ORIGINAL ARTICLE
https://doi.org/10.30773/pi.2023.0150
Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Neuroplastic and Pro-cognitive Effects of Granulocyte Colony Stimulating Factor in Healthy Adults: A Pilot Study

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Objective Granulocyte colony-stimulating factor (G-CSF) is a growth factor used to regulate the mobilization of bone marrow progenitor cells and has been shown to promote brain repair and reduce inflammation. This study aimed to investigate the pro-cognitive and neuroplastic effects of G-CSF in healthy adults.

Methods Sixteen healthy adults or donors of hematopoietic stem cell transplantation received G-CSF injections for 5 consecutive days, and their blood samples were collected before, immediately after, and 3 weeks after the G-CSF injections. Twelve subjects underwent neuropsychological testing before and 12 weeks after the G-CSF injections.

Results The study found that G-CSF administration resulted in significant improvements in cognitive function, as measured by the Rey–Osterrieth Complex Figure test for immediate recall, delayed recall, and recognition score at 12 weeks after the injections. The blood levels of brain-derived neurotrophic factor, interleukin-4, and interleukin-8 were significantly increased immediately after the injections and returned to baseline levels after 3 weeks. There was no significant change in the plasma level of Multimer Detection System-oligomerized amyloid beta.

Conclusion Our results might suggest that G-CSF has neuroplastic and pro-cognitive effects in healthy adults. However, further study containing a larger sample size is needed to confirm our findings.

Psychiatry Investig 2023;20(10):984-990

Keywords Granulocyte colony-stimulating factor; Cognition; Anti-inflammation; Neuroplasticity.

INTRODUCTION

Alzheimer's disease (AD) is a progressive and devastating neurodegenerative disorder that affects millions of people worldwide.[1] Despite the fact that AD is becoming a global pandemic, only 6 drugs indicated for AD are approved by the U.S. Food and Drug Administration (FDA).[2,3] Unfortunately, none of the classical drugs, including the cholinesterase inhibitors and the glutamate antagonist, have disease-modifying effects, and their effects are limited to symptom management.[4] The newly FDA-approved drugs, aducanumab and lecanemab, have shown potential to slow disease progression by removing amyloid-β (Aβ) deposition in the brain, but the high risk of side effects, including amyloid-related imaging abnormalities (ARIA)-edema and ARIA-hemorrhage, are of concern.[5,6] Therefore, the development of new drugs for AD remains a critical area of research.

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor that helps regulate the mobilization of bone marrow progenitor cells.[7] It has been used for more than 30 years with confirmed safety in patients with severe neutreopenia following cancer treatment as well as in stem cell mobilizations for hematopoietic stem cell transplantation (HSCT) donors. Studies showed that G-CSF may promote brain repair via an anti-apoptotic program, enhance hippocampal neurogenesis, and reduce pro-inflammatory cytokines.[8-11] The results of recent studies further suggest that G-CSF may have potential therapeutic benefits in the treatment

Received: May 10, 2023 **Revised:** July 29, 2023
Accepted: August 13, 2023

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of AD. A pilot study, which included 8 patients with AD, showed that after a 5-day schedule of G-CSF administration, patients with dementia due to AD showed improvement in paired associate learning compared to the baseline.[12] The study also showed that there were trends of changed levels of diverse interleukins after the G-CSF treatments.

Despite the above findings, no other studies were conducted to replicate the effects of G-CSF on cognition and neuroplasticity. Moreover, when developing a new drug for AD, it is important to gather data from healthy controls[13] because data from the healthy controls help ensure that the observed effects of the drug are not due to other factors, such as placebo effects or natural recovery processes.[14] Thus, more studies are needed to confirm the pro-cognitive and neuroplastic effects of G-CSF in not only patients with AD but also in healthy adults.

