



Brain connectivity correlates of cognitive dispersion in a healthy middle-aged population: influence of subjective cognitive complaints.

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Brain connectivity correlates of cognitive dispersion in a healthy middle-aged population: influence of subjective cognitive complaints.

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Abstract

Objectives

Cognitive dispersion, representing intraindividual fluctuations in cognitive performance, is associated with cognitive decline in advanced age. We sought to elucidate sociodemographic, neuropsychological, and brain connectivity correlates of cognitive dispersion in middle age, and further consider potential influences of the severity of subjective cognitive complaints (SCC).

Method

Five hundred and twenty healthy volunteers from the Barcelona Brain Health Initiative (BBHI) (aged 40-66 years; 49.6% females, 453 with magnetic resonance imaging acquisitions), were included and stratified into high and low SCC groups. Two analyses steps were undertaken, (i) for the whole sample and (ii) by groups. Generalized linear models and analysis of covariance were implemented to study associations between cognitive dispersion and performance (episodic memory, speed of processing, and executive function), white matter integrity, and resting-state functional connectivity (rs-FC) of the default mode network (DMN) and dorsal attentional networks (DAN).

Results

Across-domain dispersion was negatively related to cognitive performance, rs-FC within the DMN, and between the DMN and the DAN, but not to white matter integrity. The rs-FC values were not explained by cognitive performance. When considering groups, the above findings were significant only for those with high SCC.

Discussion

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In healthy middle-aged individuals, high cognitive dispersion was related to poorer cognition and DMN dysregulation, being these associations stronger amongst subjects with high SCC. Present results reinforce the interest in considering dispersion measures within neuropsychological evaluations, as they may be more sensitive to incipient age-related cognitive and functional brain changes than traditional measures of performance.

For Peer Review

Introduction

Cognitive intraindividual variability refers to fluctuations in cognitive behavior, more commonly found with aging (de Felice & Holland, 2018; Webber et al., 2022), and which can be measured in a neuropsychological assessment through dispersion and inconsistency. While dispersion refers to a lack of stability across tests, inconsistency is detected across trials or time in a single task (i.e., reaction time paradigms). Traditionally, cognitive status has been assessed by means of either the scores obtained in cognitive tests or composites of these. Moreover, cognitive interindividual variability has received more extensive research attention compared to intraindividual variability, particularly regarding its association with neurodegenerative brain markers, even in healthy middle-aged individuals (Ferreira et al. 2017). However, cognitive intraindividual variability has gradually acquired importance as a measure of cognitive integrity in healthy older adults (Macdonald et al., 2006).

In addition, cognitive dispersion based on instabilities within or between cognitive domains has been negatively related to education (Thaler et al., 2015; Manning et al., 2021; Yoneda et al., 2022). Likewise, higher levels of dispersion have been associated with poor quality of life and vitality amongst older adults (Watermeyer et al., 2021), and with cognitive impairment (Koscik et al., 2016) in distinct psychiatric (Manning et al., 2021) and neurologic disorders, such as Parkinson's disease (Jones et al., 2022). Furthermore, larger cognitive variability has been associated with dementia diagnoses, such as Alzheimer's Disease (AD; Halliday et al., 2018; Webber et al., 2022) and even with higher odds of mortality (Thaler et al., 2015). Recent longitudinal studies concluded that cognitive dispersion may be an independent risk factor for cognitive decline and brain atrophy in aging (Bangen et al., 2019; Scott et al., 2022), as well as a complementary marker - along with cerebrospinal fluid Tau and amyloid- β biomarkers – for mild cognitive impairment and AD (Gleason et al., 2018). Likewise, cognitive dispersion

predicted post-mortem neurofibrillary tangles in non-demented and demented individuals (Malek-Ahmadi et al., 2017).

Magnetic resonance imaging (MRI) has allowed the investigation of the neural correlates of cognitive intraindividual variability, as well as their changes across time in different populations. First, diffusion tensor imaging (DTI)-based studies found a negative association between global white matter integrity and reaction time inconsistencies (Fjell et al., 2011; Lövdén et al., 2013; Mella et al., 2013). A more recent investigation concluded that the associations between dispersion within executive function and white matter integrity were restricted to long-range tracts connecting anterior and posterior areas in young adults, whereas these structural connections were not related to cognitive performance (Sorg et al., 2021). Moreover, Halliday et al., (2019) demonstrated a link between across-domain dispersion and integrity within the corpus callosum, anterior corona radiata, and superior longitudinal fasciculus in healthy older adults. Analyses employing functional MRI (fMRI) have revealed that increasing inconsistencies associated with attentional lapses during a cognitive task were explained by default mode network (DMN) dysfunction (Kucyi et al., 2016), and a lower anti-correlation shift between task-positive and task-negative networks (Kelly et al., 2008). Using resting-state fMRI (rs-fMRI), Meeker et al., (2021) proved that higher levels of across-domain dispersion were related to functional connectivity between the DMN and the dorsal attentional network (DAN) amongst healthy middle-aged and older participants (age range: 46 to 91 years). However, the neuropsychological and neural correlates of cognitive dispersion considering several cognitive domains amongst healthy middle-aged individuals remain to be elucidated.

Subjective cognitive decline (SCD) in older adults refers to the experience of subjective cognitive complaints (SCC) without objective cognitive impairment, and it is regarded as a potential precursor to cognitive decline and dementia (Jessen et al., 2020). Notably, even in

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3 middle age, SCD has been related to a poorer quality of life and health state (Königsberg et al.,
4 2022), lower neurocognitive status, and psychoaffective symptoms (Cedres et al., 2019).
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6 Despite individuals with SCC manifested signs of cognitive internal inconsistency (Ball et al.,
7 2020), and a positive relationship between complaints and dispersion was reported in previous
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9 studies (e.g. Thaler et al., 2015), the study of cognitive inconsistency remains poorly
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11 characterized within this population. Altogether, the putative moderating role of SCD in the
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13 association between dispersion and brain measures should be further explored, with a particular
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15 focus on cognitive dispersion as a marker of brain structure and function in middle age.
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22 Based on the above, we sought to (i) investigate the associations between dispersion and
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24 sociodemographic variables (i.e., age, sex, and years of education) in a sample of healthy
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26 middle-aged individuals, as well as their relationship with cognitive composite scores; (ii) to
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28 test whether dispersion scores are related to white matter integrity and to resting state functional
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30 connectivity (rs-FC) within and between the DMN and the DAN. Finally (iii) we aimed to
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32 study whether the severity of subjective cognitive complaints (SCC) could predict putative
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34 associations between dispersion, cognition, and brain integrity. We hypothesized that (i) higher
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36 dispersion would be related to older age, lower years of education, and lower cognitive
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38 composites; (ii) increasing dispersion rates would be negatively associated with white matter
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40 integrity and dysfunctional coupling between the DMN and the DAN. Finally, (iii) we expected
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42 that if previously predicted associations were found, they would be stronger amongst those
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44 individuals presenting higher rates of SCC, as this condition has been related to low
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46 neuropsychological status in middle age.
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52 **Methods**

53 **Participants**

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Volunteers from the community-based Barcelona Brain Health Initiative (BBHI; Cattaneo et al., 2018) cohort were selected for this study. BBHI recruitment started in 2017, and it is an ongoing longitudinal study investigating the determinants of brain and mental health in healthy middle to older ages (age range 40 to 66 years), combining online and in-person data acquisition. The present work was focused on a subsample of individuals who underwent in-person medical, cognitive, and MRI assessments (Cattaneo et al., 2018, 2020). Inclusion criteria were an absence of neurological or psychiatric medical diagnoses, Mini-Mental State Examination (MMSE) equal or above 27, given the age and the educational status of our participants as recommended elsewhere (Blesa et al. 2001), and performances on neuropsychological tests no more than 1.5 SD below normative scores adjusted by age and years of education (Peña-Casanova et al., 2009). 520 participants fulfilled the criteria above, of whom 453 had MRI acquisitions that met the study requirements (rs-fMRI acquisitions for 67 volunteers had a different acquisition protocol and were not included for neuroimaging analyses), including normative neuroradiological reports (e.g., no brain tumor suspicions, stroke, or moderate to severe white matter damage). All study procedures were approved by the Institutional Review Board (IRB 00003099 - at the University of Barcelona) and *Comité d'Ètica i Investigació Clínica de la Unió Catalana d'Hospitals* in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from each participant before study enrollment.

Neuropsychological data

Neuropsychological assessment

Each participant underwent a wide neuropsychological battery assessing the main cognitive domains, as previously described (Cattaneo et al., 2018). To compute cognitive dispersion and cognitive composites, we focused on tests of episodic memory, speed of processing, and

executive function. Regarding episodic memory, we included associative memory (Face Name Associative Memory Exam, S-FNAME; Alviarez-Schulze et al., 2021) and verbal memory tasks (Spanish version of the Rey Auditory Verbal Learning Test, RAVLT). Speed of processing was obtained from the Symbol Digit Modalities Test (SDMT) and the Cancellation subtest, (WAIS-IV; Weschler, 2008) and . Finally, for executive functions, we included a phonemic verbal fluency task (letters F-A-S), two working memory tests (backward Digits and Letter-Number sequencing subtests from WAIS-IV), as well as a measure of executive control using the Trail Making Test B minus Trail Making Test A. We inverted this latter outcome to obtain better function with higher scores. Normalized scalar scores from NEURONORMA Project for the Spanish population were used for the tests included in the assessment (Peña-Casanova et al., 2009).

Cognitive dispersion indexes and cognitive composites

Both cognitive dispersion and composite measures were calculated within and across the cognitive domains of interest described above (see Supplementary Table 1). First, the dispersion index was computed using the intraindividual standard deviation (ISD) method applied in a wide range of experimental studies about cognitive dispersion (e.g., Jones et al., 2022; Meeker et al., 2021). The total direct scores of the neuropsychological tests were converted to z-scores (with the sample's mean and standard deviation [SD]) and then adjusted to T-scores (mean = 50, SD = 10). Finally, ISD of T-values were obtained for each of the three cognitive domains (i.e., episodic memory, speed of processing, executive function) and also across-domain. ISD formula has been defined as the standard deviation of the T-scores with higher values reflecting higher cognitive intraindividual variability (reviewed by Costa et al., 2019).

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$$ISD = \sqrt{\frac{\sum_{i=1}^N (T_i - \overline{T_i})^2}{N - 1}}$$

Were T_i is the cognitive T-score for each subject, and $\overline{T_i}$ is the mean of T-scores of all tests within a particular domain or across domains.

In addition, cognitive composite measures were computed through principal component analysis (PCA) in a factorial analysis using Promax rotation for each of the three cognitive domains as well as across-domain.

