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Canonical correlation analysis of synchronous neural interactions and cognitive deficits in Alzheimer's dementia

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Abstract
In previous work (Georgopoulos *et al* 2007 *J. Neural Eng.* **4** 349–55) we reported on the use of magnetoencephalographic (MEG) synchronous neural interactions (SNI) as a functional biomarker in Alzheimer's dementia (AD) diagnosis. Here we report on the application of canonical correlation analysis to investigate the relations between SNI and cognitive neuropsychological (NP) domains in AD patients. First, we performed individual correlations between each SNI and each NP, which provided an initial link between SNI and specific cognitive tests. Next, we performed factor analysis on each set, followed by a canonical correlation analysis between the derived SNI and NP factors. This last analysis optimally associated the entire MEG signal with cognitive function. The results revealed that SNI as a whole were mostly associated with memory and language, and, slightly less, executive function, processing speed and visuospatial abilities, thus differentiating functions subserved by the frontoparietal and the temporal cortices. These findings provide a direct interpretation of the information carried by the SNI and set the basis for identifying specific neural disease phenotypes according to cognitive deficits.

1. Introduction

Cognitive deficits are integral in the clinical diagnosis of Alzheimer's dementia (AD) [1, 2] and mild cognitive impairment (MCI) [3]. The cardinal cognitive complaint in AD is anterograde amnesia, yet deficits in visuospatial processing, executive function, language skills, perception, motor skills and mood are observed, especially with disease progression [1, 4]. The identification of specific cognitive deficits that will help establish the diagnosis currently requires expertise and lengthy cognitive tests. In addition, there is evidence that the pathological process in the brain starts up to ten years before the diagnosis of AD is made. For this reason there is an increasing effort in developing biomarkers for early and

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Table 1. Included NP variables[a].

NP code	NP name	Cognitive domain
'MMSE7s'	MMSE (serial 7's)	Global
'AMNARTC'	AMNART (correct)	General intelligence (premorbid)
'AMNARTIQ'	AMNART (IQ)	General intelligence (premorbid)
'DSPANF'	WAIS-III Digit Span (forwards)	Attention
'DSPANB'	WAIS-III Digit Span (backwards)	Attention
'DSPSS'	WAIS-III Digit Span (scaled score)[b]	Attention
'BD'	WAIS-III Block Design	Visuospatial
'BDSS'	WAIS-III Block Design	Visuospatial
'DSYMBL'	WAIS-III Digit Symbol	Executive/attention
'DYSMBLSS'	WAIS-III Digit Symbol	Executive/attention
'TMTA'	Trail Making Test A time	Cognitive flexibility/attention/processing speed
'TMTAERR'	Trail Making Test A errors	Cognitive flexibility/attention/processing speed
'TMTB'	Trail Making Test B time	Cognitive flexibility/attention/processing speed
'TMTBERR'	Trail Making Test B errors	Cognitive flexibility/attention/processing speed
'BNT15'	Boston Naming Test 15 item (raw)	Language
'BNT15PH'	Boston Naming Test 15 item (phonemic)	Language
'FWORDS'	Verbal Fluency: FAS	Language (verbal/linguistic)
'ANIMALS'	Verbal Fluency: Animals	Language (verbal/linguistic)
'LMAI'	WMS-R Logical Memory (story A I)	Memory (verbal)
'LMBI'	WMS-R Logical Memory (story B I)	Memory (verbal)
'LMAII'	WMS-R Logical Memory (story A II	Memory (verbal)
'LMBII'	WMS-R Logical Memory (story B II)	Memory (verbal)
'LMRETN'	WMS-R Logical Memory (% retention)	Memory (verbal)
'REYCOPY'	Rey-Osterrieth Compl. Figure (copy)	Visuospatial/planning
'REYDEL'	Rey-Osterrieth Compl. Figure (3 min recall)	Memory (visual)
'CVLTslT'	CVLT-II T normed trials total score	Memory (verbal)

[a] TMTAERR was not used in the ensuing analysis when it was shown that both its communality and loadings to the two factors were below the 0.3 cutoff.
[b] DSPSS is a combination of DSPANF and DSPANB and scaled for age.

accurate diagnosis of AD, and dementia in general [5, 6]. These biomarkers include neuropsychological tests, neuroimaging techniques, and biochemical substances, with variable levels of accuracy [5]. Beyond general accuracy levels, most researchers report the association of a biomarker with the nonspecific mini-mental state examination [7], without elucidating which specific cognitive functions that test reflects.