Multiple blood-based biomarkers are known to measure Aβ pathologies and reflect neuroplasticity. Soluble Aβ oligomers are the major toxic substances associated with the pathology of AD, which now can be measured using Multimer Detection System-oligomeric Aβ (MDS-OAβ).[15] In terms of cytokines, interleukin 4 (IL-4) and interleukin 8 (IL-8) play a crucial role in the regulation of the immune response and inflammation.[16,17] IL-4 is known to polarize microglia to the M2 form,[17] which is characterized by distal ramification, small cell bodies, strong phagocytic activity, and the secretion of anti-inflammatory cytokines.[18] IL-4 reduces inflammatory process of the brain,[19] and it also plays a critical role in higher functions of the normal brain, such as memory and learning.[20] In addition, the exogenous stimulation of the IL-4 signaling pathway promotes postinjury neuron survival, axonal regeneration, and remyelination, which results in improved functional recovery following traumatic peripheral nerve injury.[21] A more recent study human showed that the plasma IL-4 level was positively associate with left subiculum volume in patients with stable mild cognitive impairment but was negatively associate with left subiculum volume and left presubiculum volume in patients with AD.[22] IL-8 was originally recognized as a pro-inflammatory chemokine and has also been implicated in the pathogenesis of AD. Studies reported both increased and decreased IL-8 in the trajectory of AD.[23,24] Brain-derived neurotrophic factor (BDNF) is associated with the survival, differentiation, and plasticity of neurons in the brain.[25] In addition, BDNF is known to be reduced in the brains of individuals with AD, and it has been shown to promote the clearance of Aβ and protect against neuroinflammation and oxidative stress.[26]

Given that G-CSF is commonly used to mobilize hematopoietic stem cells (HSCs) in healthy donors, we conducted a pilot study to investigate the pro-cognitive and neuroplastic effects of G-CSF in HSC donors with a prospective observation study design. In order to study the possible effect of G-CSF on cognition, we investigated the neuropsychological profile before and after G-CSF administration in the donors of HSCT. We also exploratively measured blood MDS-OAβ, IL-4, IL-8, and BDNF levels to understand the neuroplastic effects of G-CSF.

METHODS

Participants

All subjects were recruited from the group of healthy donors of HSCT at Seoul St. Mary's Hospital, The Catholic University of Korea, from 2020 to 2021. The inclusion criteria were as follows: 1) subjects aged 45 years or more, 2) Mini-Mental Status Examination score ≥27, 3) global Clinical Dementia Rating score of 0, 4) Global Deterioration Scale score of 0, and 5) cognitively normal confirmed with the Consortium to Establish a Registry for Alzheimer's Disease-Korea (CERAD-K).[27] The exclusion criteria were as follows: patients having 1) presumptive diagnosis of dementia, mild cognitive impairment, or other neurological or medical conditions that cause cognitive dysfunction (e.g., hypothyroidism); 2) a history or current diagnosis of other psychiatric disorders (e.g., schizophrenia, delusional disorder, or substance abuse); 3) unstable medical conditions (e.g., poorly controlled hypertension, angina, or diabetes); and 4) patients taking any psychotropic medications (e.g., antidepressant, benzodiazepines, and antipsychotics). All subjects provided written, informed consent. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea (IRB number KC19MNSI0412).

Study design

This study was designed as a prospective observational study. Figure 1 shows a general outline of the present research.

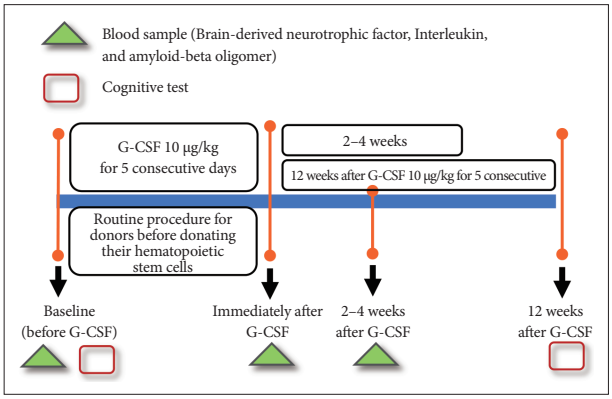

Figure 1. General outline of the experiment. G-CSF, granulocyte colony-stimulating factor.

In the Seoul St. Mary's Hospital, The Catholic University of Korea, all the donors of HSCT receive G-CSF (Filgrastim, Grasin prefilled injection; Kyowa Kirin Korea Co., Ltd., Seoul, Korea) administered subcutaneously at a dose of 10 μg/kg daily for 5 consecutive days. All subjects also underwent baseline neuropsychological testing using CERAD-K and the Rey–Osterrieth Complex Figure test (RCFT), and blood sampling, which included BDNF, IL-4, IL-8, and MDS-OAβ measurements, right before they received the first G-CSF injections. Thereafter, blood samples were collected again right after they received the last (or the 5th) G-CSF injections (immediately after G-CSF) and once more 3 (±1) weeks after the last G-CSF injections (3 weeks after G-CSF). Lastly, CERAD-K and RCFT were conducted once again 12 weeks after they received the last G-CSF injections.