Sample stratification based on SCC

Subjective cognitive complaints were measured through a subscale of the Quality of Life in Neurologic Disorders Measures (Neuro-QoL; Fieo et al., 2016) including 12 items with a Likert scale from 0 (lower severity) to 5 (higher severity) and a maximum value of 60. This questionnaire assesses self-reported difficulties perceived in the last 7 days in reasoning, memory, executive functions, concentration, and sustained attention in daily-life tasks. To the best of our knowledge, there is currently no standardized method to measure SCC and therefore no cut-off point to determine a threshold of normative complaints in healthy middle-aged individuals. Consequently, we stratified our sample into two subgroups based on the 50th percentile of the distribution (Median = 6.5), resulting in low (low-SCC; N = 260) and high SCC (high-SCC N = 260) groups. Both groups were compared in terms of global quality of life, cognitive composites, and years of education, finding significant differences in line with previous works on SCD (Cedres et al., 2019; Königsberg et al., 2022). See Table 2 of the supplementary material for further details.

MRI data

MRI acquisition parameters

MRI data were acquired in a 3T Siemens scanner (MAGNETOM Prisma) with a 32-channel head coil at the Unitat d'Imatge per Resonància Magnètica IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer) at Hospital Clínic de Barcelona, Barcelona. For all participants, high-resolution T1- and T2-weighted structural images were acquired (both with a 0.8 mm isotropic voxel), as well as a multiband diffusion-weighted image (1.5 mm × 1.5 mm × 1.5 mm, 100 directions). Finally, a multiband rs-fMRI (2 mm × 2 mm × 2 mm and TR = 0.8 s, 750 volumes) sequence was also acquired. See the supplementary material for further details regarding acquisition parameters. MRI images were examined by a senior neuroradiologist to discard any clinically significant pathology. Additionally, all acquisitions were visually inspected before analysis by two co-authors to ensure that they did not contain MRI artifacts or excessive motion.

Structural MRI preprocessing and derived measures

DTI acquisitions were preprocessed by FMRIB's Diffusion Toolbox (FDT) software from FMRIB Software Library (FSL; version 5.0.11; <http://www.fmrib.ox.ac.uk/fsl>; Jbabdi et al., 2012) and individual fractional anisotropy (FA) and mean diffusivity (MD) maps were obtained using a Diffusion Tensor Model fit (DTIFIT). The Tract-Based Spatial Statistics (TBSS) protocol was used to obtain a 4D sample skeleton to be further analyzed with the *randomise* tool from FSL. See the supplementary material for further details about diffusion preprocessing and TBSS.

Functional MRI preprocessing and derived measures

The rs-fMRI preprocessing pipeline comprised spatial standardization and nuisance correction by making use of functions from FSL, FreeSurfer (version 6.0; <https://surfer.nmr.mgh.harvard.edu>) and Statistical Parametric Mapping (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/>). As head movement may affect rs-fMRI results, frame-

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wise displacement (FWD) was computed using the vectors of rotation and translation estimated during realignment (Power et al., 2012). The FWD mean was calculated for every subject (mean = 0.165, SD = 0.086) and used as a control variable in the rs-FC analysis. After preprocessing of rs-fMRI, we computed within and between rs-FC individual values for the DMN and the DAN networks based on a mask from the Schaefer-Yeo cortical atlas with 100 nodes forming seven RSN (Schaefer et al., 2018). As a result, we obtained average values of positive rs-FC between the nodes forming each network (i.e., rs-FC within the DMN and within the DAN), and also between nodes from both networks (i.e., rs-FC between the DMN and the DAN) or each subject. See the supplementary material for further details.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics (Statistical Package for Social Sciences, version 27.0. Armonk, NY: IBM Corporation) and the *randomise* tool from FSL. Graphical representations were performed with the 3.3.6 version of the *ggplot2* package from RStudio (<https://ggplot2.tidyverse.org>). We assessed the normality of our variables of interest using the Shapiro-Wilk test. Given the non-normal distribution observed for dispersion measures and the DMN rs-FC values, we performed Generalized Linear Models (GLMs) and verified that all the derived residuals were normally distributed. To address our three goals, we performed the following analyses: (i) First, to explore the associations between dispersion and demographic data and cognitive composites in the whole sample, we first designed four univariate GLMs to implement analyses of covariance (ANCOVA), where the dependent variable was each dispersion measure, and the covariates were age, sex and years of education introduced as main effects in the model. Second, we implemented other four GLMs where the dependent variable was each of the four cognitive composites and the covariates were age, sex, years of education, and all dispersion measures introduced as main effects in the model; (ii) secondly, to study the neural correlates of dispersion in the whole sample, we obtained

structural connectivity metrics through voxel-wise statistical analyses in the whole brain using the *randomise* tool of FSL for non-parametric permutation inference in FA and MD maps. We conducted a GLM for each dispersion metric to examine associations with FA and MD (adjusting by age, sex, and years of education). A total of 5000 permutations were used, and all results were corrected by family-wise error (FWE) using the threshold-free cluster enhancement (TFCE) method. Next, for rs-FC correlates of dispersion, we designed equivalent and independent GLMs, with the four dispersion measures as dependent variables, and rs-FC values, age, sex, years of education and FWD as covariates entered as main effects in the model. We further implemented an additional analysis to examine whether rs-FC, global FA and MD values were related to cognitive composites (see Supplementary Material). (iii) Finally, third aim was based on the sample stratification to further analyze the effect of SCC on the putative associations tested. We implemented GLMs interaction models to test group interactions on the associations between dispersion, cognitive composites, and rs-FC values, controlled by age, sex, years of education, and FWD. Then, we explored dispersion-related associations for each group of SCCs (low-SCC and high-SCC) by also applying independent GLMs. All results were considered significant with a level of confidence of 95 percent, resulting in an alpha (one-tailed p-value) of 0.05.

Results

Associations between cognitive dispersion, demographics, and cognitive composites in the whole sample

The main demographics and cognitive outcomes for the whole sample (N=520, 49.6% females) are described in Table 1.

Regarding our first aim, none of our dispersion measures (i.e., episodic memory, speed of processing, executive function, across-domain) were predicted by age or years of education.

However, there were marginally significant sex differences only for the across-domain dispersion with a small effect ($F_{(1, 519)} = 3.887, p = 0.049, \eta_p^2 = 0.007$), indicating that males (mean = 8.17, SD = 2.02) exhibited greater dispersion than females (mean = 7.82, SD = 1.86). The across-domain dispersion was negatively associated with the across-domain composite ($F_{(1, 519)} = 8.837, p = 0.003$; see Fig. 1A), while episodic memory dispersion was negatively related to the speed of processing ($F_{(1, 519)} = 8.529, p = 0.004$; see Fig. 1B) and the executive functions composites ($F_{(1, 519)} = 7.518, p = 0.006$; see Fig. 1C). However, for the three cognitive domains of interest, we did not detect significant associations with any of the dispersion metrics and their corresponding composite scores.

Associations between cognitive dispersion and structural and functional brain connectivity

Voxel-wise analysis of white matter tracts did not yield any significant correlations between any dispersion measures and FA or MD values. Regarding functional connectivity analyses, negative associations were found between the across-domain dispersion and the rs-FC within the DMN ($F_{(1, 452)} = 4.283, p = 0.039$; see Fig. 2B), and between DMN and the DAN networks ($F_{(1, 452)} = 4.693, p = 0.031$; see Fig. 2A). Therefore, the higher the across-domain dispersion, the less the connectivity within the DMN as well as between the DMN and the DAN. Moreover, when we analyzed the dispersion measures for the three cognitive domains separately, a negative association between dispersion in the speed of processing and the rs-FC within DMN emerged ($F_{(1, 452)} = 4.986, p = 0.026$; see Fig. 2C).

At this point, we carried out some additional analyses to test associations between the MRI-derived measures and cognitive composites. Positive correlations emerged between global FA and the composites of the speed of processing, executive function, and across-domain. In addition, we identified a positive correlation between global MD and episodic memory

composite. However, we could not find any correlation between rs-FC values in our targeted RSNs and any of the cognitive composites (see supplementary Table 2).

Role of Subjective Cognitive Complaints in the associations between dispersion and brain measures

Finally, we tested whether observed significant associations in previous sections between dispersion, cognitive composites and MRI-derived measures could be different according to the severity of SCC (mean = 7.94, SD = 6.65). We first explored the demographical and neuropsychological data in each group (see supplementary Table 3), evidencing no significant differences between low-SCC versus high-SCC in age, sex, and dispersion indices. However, the high-SCC group had fewer years of education ($t = 2.311$, $p = 0.021$). In addition, this group showed lower across-domain performance ($F_{(1,519)} = 4.717$, $p = 0.030$) and speed of processing composite ($F_{(1,519)} = 6.121$, $p = 0.014$) than the low-SCC group, adjusted by years of education. Groups did not differ in structural (i.e., FA and MD) or functional connectivity (i.e., within and between DMN and DAN rs-FC).

We employed interaction models to analyze whether the severity of SCC moderated the previously reported associations between dispersion, cognitive composites and rs-FC values. The interaction terms were not significant when they were included in the model. To delve further into the targeted associations, we conducted the same GLMs previously described for the whole sample, but this time implemented separately for each group. The results evidenced that previous findings were driven by participants with higher subjective complaints. Specifically, only the high-SCC group showed a negative association between across-domain dispersion and across-domain composite ($F_{(1,259)} = 10.340$, $p = 0.001$; see Fig. 3A). The same was identified for the negative associations between episodic memory dispersion and speed of processing ($F_{(1,259)} = 9.344$, $p = 0.002$; see Fig. 3B) and executive functions composites ($F_{(1,$

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$_{259}) = 4.496, p = 0.035$; see Fig. 3C). Moreover, as regards functional brain correlates, negative associations between across-domain dispersion and rs-FC between the DMN-DAN ($F_{(1, 222)} = 4.521, p = 0.035$; see Fig. 4A) and within the DMN ($F_{(1, 222)} = 7.432, p = 0.007$; see Fig. 4B) were restricted to the high-SCC group. Speed of processing dispersion remained negatively associated with the rs-FC within the DMN ($F_{(1, 222)} = 7.842, p = 0.006$; see Fig. 4C) in the high-SCC group.

Discussion

The present work is, to our knowledge, the first study characterizing cognitive intraindividual variability, i.e. cognitive dispersion, by exploring its associations with neural substrates in healthy adults, and further considering the influence of SCD. Our main results showed that cognitive dispersion was negatively related to cognitive composites in an across-domain manner. This across-domain dispersion was also negatively associated with rs-FC within the DMN and between the DMN and the DAN. No associations were found between cognitive dispersion measures and structural connectivity. When considering the severity of SCC (low-SCC versus high-SCC), we observed that previous associations were only present in the high-SCC group.

