than men during the first year of follow-up. Baseline levels of inflammation were not predictive of cognitive trajectories even when they had been associated cross-sectionally. Further studies examining the temporal dynamics of inflammatory biomarker levels and how they relate to cognitive functioning over time in PwS will be necessary to further elucidate the relationship between inflammation and cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Declaration of Interest Statement

This work was supported, in part, by the National Institute of Mental Health (K23MH119375-01 to EEL, R01MH094151-01 to DVJ and LTE, R25MH101072 to Neal Swerdlow); the VA San Diego Healthcare System; and the Stein Institute for Research on Aging at the University of California San Diego. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors declare no conflict of interest.

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Highlights

- Higher baseline TNF-alpha levels predicted worse cognitive trajectories over 4.4 years, though these findings were attenuated after controlling for multiple comparisons.
- After controlling for practice effects, people with schizophrenia did not have accelerated trajectories of decline in executive functioning.
- Older age and less education were associated with worse cognitive functioning.

Figure 1.
Age at study entry (baseline, black) and each of two reassessments (red, blue).

Figure 2.
Age-aligned subgroups for modeling practice effect. Baseline visits are denoted in black, second visits in red, and third visits in blue.

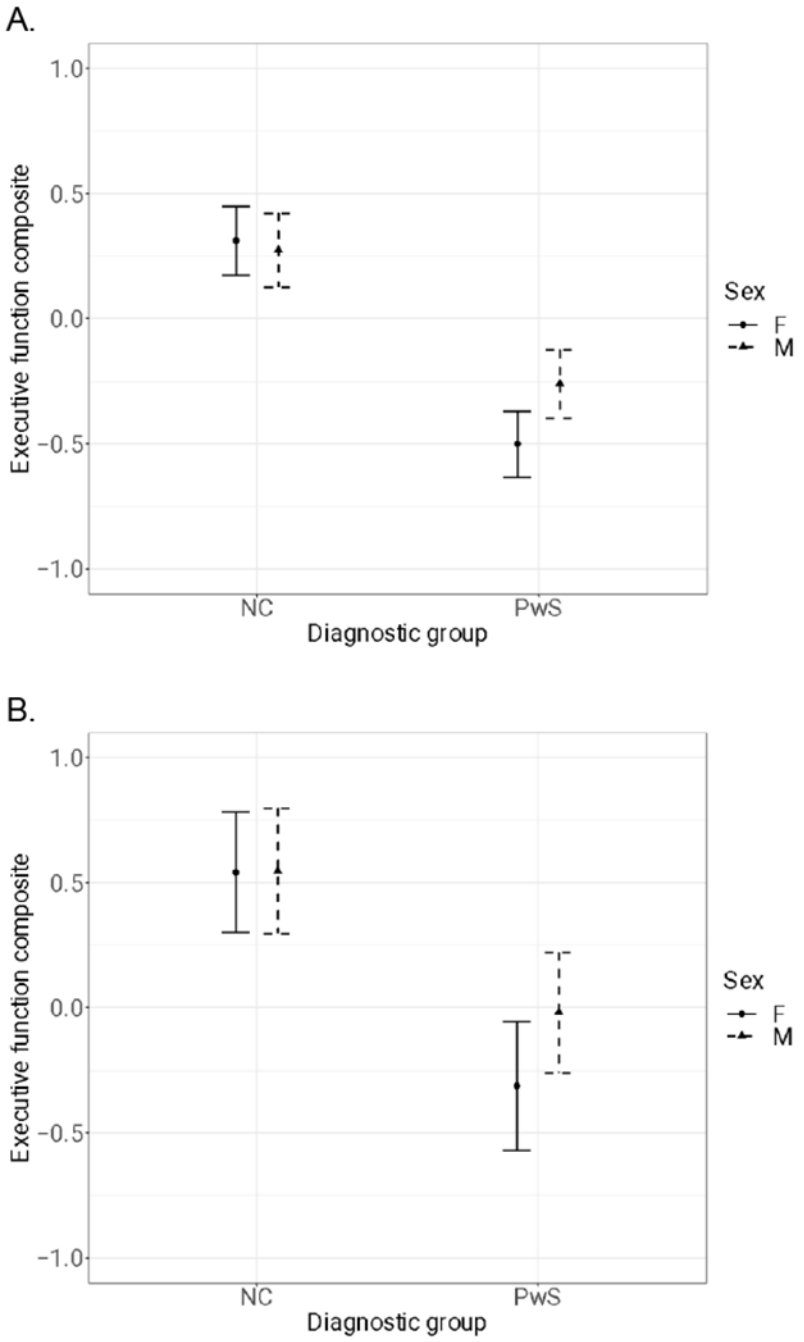

Figure 3 –. Estimated mean and 95% confidence intervals of executive functioning by sex and diagnostic group (A), accounting for practice effects (B)

NC = non-psychiatric comparison, PwS = people with schizophrenia, F= Female, M= Male.