In previous work we showed that synchronous neural interactions (SNI) of the magnetoencephalographic (MEG) signal can be used as a functional biomarker for brain disorders, including AD [8, 9]. The goal of this paper is to provide a direct link between SNI and cognitive function, as evaluated through neuropsychological scores (NP) using data from patients with AD. The current work goes beyond the general usefulness of SNI as an adjunct diagnostic test in dementia, which has been shown previously [8, 9]. Specifically, the identification of the SNI pattern that relates to cognitive function can help in providing a readily interpretable meaning to the SNI signal, which may potentially allow in the future (a) substituting lengthy NP tests with a 1 min MEG acquisition, (b) identifying specific phenotypes of cognitive disorders (amnesic versus non-amnesic MCI, AD versus frontotemporal lobar degeneration etc), and, by extension, offering (c) more accurate disease prognosis and (d) better treatment selection.

In what follows, we used canonical correlation analysis (CCA) on previously factor-analyzed SNI and NP sets of SNI and NP to identify SNI–NP relations while accounting for within-set and between-sets common information.

2. Methods

2.1. Subjects

A total of 23 AD patients (all men, age 77.8 $\pm$ 1.3 years) participated in this study as paid volunteers and were recruited at the GRECC clinic of the Minneapolis Veterans Affairs Medical Center. Subjects were diagnosed on the basis of an interdisciplinary consensus diagnosis conference. Patients met criteria for (a) diagnosis of dementia according to DSM-IV [2] and (b) possible or probable AD according to NINCDS-ADRDA criteria [1]. The study protocol was approved by the relevant institutional review boards and informed consent was obtained prior to the study according to the Declaration of Helsinki [10].

2.2. Neuropsychological score testing

Neuropsychological tests were performed on all subjects on 26 measures, the specifics of which are shown on table 1. None of the NP variables was a linear composite of others (i.e. sum or average), which allowed maximum non-overlapping information to be incorporated in the analysis without adding redundant variables. Special reference is required for the WAIS-III Scaled Digit Span score which was a nonlinear composite of the WAIS-III Digit Span Forwards score and the WAIS-III Digit Span Backwards score and scaled for age; age contributing in a nonlinear manner to the specific score derivation. Each NP score represented

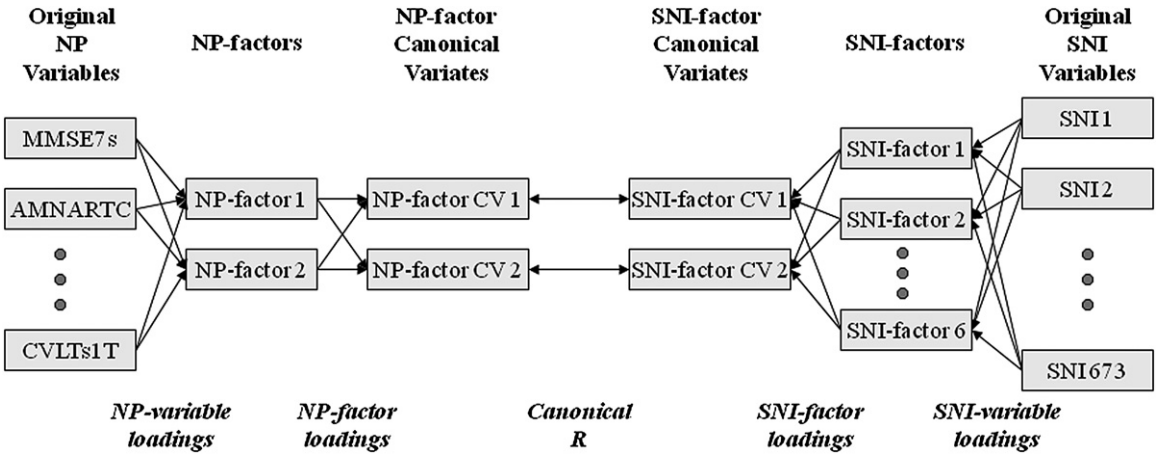


Figure 1. Flowchart depicting the steps toward the calculation of NP and SNI factor canonical correlations. Text at the top refers to boxes and text at the bottom refers to arrows.

one of seven cognitive domains (attention, visuospatial, executive, flexibility, processing speed, language and memory) or a composite of cognitive function (e.g. global deficit, intelligence).