Outcome measures

Blood-based biomarkers

MDS-OAβ is known to measure the oligomerization dynamics in plasma samples after spiking synthetic Aβ,[28] and it can selectively detect OAβ.[29,30] Thus, we used MDS-OAβ to detect subjects' plasma OAβ levels. For plasma OAβ level detection, the subjects received venipunctures, and we used in-house protocols with heparin tubes to collect blood samples. To process the samples and measure MDS-OAβ levels, we followed a previously established procedure[23]: The samples were centrifuged at 3,500 rotations per minute for 15 minutes at room temperature and then stored in 1.5 mL polypropylene tubes at -70°C to -80°C. We then sent the samples to PeopleBio Inc. (Seongnam, Korea) to measure MDS-OAβ levels. Before analysis, plasma aliquots were thawed at 37°C for 15 minutes. MDS-OAβ levels were measured using the multimer detection system, which is CE-marked and approved by the Ministry of Food and Drug Safety of the Republic of Korea.[20-23] In terms of BDNF, IL-4, and IL-8, serum blood samples were obtained from the participants via venipuncture. They were measured using an enzyme-linked immunosorbent assay by Samkwang Medical Laboratories (Seoul, Korea).[31]

Neuropsychological function

The mean changes in neuropsychological function from baseline to 12 weeks after the 5th G-CSF injections were computed to investigate the cognitive effects of G-CSF. Since we included healthy adults only, we expected that the subjects' baseline CERAD-K score would be too high to show significant differences 12 weeks after the G-CSF injections. Thus, in addition to the CERAD-K, all subjects received the RCFT test at the baseline and 12 weeks after the 5th G-CSF injections. RCFT can assess the visuo-constructional and visual memory abilities, including copying and recall tests, of neuropsychiatric disorder patients.[32] By drawing a complex figure, the RCFT has the advantage of detecting subtle changes, even in those with normal cognition.

Statistical analysis

Statistical analyses of demographic and clinical data were performed with jamovi (version 2.3.18.0; https://www.jamovi.org). Continuous and categorical variables were denoted by mean±standard deviation and number with percent among the total cohort (%), respectively. We first conducted normality testing, which confirmed that our data showed normal distribution despite small sample size. Thus, the difference in neuropsychological measures between the baseline and endpoint was evaluated using the paired t-test. In terms of blood markers, the repeated measure of analysis of variance was first utilized to investigate the overall statistical significance. Thereafter, the paired t-test with Bonferroni corrections was utilized to study differences in blood biomarkers between

Table 1. Demographic and clinical characteristics of the study participants

Variable	Value (N=16)
Age (yr)	52.70±4.86
Education (yr)	12.35±4.76
Gender, M:F	10:6
CDR	0
GDS	0
CERAD-K battery (N=11)	
VF	18.25±4.45
BNT	13.54±0.81
MMSE	28.75±1.11
WLM	21.39±3.57
CP	9.59±1.05
WLR	7.21±1.66
WLRc	9.26±0.95
CR	7.70±3.06
Total score	84.18±5.30
Rey–Osterrieth Complex Figure Test (RCFT) (N=12)	
RCFT immediate recall	18.64±6.09
RCFT delayed recall	17.23±6.81
RCFT delayed recognition	9.59±1.05

Values are presented as mean±standard deviation or number. M, male; F, female; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale; CERAD-K, the Korean version of Consortium to Establish a Registry for Alzheimer's Disease; VF, Verbal Fluency; BNT, Boston Naming Test; MMSE, Mini Mental Status Examination; WLM, Word List Memory; CP, Constructional Praxis; WLR. Word List Recall; WLRc, word list recognition; CR, Constructional Recall

two time points as a post-hoc analysis.

RESULTS

Participants characteristics

A total of 16 healthy donors of HSCT were finally enrolled. Their mean age and education were 52.70±4.86 years and 12.35±4.76 years, respectively. Among them, 4 subjects did not complete the last hospital visit for neuropsychological testing, which was 12 weeks after the G-CSF. Thus, a total of 16 subjects completed three blood biomarker tests, while 12 subjects completed two neuropsychological tests (Table 1).