Cognitive dispersion associations with demographic data and cognitive composites

Dispersion measures were not related to age and years of education in our sample. We expected to find a positive association with age because previous studies reported that older adults presented significantly more dispersion than their younger counterparts (Hultsch et al., 2002; Hilborn et al., 2009; de Felice & Holland, 2018; Sorg et al., 2021; Webber et al., 2022). The lack of age-dispersion associations could be due to the narrow distribution of age in our middle-aged sample in comparison to other studies including subjects at older ages, where the increase of cognitive dispersion may be more noticeable. Also, we expected to see a negative association

with years of education, a finding observed in some studies (Thaler et al., 2015; Manning et al., 2021). Nevertheless, associations between dispersion and demographic variables, i.e., age, sex, and years of education, are not consistent, as reported recently (Yoneda et al., 2022). Finally, our results revealed a significant association between across-domain dispersion and sex, with males showing greater dispersion scores than females, which should be cautiously interpreted due to the small effect size. This however aligns with previous evidence based on samples of middle-aged (Lin & McDonough, 2022) and older adults (Webber et al., 2022).

Regarding neuropsychological correlates of dispersion, we identified a clear association between dispersion and composite scores as an across-domain measure, as described previously in aging populations (de Felice & Holland, 2018; Yoneda et al., 2022). Yet, we did not find the same association between dispersion and composite within each cognitive domain, which is in fact in accordance with previous investigations (Hilborn et al., 2009; Halliday et al., 2019). Additionally, we found negative associations between the speed of processing and executive function composites and episodic memory dispersion, which aligns with prevalent neuropsychological models (Baudouin et al., 2009; Albinet et al., 2012). Notably, since speed of processing and executive functions start to decline early in adulthood (Salthouse, 2020), they may represent early markers of initial instability in episodic memory resources (interpreted by an increasing dispersion), even though decline in episodic memory performance tends to occur at later stages (i.e., typically from 60 onwards, reviewed in Nyberg, 2017).

Neural correlates of dispersion: functional but not structural connectivity

Structural connectivity analyses showed that white matter integrity (assessed by FA and MD) was not related to dispersion measures. To the best of our knowledge, only Halliday et al., (2019) and Sorg et al., (2021) evidenced a negative association between cognitive dispersion and long-range fasciculus proprieties in older and young adults, respectively. Furthermore, in

previous studies with different ages and collectives, tract integrity was correlated with cognitive intraindividual variability measured as inconsistency in reaction time paradigms (Fjell et al., 2011; Moy et al., 2011; Lövdén et al., 2013; Mella et al., 2013). Despite both measures of cognitive intraindividual variability (i.e., dispersion and inconsistencies) have been studied together and correlated between them (Hultsch et al., 2002; Hilborn et al., 2009), our findings suggest that cognitive dispersion might not be as sensitive as reaction time paradigms in predicting white matter status amongst middle-aged individuals.

Regarding rs-FC, our results showed that higher across-domain dispersion was related to a weaker rs-FC within the DMN and between the DMN and the DAN. These findings are consistent with previous studies where cognitive intraindividual variability showed similar associations with the DMN (Kelly et al., 2008; Kucyi et al., 2016), particularly with the work of Meeker et al. (2022), which focused on cognitive dispersion. Previous literature in the field has highlighted that both segregation and integration balance in RSN contribute to successful cognitive performance (Fukushima et al., 2018). A weaker anti-correlation between the DMN-DAN coupling has been identified with increasing age, proved in both task-based and rs-fMRI studies (Spreng et al., 2016). Furthermore, reduced rs-FC within the DMN has been found in early aging stages (reviewed in Jockwitz & Caspers, 2021) implying cognitive deficits (Farras-Permanyer et al., 2019). In addition, our analyses on each cognitive domain revealed that only dispersion in speed of processing was negatively related to the rs-FC within the DMN. This is also consistent with other reports linking speed of processing with large-scale RSNs, such as the DMN (Ng et al., 2016). In our additional analyses aiming to test whether rs-FC values were also associated with cognitive composites, no significant correlations emerged. Thus, we can conclude that compared to traditional correlates of performance, dispersion was a more sensitive marker of incipient DMN dysregulation in middle age.

Dispersion correlates were driven by high-SCC

While no differences in dispersion scores were observed between high and low SCC groups, associations with rs-FC regarding the DMN and the DAN, as well as with cognitive performance were only observed in the former. It should be noted that such associations have been previously reported amongst older adult populations (De Felice & Holland 2018; Yoenda et al., 2022; Meeker et al. 2021). Particularly, a recent neuroimaging study evidenced disrupted rs-FC among the main regions of the DMN and the DAN in older adults with SCD, suggesting an early cognitive decline (Lee et al., 2023). Therefore, our findings suggest that even in middle age, high rates of dispersion amongst high SCC may represent early indicators of incipient brain and cognitive deleterious changes. However, whether this relates to a future risk of cognitive impairment or dementia (Cedres et al., 2019; Jessen et al., 2020) cannot be ascertained through the present investigation and will require further longitudinal study designs.

Limitations

First, our cognitive domains included a limited variability of tests, with the executive functions being the most represented domain. Second, our group formation into two subgroups based on the median may not be representative of low-SCC and high-SCC in the general population. Finally, we evidenced the relevance of cognitive dispersion in high-SCC through a cross-sectional study, but longitudinal investigations are necessary to determine how the present findings may link to age-related cognitive and brain changes.

Conclusion

Among middle-aged individuals, higher cognitive dispersion was associated with intraindividual differences in cognitive performance related to DMN connectivity, but not with white matter integrity. Cognitive dispersion may be an early indicator of subtle brain functional changes over traditional performance measures. Moreover, our work highlighted that previous

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associations were particularly relevant amongst subjects with high SCC, which may reflect incipient brain changes potentially conferring increased risk for cognitive decline.

Conflict of Interest

Dr. A. P.-L. is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. He is a co-founder of Linus Health and TI Solutions AG; and serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Nexstim, and MedRhythms. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Sample description and cognitive outcomes.

	Mean	SD	Range (min-max)
Age	53.08	7.09	42 - 66
Years of education	17	3.60	8 - 28
Subjective cognitive complaints	7.94	6.65	0 - 28
<i>Cognitive dispersion</i>			
Episodic memory	6.64	2.46	1.46 – 15.67
Executive functions dispersion	7.67	3.10	0.42 – 18.03
Speed of processing dispersion	6.11	4.75	0.01 – 24.96
Across-domain dispersion	8.00	1.95	3.18 – 13.13
<i>Cognitive composite</i>			
Episodic memory	-0.006	0.723	-1.787 – 1.716
Executive functions	0.014	0.659	-2.189 – 1.815
Speed of processing	0.016	0.841	-2.446 – 2.309
Across-domain	-0.002	0.579	-1.959 – 1.541

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Figure 1. Scatter plots showing the negative relationship for the whole sample between **A)** across-domain dispersion and its composite, and **B)** episodic memory dispersion and speed of processing, also with **C)** executive functions composite. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to graphically represent our results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval.

Figure 2. Scatter plots showing the negative relationship for the whole sample between **A)** across-domain dispersion and rs-FC between the DMN and the DAN and **B)** within the DMN. As well as the negative relationship between **C)** the speed of processing dispersion and rs-FC within the DMN. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to show the results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval. **D)** Brain graphs represent the topography of the networks defined to measure rs-FC within DMN and between the DMN and the DAN (as in A). See further detail in supplementary figure 1. Abbreviations: rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network; ROI: region of interest.

Figure 3. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and cognitive composites in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced the previously reported negative correlations between **A)** across-domain dispersion and its composite, also between episodic memory dispersion and **B)** speed of processing and **C)** executive functions composites. The lines show linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints.

Figure 4. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and rs-FC values in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced a negative correlation between **A)** across-domain dispersion and rs-FC between the DMN and the DAN and **B)** within the DMN. In addition, a negative correlation between **C)** the speed of processing dispersion and rs-FC within the DMN. The lines show a linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints; rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network.

Title

Brain connectivity correlates of cognitive dispersion in a healthy middle-aged population: influence of subjective cognitive complaints.

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Abstract

Objectives

Cognitive dispersion, **representing intraindividual fluctuations in cognitive performance**, is associated with cognitive decline in advanced age. We sought to elucidate sociodemographic, neuropsychological, and brain connectivity correlates of cognitive dispersion in **middle age**, **and further consider potential influences of the severity of subjective cognitive complaints (SCC)**.

Method

Five hundred and twenty healthy volunteers from the Barcelona Brain Health Initiative (BBHI) (aged 40-66 years; 49.6% females, 453 with magnetic resonance imaging acquisitions), were included and stratified into high and low SCC groups. **Two analyses steps were undertaken, (i) for the whole sample and (ii) by groups. Generalized linear models** and analysis of covariance were implemented to study associations between cognitive dispersion and performance **(episodic memory, speed of processing, and executive function)**, white matter integrity, and **resting-state** functional connectivity **(rs-FC)** of the default mode network (DMN) and dorsal attentional networks (DAN).

Results

Across-domain dispersion was negatively related to cognitive performance, rs-FC within the DMN, and between the DMN and the DAN, but not to white matter integrity. **The** rs-FC values were not explained by cognitive performance. When considering groups, the above findings were significant only for those with high **SCC**.

Discussion

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3 In healthy middle-aged individuals, high cognitive dispersion was related to poorer cognition
4 and DMN dysregulation, being these associations stronger amongst subjects with high SCC.
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6 Present results reinforce the interest in considering dispersion measures within
7 neuropsychological evaluations, as they may be more sensitive to incipient age-related
8 cognitive and functional brain changes than traditional measures of performance.
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Introduction

Cognitive intraindividual variability refers to fluctuations in cognitive behavior, more commonly found with aging (de Felice & Holland, 2018; Webber et al., 2022), and which can be measured in a neuropsychological assessment through dispersion and inconsistency. While dispersion refers to a lack of stability across tests, inconsistency is detected across trials or time in a single task (i.e., reaction time paradigms). Traditionally, cognitive status has been assessed by means of either the scores obtained in cognitive tests or composites of these. Moreover, cognitive interindividual variability has received more extensive research attention compared to intraindividual variability, particularly regarding its association with neurodegenerative brain markers, even in healthy middle-aged individuals (Ferreira et al. 2017). However, cognitive intraindividual variability has gradually acquired importance as a measure of cognitive integrity in healthy older adults (Macdonald et al., 2006).