2.3. MEG task—data acquisition

The SNI represent steady-state relations between neuronal ensembles without the subject engaging in any complex task. For that purpose, subjects lay supine in the MEG instrument and fixated on a spot, ∼62 cm in front of them, for 45–60 s (in different subjects) while MEG data were acquired from 248 axial gradiometers (sampled at 1017.25 Hz, filtered 0.1–400 Hz; Magnes 3600WH, 4D Neuroimaging, San Diego, CA). This yielded, for each subject, a data set consisting of 248 time series with 45 000–60 000 time points. The cardiac artifact was removed from each series using event-synchronous subtraction [11].

2.4. Derivation of synchronous neural interactions

The specifics in deriving SNI have been extensively described in previous papers [8, 12]. Here we provide a concise description for parsimony. Initially, each of the 248 cardiocorrected time-series was made stationary and non-autocorrelated by 'prewhitening' using an ARIMA model (25,1,1) [13], thus avoiding spurious associations between sensors [13–15]. Next, the zero-lag cross-correlation between pairs of derived stationary and non-autocorrelated residuals was computed, and from these the partial zero-lag cross-correlation, PCC^0_{ij}, between sensors i and j was computed for all sensor pairs for each subject. Finally, PCC^0_{ij} was transformed to z^0_{ij} using Fisher's z-transformation [16] to normalize its distribution. The z^0_{ij} values were used in the ensuing analysis, providing a measure of SNI between neural cell populations. Of the total number of SNI only the ones with a significant correlation ($p < 0.001$) with at least one NP score were used in the analysis ($N = 676$). This allowed focusing on variables that relate to the cognitive domains mentioned above and rejecting variables that do not carry readily interpretable information.

2.5. Factor analysis

Factor analysis (FA) [17] was performed to address two separate issues. First, it allowed the different NP scores to be represented through latent variables (factors), making results interpretable through cognitive domains rather than individual NP scores. Second, the CCA which followed requires that the number of variables is considerably less than the number of cases to avoid spuriously correlated variable sets, and FA dimensionally reduced the variable space [18]. Specifically, we applied principal components analysis (PCA) with direct oblimin rotation and a δ of zero, followed by Humphrey–Ilgen parallel analysis [19] for component selection. All variables were initially z-scored, i.e. standardized as units of standard deviation, which led to comparable variance levels between variables. This in turn prevented variables with large variance from dominating individual principal components and allowed easier interpretation of individual variable contribution. In addition, if a variable's communalities and loadings to all factors were less than 0.3, that variable was removed from the analysis and FA was repeated without it. Thus, of 25 NP and 673 SNI variables used, this yielded 2 NP and 6 SNI factors. Each factor was interpreted based on original variable loadings larger than 0.45, and by extension a 20% level of explained variance.

2.6. Canonical correlation analysis

The steps toward acquiring the canonical correlations (CCs) are graphed in figure 1. This analysis correlated the NP-factor set with the SNI-factor set accounting for within and between set interactions [17]. From the derived canonical variate (CV) pairs, only those with (a) a large canonical R, (b) a significant Wilks' Λ ($p < 0.05$ based on Rao's approximation of an F-statistic) and (c) a dependent variable redundancy index above 0.3 were considered for further interpretation [18]. The contribution of each original variable (NP or SNI) to a CV