Blood biomarkers and neuropsychological testing

Compared to the baseline, plasma BDNF levels significantly increased immediately after the 5th G-CSF administration, which came down to the baseline level 3 weeks after the 5th G-CSF administration. However, G-CSF administration did not result in a significant change in plasma MDS-OAβ levels (Figure 2). In line with plasma BDNF levels, plasma IL-4 and IL-8 were significantly increased immediately after G-CSF compared to the baseline (Figure 3).

The average CERAD-K total score was around 84.2, confirming that the participants had normal baseline cognitive statuses. Compared to the baseline, participants did not show a significant change in the CERAD-K total score at 12 weeks after the last G-CSF administration. However, there were significant improvements in cognitive function measured using RCFT immediate recall, RCFT delayed recall, and RCFT recognition score (Figure 4).

Safety

In terms of safety, no serious adverse effects related to the use of G-CSF occurred during the study. The most common adverse effects were transient myalgia with diffuse aching that improved with acetaminophen (8/16; 50%). One subject ex-

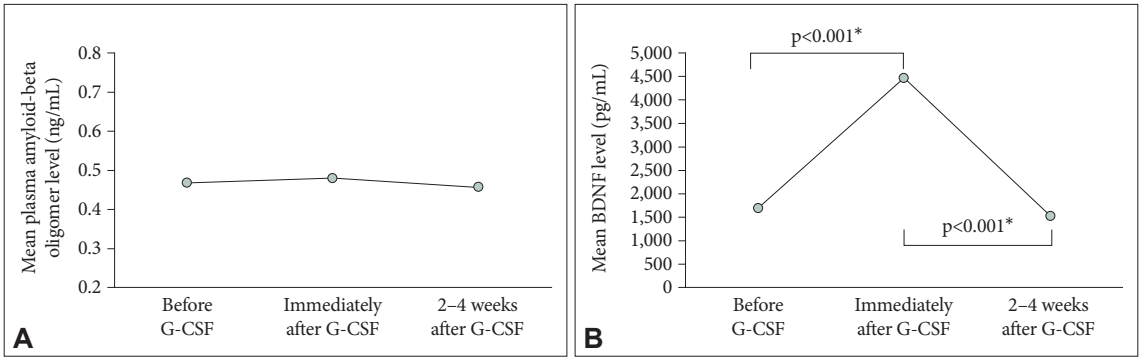

Figure 2. G-CSF administration did not cause a significant change in amyloid-beta oligomer plasma levels (A). However, compared to the baseline, plasma BDNF levels significantly increased immediately after the 5th G-CSF administration and came down to baseline 2–4 weeks after the 5th G-CSF administration (B). *repeated measure of ANOVA with Bonferroni correction. BDNF, brain-derived neurotrophic factor; G-CSF, granulocyte colony-stimulating factor; ANOVA, analysis of variance.