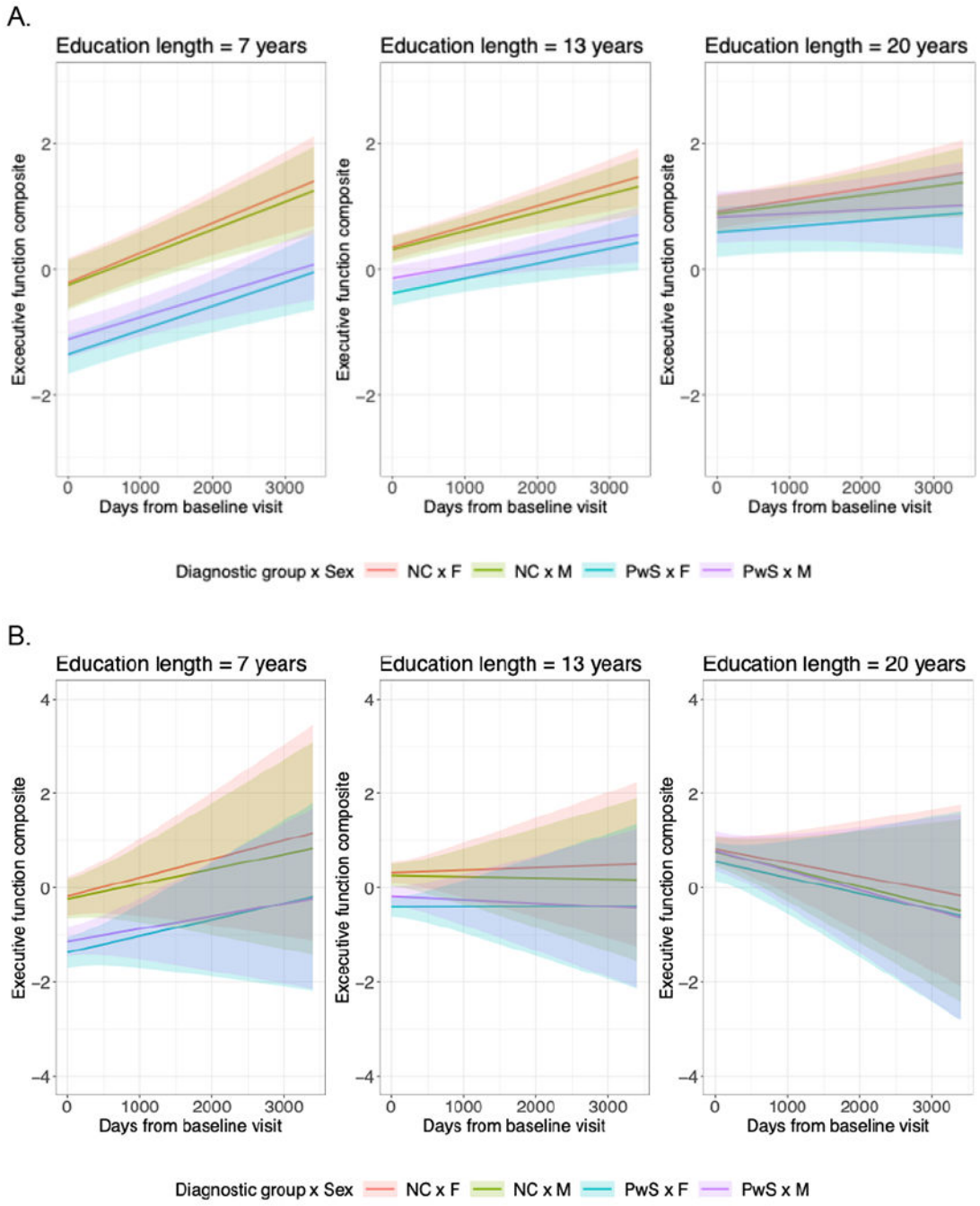

Figure 4–. Estimated mean and 95% confidence bands of executive functioning over time by education level (A), accounting for practice effects (B).

Each panel shows the modeled trajectories of executive functioning when education is fixed at three different levels (Left panel: education level = 7 years; Middle panel: education level = 13 years; Right panel: education level =20 years).

NC = non-psychiatric comparison, PwS = people with schizophrenia, F= Female, M= Male.

Table 1 –

Number of participants per number of study visits

Number of visits	Number of participants
1	350
2	298
3	231
4	193
5	155
6	115
7	68
8	22
Total	1432

Table 2 –

Demographics, cognitive, and psychopathology measures for non-psychiatric comparison participants (NCs) and people with schizophrenia (PwS)

	NC			PwS					
	N	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**t or X^2**	**df**	**p**	**Cohen's d**
Age at baseline (years)	164	47.5	11.4	186	47.9	10.2	−0.30	348	0.76	−0.03
Sex (% female)	89	54.3		91	48.9		0.52	1	0.32	
Race/ethnicity (%)							6.98	1	**0.008**	
White	99	60.4		86	46.2					
Other race/ethnicity	65	39.6		100	53.8					
Education (years)	164	14.7	2.2	186	12.3	2.1	10.23	348	**<0.001**	2.18
Executive functioning (D-KEFS)	164	0.36	0.61	186	−0.64	0.74	13.59	348	**<0.001**	0.68
Positive Symptoms (SAPS)	163	0.35	0.85	184	6.42	4.17	−18.26	345	**<0.001**	−1.96
Negative Symptoms (SANS)	159	1.57	1.95	184	7.09	4.31	−14.88	341	**<0.001**	−1.61

D-KEFS = Delis-Kaplan Executive Function System (composite of 3 scores used), SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms.