ARTICLE

Neurogranin as a predictor of memory and executive function decline in MCI patients

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Abstract

Objective

To determine whether high CSF levels of neurogranin (Ng) predict longitudinal decline in memory and executive function during early-stage Alzheimer disease (AD).

Methods

Baseline levels of CSF Ng were studied in relation to cross-sectional and longitudinal cognitive performance over 8 years. Data were obtained from the Alzheimer's Disease Neuroimaging Initiative database, and participants with normal cognition (n = 111) and mild cognitive impairment (MCI) (n = 193) were included.

Results

High levels of CSF Ng were associated with poor baseline memory scores ($\beta = -0.21$, $p < 0.0001$). CSF Ng predicted both memory and executive function decline over time ($\beta = -0.0313$, $p = 0.0068$ and $\beta = -0.0346$, $p = 0.0169$, respectively) independently of age, sex, education, and *APOE* ε4 status. When the rate of decline by tertiles was examined, CSF Ng was a level-dependent predictor of memory function, whereby the group with highest levels of Ng showed the fastest rates of decline in both memory and executive function. When examined separately, elevated Ng was associated with cognitive decline in participants with MCI but not in those with normal cognition. The levels of CSF Ng were not associated with cognitive measures when tau and amyloid 42 ($A\beta_{42}$) were controlled for in these analyses.

Conclusions

High CSF Ng associates with poor memory scores in participants with MCI cross-sectionally and with poor memory and executive function longitudinally. The association of Ng with cognitive measures disappears when tau and $A\beta_{42}$ are included in the statistical models. Our findings suggest that CSF Ng may serve as a biomarker of cognition. Synaptic dysfunction contributes to cognitive impairment in early-stage AD.

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at http://links.lww.com/WNL/A211.

Glossary

$A\beta_{42}$ = amyloid 42; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Schedule-Cognition; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ADNI-EF** = ADNI executive function; **ADNI-Mem** = ADNI memory; **CDR** = Clinical Dementia Rating; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NC** = normal cognition; **NG** = neurogranin; **t-tau** = total tau.

Alzheimer disease (AD) is the most common neurodegenerative disorder. Memory loss is an early and predominant feature of AD.[1] Patients with late-onset AD tend to display a pattern of disproportionately more impaired memory relative to executive function, yet about one-fifth of people with AD have been found to have executive predominance with executive function scores lower than memory scores.[2]

Over the last 2 decades, amyloid 42 ($A\beta_{42}$), phosphorylated tau, and total tau (t-tau) in the CSF have been identified as important biomarkers of the pathophysiologic process underlying AD.[3,4] However, the correlation of these biomarkers with the rate of cognitive deterioration is inconsistent. Searching for additional biomarkers associated with cognitive decline in AD is of critical importance in enabling earlier diagnosis, tracking mental status, and developing new treatments.

Neurogranin (Ng), a postsynaptic protein, is elevated in the CSF of patients with AD and mild cognitive impairment (MCI) compared to participants with normal cognition (NC).[5–7] High CSF Ng levels correlate with poor Mini-Mental State Examination (MMSE) scores in these participants.[8,9] Levels of Ng predict progression of MCI to AD.[10] To study the role of Ng in specific cognitive domains, we examined whether high CSF Ng would predict cognitive performance in participants at risk for AD. We hypothesized that high CSF Ng would be a sensitive predictor of memory loss and executive dysfunction. In this study, baseline levels of CSF Ng were analyzed in relation to baseline memory, executive function, global cognition, and function scores in participants with NC and MCI. The longitudinal study was performed with Ng used as a predictor of change in memory, executive function, global cognition, and function scores over an 8-year period.

Methods

Alzheimer's Disease Neuroimaging Initiative study

Data used for this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership with the primary objective of testing whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD.

Standard protocol approvals, registrations, and patient consent

As stated in the ADNI procedures manual, ADNI centers obtain local Institutional Review Board protocol approval, and patient consents are obtained at the participants' initial screening visit.

Participants

We included participants who met criteria for NC and MCI and had baseline CSF Ng samples and follow-up evaluations of memory and executive function. A total of 304 individuals were analyzed, 111 with NC and 193 with MCI. The numbers of participants present at the follow-up visits are summarized in table 1.

