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Can the clinical sign "head-turning sign" and simple questions in "Neucop-Q" predict amyloid β pathology?

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Abstract

Background To establish simple screening tests to suspect Alzheimer's disease (AD) pathology, the clinical sign "head-turning sign" (HTS), which is a patient's behavior of turning their head towards their partner to seek assistance with questions posed by the examiner during the interview, and the simple screening questionnaire for dementia named "Neucop-Q" were validated in participants diagnosed with amyloid and tau positron emission tomography (PET).

Methods We enrolled 155 patients: 47 cognitive normal, 36 with mild cognitive impairment, 64 with dementia, and 8 with psychiatric disorders. All participants underwent Neucop-Q [three questions: Consciousness/self-awareness of cognitive disabilities (C) normal/impaired (nor/imp), Pleasure/pastime (P) nor/imp, and News/knowledge on current topics (N) nor/imp] and amyloid/tau PET. Additionally, we measured plasma amyloid β (Aβ) 42/40 ratio, phosphorylated tau 181 (pTau181), glial fibrillary acidic protein (GFAP), and neurofilament light (NFL) levels and compared with HTS and Neucop-Q results.

Results The specificity and positive predictive value (PPV) of HTS positivity (HTSpos) were the highest (amyloid PET: 0.930 and 0.870, tau PET: 0.944 and 0.957, respectively), while Cimp and Nimp had a high negative predictive value (NPV) for amyloid PET (negativity) (0.750 and 0.725). Pimp showed high specificity for predicting non-AD tau positivity among non-AD participants without amyloid PET positivity (0.854). To validate these findings with PET results, we examined the correlation between well-established AD blood biomarkers and results obtained from these screening tests. HTSpos, Cimp, and Nimp were strongly associated with Aβ42/40 ratio ($P<0.0001$, $P=0.0022$, and $P=0.001$), pTau181 ($P<0.0001$, $P=0.0095$, and $P=0.001$), GFAP ($P=0.0372$, $P=0.0088$, and $P=0.0002$), and amyloid PET Centiloid ($P<0.0001$, $P=0.0210$, and $P=0.0006$), whereas Pimp increased neuroinflammation (GFAP; $P=0.0061$) and was associated with non-AD tauopathy. The combination of Neucop-Q questions showed that Cimp/Pnor/Nimp subjects

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have the highest specificity and PPV (0.972 and 0.833) and were strongly associated with Aβ42/40 ratio ($P=0.0006$), pTau181 ($P=0.0006$), and amyloid PET Centiloid ($P<0.0001$).

Conclusion HTSpos, Cimp, and Nimp have diagnostic utility in suspecting MCI due to AD and AD, and Pimp has diagnostic value in non-AD tauopathy. HTSpos, Cimp, and Nimp were associated with biomarkers of Aβ pathology. HTS and Neucop-Q may serve as powerful first-line screening in memory clinics.

Trial registration UMIN Clinical Trials Registry (UMIN-CTR) under registration numbers 000032027 (Registration date: 2018/03/31) and 000030248 (Registration date: 2018/01/01).

Keywords Mild cognitive impairment, Alzheimer's disease, Dementia, Head-turning sign, Neucop-Q, Biomarker, Amyloid PET, Tau PET

Background

The prevalence of dementia continues to rise, posing a major societal and policy challenge. According to the World Alzheimer Report, 2015 [1], there are 46.8 million people with dementia, and the number is projected to exceed 70 million by 2030, making dementia control a global issue. Therefore, establishing first-line simple and inexpensive screening procedures for Alzheimer's disease (AD) and other dementias leading to fluid biomarker testing or brain imaging is critical.

Soysal et al. have demonstrated that the head-turning sign (HTS), when a patient turns their head at least once towards their partner/primary caregiver to seek assistance with questions posed by the examiner during the medical interview, is a strong marker of dementia [2]. Larner also reported that HTS is an easily observed and categorized clinical sign in memory clinics and has good specificity for the presence of cognitive impairment [3]. Isik et al. studied three simple clinical signs—HTS, the attended-alone sign, and the applause sign—in a memory clinic and reported that the sensitivity of HTS for detecting cognitive impairment was 84.5%, the specificity was 52.3%, and the positive and negative predictive values (PPV and NPV, respectively) were 50% and 85.7%, respectively, indicating that the detection of HTS is a practical and time-saving tool for identifying cognitive impairment in patients [4].

Recently, we reported a simple set of questions referred to as Consciousness/Insight/Level of awareness, Daily Pleasure/Pastime, and Current/Recent news/Knowledge on current topics, simple screening questionnaires for dementia (Neucop-Q) [Consciousness (C) normal/impaired (nor/imp), Pleasures (P) nor/imp, and News (N) nor/imp], which has the diagnostic potential to distinguish patients with normal cognitive function from those with amnestic mild cognitive impairment (aMCI) and AD [5]. In this study, HTS displayed high specificity: 100.0% for the aMCI+AD group when compared to the cognitive normal (CN) group, and 71.8% for AD group when compared to the CN+aMCI group. As for the Neucop-Q, Cimp exhibited high sensitivity of 80.6% for discriminating the aMCI+AD group from the CN group, and 87.5% for discriminating the AD group from the CN+aMCI group. The population-attributable risk percentage of the combination of Cimp and Nimp was high, indicating the screening utility of these brief questions in assessing "Consciousness of Impairment" and "Loss of recent News" [5].

Durães et al. reported that HTS frequency in individuals with MCI was associated with higher cerebrospinal fluid (CSF) levels of total tau and phosphorylated tau 181 (pTau181), indicating potential biological correlations [6]. However, the utility of the cognitive sign HTS and the Neucop-Q questionnaire has not yet been validated against amyloid β (Aβ)/tau positron emission tomography (PET) and/or well-established blood biomarkers.

In 2023, our group conducted a study on a dementia cohort involving combined amyloid and tau PET, revealing that both PET results have a significant impact on diagnosis and subsequent management, providing highly accurate clinical data [7]. In this study, we focused on the biological correlation between the outcomes of these screening tools and suspecting pathogenic changes based on amyloid and tau PET and plasma AD biomarkers. Our aim was to study the predictability of amyloid and tau pathologies by comparing the presence of HTS and Neucop-Q results with amyloid and tau PET and plasma AD biomarkers.

