Disputes & Debates: Editors' Choice

Editors' Note: Association of Self-reflection With Cognition and Brain Health in Cognitively Unimpaired Older Adults

Dr. Demnitz-King et al. examined the association between self-reflection and markers sensitive to Alzheimer disease in 125 older adults with subjective cognitive decline and compared them with 134 cognitively unimpaired older adults in the Age-Well clinical trial. They found that self-reflection was associated with better global cognition and higher glucose metabolism in fluorodeoxyglucose positron emission tomography scans, with weak evidence that the observed associations were independent of other health and lifestyle behaviors. They concluded that longitudinal and experimental studies are needed to clarify whether self-reflection can actually help preserve cognition and cerebral glucose metabolism vs whether a lower capacity to self-reflect is a harbinger of cognitive decline and glucose hypometabolism. In response, Dr. Daly notes that the study overlooked social determinants of brain health and behaviors including those associated with self-reflection and argues that studying such determinants is potentially a higher priority for dementia research than interventional studies. Responding to these comments, the authors note that they found a higher education (an important social determinant) was associated with better self-reflection, but that the associations between self-reflection and the study outcomes remained after adjusting for education. They also report additional analyses examining the relationship between self-reflection and loneliness as well as primary occupation. They found that loneliness was associated with self-reflection, but incorporating loneliness as an additional covariate in their models did not change the associations of self-reflection with cognition and glucose metabolism. The authors counter that these findings suggest that there is utility in targeting self-reflection but agree that there may be promise in addressing such individual risk or protective factors within the broader context of social determinants of brain health. This exchange underscores the challenges of making causal inferences about protective behaviors from studies of cognitive decline or dementia-related markers, and the complexities involved in setting priorities for dementia prevention research based on such data.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD
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Reader Response: Association of Self-reflection With Cognition and Brain Health in Cognitively Unimpaired Older Adults

Timothy Daly (Paris)
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I have some issues with the claim of Demnitz-King and colleagues[1] that longitudinal and interventional studies are warranted to explicate whether self-reflection helps preserve cognition in older adults. Their assertion draws on the association of self-reflection with better global cognition and glucose metabolism and limited evidence that relationships are independent from health and lifestyle behaviors. The authors use a modified lifestyle for brain health (LIBRA) index, which provides a dementia risk score defined by empirical evidence and expert consensus.

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This claim of warrant is a value judgment calling for further investment of research resources into their hypothesis and should be stated thus, rather than its current formulation as an objective fact. In addition, the study overlooks the social determinants of brain health and behaviors such as self-reflection. Röhr et al.[2] found strong associations between the social determinants of dementia—socioeconomic factors, in particular—and the LIBRA index.

Studying the social determinants of self-reflection is arguably a higher priority for dementia research than interventional studies. Given the recognized possibility that reduced capacity to self-reflect is indicative of cognitive decline,[1] focusing only on individual behaviors and overlooking environmental drivers of reduced self-reflection strikes me as akin to fixing a leaky tap in a population-wide flood of dementia risk.

1. Demnitz-King H, Gonneaud J, Klimecki OM, et al. Association of self-reflection with cognition and brain health in cognitively unimpaired older adults. *Neurology*. 2022;99(13):e1422-e1431. doi: 10.1212/WNL.0000000000200951
2. Röhr S, Pabst A, Baber R, et al. Social determinants and lifestyle factors for brain health: implications for risk reduction of cognitive decline and dementia. *Sci Rep*. 2022;12(1):12965. doi: 10.1038/s41598-022-16771-6

Author Response: Association of Self-reflection With Cognition and Brain Health in Cognitively Unimpaired Older Adults

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We appreciate Dr. Daly's valuable comments on our article,[1] and we would like to respond to the interesting point raised about social determinants of brain health. Our article reported a positive association between education and self-reflection, yet associations between self-reflection and Alzheimer disease (AD)-sensitive markers remained after adjusting for education.

We have now conducted additional analyses examining the relationship between self-reflection and loneliness (our closest approximation of social isolation) and primary occupation. Since 93% of participants were retired, employment status was not examined as a determinant.

Only loneliness was associated with self-reflection. We, therefore, included loneliness as an additional covariate in our models examining the relationship between self-reflection and AD-sensitive markers. Associations between self-reflection and cognition (SCD-Well: adjusted-$\beta = 0.16$, $p = 0.042$; Age-Well: adjusted-$\beta = 0.21$, $p = 0.025$) and glucose metabolism (adjusted-$\beta = 0.28$, $p = 0.043$) remained unchanged.

Of the social determinants examined, not all were associated with self-reflection. Furthermore, the association of self-reflection with AD-sensitive markers persisted even after considering several social determinants of brain health. We, therefore, suggest that there is utility in targeting self-reflection. However, we do agree with Dr. Daly and propose that incorporating individual risk/protective factors within the wider context of social determinants of brain health may be a promising way to stem the tide of dementia risk.