All participants were between 55 and 90 years old at the time of inclusion, had completed at least 6 years of education, were fluent in English or Spanish, and were free of any other neurologic diseases. Participants with NC had an MMSE score ≥24 and a Clinical Dementia Rating (CDR) score of zero. Participants with MCI had an MMSE score ≥24, CDR score of 0.5, objective memory loss based on delayed recall scores of the Wechsler Memory Scale Logical memory II, and absence of dementia.

Composite memory and executive function scores

ADNI created composite memory and executive function scores derived from tests used in its neuropsychological battery. The ADNI memory composite score (ADNI-Mem) was developed from the Rey Auditory Verbal Learning Test (2 versions), Alzheimer's Disease Assessment Schedule-Cognition (ADAS-Cog, 3 versions), MMSE, and Logical Memory data.[11] The executive function score (ADNI-EF) derives from Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing.[12] Both ADNI-Mem and ADNI-EF have been validated and described to be as good as or better than any of the composite parts.[11,12] In our study, we included up to 8 years of follow-up scores.

CSF analysis

CSF Ng levels were measured with antibody-based electrochemiluminescence technology (Meso Scale Discovery, Gaithersburg, MD) with Ng 7 (a monoclonal antibody with epitope at amino acids 53–64 of Ng)[13] as the coating antibody and polyclonal Ng anti-rabbit (ab 23570, Upstate) as the detector antibody.[5]

Table 1 Demographic information of study participants

	NC (n = 111)	MCI (N = 193)	*p* Value
Age, y	75 ± 6	75 ± 7	0.472
Education, y	16 ± 3	16 ± 3	0.477
Female, %	50	33	0.004
***APOE* ε4, %**	24	53	<0.001
MMSE score	29 ± 1	27 ± 2	<0.001
CDRSB score	0 ± 0	1.5 ± 1	<0.001
CSF Ng, pg/mL	352 ± 294	494 ± 353	<0.001
$A\beta_{42}$, pg/mL	206 ± 55	166 ± 54	<0.001
t-tau, pg/mL	69 ± 30	102 ± 60	<0.001
p-tau, pg/mL	25 ± 15	36 ± 18	<0.001
Follow-up visits, n participants			
Baseline	111	193	
12 mo	107	180	
24 mo	100	154	
36 mo	93	130	
48 mo	64	68	
60 mo	54	54	
72 mo	58	51	
84 mo	47	38	
96 mo	37	31	

Abbreviations: $A\beta_{42}$ = amyloid 42; CDRSB = Clinical Dementia Rating Sum of Boxes; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = normal controls; NG = neurogranin; p-tau = phosphorylated tau; t-tau = total tau.
There is no significant difference between age and years of education between the NC and MCI groups. The MCI group has a higher percentage of men, a higher percentage of *APOE* ε4 carriers, and significantly lower MMSE and higher CDRSB score. CSF Ng is increased in the MCI group, and t-tau and p-tau are also significantly higher in the participants with MCI. $A\beta_{42}$ is lower in the MCI than the NC group.

Statistical analysis

We used *t* tests and χ^2 tests to assess differences in demographic, clinical, genotype, and CSF biomarker variables between the NC and MCI groups. To examine the cross-sectional associations between CSF Ng levels and both baseline ADNI-Mem and ADNI-EF scores, various general linear regression models were constructed: model 1 was unadjusted; model 2 was adjusted for age, sex, and years of education; model 3 was adjusted for *APOE* ε4 status; and model 4 was adjusted for t-tau and $A\beta_{42}$. To evaluate the relationship between baseline CSF Ng levels and rate of decline per year in ADNI-Mem and ADNI-EF scores, linear mixed models were fitted with the same adjustments as above. For these models, baseline CSF Ng was first assessed as a continuous variable and then categorized as tertiles to look for a gradient effect on the decline in memory and/or executive function. To determine whether clinical status had a modification effect, these analyses were conducted within each diagnostic group separately. The Pearson correlation was performed to evaluate the correlation between CSF Ng and the other biomarkers. The level of statistical significance was set at $p < 0.05$. All data analyses were performed with statistical software (SPSS, version 24, IBM, Armonk, NY; Stata, version 13, StataCorp LP, College Station, TX; or SAS, version 9.4, SAS Institute, Cary, NC).