Materials and methods

Participants and clinical measurements

A total of 165 participants were initially enrolled in this study; 155 participants (93.9%) possessed complete information and were therefore included in the final dataset for analysis. Reasons for exclusion included ineligibility due to exclusion criteria ($n=1$), mortality ($n=2$), withdrawal of consent ($n=2$), or failure to undergo PET within the specified timeframe ($n=5$). All patients visited Keio University Hospital for routine diagnostic dementia evaluations between September 2018 and July 2023 [7]. Most individuals classified as CN initially volunteered through websites. The inclusion and exclusion criteria have been previously detailed [7]. Briefly, we enrolled participants with an age at the time of the screening visit

between 40 and 85 years, ≥12 years of education, and Geriatric Depression Scale (GDS) < 6. The exclusion criterion was serious systemic and/or unstable illness. The enrollment criteria for CN, MCI, and AD participants were as follows: CN: [1] The patient must be judged as CN by a dementia specialist (neurologist or psychiatrist), and [2] the Clinical Dementia Rating (CDR) is 0. MCI: [1] The patient must be judged as having MCI by a dementia specialist; [2] CDR is 0.5; and [3] the Mini Mental State Examination (MMSE) score is ≥24 points. AD: [1] The patient must be diagnosed with AD by a dementia specialist; [2] CDR is 0.5–1.0; and [3] MMSE ≤ 23 points. All participants underwent apolipoprotein E (ApoE) genotyping, magnetic resonance imaging, amyloid PET with [^{18}F]florbetaben (FBB), and tau PET with [^{18}F] PI-2620 or [^{18}F]florzolotau ([^{18}F]PM-PBB3). Dementia specialists diagnosed each participant based on two PET results, considering suspected etiologies [MCI due to AD, MCI due to non-AD, AD, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), frontotemporal lobar degeneration (FTLD), traumatic brain injury, dementia with Lewy bodies (DLB), psychiatric disorders, or others]. Furthermore, whole-genome sequencing and analysis were performed for all participants to confirm the absence of known dominant genetic mutations in AD and frontotemporal lobar degeneration-related genes, including amyloid precursor protein, microtubule-associated protein tau, presenilin (PSEN) 1, and PSEN2.

Standard protocol approval, registration, and patient consent

The study design and protocol were approved by the Ethics Committee for Human Research of the Keio University School of Medicine (#N20170237) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was registered with the UMIN Clinical Trials Registry (UMIN-CTR) under registration numbers 000032027 and 000030248.

Examination of HTS and Neucop-Q

HTS was evaluated during a participant's visit to our memory clinic, accompanied by a study partner/primary caregiver who spent at least 10 h a week with them. The accompanying person was instructed to sit either next to or behind the patient within an angle of 45°; if a patient turned their head at least once while seeking assistance during the medical interview, they were recorded as HTS-positive (HTSpos) [2].

In Neucop-Q [5], we posed three questions to every patient (Additional file 1):

1. "Do you feel that you have more difficulties in your daily life than you used to?"
2. "Could you tell me about your daily pleasures or pastimes?"
3. "What are the most notable current/recent news/topics?"

Consciousness/Insight/self-awareness of cognitive disabilities: If a patient responded with, "Yes, I have difficulties in my daily life," they were classified as self-aware ["Consciousness normal (Cnor)"]; conversely, if they answered, "No, I do not have difficulties," they were classified as having unconsciousness or anosognosia ["Consciousness impaired (Cimp)"] in the recorded results.

Daily pleasure/pastime: A patient was reported as engaging ["Pleasure normal (Pnor)"] only when they provided a specific and concrete answer, such as "I enjoy feeding our dog and going for a walk to a nearby park with him." If the patient's response was absent or subtle/abstract (e.g., "Generally, I enjoy everything"), they were recorded as "Pleasure impaired (Pimp)."

Current/Recent news/knowledge on the current topics: A patient was noted as aware of the news ["News normal (Nnor)"] when they provided concrete, adequate, and recent news (within the past 3 months). Conversely, if the patient answered nothing or gave an abstract answer like "There have been a number of recent events" or provided news that was more than 3 months old, they were recorded as "no news (Nimp)."

Amyloid PET imaging

A 20-min static scan was conducted 90 min after the intravenous infusion of 300 MBq ± 10% [^{18}F]FBB using a PET/computed tomography (CT) system (Siemens Biograph mCT or Siemens Biograph mCT flow, Munich, Germany) [8, 9]. The manufacturing of FBB was according to good manufacturing practices at Keio University Hospital using an automated synthesizer (Synthera V2; IBA, Louvain-la-Neuve, Belgium). The acquired PET data were reconstructed using an ordered subset expectation maximization algorithm (four iterations and 24 subsets), using a matrix size of 200 × 200. A full width at half maximum Gaussian post-reconstruction filtering of 3 mm was applied, along with scatter correction. For attenuation correction and anatomic registration, CT was performed with a tube voltage of 120 kVp, a tube current of 50 mAs, 0.5 s per rotation, and a slice thickness of 2 mm. The visual assessment of the reconstructed images as Aβ-positive or Aβ-negative was conducted by a neuroradiologist who had undergone the required training. The visual assessment involved comparing signal intensity between gray and white matter in axial PET slices at the lateral temporal, frontal, and parietal lobes, as well as the posterior cingulate cortex/precuneus. Scoring was performed using the regional cortical tracer uptake (RCTU) scoring system. When tracer uptake in the gray matter

equaled or exceeded that of adjacent white matter, the RCTU score was assigned as 2 or 3, indicating positive tracer uptake, while a score of 1 meant no tracer uptake. Subsequently, the RCTU scores from the four brain regions were aggregated to determine the brain amyloid plaque load score, with Aβ positivity being determined if one or more RCTU scores exceeded 1.

Calculation of the centiloid scale

We utilized the standalone software "Amyquant" [10], specifically developed for semi-automatic quantitative analysis of brain amyloid PET, to calculate the Centiloid (CL) scale. This software allows for reliable calculation of both the global CL and amyloid accumulation (quantified as the standard uptake value ratio) in five crucial regions, including the posterior cingulate cortex and precuneus, frontal cortex, temporal cortex, parietal cortex, and striatum. Currently, it applies to five different amyloid PET tracers, including FBB. We used the entire cerebellum as the reference region [11]. The accuracy of the calculated CL values was validated by comparing the results with those available on the Global Alzheimer's Association Interactive Network website (https://www.gaain.org/centiloid-project).

Tau PET acquisition

All participants underwent [^{18}F]PI-2620 or [^{18}F]florzolotau tau PET. Sixteen participants [including CN (n=3), AD dementia (n=8), PSP (n=2), CBS (n=1), FTLD (n=1), and other non-tauopathic dementia (n=1)] underwent PET with [^{18}F]PI-2620, as previously described [9]. The [^{18}F]PI-2620 PET imaging was performed 60 min after the intravenous administration of 185 MBq±10% [^{18}F]PI-2620 using a PET/CT system (Siemens Biograph mCT or Siemens Biograph mCT flow). For the remaining 139 participants, PET scans were performed with [^{18}F] florzolotau, as detailed elsewhere [9, 12]. The determination of tau deposits in regions expected to harbor tau pathology was based on a visual assessment, which was conducted during a conference involving several neurologists and psychiatrists specializing in dementia.

Plasma biomarker measurement

Venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-2 K-containing tubes (Vacutainer™ Plastic Blood Collection Tubes with K2EDTA; BD Biosciences, Franklin Lakes, NJ) and placed on ice, following the procedures previously outlined [11]. The samples were centrifuged (1200 × g for 10 min) within 2 h of blood collection, followed by further centrifugation in different tubes (2800 × g for 10 min), resulting in the isolation of platelet-free plasma within 30 min. These plasma samples were then aliquoted into polypropylene tubes (Matrix™ 2D Barcode tube, 1.0 mL; Thermo Fisher Scientific, Waltham, MA) and stored at −80 °C until the assay. Plasma levels of pTau181, neurofilament light (NFL), and GFAP were measured using commercial assays (Simoa® ptau181 Advantage Kit, Simoa® NF-light Kit, or Simoa® GFAP Discovery Kit; Quanterix, Billerica, MA) conducted on an HD-1 analyzer or SR-X, in accordance with the manufacturer's instructions. Plasma Aβ40 and Aβ42 levels were measured using the automated high HISCL (HISCL-5000; Sysmex, Kobe, Japan), as outlined in the reference study [13, 14].

