



Polygenic Risk for Neuroticism Moderates the Association Between Objective Cognitive Performance and Subjective Memory Complaints



Hyejin Ahn¹, Min Soo Byun^{2,3}, Dahyun Yi⁴, Gijung Jung⁴, Yoonseok Oh², Woo-Jin Cha², Yura Choi², Jun Sung Kim⁴, Shiwei Liu^{5,6}, Andrew J. Saykin^{5,6,7}, Kwangsik Nho^{5,6,8}, Dong Young Lee^{1,2,3,4} and for the KBASE Research Group

¹Interdisciplinary Program of Cognitive Science, Seoul National University College of Humanities, Seoul, 08826, Republic of Korea; ²Department of Neuropsychiatry, Seoul National University Hospital, Seoul, 03080, Republic of Korea; ³Department of Psychiatry, Seoul National University College of Medicine, Seoul, 03082, Republic of Korea; ⁴Institute of Human Behavioral Medicine, Seoul National University Medical Research Center, Seoul, 03082, Republic of Korea; ⁵Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 355 W 16th St, Indianapolis, IN 46202, USA; ⁶Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, 355 W 16th St, Indianapolis, IN 46202, USA; ⁷Department of Medical and Molecular Genetics, Indiana University School of Medicine, Medical Research and Library Building, 975 W Walnut St IB 130, Indianapolis, IN 46202, USA; ⁸School of Informatics and Computing, Indiana University, 535 W Michigan St, Indianapolis, IN 46202, USA

Background

- Subjective memory complaints (SMC) reflect individuals' self-perceived concerns about cognitive functioning but do not perfectly correspond with objective cognitive performance.
- This heterogeneity suggests that SMC may capture not only current neuropsychological functioning but also individual differences in cognitive appraisal.
- Building on evidence that subjective cognitive concerns include trait-like components with genetic influences, we investigated whether genetic liability to neuroticism moderates the association between objective neuropsychological performance and SMC.

Methods

- The study included 724 adults aged 55–90 years, including cognitively normal individuals and those with mild cognitive impairment, from phases 1 and 2 of the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE).
- Neuropsychological performance was assessed using the Korean version of the CERAD battery, with global cognition indexed by the CERAD total score II (TS-II) and memory performance by a composite CERAD memory score (both expressed as z-scores). SMC was measured using the 14-item subjective memory complaint questionnaire (SMCQ).
- Neuroticism polygenic risk scores (PRS) were calculated based on published GWAS summary statistics using a clumping-and-thresholding approach ($p < 5 \times 10^{-8}$). Associations between objective cognitive performance and SMCQ, and their moderation by neuroticism PRS, were examined using linear regression models with interaction terms.



Results

Table 1. Predictors of subjective memory complaints

Objective Cognition	Model 1	Model 2	Model 3
	Cognition → SMCQ β (<i>p</i>)	PRS → SMCQ β (<i>p</i>)	Cognition × PRS → SMCQ β (<i>p</i>)
Memory	−1.000 (<.001)	0.025 (0.793)	0.296 (0.002)
Global cognition	−0.794 (<.001)	0.040 (0.674)	0.224 (0.002)