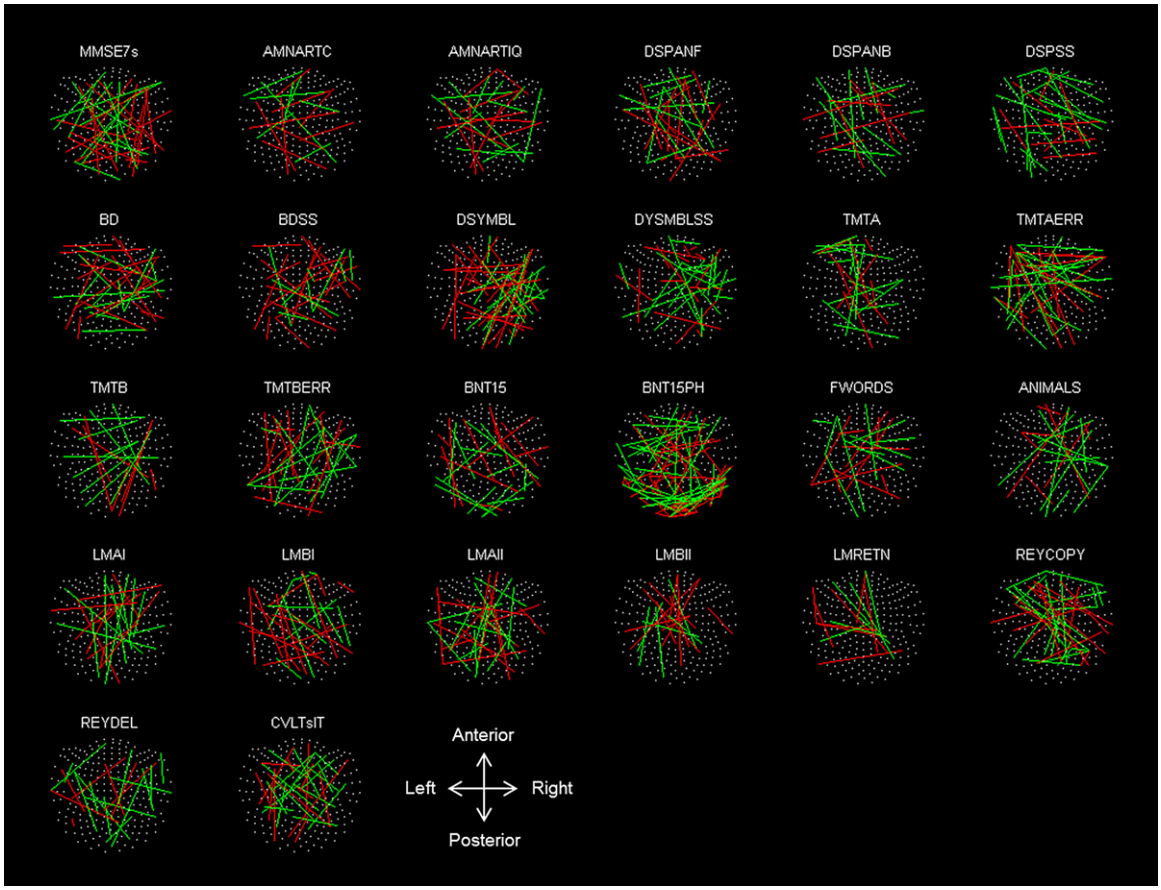


Figure 2. Serial bivariate correlations between each SNI and each NP score. Only SNI with a significant correlation with an NP score ($p < 0.001$) are plotted. Green color indicates a positive correlation and red a negative correlation between SNI and NP.

was calculated from the product of its pattern-matrix factor loading times the factor's loading to the CV (e.g. NP-factor loading $\times$ NP-variable loading). The pattern matrix loading was chosen in the above product, rather than the structure matrix loading, since it represents the unique contribution of an original variable to a factor.

All analyses were performed using MatLab code, except for direct oblimin rotation where an IMSL Fortran function was used.

3. Results

3.1. Individual correlations

An initial approach to address relations between NP and SNI was performed by taking all pairwise correlations between the two sets of variables (figure 2). The depicted SNI have a broad distribution, indicative of magnetic field correlations throughout the sensor space and not necessarily clustered at a specific location. Specifically, many more variables relate to memory function scores, while a considerable number of variables relate to attention, cognitive flexibility and executive function. In general, NP within tests have similar distributions of SNI (e.g. WMS-R Logical Memory). On the other hand, the Boston Naming Test scores revealed significant differences between the phonemic and non-phonemic version. In addition, verbal fluency patterns depended on differences between phonetic and semantic tasks (FWORDS versus ANIMALS). All the above indicate that cognitive domains have functional counterparts in the SNI measurements. However, the pairwise correlations do not account for common information carried within the NP and SNI sets, and only relate SNI to specific NP scores rather than to cognitive domains in general. These were issues addressed through CCA.

3.2. Factor analysis

After dimensionally reducing our data through FA, two NP and six SNI factors were retained. The NP factors explained 54.52% and the SNI factors explained 57.47% of the variance carried in the respective original variables. Since oblique rotation was performed, factors in the same set explained common elements of the original variance. However, both NP and SNI within-set factor correlations were small, with maximum common variance of 3.5% observed between the two NP-factors. This indicates that individual factors in both sets practically represent different aspects of the original variable space.