Statistical analysis

We conducted statistical analyses using JMP version 17 (SAS Institute, Cary, NC). For descriptive statistics, we assessed differences between the CN and other groups using the Wilcoxon test for continuous variables and the chi-squared test for categorical variables (Table 1). In Figs. 1, 2, 3 and 4, we employed the Wilcoxon test to evaluate differences between groups categorized as battery pos vs. neg or nor vs. imp. A Bonferroni-corrected significance level threshold (Figs. 1, 2, 3 and 4, and Additional files) or p-values<0.05 (Table 1) were considered statistically significant.

Results

Participant characteristics

The participants' demographic data are presented in Table 1. As previously described, 155 participants provided the complete information required for this study.

Table 1 Characteristics and diagnoses of patients

	n	Male (%)	Age (years)	education(y)	CDRsum	MMSE	ADAS	FAQ	ApoE4+(%)
total	155	77(49.7)	69.5±10.3	14.6±2.0	1.75±3.00	25.5±5.4	10.3±10.3	2.84±4.57	36.8
CN	47	26(55.3)	70.2±7.7	15.0±2.2	0.01±0.07	29.0±1.1	4.3±2.3	0.43±1.04	31.9
MCI due to AD	19	8(42.1)	72.5±10.0	14.2±1.9	0.63±1.10*	27.2±2.4*	6.4±4.4*	1.33±3.59*	52.6
MCI due to non AD	17	12(70.59)	73.2±9.2	14.9±2.0	0.85±0.68*	27.2±1.9*	7.2±3.7*	0.71±1.05*	29.4
AD	31	13(41.9)	73.7±9.1*	14.3±1.8	3.87±3.47*	18.9±6.2*	20.8±10.3*	6.55±5.58*	54.8†
non-AD dementia	33	16(48.5)	62.2±11.7*	14.7±1.9	3.36±4.25*	24.2±5.4*	13.7±14.6*	5.00±5.58*	24.2
psychiatric disorders	8	3(30.0)†	64.6±10.8	14.4±2.3	0.13±0.23*	28.1±1.9	4.04±1.4	0.25±0.71	0

Abbreviations: MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; ADAS, Alzheimer's Disease Assessment Scale; ApoE, apolipoprotein E; CN: cognitive normal, AD: Alzheimer's disease, MCI: mild cognitive impairment, A/T: amyloidβ/tau pathology

Notes: Data are presented as mean (SD or %). *; Differences from CN were assessed using the Wilcoxon test. p<0.05, †; Differences between each two groups were assessed using χ2 test

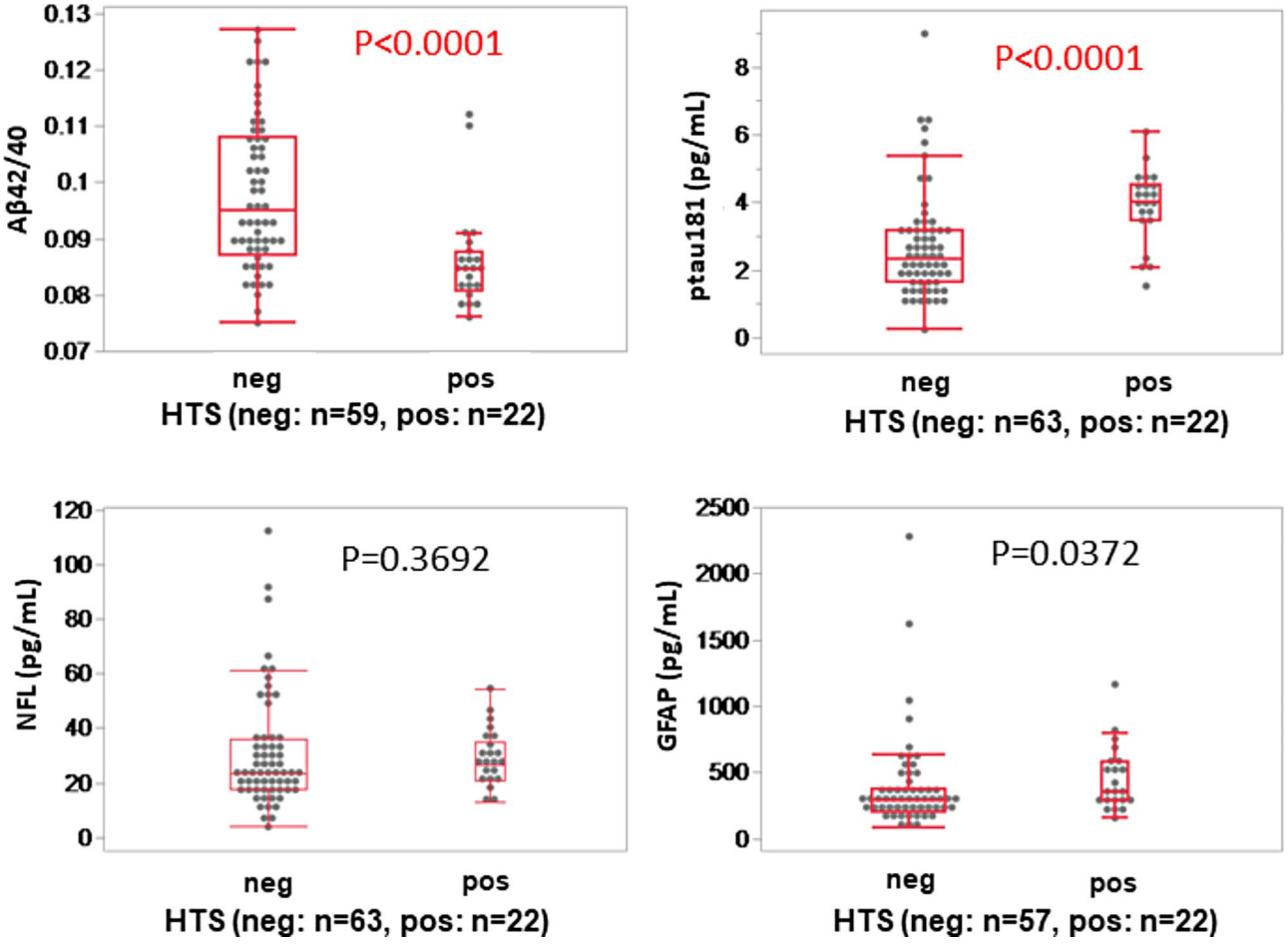

Fig. 1 Boxplots comparing plasma Aβ42/40 ratio, pTau181, GFAP, and NFL on HTS neg/pos. Boxplots were constructed from five values: the minimum above the lower fence, first quartile, median, third quartile, and maximum below the upper fence. Outliers are any observation that is more than 1.5 IQR away from the first or third quartile. The Wilcoxon test was used to compare neg vs. pos. A Bonferroni-corrected significance level threshold of $\alpha = 0.05/4 = 0.0125$ was considered statistically significant. Aβ: amyloid β, pTau181: phosphorylated tau 181, GFAP: glial fibrillary acidic protein, NFL: neurofilament light, HTS: head-turning sign