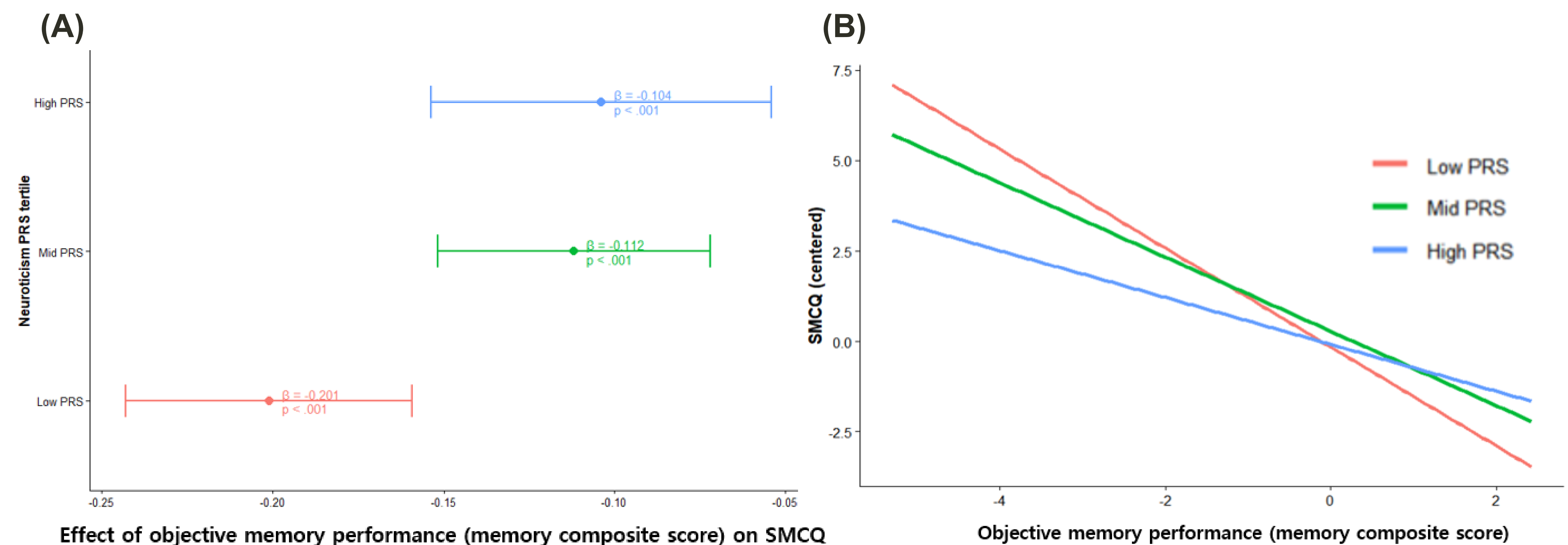
Memory= composite CERAD memory z-score; Global cognition = CERAD total score II(TS-II) z-score. PRS indicates neuroticism polygenic risk score. Models tested main effects and NP × PRS interactions predicting SMCQ.

Table 2. Level-specific associations between cognitive performance and SMCQ according to neuroticism PRS

Objective Cognition	Neuroticism PRS level	β (Cognition → SMCQ)	SE	95% CI	<i>p</i> -value
Memory	Low	−0.201	0.021	−0.243 to −0.159	<.001
	Intermediate	−0.112	0.020	−0.152 to −0.072	<.001
	High	−0.104	0.025	−0.154 to −0.054	<.001
Global Cognition	Low	−0.258	0.027	−0.311 to −0.204	<.001
	Intermediate	−0.141	0.025	−0.191 to −0.092	<.001
	High	−0.132	0.032	−0.194 to −0.069	<.001

Neuroticism PRS was calculated using genome-wide significant variants ($p < 5 \times 10^{-8}$) and stratified into tertiles (low, intermediate, and high levels). Memory= composite CERAD memory z-score; Global cognition= CERAD total score II (TS-II) z-score.

Figure 1. Graded attenuation of the association between memory performance and subjective memory complaints across neuroticism PRS levels.



- (A) Standardized regression coefficients(β) for the association between memory domain performance and SMCQ across neuroticism PRS tertiles.
(B) Simple slopes illustrating the interaction between memory performance and neuroticism PRS on SMCQ.

Conclusion

- Neuroticism polygenic risk moderated the association between objective cognitive performance and SMCQ, with the strongest association observed at lower levels of genetic liability.
- This suggests that when trait-related neuroticism is low, objective cognitive performance more strongly predicts SMC, whereas higher genetic liability attenuates this relationship.

Acknowledgment

This work was supported by grants from the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (No. RS-2022-00165636 and 2014M3C7A1046042); the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare (No. HI18C0630 and HI19C0149); the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (No. RS-2023-KH136195); and the National Institute of Aging, USA (U01AG072177).