Results

Demographic information

Within the ADNI dataset, participants with MCI (n = 193) and NC (n = 111) were analyzed (table 1). Compared with healthy controls, participants with MCI were more likely to be male and *APOE* ε4 carriers and had greater CDR Sum of Boxes scores, lower MMSE scores, and higher levels of CSF Ng, t-tau, and phosphorylated tau but lower levels of $A\beta_{42}$. No significant difference was found in age or education attainment between the 2 groups (table 1).

Association of CSF Ng levels with memory scores in cross-sectional study

There was a significant association between baseline levels of CSF Ng and baseline memory scores in the pooled participants with NC and MCI (table 2). Increased CSF Ng was associated with lower baseline memory scores (β = −0.21, $p < 0.0001$). This association remained after adjustment for age, sex, and education in model 2 (β = −0.23, $p < 0.0001$) and after adjustment for *APOE* ε4 in model 3 (β = −0.16, $p = 0.002$). The levels of CSF Ng were not associated with baseline memory when tau and $A\beta_{42}$ were controlled for in model 4 (β = 0.01, $p = 0.786$). There was no association between baseline CSF Ng and baseline executive function in both unadjusted and multivariable-adjusted models (table 2).

Association of CSF Ng levels with memory and executive scores over a period of 8 years

Longitudinal analysis of NC and MCI participants showed that baseline CSF Ng levels predicted decline in both memory and executive function over an 8-year period. Table 3 demonstrates that baseline CSF Ng was associated with memory decline per year (β = −0.049, $p < 0.0001$), and after accounting for age, sex, education, and *APOE* ε4 status, this association remained (β = −0.031, $p = 0.0068$). There was an association of baseline CSF Ng with executive function decline per year (β = −0.056, $p < 0.0001$), and this association remained after adjustment for age, sex, education, and *APOE* ε4 status in model 3 (β = −0.035, $p = 0.0169$). As shown in model 4, when CSF $A\beta_{42}$ and tau levels were corrected for, CSF Ng was no longer a predictor of longitudinal memory or executive function decline (β = 0.017, $p = 0.238$ and β = 0.015, $p = 0.403$, respectively).

When the participants were divided into tertiles based on CSF Ng levels, there was a clear gradient relationship between baseline CSF Ng levels and the rate of memory decline (figure). The rate of memory decline could be differentially predicted by all CSF Ng tertiles. Tertiles 2 and 3 showed incrementally faster rates of decline in memory function compared to tertile 1. Executive function decline could be differentially predicted only by the top CSF Ng tertile (tertile 3). The rate of decline in executive function was not different between the tertile 2 and 1 groups (figure).

Association of CSF Ng with global cognition and function

The baseline and longitudinal associations between CSF Ng and multiple global cognitive measures, including

Table 2 Association of the CSF Ng with baseline memory function and executive function in the pooled sample

	Models							
	1		2		3		4	
	β	*p* Value	β	*p* Value	β	*p* Value	β	*p* Value
Baseline memory function								
CSF Ng	−0.21	<0.0001	−0.23	<0.0001	−0.16	0.002	0.01	0.786
Age			0.02	0.665	0.005	0.914	0.02	0.676
Female vs male			−0.28	<0.0001	−0.26	<0.0001	−0.24	<0.0001
Education			−0.13	0.016	0.12	0.020	0.13	0.010
***APOE* ε4 status**					−0.23	<0.0001	−0.09	0.096
t-tau							−0.21	0.003
$A\beta_{42}$							0.22	<0.0001
Baseline executive function								
CSF Ng	−0.09	0.103	−0.09	0.090	−0.07	0.198	0.12	0.099
Age			−0.08	0.127	−0.09	0.104	−0.07	0.167
Female vs male			−0.21	<0.0001	−0.20	<0.0001	−0.17	0.002
Education			0.22	<0.0001	0.22	<0.0001	0.23	<0.0001
***APOE* ε4 status**					−0.07	0.195	0.08	0.152
t-tau							−0.21	0.005
$A\beta_{42}$							0.26	<0.0001

Abbreviations: $A\beta_{42}$ = amyloid 42; Ng = neurogranin; t-tau = total tau.
A higher baseline CSF Ng is associated with a lower baseline memory score. This association remains in model 2 in which age, sex, and education are accounted for and in model 3 in which *APOE* ε4 status is accounted for, but not when $A\beta_{42}$ and t-tau are corrected for. There is no association of a baseline CSF Ng with baseline executive function.