Among them, 36 patients were diagnosed with MCI, with 19 of them attributed to MCI due to AD and 17 to MCI due to non-AD. Additionally, 64 patients were diagnosed with dementia (31 patients with AD and 33 with dementia due to non-AD). Eight were diagnosed with psychiatric disorders (Table 1). The sex ratio (female/male), age, duration of education, CDR-Sum of Boxes, MMSE scores, Alzheimer's Disease Assessment Scale (Japanese version) cognitive subscale (ADAS-Jcog), Functional Activities Questionnaire (FAQ), and ApoE4 positivity are shown in Table 1. The groups displayed significant differences in terms of age between CN and AD ($P=0.0265$) and between CN and non-AD dementia ($P=0.0022$). Furthermore, sex differences were observed between CN and psychiatric disorders ($P=0.0035$). Significant differences were evident across all cognitive and functional assessments, including the MMSE, CDR-Sum of Boxes, FAQ, and ADAS-Jcog, when comparing CN with MCI due to AD, MCI due to non-AD, AD, and non-AD dementia ($P<0.0001$), except for FAQ in MCI due to non-AD ($P=0.0177$). ApoE4 positivity rates were significantly different between the CN and AD groups ($P=0.0044$).

Diagnostic utility of HTS and Neucop-Q

Firstly, the association between HTS and Neucop-Q results and cognitive status (CN, MCI, and dementia) was evaluated. As shown in Additional file 2, HTS and partially "N" and "Cimp/Pimp/Nimp" in Neucop-Q, demonstrated significant differences in cognitive status in all participants, confirming the validity of these simple screening tests [5]. HTS and "Cimp/Pimp/Nimp" in Neucop-Q lost significance when AD dementia and MCI due to AD were excluded, suggesting that these simple screening tests might be specific to cognitive impairment due to AD. (Additional file 3, right) Among participants excluded from non-AD dementias and MCI due to non-AD, thus focusing on AD pathology, "P" did not show significance, suggesting that Pimp is not related to cognitive

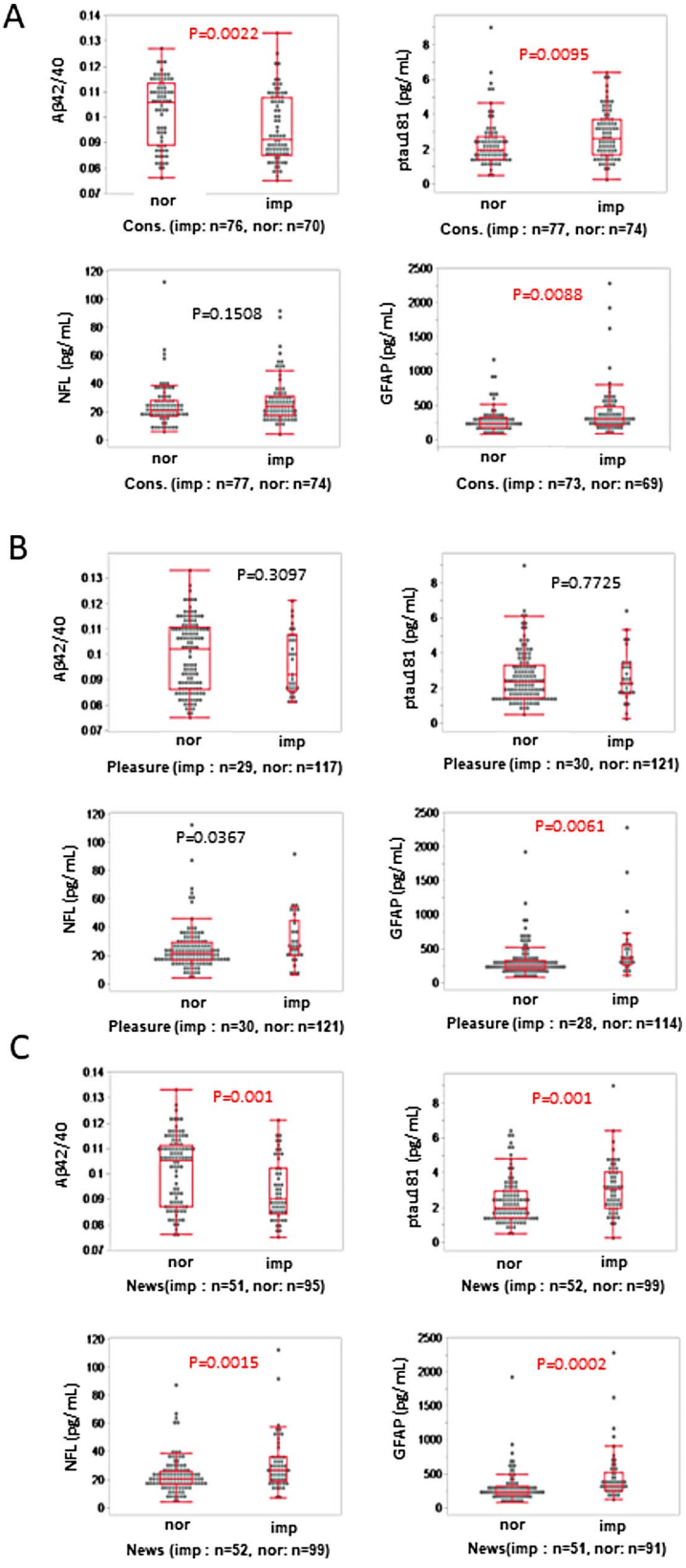

Fig. 2 Boxplots comparing plasma Aβ42/40 ratio, pTau181, GFAP, and NFL on Neucop-Q. **(A)** Consciousness imp/nor, **(B)** pleasure imp/nor, **(C)** news imp/nor. The Wilcoxon test was used to assess the differences between the two groups (imp vs. nor). A Bonferroni-corrected significance level threshold of α = 0.05/4 = 0.0125 was considered statistically significant. Aβ: amyloid β, pTau181: phosphorylated tau 181, GFAP: glial fibrillary acidic protein, NFL: neurofilament light