NP-factor 1 relates mostly to aspects of executive function, visuospatial function, attention and processing speed, NP-factor 2 relates mostly to aspects of memory (typical changes in AD) and phonemic elements of language (table 2). SNI which relate most to each of the SNI-factors are depicted in figure 3. Distributed networks across the sensor-space are

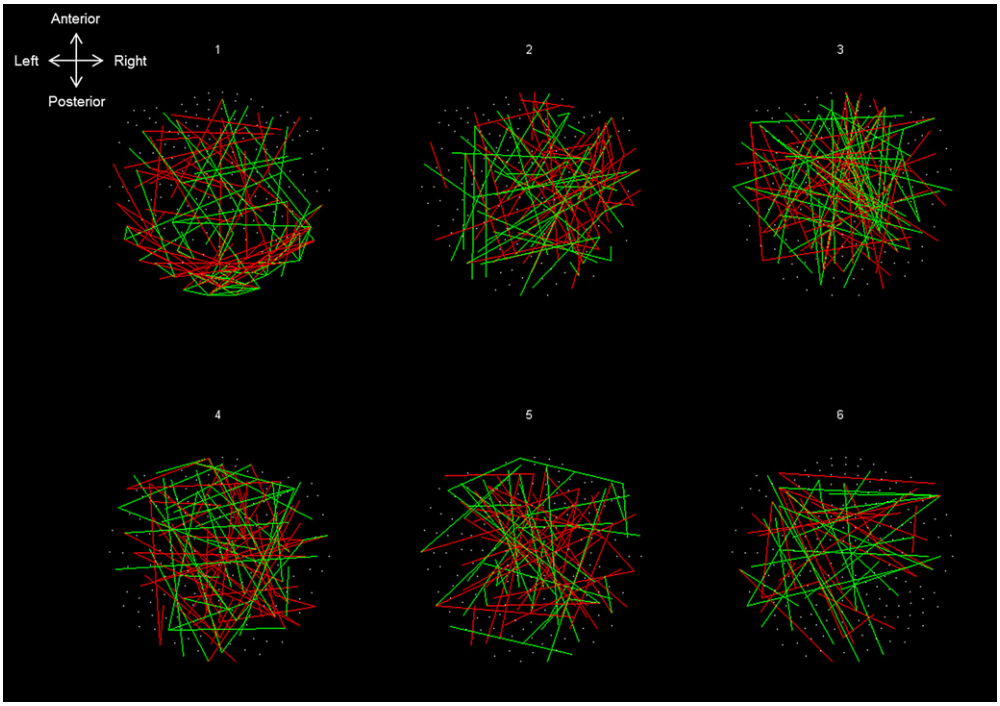


Figure 3. SNI contributing to each of the six SNI-factors. SNI with factor loadings >0.45 in both the structure and pattern matrix are plotted. Differences are observed in both the number of SNI that relate most to a factor, and the positive or negative relation of an SNI to a factor.

observed for all SNI-factors. Differences between SNI-factors are observed in the number and sign of SNI. For certain SNI-factors the SNI pattern is similar to certain patterns observed in figure 2 (e.g. SNI-factor 1 versus SNI relating to Boston Naming Test phonemic scores, SNI-factor 5 versus SNI relating to Rey-Osterrieth Complex Figure copy).

3.3. Canonical correlation analysis

To address the relationship between the two sets of variables (NP and SNI), a CCA was performed between the two NP-factors and the six SNI-factors. The CCs, their statistical significance and the dependent variable redundancy indices are tabulated in table 3. It can be seen that both CCs have a large magnitude (R), are significant according to Wilks' Λ and have a substantial redundancy index; all of which are recommended criteria prior to interpreting a CC [18].

We followed two approaches in interpreting the CVs (NP-CV and SNI-CV) of each CC: (a) for the NP-CV we identified which NP-factors had the largest loadings (L), thus allowing data interpretation via cognitive domains, and (b) for the SNI-CV we identified which SNI had the largest contribution (see section 2.6), thus allowing a direct reference to the original SNI measures and the sensor-space.