Table 3 Longitudinal follow-up of memory and executive function with Ng as a predictor in the pooled sample

	Models							
	1		2		3		4	
	β	*p* Value	β	*p* Value	β	*p* Value	β	*p* Value
Memory decline per year								
CSF Ng	−0.0492	<0.0001	−0.0447	<0.0001	−0.0313	0.0068	0.017	0.238
Age			0.0011	0.9212	−0.0076	0.4932	−0.002	0.826
Female vs male			−0.0131	0.2344	−0.0187	0.0784	−0.022	0.026
Education			−0.0173	0.1131	−0.0205	0.0499	−0.016	0.094
***APOE* ε4 status**					−0.0530	<0.0001	−0.022	0.054
t-tau							−0.063	0.001
$A\beta_{42}$							0.049	<0.0001
Executive function decline per year								
CSF Ng	−0.0563	<0.0001	−0.0520	0.0002	−0.0346	0.0169	0.015	0.403
Age			0.0376	0.0072	0.0246	0.0674	0.027	0.0365
Female vs male			−0.0132	0.3373	−0.0215	0.0994	−0.027	0.0273
Education			−0.0227	0.0959	−0.0281	0.0291	−0.025	0.0394
***APOE* ε4 status**					−0.0746	<0.0001	−0.034	0.0181
t-tau							−0.057	0.0152
$A\beta_{42}$							0.069	<0.0001

Abbreviations: $A\beta_{42}$ = amyloid 42; Ng = neurogranin; t-tau = total tau.
Increased CSF Ng levels can predict decline in both memory and executive function. CSF Ng is associated with memory decline per year when age, sex, education, and *APOE* ε4 status are accounted for, but the association is not present when t-tau and $A\beta_{42}$ are corrected for. Similarly, higher CSF Ng is associated with a decline in executive function over time. The association between CSF Ng and executive function is present when age, sex, and education are accounted for, but the association is not present when *APOE* ε4 status, t-tau, and $A\beta_{42}$ are accounted for.

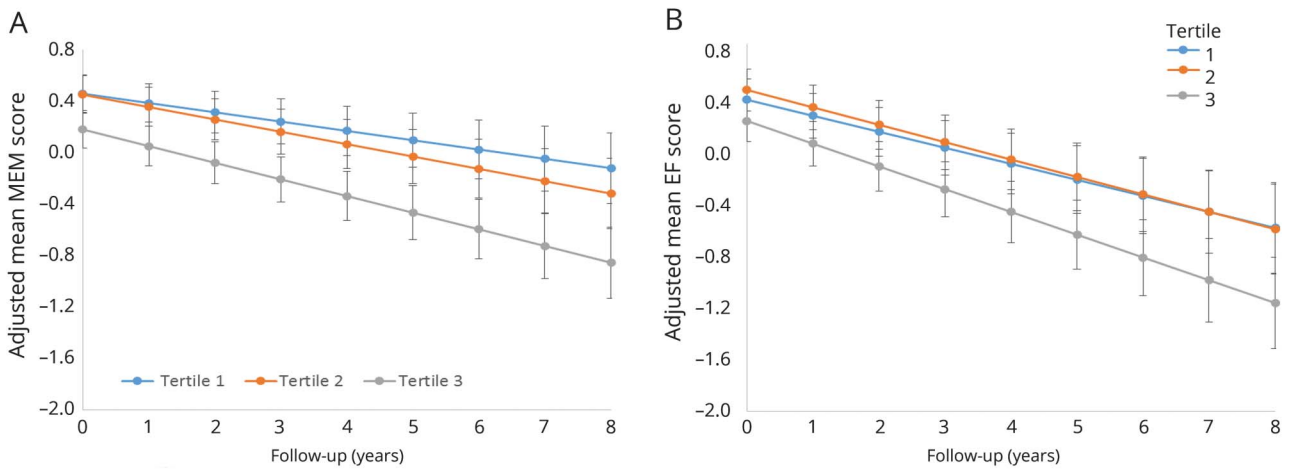
ADAS-Cog 11, ADAS-Cog 13, MMSE, and CDR Sum of Boxes, were studied (tables e-1–e-12, http://links.lww.com/WNL/A210). At baseline, CSF Ng is associated with ADAS-Cog 11 ($\beta = 0.13$, $p = 0.02$), ADAS-Cog 13 ($\beta = 0.17$, $p < 0.01$), and CDR Sum of Boxes scores ($\beta = 0.12$, $p = 0.03$). These associations remained when age, sex, and years of education were accounted for. However, only baseline ADAS-Cog 13 was associated with CSF Ng when *APOE* ε4 status was corrected for ($\beta = 0.11$, $p = 0.04$). In model 4, CSF Ng was not associated with any of these cognitive measures after adjustment for tau and $A\beta_{42}$.