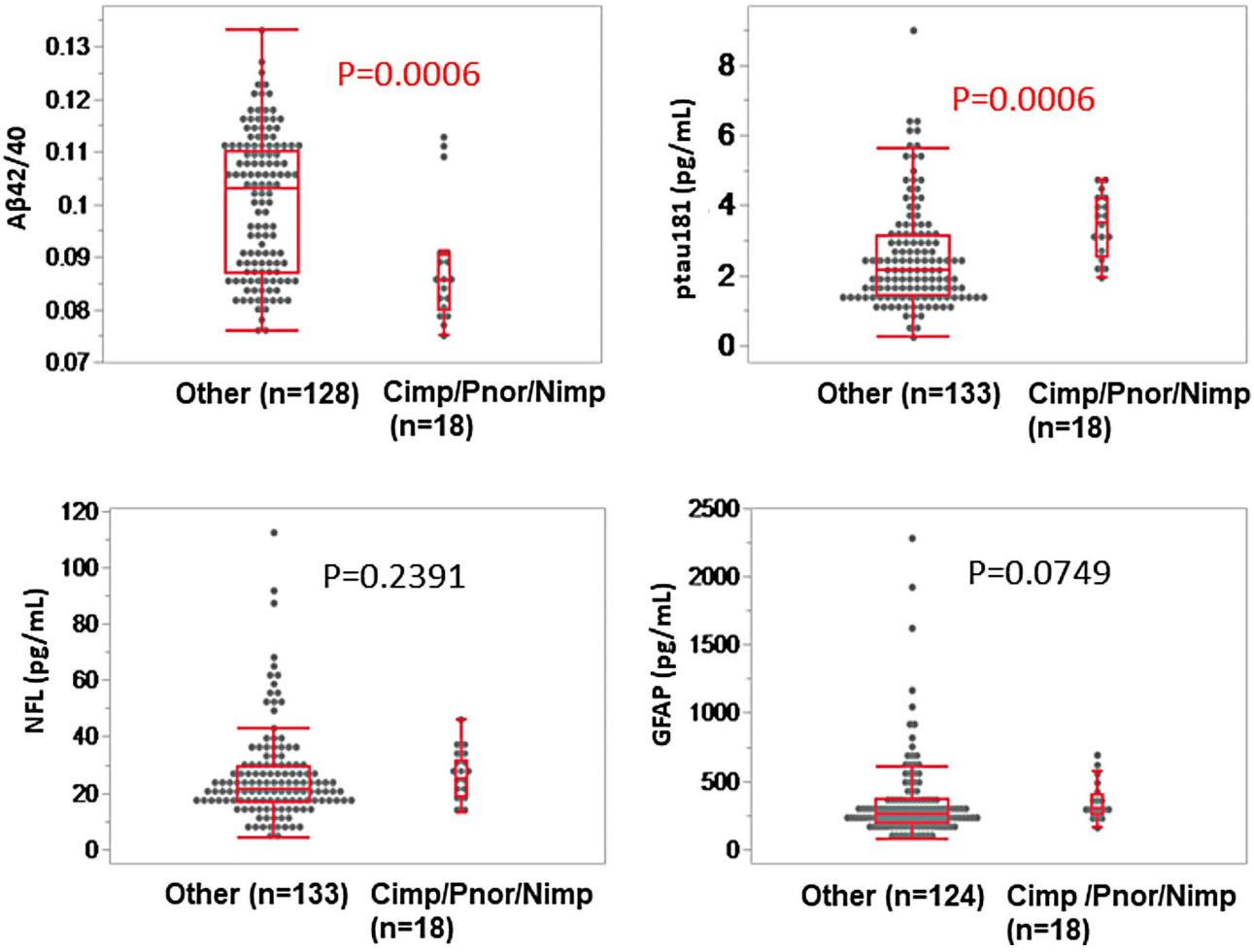

Fig. 3 Boxplots comparing plasma Aβ42/40 ratio, pTau181, GFAP, and NFL and between the Cimp/Pnor/Nimp group and the other groups. The Wilcoxon test was used to assess the differences (imp vs. nor). A Bonferroni-corrected significance level threshold of α = 0.05/4 = 0.0125 was considered statistically significant. Aβ: amyloid β, pTau181: phosphorylated tau 181, GFAP: glial fibrillary acidic protein, NFL: neurofilament light

status related to AD. (Additional file 3, left) Moreover, the likelihood ratio test was conducted on HTS and NeuroQ subscores with cognitive status (cognitively unimpaired, MCI, dementia) and amyloid PET (positive versus negative) as factors. "N" and "Cimp/Pimp/Nimp" were associated with cognitive status, and HTS and "Cimp/Pimp/Nimp" with amyloid PET results, indicating that HTS is specific to Alzheimer's pathology. (Additional file 4)

Table 2 shows the sensitivity, specificity, PPV, and NPV of HTSpos, Cimp, Pimp, and Nimp for predicting amyloid FBB PET and tau PET positivity using [^{18}F]PI-2620 or [^{18}F]florzolotau. These assessments are crucial for the diagnosis of non-AD tauopathies [9, 12, 15–19].

For participants with amyloid or tau PET positivity, HTSpos exhibited the highest specificity and PPV (amyloid PET: 0.930 and 0.870, tau PET: 0.944 and 0.957, respectively). Cimp and Nimp showed a high NPV for predicting amyloid PET result (negativity) (0.750 and 0.725, respectively). Similar results were observed in patients with cognitive impairment due to AD (AD-dementia or MCI due to AD), which is crucial for determining indications for AD disease-modifying treatments (Additional file 5). For predicting tau PET positivity among all participants, HTS, followed by Nimp, showed a high PPV (0.957 and 0.811, respectively) due to an increase in the number of PET-positive subjects. Notably, Pimp showed high specificity for predicting non-AD tauopathy among non-AD participants with amyloid PET negativity (0.854). Collectively, HTSpos, Cimp, and Nimp have diagnostic utility in predicting amyloid pathology, and Pimp has diagnostic value in non-AD tauopathy.

Finally, we assessed the sensitivity, specificity, PPV, and NPV of various combinations of "Cnor/imp," "Pnor/imp," and "Nnor/imp" to detect AD or MCI due to AD (Table 3). Among all the combinations (Cimp/Pimp/Nimp, Cnor/Pimp/Nimp, Cimp/Pnor/Nimp, Cimp/Pimp/Nnor, Cnor/Pnor/Nimp, Cnor/Pimp/Nnor, Cimp/Pnor/Nnor, and Cnor/Pnor/Nnor), Cimp/Pnor/Nimp