In addition, cognitive dispersion based on instabilities within or between cognitive domains has been negatively related to education (Thaler et al., 2015; Manning et al., 2021; Yoneda et al., 2022). Likewise, higher levels of dispersion have been associated with poor quality of life and vitality amongst older adults (Watermeyer et al., 2021), and with cognitive impairment (Koscik et al., 2016) in distinct psychiatric (Manning et al., 2021) and neurologic disorders, such as Parkinson’s disease (Jones et al., 2022). Furthermore, larger cognitive variability has been associated with dementia diagnoses, such as Alzheimer’s Disease (AD; Halliday et al., 2018; Webber et al., 2022) and even with higher odds of mortality (Thaler et al., 2015). Recent longitudinal studies concluded that cognitive dispersion may be an independent risk factor for cognitive decline and brain atrophy in aging (Bangen et al., 2019; Scott et al., 2022), as well as a complementary marker - along with cerebrospinal fluid Tau and amyloid-β biomarkers – for mild cognitive impairment and AD (Gleason et al., 2018). Likewise, cognitive dispersion

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3 predicted post-mortem neurofibrillary tangles in non-demented and demented individuals
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5 (Malek-Ahmadi et al., 2017).
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9 Magnetic resonance imaging (MRI) has allowed the investigation of the neural correlates of
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11 cognitive intraindividual variability, as well as their changes across time in different
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13 populations. First, diffusion tensor imaging (DTI)-based studies found a negative association
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15 between global white matter integrity and reaction time inconsistencies (Fjell et al., 2011;
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17 Lövdén et al., 2013; Mella et al., 2013). A more recent investigation **concluded** that the
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19 associations between **dispersion within** executive function and white matter integrity were
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21 restricted to long-range tracts connecting anterior and posterior areas in young adults, whereas
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23 these structural connections were not related to cognitive performance (Sorg et al., 2021).
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25 Moreover, Halliday et al., (2019) demonstrated a link between across-domain dispersion and
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27 integrity within the corpus callosum, anterior corona radiata, and superior longitudinal
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29 fasciculus in healthy older adults. Analyses employing functional MRI (fMRI) have revealed
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31 that increasing inconsistencies associated with attentional lapses during a cognitive task were
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33 explained by default mode network (DMN) dysfunction (Kucyi et al., 2016), and a lower anti-
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35 correlation shift between task-positive and task-negative networks (Kelly et al., 2008). Using
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37 resting-state fMRI (**rs-fMRI**), Meeker et al., (2021) proved that higher levels of across-domain
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39 dispersion were related to functional connectivity between the DMN and the dorsal attentional
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41 network (DAN) **amongst healthy middle-aged and older participants (age range: 46 to 91**
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43 **years)**. However, the neuropsychological and neural correlates of **cognitive** dispersion
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45 considering several cognitive domains amongst healthy middle-aged individuals remain to be
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47 elucidated.
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55 **Subjective cognitive decline (SCD) in older adults refers to the experience of subjective**
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57 **cognitive complaints (SCC) without objective cognitive impairment, and it is regarded as a**
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59 **potential precursor to cognitive decline and dementia (Jessen et al., 2020). Notably, even in**
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middle age, SCD has been related to a poorer quality of life and health state (Königsberg et al., 2022), lower neurocognitive status, and psychoaffective symptoms (Cedres et al., 2019). Despite individuals with SCC manifested signs of cognitive internal inconsistency (Ball et al., 2020), and a positive relationship between complaints and dispersion was reported in previous studies (e.g. Thaler et al., 2015), the study of cognitive inconsistency remains poorly characterized within this population. Altogether, the putative moderating role of SCD in the association between dispersion and brain measures should be further explored, with a particular focus on cognitive dispersion as a marker of brain structure and function in middle age.

Based on the above, we sought to (i) investigate the associations between dispersion and sociodemographic variables (i.e., age, sex, and years of education) in a sample of healthy middle-aged individuals, as well as their relationship with cognitive composite scores; (ii) to test whether dispersion scores are related to white matter integrity and to resting state functional connectivity (rs-FC) within and between the DMN and the DAN. Finally (iii) we aimed to study whether the severity of subjective cognitive complaints (SCC) could predict putative associations between dispersion, cognition, and brain integrity. We hypothesized that (i) higher dispersion would be related to older age, lower years of education, and lower cognitive composites; (ii) increasing dispersion rates would be negatively associated with white matter integrity and dysfunctional coupling between the DMN and the DAN. Finally, (iii) we expected that if previously predicted associations were found, they would be stronger amongst those individuals presenting higher rates of SCC, as this condition has been related to low neuropsychological status in middle age.

Methods

Participants

Volunteers from the community-based Barcelona Brain Health Initiative (BBHI; Cattaneo et al., 2018) cohort were selected for this study. BBHI recruitment started in 2017, and it is an ongoing longitudinal study investigating the determinants of brain and mental health in healthy middle to older ages (age range 40 to 66 years), combining online and in-person data acquisition. The present work was focused on a subsample of individuals who underwent in-person medical, cognitive, and MRI assessments (Cattaneo et al., 2018, 2020). Inclusion criteria were an absence of neurological or psychiatric medical diagnoses, Mini-Mental State Examination (MMSE) equal or above 27, given the age and the educational status of our participants as recommended elsewhere (Blesa et al. 2001), and performances on neuropsychological tests no more than 1.5 SD below normative scores adjusted by age and years of education (Peña-Casanova et al., 2009). 520 participants fulfilled the criteria above, of whom 453 had MRI acquisitions that met the study requirements (rs-fMRI acquisitions for 67 volunteers had a different acquisition protocol and were not included for neuroimaging analyses), including normative neuroradiological reports (e.g., no brain tumor suspicions, stroke, or moderate to severe white matter damage). All study procedures were approved by the Institutional Review Board (IRB 00003099 - at the University of Barcelona) and *Comité d'Ètica i Investigació Clínica de la Unió Catalana d'Hospitals* in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from each participant before study enrollment.

Neuropsychological data

Neuropsychological assessment

Each participant underwent a wide neuropsychological battery assessing the main cognitive domains, as previously described (Cattaneo et al., 2018). To compute cognitive dispersion and cognitive composites, we focused on tests of episodic memory, speed of processing, and

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executive function. Regarding episodic memory, we included associative memory (Face Name Associative Memory Exam, S-FNAME; Alviarez-Schulze et al., 2021) and verbal memory tasks (Spanish version of the Rey Auditory Verbal Learning Test, RAVLT). Speed of processing was obtained from the Symbol Digit Modalities Test (SDMT) and the Cancellation subtest, (WAIS-IV;Weschler, 2008) and . Finally, for executive functions, we included a phonemic verbal fluency task (letters F-A-S), two working memory tests (backward Digits and Letter-Number sequencing subtests from WAIS-IV), as well as a measure of executive control using the Trail Making Test B minus Trail Making Test A. We inverted this latter outcome to obtain better function with higher scores. Normalized scalar scores from NEURONORMA Project for the Spanish population were used for the tests included in the assessment (Peña-Casanova et al., 2009).

Cognitive dispersion indexes and cognitive composites

Both cognitive dispersion and composite measures were calculated within and across the cognitive domains of interest described above (see Supplementary Table 1). First, the dispersion index was computed using the intraindividual standard deviation (ISD) method applied in a wide range of experimental studies about cognitive dispersion (e.g., Jones et al., 2022; Meeker et al., 2021). The total direct scores of the neuropsychological tests were converted to-z-scores (with the sample’s mean and standard deviation [SD]) and then adjusted to T-scores (mean = 50, SD = 10). Finally, ISD of T-values were obtained for each of the three cognitive domains (i.e., episodic memory, speed of processing, executive function) and also across-domain. ISD formula has been defined as the standard deviation of the T-scores with higher values reflecting higher cognitive intraindividual variability (reviewed by Costa et al., 2019).

$$ISD = \sqrt{\frac{\sum_{i=1}^N (T_i - \bar{T}_i)^2}{N - 1}}$$

Were T_i is the cognitive T-score for each subject, and $\bar{T}_i$ is the mean of T-scores of all tests within a particular domain or across domains.

In addition, cognitive composite measures were computed through principal component analysis (PCA) in a factorial analysis using Promax rotation for each of the three cognitive domains as well as across-domain.

Sample stratification based on SCC

Subjective cognitive complaints were measured through a subscale of the Quality of Life in Neurologic Disorders Measures (Neuro-QoL; Fieo et al., 2016) including 12 items with a Likert scale from 0 (lower severity) to 5 (higher severity) and a maximum value of 60. This questionnaire assesses self-reported difficulties perceived in the last 7 days in reasoning, memory, executive functions, concentration, and sustained attention in daily-life tasks. To the best of our knowledge, there is currently no standardized method to measure SCC and therefore no cut-off point to determine a threshold of normative complaints in healthy middle-aged individuals. Consequently, we stratified our sample into two subgroups based on the 50th percentile of the distribution (Median = 6.5), resulting in low (low-SCC; N = 260) and high SCC (high-SCC N = 260) groups. Both groups were compared in terms of global quality of life, cognitive composites, and years of education, finding significant differences in line with previous works on SCD (Cedres et al., 2019; Königsberg et al., 2022). See Table 2 of the supplementary material for further details.

MRI data

MRI acquisition parameters

MRI data were acquired in a 3T Siemens scanner (MAGNETOM Prisma) with a 32-channel head coil at the Unitat d'Imatge per Resonància Magnètica IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer) at Hospital Clínic de Barcelona, Barcelona. For all participants, high-resolution T1- and T2-weighted structural images were acquired (both with a 0.8 mm isotropic voxel), as well as a multiband diffusion-weighted image (1.5 mm × 1.5 mm × 1.5 mm, 100 directions). Finally, a multiband rs-fMRI (2 mm × 2 mm × 2 mm and TR = 0.8 s, 750 volumes) sequence was also acquired. See the supplementary material for further details regarding acquisition parameters. MRI images were examined by a senior neuroradiologist to discard any clinically significant pathology. Additionally, all acquisitions were visually inspected before analysis by two co-authors to ensure that they did not contain MRI artifacts or excessive motion.

Structural MRI preprocessing and derived measures

DTI acquisitions were preprocessed by FMRIB's Diffusion Toolbox (FDT) software from FMRIB Software Library (FSL; version 5.0.11; <http://www.fmrib.ox.ac.uk/fsl>; Jbabdi et al., 2012) and individual fractional anisotropy (FA) and mean diffusivity (MD) maps were obtained using a Diffusion Tensor Model fit (DTIFIT). The Tract-Based Spatial Statistics (TBSS) protocol was used to obtain a 4D sample skeleton to be further analyzed with the *randomise* tool from FSL. See the supplementary material for further details about diffusion preprocessing and TBSS.