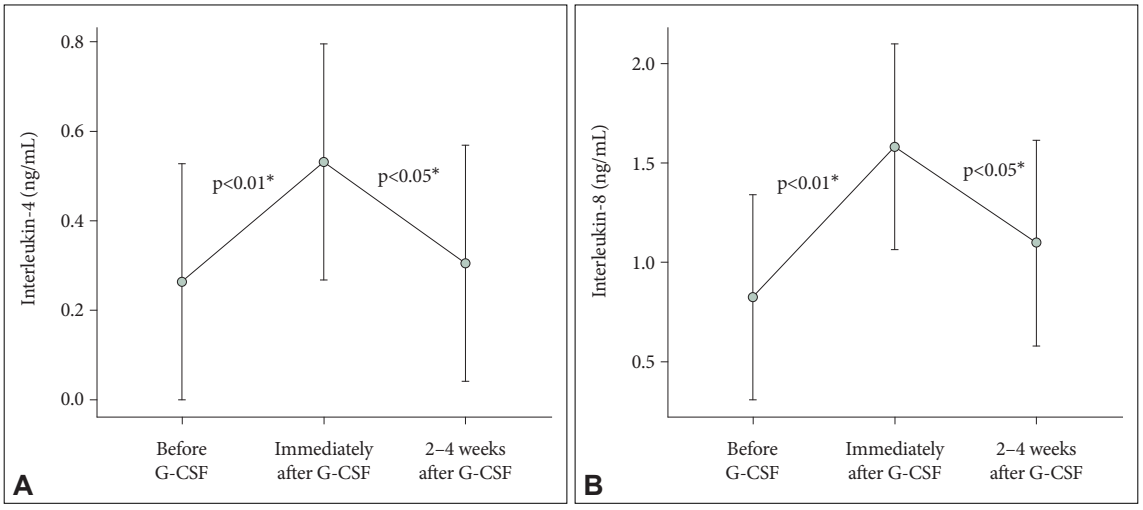

Figure 3. Compared to the baseline, plasma IL-4 (A) and IL-8 (B) levels were significantly increased immediately after the 5th G-CSF administration and came down to baseline 2–4 weeks after the 5th G-CSF administration. *repeated measure of ANOVA with Bonferroni correction. G-CSF, granulocyte colony-stimulating factor; IL-4, interleukin-4; IL-8, interleukin-8; ANOVA, analysis of variance.

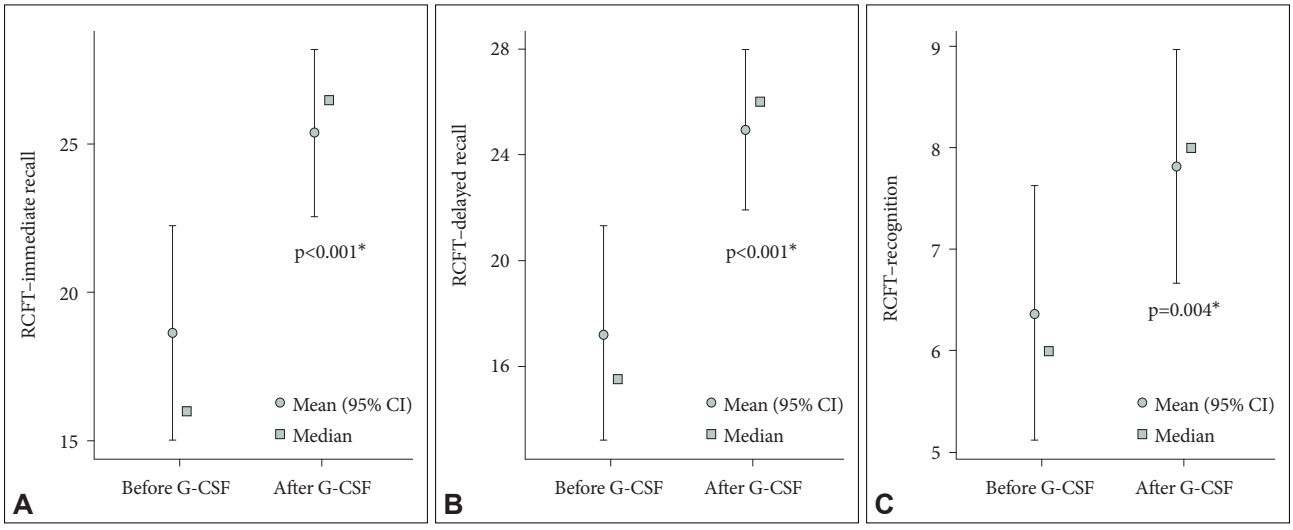

Figure 4. Compared to the baseline, immediate recall (A), delayed recall (B), and recognition (C) in the Rey–Osterrieth Complex Figure Test (RCFT) were significantly improved 12 weeks after G-CSF administration. *statistical analysis using the paired samples Wilcoxon test. G-CSF, granulocyte colony-stimulating factor; CI, confidence interval.

perienced a mild headache, which resolved without any medications. Mild nausea was noted for 2 subjects, which again resolved without any interventions.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the effects of G-CSF on cognition, blood biomarkers of AD pathology, and neuroplasticity in healthy adults or donors of HSCT. In line with our initial hypothesis, compared to the baseline, the subjects' cognitive functions were improved 12 weeks after G-CSF administration. However, the cognitive functions between baseline and 12 weeks after the G-CSF were significantly improved only regarding the RCFT but not the CERAD-K. The CERAD-K is useful in diagnosing patients with dementia and mild cognitive impairment from normal subjects, but it is not effective in detecting subtle cognitive changes in cognitively normal individuals.[33] Since the mean CERAD-K total score for our study subjects was already high (84 out of 100), it might have been difficult to yield statistically significant improvements. In contrast, the RCFT is more effective in detecting cognitive improvements, even in those with normal cognition, because it has a more broad range of scores to represent those with normal cognition.[32] Thus, the sensitivity differences and varying difficulty of the two tests could have been the cause of our subjects showing cognitive improvement after the G-CSF when measured with the RCFT but not with the CERAD-K.