Longitudinal analysis revealed an association between CSF Ng and all of the cognitive scores analyzed: ADAS-Cog 11 ($\beta = 4.77$, $p < 0.01$), ADAS-Cog 13 ($\beta = 5.42$, $p < 0.001$), MMSE ($\beta = -2.07$, $p < 0.001$), and CDR Sum of Boxes ($\beta = 1.215$, $p < 0.001$). In models 2 and 3 in which demographic information and *APOE* ε4 status were corrected, the longitudinal associations remained significant. As with the baseline associations, CSF Ng was not significantly associated with longitudinal ADAS-Cog 11, ADAS-Cog 13, MMSE, or CDR Sum of Boxes scores when t-tau and $A\beta_{42}$ were additionally corrected for in model 4.

High levels of CSF Ng are associated with memory and executive function decline in participants with MCI but not those with NC over an 8-year period.

To explore the potential modification effect of baseline diagnostic status, the relationship between CSF Ng and memory and executive function decline was examined in participants with MCI and healthy controls separately. Table 4 reveals that baseline CSF Ng was not associated with longitudinal memory decline in healthy controls ($\beta = -0.029$, $p = 0.133$) but was associated with memory decline in participants with MCI ($\beta = -0.068$, $p = 0.0031$). The association in the MCI group remained after accounting for age, sex, and education ($\beta = -0.056$, $p = 0.020$) but not after accounting for *APOE* ε4 status ($\beta = -0.037$, $p = 0.113$). Baseline CSF Ng predicted a decline in executive function for participants with MCI ($\beta = -0.056$, $p = 0.006$) but not for healthy controls ($\beta = -0.0048$, $p = 0.736$). Baseline CSF Ng was not associated with executive function decline in the MCI group after adjustment for confounders.

Figure Pattern of memory and executive function decline with Ng as a function in the pooled sample



Three tertiles were created based on baseline CSF neurogranin (Ng) level. Tertile 1 comprises the lowest level CSF Ng; tertile 2 is intermediate; and tertile 3 includes the highest level of CSF Ng. Trajectories of memory (MEM) and executive function (EF) decline over time, showing that Ng is an effective longitudinal predictor for cognitive function over an 8-year period. (A) The rate of memory decline is fastest for the highest CSF Ng level, and the rate of decline is faster in the intermediate tertile than the lowest tertile. (B) For executive function, the highest level of CSF Ng predicts a faster rate of executive function decline, but the rates for the 2 lower tertiles are very similar.

Correlation of CSF Ng levels with t-tau and $A\beta_{42}$ levels

To evaluate the relationship between CSF Ng and t-tau and $A\beta_{42}$, a Pearson correlation test was performed. Increasing levels of CSF Ng were associated with increasing t-tau levels ($r = 0.69$, $p < 0.0001$). Conversely, increasing levels of CSF Ng were associated with decreasing $A\beta_{42}$ levels ($r = -0.33$, $p < 0.0001$).