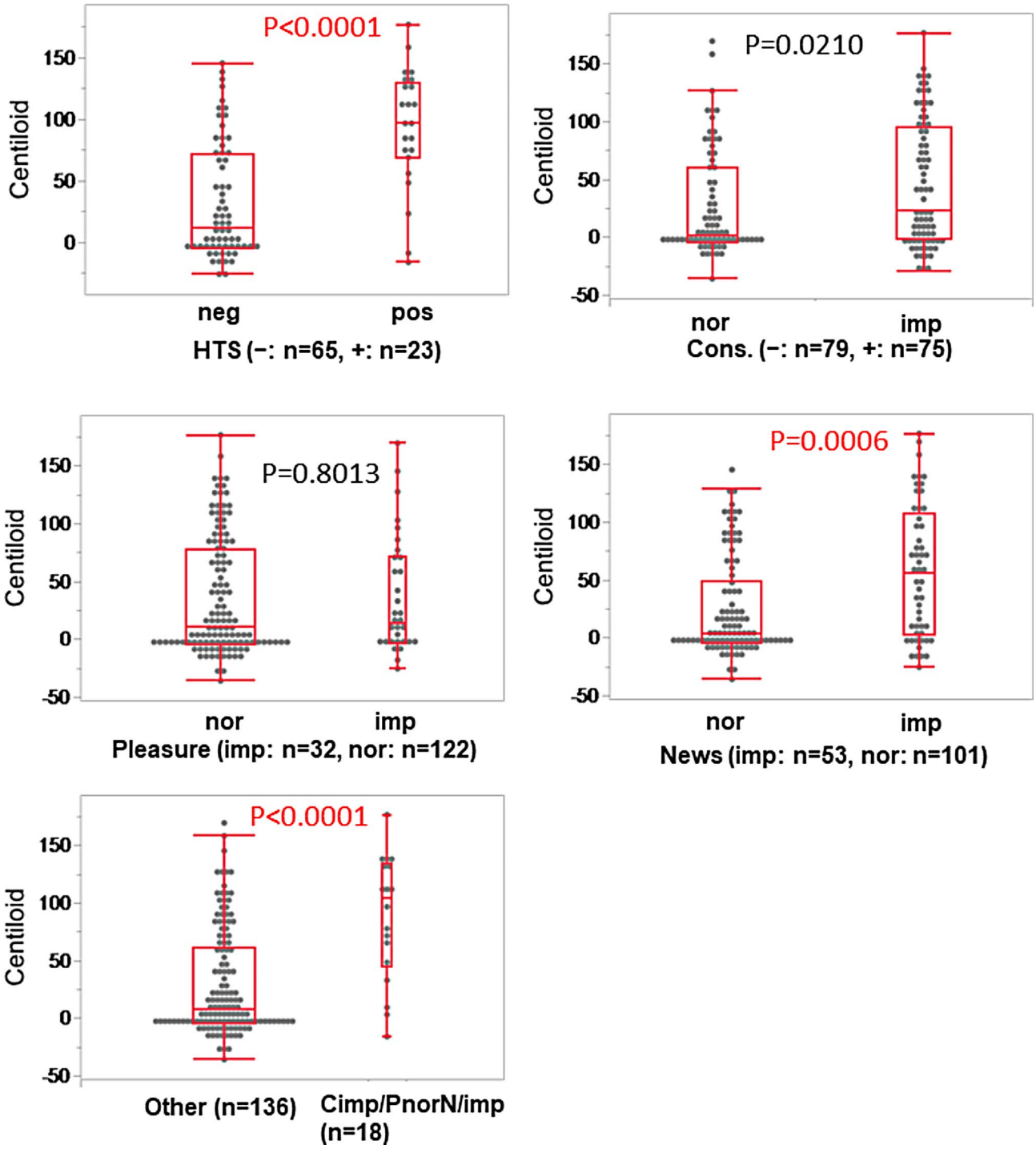

Fig. 4 Boxplots comparing FBB CL between the HTS/Neucop-Q groups. The Wilcoxon test was used to evaluate the differences (neg vs. pos, imp vs. nor). A Bonferroni-corrected significance level threshold of $\alpha = 0.05/5 = 0.01$ was considered statistically significant. CL, Centiloid, HTS: head-turning sign

Table 2 Diagnosis utility of HTS and Neucop-Q on account of amyloid or tau PET positivity

		Amyloid PET						**Tau PET**						**non-AD Tau PET**			
		(+)	(-)					(+)	(-)					(+)	(-)		
HTS	pos	20	3	0.870	PPV	HTS	pos	22	1	0.957	PPV	HTS	pos	2	1	0.667	PPV
	neg	25	40	0.615	NPV		neg	48	17	0.262	NPV		neg	24	16	0.400	NPV
		0.444	0.930					0.314	0.944					0.077	0.941		
		sens.	spec.					sens.	spec.					sens.	spec.		
		Amyloid PET						Tau PET						non-AD Tau PET			
		(+)	(-)					(+)	(-)					(+)	(-)		
Consc.	imp	39	40	0.494	PPV	Consc.	imp	58	21	0.734	PPV	Consc.	imp	20	20	0.500	PPV
	nor	19	57	0.750	NPV		nor	48	28	0.368	NPV		nor	29	28	0.491	NPV
		0.672	0.588					0.547	0.571					0.408	0.583		
		sens.	spec.					sens.	spec.					sens.	spec.		
		Amyloid PET						Tau PET						non-AD Tau PET			
		(+)	(-)					(+)	(-)					(+)	(-)		
Pleas.	imp	11	21	0.344	PPV	Pleas.	imp	25	7	0.781	PPV	Pleas.	imp	14	7	0.667	PPV
	nor	47	76	0.618	NPV		nor	81	42	0.341	NPV		nor	35	41	0.539	NPV
		0.190	0.784					0.236	0.857					0.286	0.854		
		sens.	spec.					sens.	spec.					sens.	spec.		
		Amyloid PET						Tau PET						non-AD Tau PET			
		(+)	(-)					(+)	(-)					(+)	(-)		
News	imp	30	23	0.566	PPV	News	imp	43	10	0.811	PPV	News	imp	13	10	0.565	PPV
	nor	28	74	0.725	NPV		nor	63	39	0.382	NPV		nor	36	38	0.514	NPV
		0.517	0.763					0.406	0.796					0.265	0.792		
		sens.	spec.					sens.	spec.					sens.	spec.		

Cons.: consciousness, Pleas.: pleasure, imp: impaired, normal: nor, sens.: sensitivity, spec.: specificity, PET: positron emission tomography, PPV: positive predictive value, NPV: negative predictive value, HTS: head-turning sign

Table 3 Diagnosis utility of combination of Neucop-Q on account of amyloid or tau PET positivity

All participants					**Participants without Amyloid PET +**			
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cimp/Pimp/Nimp	6	11	0.353	PPV	Cimp/Pimp/Nimp	5	5	0.500
other	43	95	0.688	NPV	other	44	43	0.494
	0.122	0.896				0.102	0.896	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cnor/Pimp/Nimp	2	3	0.400	PPV	Cnor/Pimp/Nimp	2	1	0.667
other	47	103	0.687	NPV	other	47	47	0.500
	0.041	0.972				0.041	0.979	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cimp/Pnor/Nimp	15	3	0.833	PPV	Cimp/Pnor/Nimp	1	2	0.333
other	34	103	0.752	NPV	other	48	46	0.489
	0.306	0.972				0.020	0.958	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cimp/Pimp/Nnor	2	5	0.286	PPV	Cimp/Pimp/Nnor	4	1	0.800
other	47	101	0.682	NPV	other	45	47	0.511
	0.041	0.953				0.082	0.979	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cnor/Pnor/Nimp	5	8	0.385	PPV	Cnor/Pnor/Nimp	5	2	0.714
other	44	98	0.690	NPV	other	44	46	0.511
	0.102	0.925				0.102	0.958	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cnor/Pimp/Nnor	0	3	0.000	PPV	Cnor/Pimp/Nnor	3	0	∞
other	49	103	0.678	NPV	other	46	48	0.511
	0.000	0.972				0.061	∞	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cimp/Pnor/Nnor	10	27	0.270	PPV	Cimp/Pnor/Nnor	10	12	0.455
other	39	79	0.669	NPV	other	39	36	0.480
	0.204	0.745				0.204	0.750	
	sens.	spec.				sens.	spec.	
	AD or AD-MCI					non-AD Tau PET		
	(+)	(-)				(+)	(-)	
Cnor/Pnor/Nnor	9	46	0.164	PPV	Cnor/Pnor/Nnor	19	25	0.432
other	40	60	0.600	NPV	other	30	23	0.434
	0.184	0.566				0.388	0.479	
	sens.	spec.				sens.	spec.	