Multiple studies showed that G-CSF has immunomodulatory actions by increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines.[34,35] Since IL-4 is a well-known anti-inflammatory, our findings suggest that G-CSF might attenuate inflammation by increasing IL-4 levels. Moreover, previous studies showed that plasma IL-4 promotes the proliferation of neural stem/progenitor cells, and participates in memory and learning.[19,20] In addition, IL-4 was found to induces the clearance of OAβ by primary rat microglial cells via increased expression of CD36 receptor and the Aβ-degrading enzymes neprilysin.[36] Furthermore, in vivo injection of IL-4, with IL-13, resulted in reduction of cerebral Aβ levels and subtle improvement in cognitive function in amyloid precursor protein transgenic mice.[17] Thus, our results might provide baseline data suggesting its potential efficacy in AD. In line with our speculation and results, a previous study showed that plasma IL-4 levels were increased immediately after G-CSF injections, coming back down to the baseline 2 weeks after the G-CSF injections in patients with AD.[12] However, further study with a larger sample size in patients with AD continuum are needed to confirm our hypothesis.

We observed increased levels of IL-8 after G-CSF. Other studies have reported conflicting results, both upregulation and downregulation of IL-8 in AD patients compared to control participants.[37,38] Nevertheless, studies showed that IL-8 is a microglia-derived chemokine that induces the chemotaxis of cells to sites of injury.[39] Moreover, IL-8 promotes increased survival of neuronal cultures and angiogenesis.[40,41] Thus, G-CSF might have induced IL-8 to promote neuroprotective and angiogenetic processes. However, further studies investigating the underlying biological mechanisms are needed to confirm our speculations.

BDNF, a member of the neurotrophin family of growth factors, is known to support the survival of existing neurons and

encourage the growth and differentiation of new neurons and synapses.[25] Previous results consistently reported that G-CSF increases BDNF, and this increment of BDNF is associated with the activation of microglia and astrocytes, as well as improved cognition.[42] Likewise, our results also showed upregulation of BDNF after the G-CSF injections. Taken together, our results suggest that G-CSF not only promotes anti-inflammation and neuronal recovery, but it also enhances neuroprotection. Others also showed that the complex and multifaceted association among G-CSF, BDNF, and interleukins contributes to precognitive and neuroplastic effects.[43] More translational studies are needed to elucidate this important issue. Moreover, since the blood levels of IL-4, IL-8, and BDNF rose transiently immediately after G-CSF and later came back down to the baseline level, further studies are needed to confirm whether boosting injections can be more effective than a one-shot protocol.

Interestingly, the OAβ level in our subjects did not change after G-CSF injections. Previous studies on MDS-OAβ recognize levels less than 0.78 ng/mL as representing a low risk of having Aβ pathology.[44] Since the average level of MDS-OAβ was around 0.48 ng/mL, which was much lower than the cut-off value of 0.78, further decrement of MDS-OAβ levels might not have been possible due to the basement effect or floor effect. Studies including subjects with high baseline Aβ pathology or OAβ levels are needed to confirm whether G-CSF can attenuate cerebral Aβ levels.

Our study has multiple limitations. First, the small sample size was our major shortcoming. Since the study included donors of HSCT who routinely receive G-CSF injections, it was not possible to compare the effects using a placebo. Second, although we found neuroplastic effects of G-CSF using blood biomarkers, we were not able to investigate them using neuroimaging measures. Due to the short study duration, we were also unable to investigate longer-term effects of G-CSF in cognition and whether blood biomarkers persisted. Thus, a longer-term study including a larger sample is needed to compare the effects of G-CSF and placebo on cognition and neuroplasticity.

In conclusion, our study showed that G-CSF administration did not show clinically significant side effects, and it induced a transient increase in BDNF, IL-4, and IL-8, which are associated with enhanced neuroplasticity, anti-inflammatory processes, and neuronal repair. Memory functions including immediate recall, delayed recall, and recognition abilities were also improved after G-CSF injections. Thus, our results might suggest that G-CSF has neuroplastic and pro-cognitive effects in healthy adults. However, further study containing a larger sample size is needed to confirm our findings.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Hyun Kook Lim, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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Funding Statement

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (NRF-2019R1C1C1011664). The authors also wish to acknowledge the financial support of the Catholic Medical Center Research Foundation made in the program year of 2022. Lastly, we thank Seo Hyeon Kim for his contribution to this work.

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