Functional MRI preprocessing and derived measures

The rs-fMRI preprocessing pipeline comprised spatial standardization and nuisance correction by making use of functions from FSL, FreeSurfer (version 6.0; <https://surfer.nmr.mgh.harvard.edu>) and Statistical Parametric Mapping (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/>). As head movement may affect rs-fMRI results, frame-

wise displacement (FWD) was computed using the vectors of rotation and translation estimated during realignment (Power et al., 2012). The FWD mean was calculated for every subject (mean = 0.165, SD = 0.086) and used as a control variable in the rs-FC analysis. After preprocessing of rs-fMRI, we computed within and between rs-FC individual values for the DMN and the DAN networks based on a mask from the Schaefer-Yeo cortical atlas with 100 nodes forming seven RSN (Schaefer et al., 2018). As a result, we obtained average values of positive rs-FC between the nodes forming each network (i.e., rs-FC within the DMN and within the DAN), and also between nodes from both networks (i.e., rs-FC between the DMN and the DAN) or each subject. See the supplementary material for further details.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics (Statistical Package for Social Sciences, version 27.0. Armonk, NY: IBM Corporation) and the *randomise* tool from FSL. Graphical representations were performed with the 3.3.6 version of the *ggplot2* package from RStudio (<https://ggplot2.tidyverse.org>). We assessed the normality of our variables of interest using the Shapiro-Wilk test. Given the non-normal distribution observed for dispersion measures and the DMN rs-FC values, we performed Generalized Linear Models (GLMs) and verified that all the derived residuals were normally distributed. To address our three goals, we performed the following analyses: (i) First, to explore the associations between dispersion and demographic data and cognitive composites in the whole sample, we first designed four univariate GLMs to implement analyses of covariance (ANCOVA), where the dependent variable was each dispersion measure, and the covariates were age, sex and years of education introduced as main effects in the model. Second, we implemented other four GLMs where the dependent variable was each of the four cognitive composites and the covariates were age, sex, years of education, and all dispersion measures introduced as main effects in the model; (ii) secondly, to study the neural correlates of dispersion in the whole sample, we obtained

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3 structural connectivity metrics through voxel-wise statistical analyses in the whole brain using
4 the *randomise* tool of FSL for non-parametric permutation inference in FA and MD maps. We
5 conducted a GLM for each dispersion metric to examine associations with FA and MD
6 (adjusting by age, sex, and years of education). A total of 5000 permutations were used, and
7 all results were corrected by family-wise error (FWE) using the threshold-free cluster
8 enhancement (TFCE) method. Next, for rs-FC correlates of dispersion, we designed equivalent
9 and independent GLMs, with the four dispersion measures as dependent variables, and rs-FC
10 values, age, sex, years of education and FWD as covariates entered as main effects in the model.
11 We further implemented an additional analysis to examine whether rs-FC, global FA and MD
12 values were related to cognitive composites (see Supplementary Material). (iii) Finally, third
13 aim was based on the sample stratification to further analyze the effect of SCC on the putative
14 associations tested. We implemented GLMs interaction models to test group interactions on
15 the associations between dispersion, cognitive composites, and rs-FC values, controlled by age,
16 sex, years of education, and FWD. Then, we explored dispersion-related associations for each
17 group of SCCs (low-SCC and high-SCC) by also applying independent GLMs. All results were
18 considered significant with a level of confidence of 95 percent, resulting in an alpha (one-tailed
19 p-value) of 0.05.

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43 **Results**

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46 Associations between cognitive dispersion, demographics, and cognitive composites in the
47 whole sample

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51 The main demographics and cognitive outcomes for the whole sample (N=520, 49.6% females)
52 are described in Table 1.

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56 Regarding our first aim, none of our dispersion measures (i.e., episodic memory, speed of
57 processing, executive function, across-domain) were predicted by age or years of education.

However, there were marginally significant sex differences only for the across-domain dispersion **with a small effect** ($F_{(1, 519)} = 3.887$, $p = 0.049$, $\eta_p^2 = 0.007$), indicating that males (mean = 8.17, SD = 2.02) exhibited greater dispersion than females (mean = 7.82, SD = 1.86). The across-domain dispersion was negatively associated with the across-domain composite ($F_{(1, 519)} = 8.837$, $p = 0.003$; see Fig. 1A), **while** episodic memory dispersion was negatively related to the speed of processing ($F_{(1, 519)} = 8.529$, $p = 0.004$; see Fig. 1B) and the executive functions composites ($F_{(1, 519)} = 7.518$, $p = 0.006$; see Fig. 1C). However, for the three cognitive domains of interest, we did not detect significant associations with any of the dispersion metrics **and** their corresponding composite scores.

Associations between cognitive dispersion and structural and functional brain connectivity

Voxel-wise analysis of white matter tracts did not yield any significant correlations between any dispersion measures and FA or MD values. Regarding functional connectivity analyses, negative associations were found between the across-domain dispersion and the rs-FC within the DMN ($F_{(1, 452)} = 4.283$, $p = 0.039$; see Fig. 2B), and between DMN and the DAN networks ($F_{(1, 452)} = 4.693$, $p = 0.031$; see Fig. 2A). Therefore, the higher the across-domain dispersion, the less the connectivity within the DMN as well as between the DMN and the DAN. Moreover, when we analyzed the dispersion measures for the three cognitive domains separately, a negative association between dispersion in the speed of processing and the rs-FC within DMN emerged ($F_{(1, 452)} = 4.986$, $p = 0.026$; see Fig. 2C).

At this point, we carried out some additional analyses to test associations between the MRI-derived measures and cognitive composites. Positive correlations emerged between global FA and the composites of the speed of processing, executive function, and across-domain. In addition, we identified a positive correlation between global MD and episodic memory

composite. However, we could not find any correlation between rs-FC values in our targeted RSNs and any of the cognitive composites (see supplementary Table 2).

Role of Subjective Cognitive Complaints in the associations between dispersion and brain measures

Finally, we tested whether observed significant associations in previous sections between dispersion, cognitive composites and MRI-derived measures could be different according to the severity of SCC (mean = 7.94, SD = 6.65). We first explored the demographical and neuropsychological data in each group (see supplementary Table 3), evidencing no significant differences between low-SCC versus high-SCC in age, sex, and dispersion indices. However, the high-SCC group had fewer years of education ($t = 2.311$, $p = 0.021$). In addition, this group showed lower across-domain performance ($F_{(1,519)} = 4.717$, $p = 0.030$) and speed of processing composite ($F_{(1,519)} = 6.121$, $p = 0.014$) than the low-SCC group, adjusted by years of education. Groups did not differ in structural (i.e., FA and MD) or functional connectivity (i.e., within and between DMN and DAN rs-FC).

We employed interaction models to analyze whether the severity of SCC moderated the previously reported associations between dispersion, cognitive composites and rs-FC values. The interaction terms were not significant when they were included in the model. To delve further into the targeted associations, we conducted the same GLMs previously described for the whole sample, but this time implemented separately for each group. The results evidenced that previous findings were driven by participants with higher subjective complaints. Specifically, only the high-SCC group showed a negative association between across-domain dispersion and across-domain composite ($F_{(1,259)} = 10.340$, $p = 0.001$; see Fig. 3A). The same was identified for the negative associations between episodic memory dispersion and speed of processing ($F_{(1,259)} = 9.344$, $p = 0.002$; see Fig. 3B) and executive functions composites ($F_{(1,$

$_{259} = 4.496, p = 0.035$; see Fig. 3C). Moreover, as regards functional brain correlates, negative associations between across-domain dispersion and rs-FC between the DMN-DAN ($F_{(1, 222)} = 4.521, p = 0.035$; see Fig. 4A) and within the DMN ($F_{(1, 222)} = 7.432, p = 0.007$; see Fig. 4B) were restricted to the high-SCC group. Speed of processing dispersion remained negatively associated with the rs-FC within the DMN ($F_{(1, 222)} = 7.842, p = 0.006$; see Fig. 4C) in the high-SCC group.

Discussion

The present work is, to our knowledge, the first study characterizing **cognitive intraindividual variability, i.e. cognitive dispersion, by** exploring its associations with neural substrates in healthy adults, and further considering the influence of SCD. Our main results showed that cognitive dispersion was negatively related to cognitive composites in an across-domain manner. This across-domain dispersion was also negatively associated with rs-FC within the DMN and between the DMN and the DAN. No associations were found between cognitive dispersion measures and structural connectivity. When considering the severity of SCC (low-SCC versus high-SCC), we observed that previous associations were only present in the high-SCC group.

Cognitive dispersion associations with demographic data and cognitive composites

Dispersion measures were not related to age and years of education in our sample. We expected to find a positive association with age because previous studies reported that older adults presented significantly more dispersion than their younger counterparts (Hultsch et al., 2002; Hilborn et al., 2009; de Felice & Holland, 2018; Sorg et al., 2021; Webber et al., 2022). **The lack of age-dispersion associations could be due to the narrow distribution of age in our middle-aged sample in comparison to other studies including subjects at older ages, where the increase of cognitive dispersion may be more noticeable.** Also, we expected to see a negative association

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with years of education, a finding observed in some studies (Thaler et al., 2015; Manning et al., 2021). Nevertheless, associations between dispersion and demographic variables, i.e., age, sex, and years of education, are not consistent, as reported recently (Yoneda et al., 2022). Finally, our results revealed a significant association between across-domain dispersion and sex, with males showing greater dispersion scores than females, which should be cautiously interpreted due to the small effect size. This however aligns with previous evidence based on samples of middle-aged (Lin & McDonough, 2022) and older adults (Webber et al., 2022).

Regarding neuropsychological correlates of dispersion, we identified a clear association between dispersion and composite scores as an across-domain measure, as described previously in aging populations (de Felice & Holland, 2018; Yoneda et al., 2022). Yet, we did not find the same association between dispersion and composite within each cognitive domain, which is in fact in accordance with previous investigations (Hilborn et al., 2009; Halliday et al., 2019). Additionally, we found negative associations between the speed of processing and executive function composites and episodic memory dispersion, which aligns with prevalent neuropsychological models (Baudouin et al., 2009; Albinet et al., 2012). Notably, since speed of processing and executive functions start to decline early in adulthood (Salthouse, 2020), they may represent early markers of initial instability in episodic memory resources (interpreted by an increasing dispersion), even though decline in episodic memory performance tends to occur at later stages (i.e., typically from 60 onwards, reviewed in Nyberg, 2017).

Neural correlates of dispersion: functional but not structural connectivity

Structural connectivity analyses showed that white matter integrity (assessed by FA and MD) was not related to dispersion measures. To the best of our knowledge, only Halliday et al., (2019) and Sorg et al., (2021) evidenced a negative association between cognitive dispersion and long-range fasciculus proprieties in older and young adults, respectively. Furthermore, in

previous studies with different ages and collectives, tract integrity was correlated with cognitive intraindividual variability measured as inconsistency in reaction time paradigms (Fjell et al., 2011; Moy et al., 2011; Lövdén et al., 2013; Mella et al., 2013). Despite both measures of cognitive intraindividual variability (i.e., dispersion and inconsistencies) have been studied together and correlated between them (Hultsch et al., 2002; Hilborn et al., 2009), our findings suggest that cognitive dispersion might not be as sensitive as reaction time paradigms in predicting white matter status amongst middle-aged individuals.