Discussion

In this study, cross-sectional analysis showed that high CSF Ng was significantly associated with lower memory scores in pooled participants with NC and MCI. Longitudinal analysis revealed that baseline CSF Ng was significantly associated with both memory and executive function decline in the pooled sample. In addition, Ng predicted memory, executive function, and global cognitive decline over an 8-year period. Finally, a significant association of CSF Ng with memory and executive function decline was associated only with individuals with MCI.

In AD, memory impairment is an initial and central presentation in most patients.[1,14] Amnestic MCI has a higher likelihood of progression to AD compared to nonamnestic MCI.[15] This is consistent with neuropathologic studies showing that the limbic system has degenerative changes in the early stage of AD.[16] Although a clear, disproportionately severe episodic memory disorder was observed in patients with amnestic MCI, increasing evidence also shows that there is a dysexecutive form of MCI associated with AD.[2,17,18] The molecular mechanism underlying memory and executive dysfunction remains unclear.

Ng, a postsynaptic protein, has been shown to be associated with synaptic plasticity.[19] Deletion of the Ng gene in mice results in decreased short- and long-term plasticity and impaired spatial memory.[19,20] Ng influences synaptic plasticity by regulating the level of calmodulin and the pattern of calcium/calmodulin–dependent postsynaptic signaling at dendritic spines.[21] In AD, a marked reduction in Ng levels is found in the hippocampus and frontal cortex.[22]

In this study, high CSF Ng was significantly associated with poor memory scores in both cross-sectional and longitudinal analyses. This finding suggests that Ng plays an important role in memory dysfunction in AD. Given the fact that excitatory synapses terminating on dendritic spines are involved in the formation of new memories and are damaged in AD, changes of the levels of postsynaptic proteins in CSF in relation to memory function are to be expected.[23,24]

However, high CSF Ng levels were associated with worse executive function only in the longitudinal analysis, not the cross-sectional analysis. This finding raises several possibilities. First, the participants with MCI in this study may have had a relatively subtle deficit of executive function at baseline. Alternatively, the neuropsychological battery used in this study may have been too insensitive to detect dysexecutive function in MCI. Another possible explanation is that our MCI group is composed of a more amnestic phenotype than dysexecutive phenotype because our population has a high percentage of *APOE* ε4 carriers in the MCI group (53%). A previous study noted that *APOE* ε4 carriers were more common in the amnestic group than the dysexecutive phenotype.[17] As a result, the association of memory dysfunction with CSF Ng was readily apparent.

Table 4 Memory and executive function decline as a function of Ng in the participants with NC and MCI

	Models					
	1		2		3	
	β	*p* Value	β	*p* Value	β	*p* Value
Memory decline per year						
Control						
CSF Ng	−0.029	0.1332	−0.023	0.2127	−0.0023	0.293
Age			−0.022	0.2459	−0.022	0.2423
Female vs male			−0.005	0.7736	−0.010	0.5767
Education			0.002	0.926	−0.003	0.8827
***APOE* ε4 status**					−0.024	0.188
MCI						
CSF Ng	−0.068	0.0031	−0.0556	0.0204	−0.037	0.1131
Age			−0.010	0.6575	−0.023	0.3223
Female vs male			−0.055	0.0246	−0.053	0.0256
Education			−0.037	0.1059	−0.039	0.0751
***APOE* ε4 status**					−0.074	0.0011
Executive function decline per year						
Control						
CSF Ng	−0.0048	0.7363	−0.004	0.8235	0.0008	0.9657
Age			−0.014	0.4468	−0.0140	0.4478
Female vs male			0.012	0.5025	0.0046	0.7978
Education			−0.009	0.6008	−0.0147	0.3926
***APOE* ε4 status**					−0.0349	0.0558
MCI						
CSF Ng	−0.0557	0.0064	−0.037	0.0734	−0.0232	0.2664
Age			0.029	0.1557	0.0176	0.3882
Female vs male			−0.066	0.0022	−0.0651	0.0017
Education			−0.028	0.1646	−0.0307	0.1134
***APOE* ε4 status**					−0.0486	0.0013

Abbreviations: MCI = mild cognitive impairment; NC = normal controls; NG = neurogranin.
CSF Ng is not significantly associated with memory or executive function decline over time in NC. In participants with MCI, CSF Ng is an effective predictor of decline in memory and executive function without adjustment. When age, sex, and education are adjusted for, memory decline is still predicted by Ng, but executive function no longer is. When *APOE* ε4 status is adjusted for in additional to the confounders, Ng is not a significant predictor for memory or executive function.