1. Demnitz-King H, Gonneaud J, Klimecki OM, et al. Association of self-reflection with cognition and brain health in cognitively unimpaired older adults. *Neurology*. 2022;99(13):e1422-e1431. doi: 10.1212/WNL.0000000000200951

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Editors' Note: An International Perspective on Preceding Infections in Guillain-Barré Syndrome: The IGOS-1000 Cohort

Dr. Leonhard et al. analyzed the presence of several recent bacterial and viral infections in 768 patients included in the International Guillain-Barré syndrome (GBS) Outcome Study (IGOS) with available biosamples. They found serologic evidence of a recent infection with *Campylobacter jejuni* in 228 patients (30%), *Mycoplasma pneumoniae* in 77 (10%), hepatitis E virus in 23 (3%), cytomegalovirus in 30 (4%), and Epstein-Barr virus in 7 (1%), but interestingly, the proportion of patients reporting symptoms of antecedent infections did not significantly differ between those testing positive or negative for these recent infections. The authors found that the distribution of infections was similar across geographic regions, but the association between infection and clinical phenotype differed. The sensorimotor variant and demyelinating electrophysiologic subtype were most frequent across all infection groups, and the *Campylobacter jejuni*–positive patients were more severely affected. Among *Campylobacter jejuni*–positive patients, the pure motor variant and axonal electrophysiologic subtype were more frequent in Asian compared with American or European patients. The authors concluded that broad serologic testing of patients with GBS was important to identify the most likely infectious triggers, given the mismatch between symptom reporting and serologic results, and noted that these infections can have value in future prognostic models. In response, Drs. Debnath and Nagappa noted that most patients in this study were from temperate regions, pointing to the high prevalence of arboviral infections (not tested in this study) such as dengue, chikungunya, Japanese encephalitis, and Zika virus in the tropics, which have been associated with GBS in prior studies. In particular, they cited their recent study from India in which 66.7% of patients were seropositive for chikungunya vs 32% for *Campylobacter jejuni*. They called for studies with broader infection panels including arboviruses, increased representation of patients with GBS from tropic countries, and simultaneous testing of contemporary population controls. Responding to these comments, the authors agreed that the results of their study do not reflect GBS statistics worldwide, but noted that they found similar distributions of their 5 study pathogens across participating countries including Bangladesh, Malaysia, and Japan. They pointed out that 45% of controls in the aforementioned Indian study also had evidence of chikungunya while the proportion of dengue and Japanese encephalitis virus was lower in patients than controls and noted that the high proportion of patients with evidence of multiple infections (66% vs 6% in IGOS) may reflect cross-reactive antibodies due to other prior Flavivirus infection or vaccination. They agreed that controlled studies with international collaboration will be important to better identify GBS-associated infections. This discussion highlights the geographic and methodological complexities involved in studying the interplay between infections and the development of GBS.

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Reader Response: An International Perspective on Preceding Infections in Guillain-Barré Syndrome: The IGOS-1000 Cohort

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Leonhard et al. analyzed the pattern of preceding infections in a large cohort of 768 patients with Guillain-Barré syndrome (GBS) from 19 countries spread over 5 continents.[1] To some extent, this study is biased because the majority of the patients were from temperate regions and testing for preceding infections was limited to only 5 microorganisms (*Campylobacter jejuni*,

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hepatitis E virus, *Mycoplasma pneumoniae*, cytomegalovirus, and Epstein-Barr virus). The burden of infections varies significantly across tropical and temperate regions, with arboviral infections being quite prevalent in the tropics. Dengue, chikungunya, Japanese encephalitis, and zika have consistently been associated with GBS.[2-4]

In our recent study, *C. jejuni*, dengue, and chikungunya were associated with GBS; however, the number of patients with GBS seropositive for chikungunya was much higher than *C. jejuni* (66.7% vs 32%).[5] Therefore, the findings by Leonhard et al. may not truly reflect the international occurrence rate. A balanced study design with an examination of a wider infection panel including arboviruses, increased representation of patients with GBS from tropical countries, particularly India and China, and simultaneous testing of population controls selected from the same period will add strength to the current understanding of the interplay between infections and development of GBS.

1. Leonhard SE, van der Eijk AA, Andersen H, et al. An international perspective on preceding infections in Guillain-Barré syndrome: the IGOS-1000 cohort. *Neurology*. 2022;99(12):e1299-e1313. doi: 10.1212/WNL.0000000000200885
2. Leonhard SE, Tan CY, Eijk AA, et al. Antecedent infections in Guillain-Barré syndrome in endemic areas of arbovirus transmission: a multinational case-control study. *J Peripher Nerv Syst.* 2021;26(4):449-460. doi: 10.1111/jns.12469
3. Keesen TSL, de Almeida RP, Gois BM, et al. Guillain-Barré syndrome and arboviral infection in Brazil. *Lancet Infect Dis.* 2017;17(7):693-694. doi: 10.1016/S1473-3099(17)30333-X
4. Ravi V, Taly AB, Shankar SK, et al. Association of Japanese encephalitis virus infection with Guillain-Barré syndrome in endemic areas of south India. *Acta Neurol Scand.* 2009;90(1):67-72. doi: 10.1111/j.1600-0404.1994.tb02681.x
5. Dutta D, Debnath M, Nagappa M, et al. Antecedent infections in Guillain-Barré syndrome patients from south India. *J Peripher Nervous Syst.* 2021;26(3):298-306. doi: 10.1111/jns.12459