For the NP-set we found the following. The first CC related most to NP-factor 2 ($L = -0.99$; memory and language), and less to NP-factor 1 ($L = -0.25$; executive function, visuospatial function, attention and processing speed), thus representing mostly a memory component (the hallmark of AD). The second CC received most of its NP-factor contribution from NP-factor 1 ($L = 0.97$), without any substantial contribution from NP-factor 2 ($L = -0.06$), relating mostly to aspects of executive function, attention, processing speed and visuospatial skill. The SNI that contributed most (see sections 2.5 and 2.6) to the first and second CCs are depicted in figure 4. A distributed pattern is observed between distant pairs of sensors, with certain sensors contributing to more than one SNI.

4. Discussion

The main goal of this paper was to apply CCA as a tool by which to uncover readily interpretable relations between SNI and NP-assessed cognitive functions in AD. It seemed reasonable to correlate SNI with NP for two reasons. First, both SNI and NP represent the brain's functional state and it was thus more probable that they would both explain common elements of information. Second, it is important for the clinician to have a biomarker linked more directly to cognitive decline rather than to a localized structural brain abnormality that may or may not lead to a deficit. In addition, the relation of NP to SNI also allows for the potential substitution of lengthy NP tests with a fast 1 min MEG recording.

The results obtained showed that all cognitive domains tested were represented through SNI to a variable degree. When individual NP and SNI were compared, many more SNI related to memory tests than to other cognitive tests (figure 2). This is an indication that individual SNI mostly reflect the cardinal feature of AD, namely memory deficit. In addition, these specific SNI could potentially be useful in the diagnosis of AD and MCI, but they could prove even more useful in the differentiation of amnesic from non-amnesic MCI, or AD from frontotemporal lobar degeneration. Similarly, for diagnosing

Table 2. NP score loadings for each NP factor[a].

	Structure matrix		Pattern matrix	
NP score	Factor 1	Factor 2	Factor 1	Factor 2
'MMSE7s'	**−0.57**	**−0.65**	**−0.46**	**−0.57**
'AMNARTC'	**−0.54**	−0.30	**−0.50**	−0.20
'AMNARTIQ'	**−0.55**	−0.34	**−0.50**	−0.24
'DSPANF'	−0.44	0.23	**−0.50**	0.33
'DSPANB'	**−0.57**	−0.16	**−0.56**	−0.06
'DSPSS'	**−0.72**	0.21	**−0.79**	0.36
'BD'	**−0.79**	−0.09	**−0.80**	0.07
'BDSS'	**−0.81**	−0.11	**−0.82**	0.04
'DSYMBL'	**−0.69**	−0.06	**−0.71**	0.08
'DYSMBLSS'	**−0.63**	−0.12	**−0.63**	0.00
'TMTA'	**0.66**	−0.04	**0.69**	−0.17
'TMTB'	**0.85**	0.22	**0.83**	0.07
'TMTBERR'	**0.65**	0.25	**0.62**	0.14
'BNT15'	−0.29	−0.36	−0.23	−0.32
'BNT15PH'	−0.26	**−0.54**	−0.16	**−0.51**
'FWORDS'	**−0.79**	−0.28	**−0.77**	−0.14
'ANIMALS'	**−0.65**	−0.37	**−0.60**	−0.26
'LMAI'	−0.31	**−0.83**	−0.16	**−0.80**
'LMBI'	0.22	**−0.78**	0.38	**−0.85**
'LMAII'	0.01	**−0.88**	0.18	**−0.92**
'LMBII'	−0.12	**−0.92**	0.05	**−0.93**
'LMRETN'	−0.13	**−0.86**	0.03	**−0.87**
'REYCOPY'	**−0.53**	−0.25	**−0.50**	−0.16
'REYDEL'	−0.32	**−0.67**	−0.21	**−0.63**
'CVLTslT'	−0.44	**−0.50**	−0.36	−0.43

[a] The structure matrix reflects the raw correlation of each NP score to each factor, and the pattern matrix its unique contribution to each factor. Loadings in bold have an absolute value > 0.45, which in turn signifies that more than 20% of the respective NP score's variance is explained by the respective factor. The larger the absolute value of a loading, the stronger the relation of a factor to the respective cognitive domain.

Table 3. Canonical correlations.