Finally, it is possible that there is a temporal relationship between involvement of memory and executive function in the pathophysiologic process of AD. Declining performance on episodic memory was found to occur 7 years before diagnosis, while declining performance on executive function was found to accelerate 2 to 3 years before diagnosis.[25] Nevertheless, our findings provide evidence that Ng is involved in executive dysfunction in patients with MCI.

In this study, we further investigated the utility of CSF Ng as a maker for global cognition and functional status. We confirmed that high CSF Ng was associated with global cognitive impairment cross-sectionally and longitudinally. In addition, high CSF Ng was associated with poor functional scores longitudinally. These findings suggest that CSF Ng has potential to monitor the progress of this disease, serving as a biomarker for assessing the effect of treatment.

In this study, the association of Ng with memory, executive function, and global cognitive and functional measures was no longer present when tau and $A\beta_{42}$ were controlled for in the cross-sectional and longitudinal analyses. It is suggested that tau and $A\beta_{42}$ are the key factors involved in postsynaptic injury in patients with MCI. This finding is supported by our correlation analysis. A recent study also reports that the association of Ng with regional brain atrophy was found in individuals with Aβ pathology.[26] Emerging evidence suggests that Aβ-induced synaptic dysfunction is dependent on NMDA receptor–mediated pathways, leading to dendritic spine loss.[27–29] Tau pathology has been reported to contribute more to synapse degeneration and resultant dementia.[30,31] The involvement of amyloid and tau pathology in synaptic damage requires further investigation.

Finally, in this study, we show that Ng was associated with memory and executive scores over time only in patients with MCI. It is suggested that elevated CSF Ng levels are especially related to the pathologic process of cognitive impairment in the early stage of the disease. Our findings are consistent with a recent study showing that individuals with progressive MCI have elevated CSF Ng levels that are associated with accelerated deterioration in the ADAS-Cog subscale.[9] In the NC subgroup, there were no significant associations between cognitive function and Ng. Ng may therefore serve as a useful marker in conjunction with $A\beta_{42}$ and t-tau to distinguish between MCI and NC. Ng has also been reported to be a useful biomarker for differentiating NC from MCI.[8]

This study has limitations. First, as with any longitudinal study of the elderly, attrition rate is a concern. We conducted an association study at the 36-month follow-up when dropout rate is less of an issue than at the 96-month follow-up (tables e-1–e-12, http://links.lww.com/WNL/A210). We also performed an analysis in the participants who completed the 96-month follow-up. We found that Ng also predicts memory and executive function decline longitudinally then. Nevertheless, we are aware that high dropout rates can cause the remaining participants to constitute a biased sample. The data should be interpreted with caution. Second, we examined the association of Ng only with memory, executive function, ADAS-Cog 11 and 13, MMSE, and CDR Sum of Boxes scores. It would be interesting to examine a more complete cognitive profile, including visuospatial and language domains, to see the timing and degree of association between CSF Ng and additional measures. Third, the findings relating Ng to cognitive measures disappear when tau and $A\beta_{42}$ are included in the statistical models. It would be important to replicate these findings with other statistical models. The interactions and common pathways between Ng and $A\beta_{42}$ and t-tau warrant further exploration. Fourth, data are also needed to clarify the temporal course of CSF Ng across the spectrum of MCI and AD and whether the rate of CSF Ng change parallels declines in cognition. Finally, because the ADNI cohort is a selected convenience sample of volunteers, sample selection bias should be taken into consideration in the interpretation of the data.