C: Consciousness, P: Pleasure, N: News, imp: impaired, normal: nor, sens.: sensitivity, spec.: specificity, PET: positron emission tomography, PPV, positive predictive value, NPV: negative predictive value, AD: Alzheimer's disease, MCI: mild cognitive impairment

exhibited the highest specificity, PPV, and NPV (0.972, 0.833, and 0.752, respectively). Meanwhile, Cimp/Pimp/Nnor displayed the highest specificity and PPV among non-AD participants without amyloid PET + (0.979 and 0.800, respectively); however, caution should be exercised in interpreting these results as the number of cases ($n=5$) was limited.

Correlation with plasma biomarkers and outcomes of HTS and Neucop-Q

Recently, considerable progress has been made in the field of blood biomarkers for neurodegenerative dementias [11]. Biomarkers specific to AD pathology include the Aβ42/40 ratio [11, 14, 20, 21]. pTau181 [22–24] exhibits a strong correlation with Aβ toxicity. Other neurodegenerative biomarkers include GFAP [25, 26], which serves as a marker for glial activation and neuroinflammation, and NFL [27], which is indicative of axonal damage. As shown in Additional file 6 and 7, all well-established biomarkers showed a significant difference in cognitive status (CN, MCI, and dementia), consistent with previous publications [11, 28], and also showed significant correlation between biomarkers, except between NFL vs. Aβ42/40 and Centiloid (Additional file 8).

Next, we investigated the correlation between plasma AD biomarkers and results obtained from the HTS and simple questions in Neucop-Q (Figs. 1, 2, 3 and 4). Wilcoxon tests revealed that the plasma Aβ42/40 ratio was significantly lower and pTau181 were higher in patients with HTSpos than in patients with HTSneg [neg vs. pos, Aβ42/40: 0.098±0.013 vs. 0.086±0.009 pg/mL ($P<0.0001$); pTau181: 2.69±1.57 vs. 3.86±1.09 pg/mL ($P<0.0001$)] (Fig. 1). Similarly, differences were observed between patients with Cnor and Cimp [nor vs. imp, Aβ42/40: 0.102±0.013 vs. 0.095±0.013 pg/mL ($P=0.0022$); pTau181: 2.35±1.43 vs. 2.84±1.40 pg/mL ($P=0.0095$); GFAP: 287.9±200.2 vs. 401.1±370.7 pg/mL ($P=0.0088$)] (Fig. 2A). Conversely, patients with Pimp exhibited significant differences in GFAP [nor vs. imp, GFAP: 310.8±239.3 vs. 489.8±466.7 pg/mL ($P=0.0061$)] but not in the Aβ42/40 ratio or pTau181 (Fig. 2B). In the case of Nimp, all plasma biomarkers showed significantly positive values for pathology [nor vs. imp, Aβ42/40: 0.102±0.014 vs. 0.093±0.012 pg/mL ($P=0.0010$); pTau181: 2.34±1.29 vs. 3.09±1.56 pg/mL ($P=0.0010$); NFL: 22.9±13.1 vs. 31.2±19.2 pg/mL ($P=0.0015$); GFAP: 291.2±234.4 vs. 444.1±383.7 pg/mL ($P=0.0002$)] (Fig. 2C). Overall, HTSpos, Cimp, and Nimp were strongly associated with biomarkers of Aβ pathology, whereas Pimp was associated with biomarkers of neuroinflammation but not Aβ pathology.

In combinations of Neucop-Q, Cimp/Pnor/Nimp was strongly associated with biomarkers of Aβ pathology, such as plasma Aβ42/40 ratio and pTau181, supporting the abovementioned findings [other vs. Cimp/Pnor/Nimp: Aβ42/40 ratio, 0.100±0.013 vs. 0.088±0.011 pg/mL ($P=0.0006$), pTau181, 2.50±1.46 vs. 3.38±0.89 pg/mL ($P=0.0006$)] (Fig. 3).

Next, we analyzed the association between HTS/Neucop-Q and the CL scale of amyloid PET. As shown in (Fig. 4), HTSpos, Nimp, and "Cimp/Pnor/Nimp" showed significantly higher CL values, consistent with the findings related to plasma biomarkers [HTSneg vs. HTSpos: 32.3±46.9 vs. 93.0±49.3 ($P<0.0001$); Nimp vs. Nnor: 56.7±57.0 vs. 24.0±43.0 ($P=0.0006$); other vs. Cimp/Pnor/Nimp: 28.4±46.0 vs. 87.0±54.9 ($P<0.0001$)].

Finally, we have also performed Logistic regression analysis assessing factors associated between blood biomarker status and head-turning sign or Neucop-Q. (Additional file 9). There were significant interactions between pTau181 and Cimp. On the other hand, the lack of independent effect for a single biomarker for other signs could be interpreted as a general effect of Alzheimer's pathology.

Discussion

In our earlier study [5], we reported that HTSpos is a strong indicator for detecting cognitive impairment. Furthermore, we demonstrated that Neucop-Q, a set of three simple questions and their corresponding answers (Cnor/imp, Pnor/imp, and Nnor/imp), has similar diagnostic power for identifying AD-spectrum cognitive disorder. This tool provides reliable information, especially when patients are unaccompanied by family members or caregivers. In the present study, we have biologically validated the correlation between HTSpos and Neucop-Q outcomes and AD pathology. This validation is supported by PET and plasma AD biomarkers, demonstrating the diagnostic utility of these clinical signs and questionnaires.

Plasma biomarkers have recently emerged as expected screening tools for AD. A reduced plasma Aβ42/40 ratio in blood plasma serves as a specific peripheral biomarker for the cerebral amyloid deposits observed in AD [11, 14, 20, 21]. pTau181 levels increase with cortical amyloid deposition in AD, preceding tau accumulation detected by tau PET, although they are not correlated with non-AD tau pathology [22–24]. Plasma GFAP, an early and independent marker of astrocytosis associated with Aβ pathology, has been proposed as a biomarker for AD in memory clinic cohorts [25, 26]. In our previous work, we compared the performance of plasma Aβ42/40, pTau181, GFAP, and NFL simultaneously in a cohort study and showed that plasma Aβ42/40 (with an area under the receiver operating characteristic curve of 0.950) had excellent performance in detecting Aβ accumulation in the brain [11]. Additional file 5 and 6 also demonstrates that the values of biomarkers are associated with cognitive status. Our present data clearly show that HTSpos,

Cimp, and Nimp, but not Pimp, are strongly associated with these biomarkers of Aβ pathology. (Figures 1 and 2) This supports the significance of the combination set Cimp/Pnor/Nimp, which exhibited significant differences in plasma Aβ42/40 peptide ratio, pTau181 levels, and amyloid PET CL. (Fig. 3)

HTS is an easily observable, categorized sign that may indicate cognitive impairment [29]. Larner examined an operationalized HTS in the memory clinic and reported that diagnostic parameters for HTS are overall test accuracy: 0.83, sensitivity: 0.60, specificity: 0.98, positive predictive value: 0.94, negative predictive value: 0.79 [3]. On the other hand, similar to our results, he pointed out the low sensitivity of HTSpos as a weakness in screening. Fukui et al. reported that the incidence of HTS was significantly higher in the AD-related group (clinical AD+amnestic MCI) compared to other dementias, DLB, PSP, and VaD (AD-related 41% and other dementias 17%; $p=0.002$) [30]. They suggested that HTS may be the consequence of an imbalance between memory impairment and preserved executive function. As frontal executive dysfunction may be spared in AD, HTS may be a clinical marker of the AD population. Therefore, together with the results of the present study, HTS can be considered quite specific for Alzheimer's pathology.