Author Response: An International Perspective on Preceding Infections in Guillain-Barré Syndrome: The IGOS-1000 Cohort

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We thank the readers for their comments on our article.[1] The results of the International Guillain-Barré syndrome (GBS) Outcome Study (IGOS) do not reflect GBS statistics worldwide. We focused on 5 pathogens consistently associated with GBS in case-control studies and found similar distributions across participating countries including Bangladesh, Malaysia, and Japan.[1] In 59% of patients, no evidence of infection was found, which suggests other triggers.

In the study from South India, recent *Campylobacter jejuni* infection was identified in ~30% of patients, similar to the findings in IGOS.[1,2] The study suggests chikungunya, dengue, and Japanese encephalitis virus as triggers of GBS in endemic areas. It notes evidence of chikungunya in 67% of patients but also in 45% of controls, whereas the proportion of dengue and Japanese encephalitis virus was lower in patients than controls.[2] Evidence of multiple infections was found in 66%, vs 6% of patients in IGOS.[1,2] This may indicate true coinfections, but it may also reflect cross-reactive antibodies, especially for flaviviruses, due to other flavivirus prior infection or vaccination.[3] This is further exemplified by the finding that all dengue immunoglobulin M-positives were also positive for other agents. Exposure to GBS-related infections varies in region and time, and controlled studies to identify these infections can best occur through long-standing international collaboration.

1. Leonhard SE, van der Eijk AA, Andersen H, et al. An international perspective on preceding infections in Guillain-Barré syndrome: the IGOS-1000 cohort. *Neurology*. 2022;99(12):e1299-e1313. doi: 10.1212/WNL.0000000000200885
2. Dutta D, Debnath M, Nagappa M, et al. Antecedent infections in Guillain-Barré syndrome patients from south India. *J Peripher Nerv Syst.* 2021;26(3):298-306. doi: 10.1111/jns.12459
3. Leonhard SE, Tan CY, Eijk AA, et al. Antecedent infections in Guillain-Barré syndrome in endemic areas of arbovirus transmission: a multinational case-control study. *J Peripher Nerv Syst.* 2021;26(4):449-460. doi: 10.1111/jns.12469

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CORRECTIONS

Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology

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In the Research Article previously titled "Gender Representation Among Physician Authors of American Academy of Neurology Clinical Practice Guidelines" by Ross et al.,[1] several changes were made after online-first publication of the accepted manuscript before final publication. The article title was revised, along with the titles of Figures 1, 2, 3, and 4. Wording changes were made throughout the article, along with the additions of new paragraphs in the Results and Discussion, an eAppendix, the "Subanalysis of AAN Developed PGs" subsection, and Figure 5 in the Results. The authors regret the confusion.

Reference

1. Ross L, Hassett C, Brown P, et al. Gender representation among physician authors of practice guidelines developed, endorsed, or affirmed by the American Academy of Neurology. *Neurology*. 2023;100(5):e465-e472.

Impulsivity Trait Profiles in Patients With Cerebellar Ataxia and Parkinson Disease

Neurology® 2023;100:265. doi:10.1212/WNL.0000000000201691

In the Research Article "Impulsivity Trait Profiles in Patients With Cerebellar Ataxia and Parkinson Disease" by Chen et al.,[1] Figure 2A should be labeled "First-order factors: CA vs control." The editorial staff regret the error.

Reference

1. Chen TX, Lin CYR, Aumann MA, et al. Impulsivity trait profiles in patients with cerebellar ataxia and Parkinson disease. *Neurology*. 2022;99(2):e176-e186. doi: 10.1212/WNL.0000000000200349.

CORRECTION & REPLACEMENT

Association Between Anatomical Location of Surgically Induced Lesions and Postoperative Seizure Outcome in Temporal Lobe Epilepsy

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In the Research Article "Association Between Anatomical Location of Surgically Induced Lesions and Postoperative Seizure Outcome in Temporal Lobe Epilepsy" by Gleichgerrcht et al.,[1] Dr. Bernd Weber was inadvertently omitted as an author. The article has now been replaced by a corrected version with Dr. Weber included. Dr. Weber's full disclosures may be viewed at Neurology.org/N. The original version with the changes highlighted is available from a link in the corrected article. The authors regret the omission.

Reference

1. Gleichgerrcht E, Drane DL, Keller SS, et al. Association between anatomical location of surgically induced lesions and postoperative seizure outcome in temporal lobe epilepsy. *Neurology*. 2022;98(2):e141-e151.

Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology

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