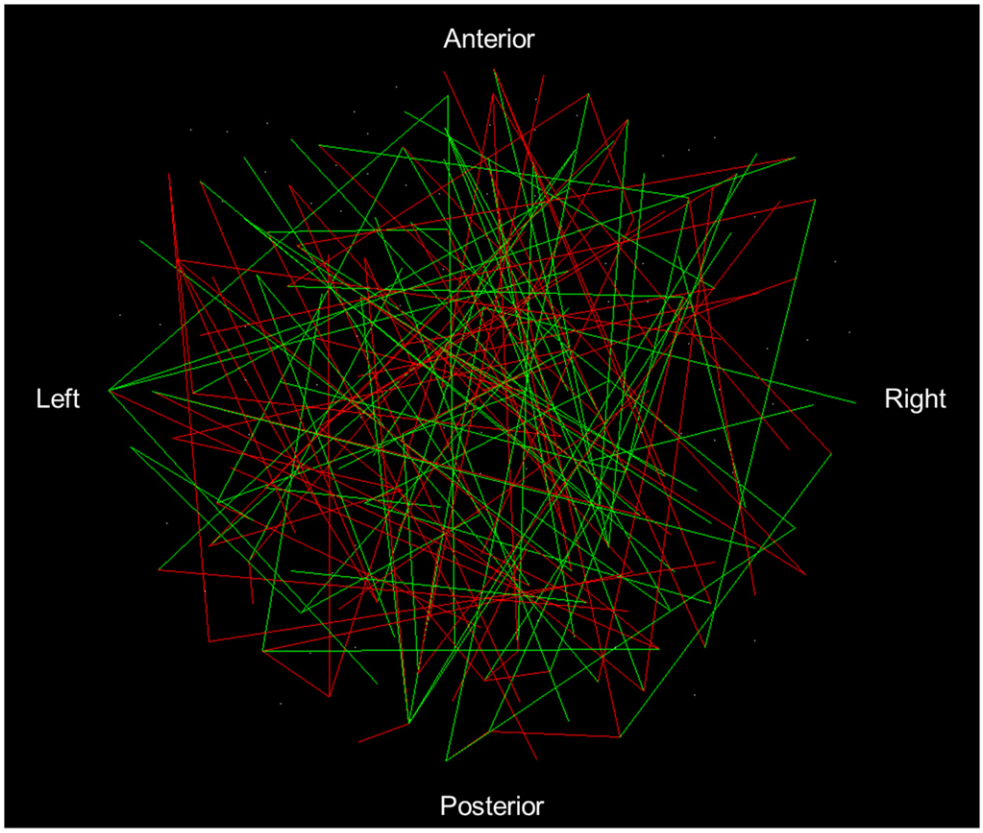
Canonical variate pair	1	2
Canonical R	0.98	0.97
Wilks' Λ (p)	0.002 (7×10^{-17})	0.053 (1.3×10^{-9})
Redundancy index	0.51	0.45
Factor contributions (L)		
NP-factor 1	−0.25	0.97
NP-factor 2	−0.99	−0.06
SNI-factor 1	−0.42	0.06
SNI-factor 2	−0.06	0.60
SNI-factor 3	0.91	0.16
SNI-factor 4	0.10	−0.76
SNI-factor 5	0.36	−0.43
SNI-factor 6	0.03	0.27

non-amnesic MCI, cognitive deficits other than memory have to be identified by the clinician, and that process requires time and expertise. Those domains that are less studied in relation to dementia biomarkers are also represented in the SNI signal to a considerable extent. Thus, non-amnesic MCI and other types of dementia (frontotemporal dementia, primary progressive aphasia etc) could potentially be effectively diagnosed through the SNI test.