Regarding rs-FC, our results showed that higher across-domain dispersion was related to a weaker rs-FC within the DMN and between the DMN and the DAN. These findings are consistent with previous studies where cognitive intraindividual variability showed similar associations with the DMN (Kelly et al., 2008; Kucyi et al., 2016), particularly with the work of Meeker et al. (2022), which focused on cognitive dispersion. Previous literature in the field has highlighted that both segregation and integration balance in RSN contribute to successful cognitive performance (Fukushima et al., 2018). A weaker anti-correlation between the DMN-DAN coupling has been identified with increasing age, proved in both task-based and rs-fMRI studies (Spreng et al., 2016). Furthermore, reduced rs-FC within the DMN has been found in early aging stages (reviewed in Jockwitz & Caspers, 2021) implying cognitive deficits (Farras-Permanyer et al., 2019). In addition, our analyses on each cognitive domain revealed that only dispersion in speed of processing was negatively related to the rs-FC within the DMN. This is also consistent with other reports linking speed of processing with large-scale RSNs, such as the DMN (Ng et al., 2016). In our additional analyses aiming to test whether rs-FC values were also associated with cognitive composites, no significant correlations emerged. Thus, we can conclude that compared to traditional correlates of performance, dispersion was a more sensitive marker of incipient DMN dysregulation in middle age.

Dispersion correlates were driven by high-SCC

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While no differences in dispersion scores were observed between high and low SCC groups, associations with rs-FC regarding the DMN and the DAN, as well as with cognitive performance were only observed in the former. It should be noted that such associations have been previously reported amongst older adult populations (De Felice & Holland 2018; Yoenda et al., 2022; Meeker et al. 2021). **Particularly, a recent neuroimaging study evidenced disrupted rs-FC among the main regions of the DMN and the DAN in older adults with SCD, suggesting an early cognitive decline (Lee et al., 2023).** Therefore, our findings suggest that even in middle age, high rates of dispersion amongst high SCC may represent early indicators of incipient brain and cognitive deleterious changes. However, whether this relates to a future risk of cognitive impairment or dementia (Cedres et al., 2019; Jessen et al., 2020) cannot be ascertained through the present investigation and will require further longitudinal study designs.

Limitations

First, our cognitive domains included a limited variability of tests, with the executive functions being the most represented domain. Second, our group formation into two subgroups based on the median may not be representative of low-SCC and high-SCC in the general population. Finally, we evidenced the relevance of cognitive dispersion in high-SCC through a cross-sectional study, but longitudinal investigations are necessary to determine how the present findings may link to age-related cognitive and brain changes.

Conclusion

Among middle-aged individuals, higher cognitive dispersion was associated with intraindividual differences in cognitive performance related to DMN connectivity, but not with white matter integrity. Cognitive dispersion may be an early indicator of subtle brain functional changes over traditional performance measures. Moreover, our work highlighted that previous

associations were particularly relevant amongst subjects with high SCC, which may reflect incipient brain changes potentially conferring increased risk for cognitive decline.

Conflict of Interest

Dr. A. P.-L. is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. He is a co-founder of Linus Health and TI Solutions AG; and serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Nexstim, and MedRhythms.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Sample description and cognitive outcomes.

	Mean	SD	Range (min-max)
Age	53.08	7.09	42 - 66
Years of education	17	3.60	8 - 28
Subjective cognitive complaints	7.94	6.65	0 - 28
<i>Cognitive dispersion</i>			
Episodic memory	6.64	2.46	1.46 – 15.67
Executive functions dispersion	7.67	3.10	0.42 – 18.03
Speed of processing dispersion	6.11	4.75	0.01 – 24.96
Across-domain dispersion	8.00	1.95	3.18 – 13.13
<i>Cognitive composite</i>			
Episodic memory	-0.006	0.723	-1.787 – 1.716
Executive functions	0.014	0.659	-2.189 – 1.815
Speed of processing	0.016	0.841	-2.446 – 2.309
Across-domain	-0.002	0.579	-1.959 – 1.541

Figure 1. Scatter plots showing the negative relationship for the whole sample between **A)** across-domain dispersion and its composite, and **B)** episodic memory dispersion and speed of processing, also with **C)** executive functions composite. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to graphically represent our results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval.

Figure 2. Scatter plots showing the negative relationship for the whole sample between **A)** across-domain dispersion and rs-FC between the DMN and the DAN and **B)** within the DMN. As well as the negative relationship between **C)** the speed of processing dispersion and rs-FC within the DMN. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to show the results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval. **D)** Brain graphs represent the topography of the networks defined to measure rs-FC within DMN and between the DMN and the DAN (as in A). See further detail in supplementary figure 1. Abbreviations: rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network; ROI: region of interest.

Figure 3. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and cognitive composites in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced the previously reported negative correlations between **A)** across-domain dispersion and its composite, also between episodic memory dispersion and **B)** speed of processing and **C)** executive functions composites. The lines show linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints.

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Figure 4. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and rs-FC values in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced a negative correlation between **A)** across-domain dispersion and rs-FC between the DMN and the DAN and **B)** within the DMN. In addition, a negative correlation between **C)** the speed of processing dispersion and rs-FC within the DMN. The lines show a linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints; rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network.

For Peer Review

Supplementary material for:

Brain connectivity correlates of cognitive dispersion in a healthy middle-aged population: influence of subjective cognitive complaints.

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METHODS

1. Cognitive dispersion indexes and cognitive composites

Table 1
Neuropsychological tests included in the dispersion and cognitive composite measures (N = 520)

	Tests and outcomes	Score	Mean ± SD	Range (min – max)
Episodic memory	RAVLT leaning recall	Total	52.23 ± 8.63	26 – 71
	RAVLT delayed recall	Total	11.35 ± 2.64	5 – 15
	RAVLT recognition	Total	14.39 ± 1.07	8 – 15
	S-FNAME Initial learning name	Total	6.72 ± 3.48	0 – 16
	S-FNAME. Initial learning occupation	Total	9.38 ± 3.26	0 – 16
	S-FNAME immediate cued recall names	Total	5.08 ± 3.48	0 – 16
	S-FNAME immediate cued recall occupation	Total	8.79 ± 3.33	0 – 16
	S-FNAME delayed cued recall names	Total	5.02 ± 3.49	0 – 16
	S-FNAME delayed cued recall occupation	Total	8.56 ± 3.39	0 – 16
	Episodic memory dispersion	ISD	6.64 ± 2.46	1.46 – 15.67
	Episodic memory composite	Z	-0.0057 ± 0.7225	-1.7865 – 1.7160
Speed of processing	Cancellation test	Hits	41.75 ± 8.55	19 – 65
	SDMT	Total	78.96 ± 13.38	38 – 114
	Speed of processing dispersion	ISD	6.11 ± 4.75	0.01 – 24.96
	Speed of processing composite	Z	0.0158 ± 0.8410	-2.4456 – 2.3088
Executive functions	TMTB-TMTA	Time in seconds	88.13 ± 22.40	0 – 126
	Backward digits	Span	4.90 ± 1.11	2 – 8

	Phonemic fluency (F-A-S)	Total	18.50 ± 4.35	6 – 32
	Letter and number sequencing	Span	5.79 ± 1.03	3 – 8
	Executive functions dispersion	ISD	7.67 ± 3.10	0.42 – 18.03
	Executive functions composite	Z	0.01374 ± 0.6586	-2.1890 – 1.8154
Across domain	Across-domain dispersion	ISD	8.00 ± 1.95	3.18 – 13.13
	Across-domain composite	Z	-0.0024 ± 0.5793	-1.9588 – 1.5414

Note. SD, Standard Deviation; ISD, Intraindividual Standard Deviation; PCA, Principal Component Analyses; S-FNAME, Face Name Associative Memory Exam; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trial Making Test; SDMT, Symbol Digit Modalities Test.

2. Sample stratification based on SCC

Table 2

Low-SCC (N= 260) and high-SCC (N= 260) differences in quality of life, objective cognition, and years of education

	Low-SCC group	High-SCC group	Statistic, <i>p</i> -value
	Mean ± SD	Mean ± SD	
Quality of life	40.57 ± 5.76	36.11 ± 5.98	<i>t</i> = 8.663, <i>p</i> < 0.001***
Episodic memory composite	0.065 ± 0.739	-0.077 ± 0.700	<i>F</i> _(1,519) = 2.953, <i>p</i> = 0.086
Speed of processing composite	0.059 ± 0.676	-0.031 ± 0.639	<i>F</i> _(1,519) = 6.121, <i>p</i> = 0.014*
Executive functions composite	0.115 ± 0.872	-0.084 ± 0.798	<i>F</i> _(1,519) = 1.588, <i>p</i> = 0.208
Across-domain composite	0.701 ± 0.595	-0.065 ± 0.556	<i>F</i> _(1,519) = 4.717, <i>p</i> = 0.030*
Years of education	17.36 ± 3.44	16.63 ± 3.72	<i>t</i> = 2.311, <i>p</i> = 0.021*

Note. Cognitive composite differences between groups were adjusted by years of education. SD, Standard Deviation; SCC, subjective cognitive complaints.

3. MRI acquisition parameters

For all participants, a high-resolution T1-weighted structural image was obtained with a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) three-dimensional protocol [repetition time (TR) = 2,400 ms, echo time (TE) = 2.22 ms, inversion time = 1,000 ms, field of view (FOV) = 256 mm, 0.8-mm isotropic voxel]. Diffusion-weighted

image data were acquired with two multiband acquisitions (anterior-posterior; acceleration factor = 4), sensitized in 99 monopolar directions with a b-value of 3000 s/mm² in an echo-planar imaging sequence (TR = 3230 ms; TE = 89.20 ms; section thickness = 1.5 mm; voxel size = 1.5 × 1.5 × 1.5 mm; FOV = 210 mm). Additionally, a high-resolution 3D SPC T2-weighted structural brain MRI was undertaken (TR = 3,200 ms, TE = 563 ms, flip angle = 120°, 0.8 mm isotropic voxel, FOV = 256 mm). Finally, they also underwent resting-state fMRI (rs-fMRI) multiband (anterior-posterior phase-encoding; acceleration factor = 8) interleaved acquisitions [T2*-weighted EPI scans, TR = 800 ms, TE = 37 ms, 750 volumes, 72 slices, slice thickness = 2 mm, FOV = 208 mm].

4. DTI preprocessing and TBSS

Prior to analysis, DTI acquisitions were preprocessed by FMRIB's Diffusion Toolbox (FDT) software from FMRIB Software Library (FSL; version 5.0.11; <http://www.fmrib.ox.ac.uk/fsl>; Jbabdi et al., 2012). We applied eddy current, motion correction, and brain extraction (Smith, 2002). Then, individual fractional anisotropy (FA) and mean diffusivity (MD) maps were obtained using a Diffusion Tensor Model fit (DTIFIT). We introduced individual maps to our group analysis using the Tract-based spatial statistics (TBSS) protocol (Smith et al., 2006). TBSS performs nonlinear registration (FNIRT) of FA images to the Montreal Neurological Institute (MNI) standard space, which generates a mean FA skeleton representing the center of all common tracts to the entire sample. Then, the aligned FA image for each subject was projected onto the skeleton by filling it with FA values from the nearest relevant tract center. FA and MD maps were co-registered and projected to the sample skeleton from TBSS to be further analyzed using the *randomise* tool from FSL (Winkler et al., 2014). Continuously, taking advantage of FA analyses TBSS projects non-FA data onto the FA skeleton already done, allowing us to achieve the nonlinear registration and skeletonisation stages in other DTI-derived as we did in MD maps.