Author contributions

Dr. Sun had full access to all of the data in the study, initiated the study concept, was involved in study design, interpreted data, and edited the manuscript. Data analysis and drafting of the manuscript: Drs. Headley and DeLeon-benedetti. Study design, statistical analysis, and interpretation of data: Dr. Dong. Data analysis: Dr. Camargo. Acquisition, analysis, or interpretation of data: Drs. Blennow and Zetterberg. Interpretation of data and critical revision of the manuscript to enhance intellectual content: Drs. Levin, Blennow, Zetterberg, Loewenstein, Rundek, and Wright.

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Disclosure

A. Headley, A. DeLeon-benedetti, C. Dong, B. Levin, D. Loewenstein, C. Camargo, and T. Rundek report no disclosures relevant to the manuscript. H. Zetterberg is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Holding–based platform company at the University of Gothenburg. K. Blennow has served as a consultant for Eli Lilly, Novartis, and Roche Diagnostics; has served on Advisory Boards for Amgen and IBL International; has given lectures for Fujirebio Europe and Lundbeck; and is

a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Holding–based platform company at the University of Gothenburg, Sweden. C. Wright and X. Sun report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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FULL-LENGTH ARTICLE NPub.org/cu8y1e

Neurogranin as a predictor of memory and executive function decline in MCI patients

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Study question

Do Neurogranin (Ng) levels in CSF reliably predict progressive cognitive declines in adults with mild cognitive impairment (MCI)?

Summary answer

CSF NG levels consistently reflect progressive changes in memory and executive function in adults with MCI compared to adults with normal cognition (NC), and in a manner that is independent of age, sex, education and *APOE* ε4 status.

What is known and what this paper adds

Other biomarkers (Aβ42, p-tau, t-tau) do not show consistent correlation with cognitive deterioration rates. This study examines CSF Ng as a reliable predictor of cognitive decline in adults who are at risk for developing Alzheimer disease (AD).

Participants and setting

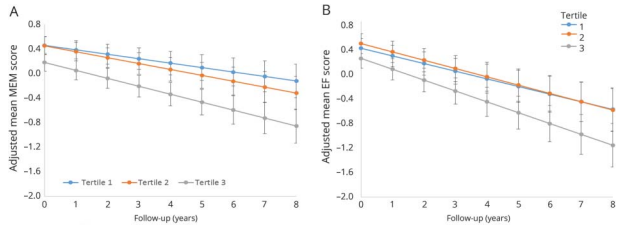
A total of 304 individuals, aged 55–90 years, were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The MCI group (n = 193) had a Clinical Dementia Rating (CDR) score of ≥0.5 and a delayed recall deficit. The NC group (n = 111) had a CDR score of 0 and no delayed recall deficit.

Design, size and duration

CSF Ng levels were measured at baseline using electrochemiluminescence technology. Memory and executive function were measured at baseline and follow-up over 8 years using ADNI memory composite scores (ADNI-Mem) and ADNI executive function scores (ADNI-EF).

Primary outcomes

There was an association between elevated CSF Ng levels and progressive memory loss and executive dysfunction, as well as high CSF Ng levels and baseline poor memory scores. Associations of high CSF Ng levels with these cognitive measures were significant regardless of age, sex, education and *APOE* ε4 status but not significant after controlling for tau and Aβ42.



Main results and the role of chance

High CSF Ng levels were associated with progressive declines in memory and executive function ($\beta = -0.0313$, $p = 0.0068$ and $\beta = -0.0346$, $p = 0.0169$, respectively), with the highest CSF Ng levels showing the fastest decline. High CSF Ng baseline levels were correlated with poor memory scores ($\beta = -0.21$, $p < 0.0001$). NC controls show no association between CSF Ng levels and cognitive function or decline.

Bias, confounding and other reasons for caution

Mechanisms underlying memory loss and executive dysfunction are not well understood. CSF Ng may interact with other postsynaptic proteins. Subtle cognitive defects may have gone undetected. The MCI group had a higher percentage of *APOE* ε4 phenotypes. Memory and executive function deteriorate at different rates.

Generalizability to other populations

CSF Ng monitoring could be applied across multiple demographics (age, sex, education, phenotypes) to detect early stage AD cognitive changes and assess treatment effectiveness.

Study funding/potential competing interests

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A draft of the short-form article was written by A.Y. Tsuchiya, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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