Patients with dementia frequently attempt to maintain a normal external and superficial appearance to conceal their mistakes or evade responsibility. This behavior is referred to as saving appearance responses/behaviors (SARs) [31]. Matsushita et al. found that SARs were exhibited by 57.9% of individuals with AD, whereas only 20.0% of those with DLB displayed such behavior. This suggests that SARs are a typical communication pattern in patients with AD.

We propose that HTS and Cimp may be reflective of SARs, thus explaining their strong correlation with AD pathology. In contrast, Pimp is not associated with AD biomarkers and exhibits the highest specificity for non-AD tauopathies detected by tau PET. Pimp may reflect apathy and inertia commonly observed in non-AD tauopathies, such as FTLD-tau [32]. Patients with AD, on the other hand, would respond to the question of "pleasure" with SARs.

There are several limitations to this study. First, it was a single-center, retrospective study with a small sample size. All participants were Japanese individuals living in urban areas and covered by specific health insurance, which may not fully represent broader populations. The Japanese population is known for being particularly conscious of how others perceive their behavior, which could influence the prevalence of SARs observed in this study [31]. Furthermore, the participants in this study had higher educational attainment than the average population in Japan or worldwide, which may have influenced the outcomes of HTS and Neucop-Q. Therefore, the results of this study may not be directly applicable to other countries or populations. Larger, more comprehensive studies involving participants from diverse cultural, ethnic, and regional backgrounds, as well as multiple institutions, should be conducted to validate these findings.

Second, a Turkish study reported that the positivity of HTS patients with AD+MCI was higher in consecutive outpatients in a memory clinic than in that of our study (76.3% vs. 47.6%) [4]. Our study consists of patients recruited to a cohort study for PET and biomarkers in a memory clinic and CN subjects recruited from the website under inclusion and exclusion criteria [7], rather than exact consecutive patients.

Third, because this study was conducted in a specialized medical setting, a university hospital, which is required to provide advanced medicine for cases that are difficult to diagnose and treat, the average age of the subjects was around 70 years, much younger than the average age of patients seen in a general memory clinic. It is expected that non-AD dementia will have a high proportion of early-onset dementia (FTLD and primary tauopathy) and a low proportion of late-onset dementia (argyrophilic grain dementia and primary age-related tauopathy), given the average age of non-AD dementia of 62.2 years. It is therefore possible that sample size and selection bias may have had a significant impact on the present results and that this study simply cannot be applied to patients seen in a general memory clinic.

Fourth, HTS is not indicated for patients attending the clinic alone, and a significant portion of CN participants visited the clinic alone, making them ineligible for the HTS test.

Fifth, as the CN subjects in this study were mainly recruited online, the diagnostic accuracy values may not be applicable in a real outpatient setting, where there are essentially no truly healthy individuals without symptoms.

Finally, previous research has shown a significant correlation between HTS frequency and CSF total tau levels in MCI subgroups [6]. Since plasma biomarkers are still not well established as predictive indicators of AD pathology and CSF AD biomarkers are generally considered to be more sensitive and reliable than plasma biomarkers, future studies should aim to verify the correlation between HTS and CSF AD biomarkers.

Conclusion

Early screening for AD is crucial for timely intervention, including disease-modifying therapy. As gold-standard tests, CSF or PET scans are costly and invasive, and a safe and easy screening method is desired. Although caution is warranted before reaching a conclusion, our study

suggests that HTS and Neucop-Q have the potential to be a powerful first-line screening sign and tool for suspecting MCI due to AD and AD in memory clinics.

Abbreviations

Aβ	Amyloidβ
AD	Alzheimer's disease
ADAS-Jcog	Alzheimer Disease Assessment Scale (Japanese version) cognitive subscale
ApoE	Apolipoprotein E
C	Consciousness
CBS	Corticobasal syndrome
CDR	Clinical Dementia Rating
Cimp	Consciousness impaired
CL	Centiloid
CN	Cognitive normal
Cnor	Consciousness normal
CT	Computed tomography
FAQ	Functional Activities Questionnaire
FTLD	Frontotemporal lobar degeneration
GFAP	Glial fibrillary acidic protein
HTS	Head turning sign
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N	News
NFL	Neurofilament light chain
Nnor	News normal
Nimp	News impaired
NPV	Negative predictive value
P	Pleasure
PET	Positron emission tomography
Pimp	Pleasure impaired
Pnor	Pleasure normal
PPV	Positive predictive value
PSEN	Presenilin
PSP	Progressive supranuclear palsy
pTau	Phosphorylated tau

Supplementary Information

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Supplementary Material 1: Fig. 1. Boxplots comparing plasma Aβ42/40 ratio, pTau181, GFAP, and NFL on cognitive status. Fig. 2. Correlation of plasma biomarkers, Aβ42/40 ratio, pTau181, GFAP, and NFL.

Supplementary Material 2: Table 1. Clinical sign "head-turning sign" and simple set of questions in Neucop-Q. Table 2. Chi-squared test of the association between head-turning sign or Neucop-Q results and cognitive status in all participants. Table 3. Chi-square test of the association between HTS or Neucop-Q results and cognitive status. Table 4. Likelihood ratio test of the association between HTS or Neucop-Q results and cognitive status (CN, MCI, Dementia), amyloid PET (+/-) in all participants. Table 5. Diagnosis utility of head-turning sign and Neucop-Q in Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease. Table 6. Chi-squared test of the association between cut-off of blood biomarkers or amyloid positron emission tomography Centiloid and cognitive status using the cut-off derived from previous studies in all participants. Table 7. Logistic regression analysis assessing factors associated between blood biomarker status and head-turning sign or Neucop-Q.

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Author contributions

YD, HT, and DI contributed to study conception (lead contributor was DI). SB, MK, YMomota, YI, TT, MS, YY, RS, SK, YMimura, SS, contributed to participant recruitment. KT, TH contributed to data curation, including activities to clean and maintain research data. NS, AM, AO, YH contributed to administrative, technical, or material support. All authors interpreted the results and critically reviewed the manuscript. MJ, and MM contributed to supervision.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Certified Review Board of Keio University (#N20170237) approved the study design and protocol. The study was conducted in accordance with the Declaration of Helsinki. All participants (plus their proxies as needed) provided written informed consent for participation in the study. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; https://www.umin.ac.jp/ctr/index.htm, ID# UMIN000032027) and Japan Registry of Clinical Trials (jRCT; https://jrct.niph.go.jp/, ID# jRCTs031180225).

Consent for publication

Not applicable.

Competing interests

Daisuke Ito has received honorariums from Daiichi Sankyo, Nihon Medi-Physics, KOWA, and Eizai; there are no other relationships or activities that could appear to have influenced the submitted work.

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