5. Rs-fMRI preprocessing and rs-FC calculation

rs-fMRI preprocessing pipeline comprised spatial standardization and nuisance correction by making use of functions from FMRIB Software Library (FSL; version 5.0.11; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), FreeSurfer (version 6.0; <https://surfer.nmr.mgh.harvard.edu>) and Statistical Parametric Mapping (SPM12;

<https://www.fil.ion.ucl.ac.uk/spm/>). To start with, the first 10 scans were removed to ensure magnetization equilibrium. After that, all images were field inhomogeneity corrected (FSL top-up tool), all scans realigned to a reference image (FSL MCFLIRT), and then standardized into native T1-weighted space (SPM Coregister). Finally, normalization (SPM Normalize) of all fMRI images to Montreal Neuroscience Institute (MNI152) standard space was performed to ensure among-subjects comparability. As for nuisance correction, different components were defined and manually removed from the rs-fMRI images by the “fsl_regfilt” tool implemented in FSL. These components correspond to (i) motion regressors of rotation, translation, and their derivatives, as estimated during scans’ realignment, (ii) a drift estimated by a discrete cosine transform as a low-pass frequency filter (<0.01), and (iii) signals from WM and cerebrospinal fluid. To extract these, cerebrospinal fluid and WM masks were obtained from automatic subcortical segmentation of brain volume, based on the existence of an atlas containing probabilistic information on the location of structures (Fischl et al., 2002; Power et al., 2012, 2014, 2015). This step was part of the FreeSurfer ‘recon-all’ processing stream, which was run with default parameters, except for the addition of the T2 flag for the improvement of pial surfaces reconstruction. Exactly, both T1- and T2-weighted images were used for processing anatomical information.

We quantified within and between rs-FC individual values in the DMN and the DAN based on the Schaefer-Yeo cerebral cortical atlas of 100 nodes forming 7 RSN (Schaefer et al., 2018). Specifically, both large-scale RSN comprise multiple cortical areas in both hemispheres. The DMN is based on 24 nodes, and the DAN is based on 15 nodes (see figure 1 below) (https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal). As a result, these 39 nodes defined our regions of interest (ROI) in our analyses. After rs-fMRI preprocessing, we extracted the blood-oxygen-level-dependent (BOLD) signal in each voxel in our functional images. Then, we averaged the BOLD signal in ROIs voxels and extracted ROI-to-ROI Pearson correlations which were Fisher-z transformed to improve matrices normality. Next in order, only positive correlations were used to average correlation coefficients. Subsequently, as this method required, negative correlations were set to zero, and autocorrelations were not considered, as other authors defined (Sporns, 2018) and did to explore rs-FC in RSN (Meeker et al., 2021). As a result, we obtained values of positive

rs-FC between the nodes in each network (i.e., rs-FC within DMN and within DAN), and also between nodes from both RSN (i.e., rs-FC between DMN-DAN).

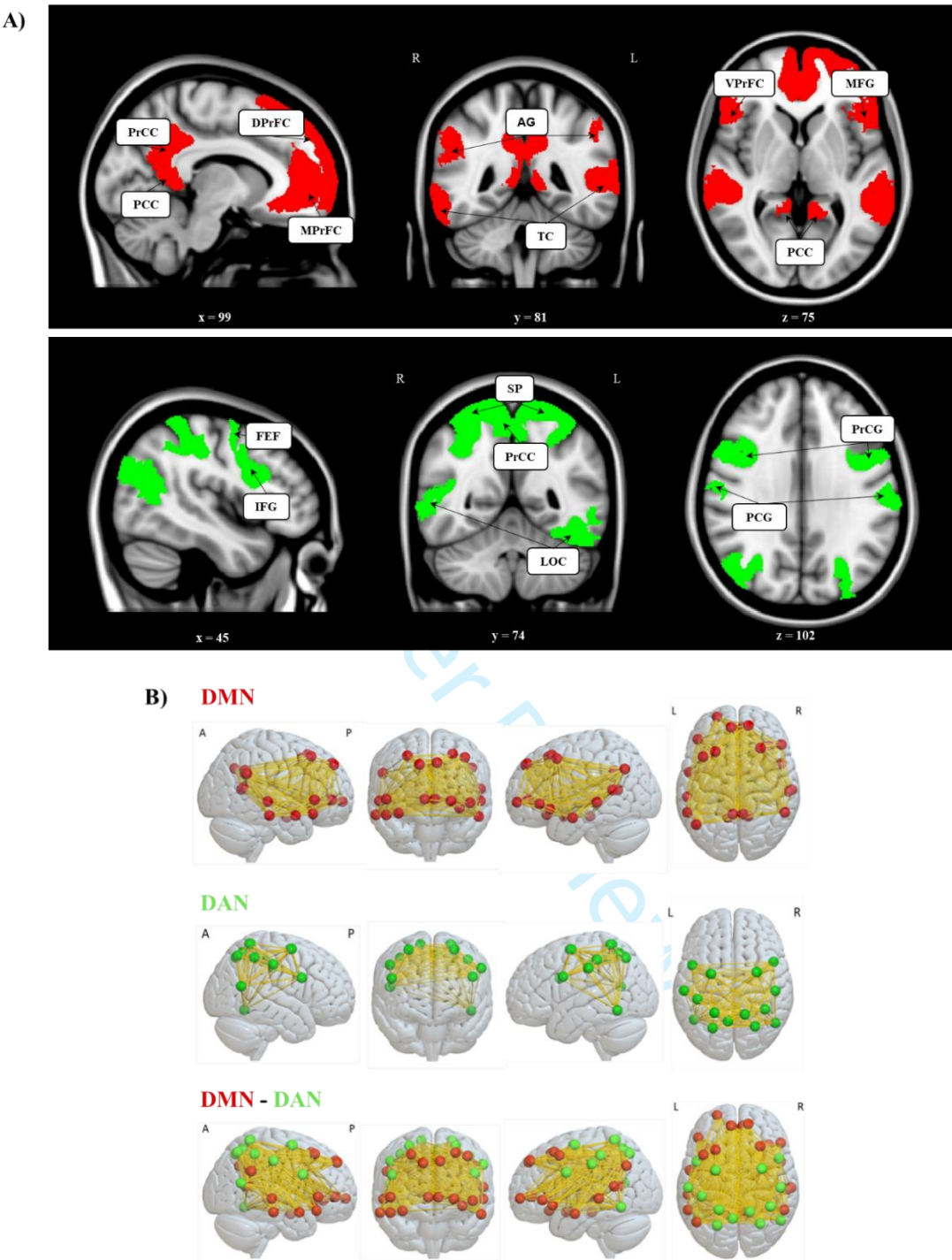


Figure 1. Schaefer-Yeo cortical areas of the DMN and the DAN over an MNI template and our rs-FC maps of interest. **A)** Representation of Schaefer-Yeo cortical regions becoming our ROIs in the rs-FC analyses. The 24 regions of the DMN are in red, and the 15 regions of the DAN are in green. The DMN and the DAN are both large-scale networks compromising distant anterior and posterior cortical regions. The DMN recruits mainly

the medial prefrontal cortex (MPrFC) associated with social behavior, emotional processing, self-perception, and motivation; and the precuneus cortex (PrCC) and the posterior cingulate cortex (PCC), associated with autobiographic memory (Raichle, 2015). The DAN recruits regions linked to goal-directed attentional processing such as the frontal eye fields (FEF) next to the precentral gyrus (PrCG), intraparietal sulcus, and superior parietal lobule (SP) (Allan et al., 2019). **B)** Representation of rs-FC maps extrapolating our ROIs connectivity. The nodes represent our ROIS and the edges are the connectivity between them and are spatially located according to the center of gravity of each parcel. DMN. The 24 nodes of the DMN are in red and the 15 nodes of the DAN are in green. The edges were colored yellow. We obtained ROI-to-ROI Pearson correlations among the nodes in each network for the ‘within rs-FC’ values and among the nodes from both networks for the ‘between rs-FC’ values. rs-FC maps were represented using the Surfe Ice tool (<https://www.nitrc.org/projects/surfeice/>). Abbreviations: DMN, default mode network; DAN, dorsal attentional network; rs-FC, resting-state functional connectivity; ROI, region of interest; PrCC, precuneous cortex; DPrFC, dorsal prefrontal cortex; PPC, posterior parietal cortex; MPrFC, medial prefrontal cortex; AG, angular gyrus; TM, temporal cortex; VPrFC, ventral prefrontal cortex; MDG, Middle Frontal Gyrus; PCC, Posterior Cingulate Cortex; FEF, Frontal Eye Fields; IFG, inferior frontal gyrus; SP, superior parietal; LOC, lateral occipital cortex; PCG, postcentral gyrus; PrCG, precentral gyrus.

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RESULTS

1. Associations between MRI-derived data and cognitive composites

As a complementary analysis, we wanted to test whether global FA and MD and rs-FC values concerning the DMN and the DAN could be correlated with cognitive composites. Global FA and MD were individual values extracted based on the mean of the whole skeleton map.

Table 2

Spearman correlations performed between MRI-derived data and cognitive composites (N= 453)

	Speed of processing composite	Episodic memory composite	Executive functions composite	Across- domain composite
Global FA	0.149***	0.049	0.099*	0.090*
Global MD	0.020	0.125**	-0.036	0.084
rs-FC within DMN	-0.016	-0.050	-0.031	-0.047
rs-FC within DAN	-0.052	-0.063	-0.068	-0.077
rs-FC between DMN-DAN	-0.064	-0.065	-0.073	-0.078

Note. FA, fractional anisotropy; MD, mean diffusivity; rs-FC, resting-state functional connectivity; DMN, default mode network; DAN, dorsal attentional network (*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$).

2. Demographics, cognitive dispersion, and cognitive composites for each group of subjective cognitive complaints

Table 3

Demographical and neuropsychological data for each group of subjective cognitive complaints

	Low-SCC (N= 260)			High-SCC (N= 260)		
	<i>Mean ± SD</i>	<i>Range (min-max)</i>	<i>%</i>	<i>Mean ± SD</i>	<i>Range (min-max)</i>	<i>%</i>
Age	52.83 ± 7.21	42 – 66		53.33 ± 6.99	42 – 66	
Gender (females)			49.6			49.6
Years of education	17.36 ± 3.44	9 – 28		16.63 ± 3.72	8 – 27	
Episodic memory dispersion	6.71 ± 2.37	2.7 – 18.90		6.58 ± 2.57	1.46 – 15.67	
Executive functions dispersion	7.63 ± 3.13	0.42 – 13.71		7.70 ± 3.08	0.80 – 18.03	
Speed of processing dispersion	5.82 ± 4.27	0.20 – 22.77		6.41 ± 5.18	0.1 – 24.96	
Across-domain dispersion	8.02 ± 1.97	3.37 – 13.13		7.97 ± 1.92	3.18 – 13.01	
Episodic memory composite	0.065 ± 0.739	-1.659 – 1.716		-0.077 ± 0.700	-1.786 – 1.623	
Executive functions composite	0.059 ± 0.676	-1.792 – 1.815		-0.031 ± 0.639	-2.189 – 1.619	
Speed of processing composite	0.115 ± 0.872	-1.969 – 2.309		-0.084 ± 0.798	-2.446 – 1.962	
Across-domain composite	0.701 ± 0.595	-1.363 – 1.541		-0.065 ± 0.556	-1.959 – 1.252	

Note. SCC, subjective cognitive complaints; CD, cognitive dispersion; CC, cognitive composite; EM, episodic memory; SOP, speed of processing; EF, executive functions; SD, standard deviation.