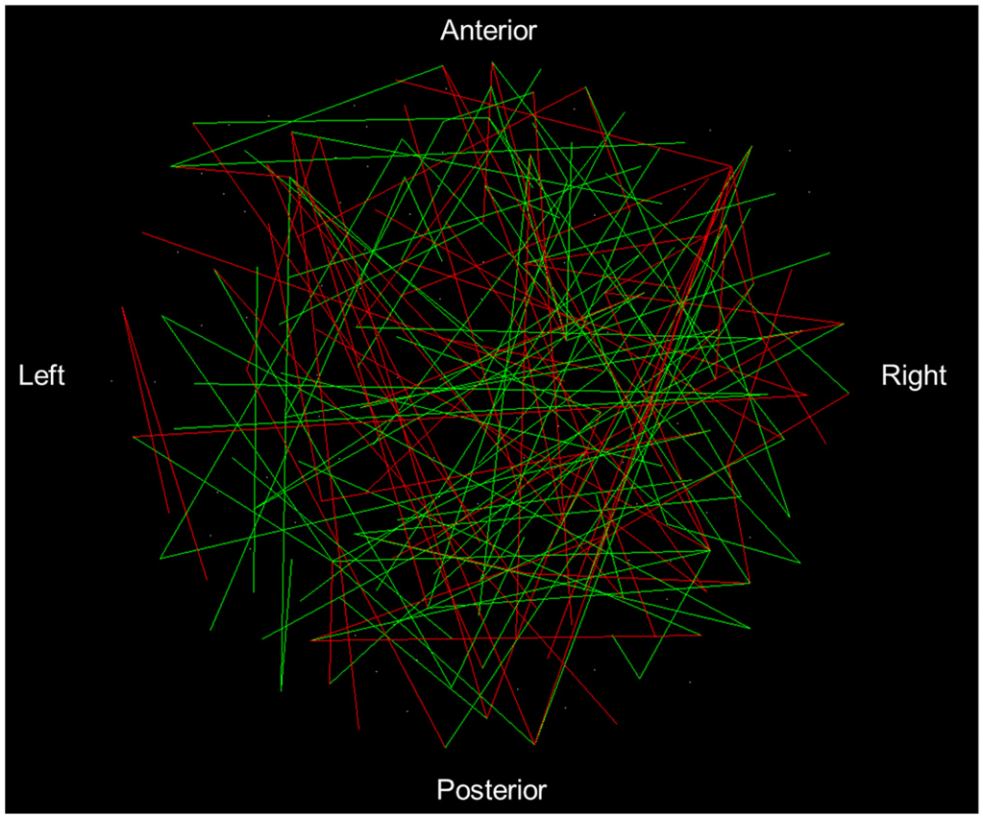
CCA revealed other interesting aspects of the SNI and their relation to cognitive domains. A defining characteristic of the CCA is that the relationship between the two sets of variables was evaluated as a whole and not on an individual variable basis. This allowed accounting for within-set and between-set relationships simultaneously, leading to an optimal correlation between sets of interrelated variables. Also, even though we dimensionally reduced our original variable space into factors to address the statistical requirements of CCA, we compared a high proportion of the original variance for both sets. Even more, through FA, NP were combined into factors which now represented specific cognitive domains more completely than individual scores. When looking at the relationship of the SNI set to the NP set through CCA, the most prominent relation of the SNI network was to memory and language functions. This was consistent also with the results obtained from individual variable correlations, where memory was the domain most prominently represented. The difference interpreting results between individual variable correlations and CCA though lies in that the network of SNI in the CCA relates to a cognitive domain and not a specific cognitive test. Thus, the combined SNI signal of the first CC mostly reflects memory and language cognitive domains, but also relates to executive, visuospatial and other domains to a much lesser extent as indicated by the loadings of each NP-factor to the first CC. Conversely, the second CC incorporated mostly aspects of executive function and visuospatial abilities. As such, there are two SNI patterns, each one reflecting different cognitive domains; executive and visuospatial domains on one hand, and memory and language on the other (figure 4).

Furthermore, cognitive domains whose functions are subserved by nearby brain areas, such as the temporal lobe for memory and language and the frontoparietal area for executive function and visuospatial ability, factored together. This is possibly related to the patient population of AD, where cognitive deficits reflecting temporal lobe pathology will have a similar progression compared to deficits reflected in frontal and parietal lobes. On the other hand, the distributed pattern observed in the SNI that contributed most to each CC indicates that the MEG signal, as represented by z_{ij}^0, does not fall tightly under area constraints but rather represents a functional marker above all.

Finally, the results and their interpretation are limited to male individuals with possible or probable AD, a constraint imposed by the fact our volunteer subjects were recruited through the Veterans Affairs Health System. At the same time, great care was taken to avoid overfitting of results in order to identify factor structures that represent the broader male AD population, by including significantly more subjects in the CCA than the number of variables; a low ratio of number of subjects to number of variables being a common reason for overfitting otherwise (see 2.5 and [18]). The gold standard for verification of results for the general population, however, would require an independent follow-up study on a larger population of AD subjects, ideally including females and patients with prodromal disease, and for which different statistical approaches (e.g. classification analysis) would be



(a)



(b)

Figure 4. SNI relating most to (a) the first and (b) the second canonical correlations.

required. Although the aims of this study did not involve the identification of SNI networks for AD diagnosis, additional work on the specific variables might allow such a potential application.

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