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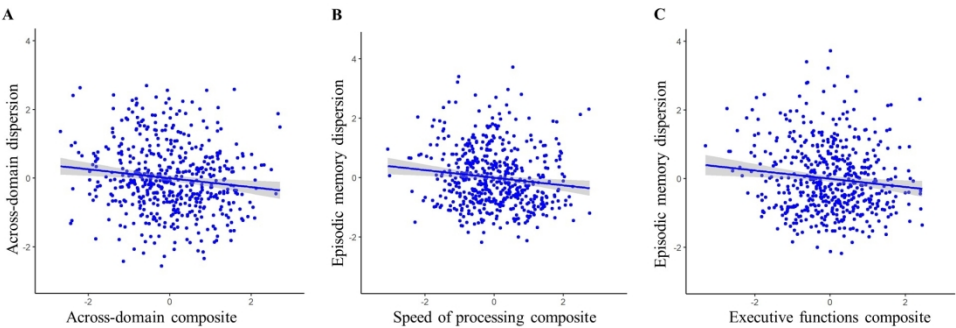


Figure 1. Scatter plots showing the negative relationship for the whole sample between A) across-domain dispersion and its composite, and B) episodic memory dispersion and speed of processing, also with C) executive functions composite. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to graphically represent our results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval.

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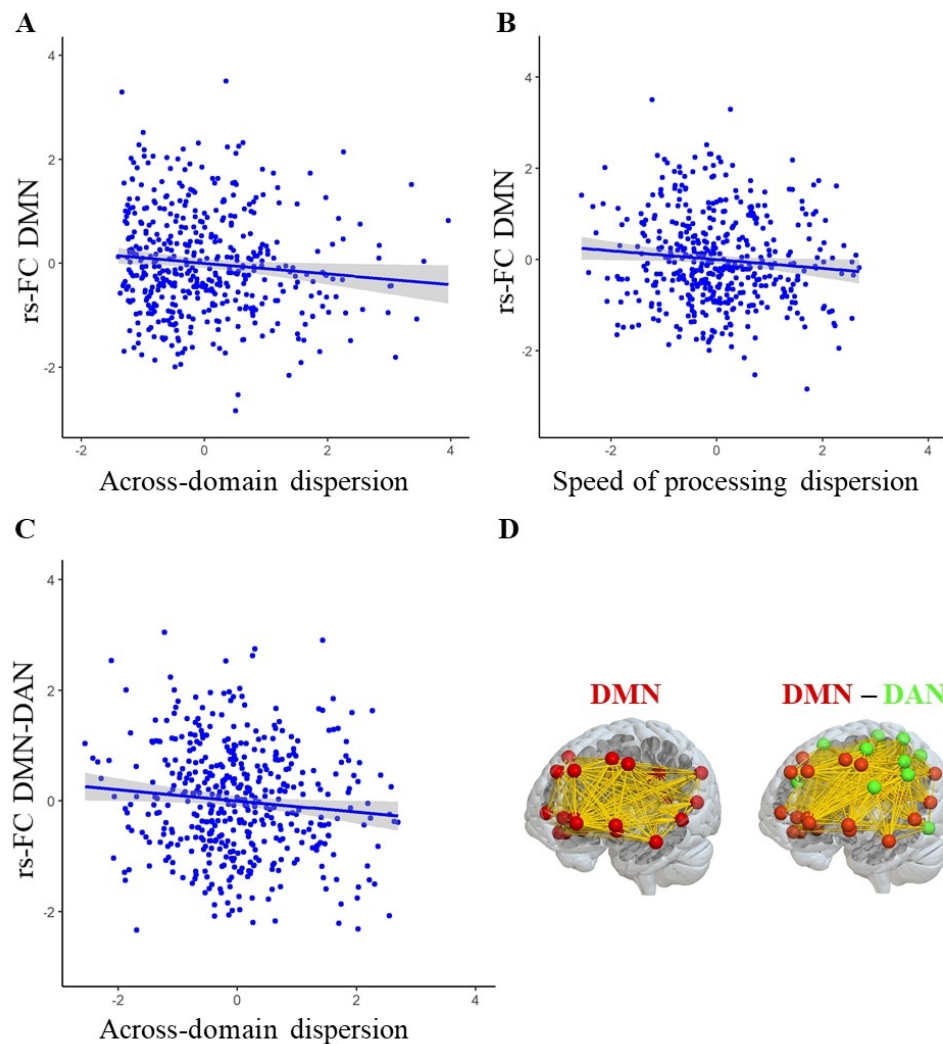


Figure 2. Scatter plots showing the negative relationship for the whole sample between A) across-domain dispersion and rs-FC between the DMN and the DAN and B) within the DMN. As well as the negative relationship between C) the speed of processing dispersion and rs-FC within the DMN. Standardized residuals of dependent and independent variables from general linear models were saved and linearly regressed to show the results. Blue lines show linear regression fit to the data, and gray areas represent the confidence interval. D) Brain graphs represent the topography of the networks defined to measure rs-FC within DMN and between the DMN and the DAN (as in A). See further detail in supplementary figure 1. Abbreviations: rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network; ROI: region of interest.

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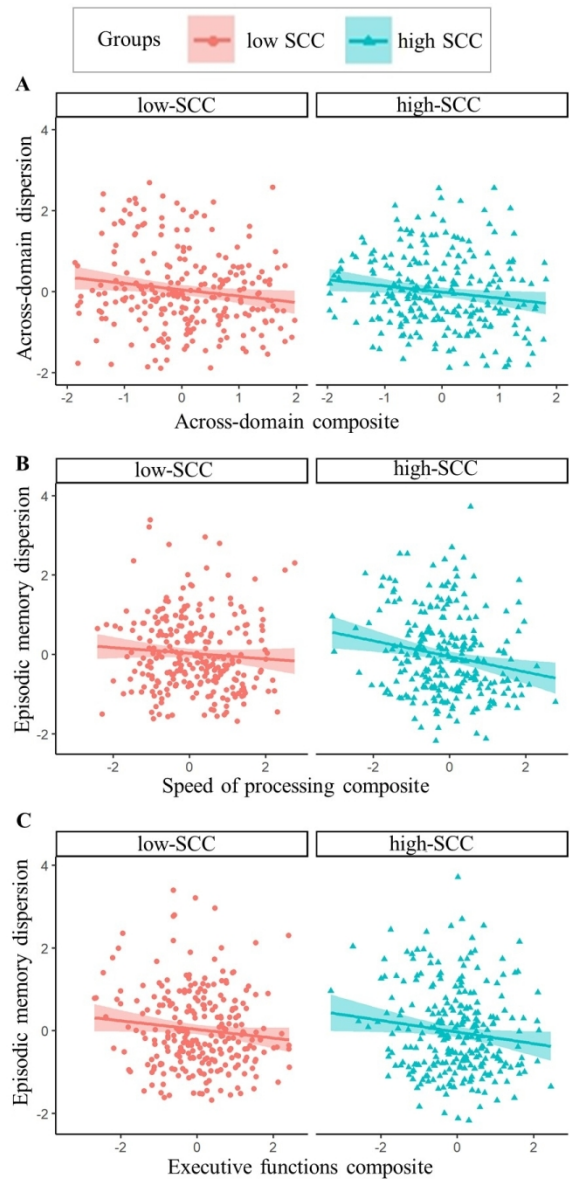


Figure 3. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and cognitive composites in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced the previously reported negative correlations between A) across-domain dispersion and its composite, also between episodic memory dispersion and B) speed of processing and C) executive functions composites. The lines show linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints.

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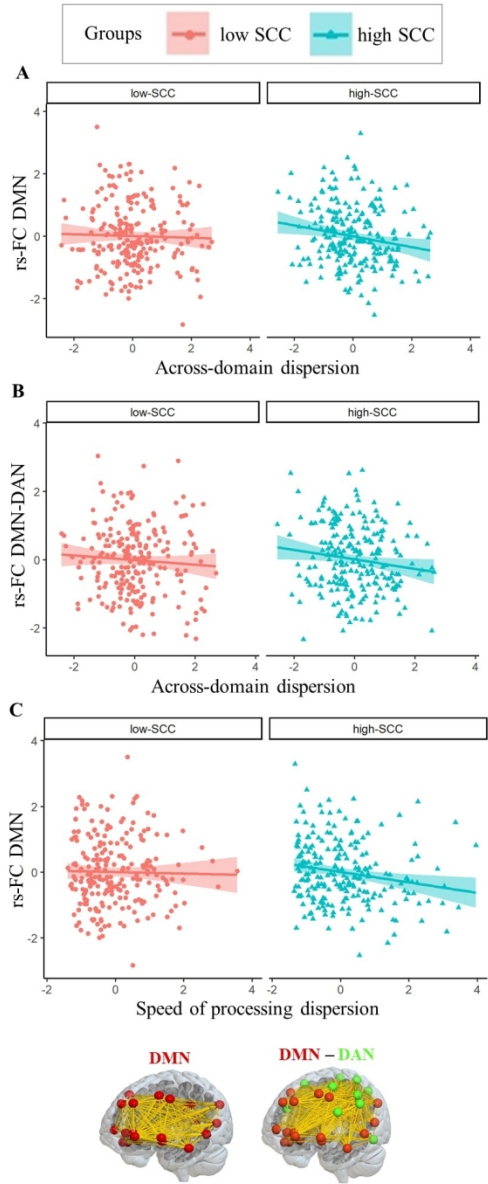


Figure 4. Scatter plots showing the negative relationships among standardized residuals of dispersion measures and rs-FC values in the low-SCC (in red) and the high-SCC (in blue) groups. Only the high-SCC group evidenced a negative correlation between A) across-domain dispersion and rs-FC between the DMN and the DAN and B) within the DMN. In addition, a negative correlation between C) the speed of processing dispersion and rs-FC within the DMN. The lines show a linear regression fit to the data, and shadowed areas represent the confidence interval. Abbreviations: SCC, subjective cognitive complaints; rs-FC: resting-state functional connectivity; DMN: default mode network; DAN: dorsal attentional network.

82x170mm (300 x 300 DPI)