Age-dependent contribution of domain-general network interactions to semantic cognition

Running title: Age-dependent interactions of domain-general networks

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Abstract

Aging is characterized by a decline of cognitive control. In semantic cognition, this leads to the paradox that older adults usually show poorer task performance than young adults despite their greater semantic knowledge. So far, the underlying neural changes of these behavioral differences are poorly understood. In the current neuroimaging study, we investigated the interplay of domain-specific and domain-general networks in young and older adults during a verbal semantic fluency task. In both age groups, task processing was characterized by a strong interaction between the domain-general multiple-demand and the default mode system during semantic fluency. However, the behavioral relevance of strengthened connectivity differed between groups: While within- and between-network functional connectivity predicted better performance in young adults, these increases were associated with a performance decline in older adults. Our findings lend novel support to the notion of reduced efficiency in the aging brain, due to neural dedifferentiation in semantic cognition.

Keywords: aging, default mode network, multiple-demand network, connectivity, language production

Introduction

Semantic cognition is a fundamental human ability that is central to communication across life span. Key facets of semantic cognition refer to our knowledge of the world and the meaning of words and sentences. With respect to cognitive changes across the adult life span, cognitive control processes – also referred to as fluid intelligence – are well established to steadily decline with increasing age (Hedden & Gabrieli, 2004) whereas semantic knowledge (so-called crystallized intelligence) has been shown to remain stable or might even increase with age due to the ongoing accrual of knowledge and experience across the life course (Verhaegen, 2003). In the domain of semantic cognition, the impact of aging thus seems to depend on both the specific cognitive demand of a task and the individual semantic knowledge.

At the neural level, cognitive changes with age are mirrored by large-scale reorganization processes at the structural and functional levels (Grady, 2012; Morcom & Johnson, 2015). Task-related performance changes in older adults have been associated with a pattern of dedifferentiation of neural activity (Park et al., 2004; Li et al., 2001) which is reflected by an under-recruitment of domain-specific regions (Lövdén et al., 2010) and reduced task-specific lateralization (Cabeza, 2002), as well as an increased recruitment of areas in the domain-general multiple-demand network (MDN; Lövdén et al., 2010) and a reduced deactivation of regions in the default mode network (DMN; Andrews-Hanna et al, 2007; Damoiseaux et al., 2008; Persson et al., 2007). A recent meta-analysis that investigated age-related effects on the neural substrates of semantic cognition confirmed the upregulation of the MDN in older adults for a variety of semantic tasks (Hoffman & Morcom, 2018).

In addition to local changes in task-related activity, alterations in the functional connectivity of large-scale neural networks have become a hallmark of brain aging (Damoiseaux et al., 2017; Li et al., 2015; Spreng et al., 2016). A common observation is that functional network segregation declines with age which is evident in the form of decreased within- and increased between-network functional connectivity (Chan et al., 2014; Geerligs et al., 2015; Spreng et al., 2016). These changes have been interpreted as dedifferentiation of network interactions, paralleling local task-related neural changes (Spreng & Turner, 2019). However, the majority of studies investigated these changes at rest and it is thus less clear how aging affects task-related functional connectivity and how this is associated with behavior.

The recently proposed default-executive coupling hypothesis of aging (DECHA; Turner & Spreng, 2015; Spreng & Turner, 2019) suggests that the observed activity increase in MDN regions

and the reduced deactivation of the DMN co-occur and are functionally coupled in older adults. This shift in network coupling is based on the accrual of semantic knowledge and the parallel decline of cognitive control abilities, letting older adults rely more strongly on their preserved semantic knowledge which is reflected by a reduced deactivation of DMN regions compared to young adults. According to this hypothesis, context and cognitive demand of a task determine if this increased default-executive coupling in older adults is beneficial or maladaptive. On this basis, the framework predicts a stable performance in older adults for tasks that rely on crystallized intelligence in the form of intrinsic prior knowledge and require little cognitive control whereas externally-directed cognitive tasks result in poorer performance in older adults due to their dependence on control resources.

So far, the integration of domain-general networks in semantic word retrieval in older adulthood is poorly understood. In this context, semantic fluency tasks, which require participants to generate words that belong to a specific category within a given time, provide a unique opportunity since they require an interaction of verbal semantic and general cognitive control processes (Gordon et al., 2018; Schmidt et al., 2017; Whiteside et al., 2016). Semantic fluency tasks test a natural and important communicative ability as they rely on accessing related concepts to retrieve words. Furthermore, semantic fluency is of high ecological validity, for example when writing a shopping list (Shao et al., 2014), and is frequently implemented as a measure of language and neuropsychological abilities in healthy as well as clinical populations (Schmidt et al., 2017). The impact of aging on semantic fluency is especially interesting since its strong link to semantic memory would predict preserved performance for older adults. Yet, the opposite pattern is usually observed, suggesting a high load on cognitive control processes for this task (e.g., Kavé & Knafo-Noam, 2015; Gordon et al., 2018; Troyer et al., 1997). Most studies that implemented semantic fluency tasks in neuroimaging experiments reported age-related changes within domain-specific networks (Baciu et al., 2016; Marsolais et al., 2014) or pre-defined regions of interest, mainly in the prefrontal cortex (Meinzer et al., 2009; Meinzer et al., 2012a; Meinzer et al., 2012b). However, based on the outlined changes in semantic and cognitive control abilities, older adults could show a shift in network coupling with a stronger engagement of domain-general networks which might be additionally modulated by task demand.

Thus, the aim of the present study was to explore and compare the interplay of domain-specific and domain-general networks during word retrieval in healthy young and older adults. We implemented an fMRI study with a paced overt semantic fluency task, which included an explicit modulation of task difficulty. A counting task was used as a low-level verbal control task. First, we

were interested in delineating the network for semantic fluency and its interaction with task demand. Secondly, we asked whether age modulates both activation patterns and behavioral performance. Finally, we were interested in task-related functional interactions between domain-specific and domain-general networks. To this end, we combined univariate whole-brain analyses with generalized psycho-physiological interaction (gPPI) analyses. We applied traditional gPPI analyses to explore the functional coupling of the strongest activation peaks for semantic fluency. This allowed us to investigate the age-related contribution of domain-general networks to language processing. Furthermore, we used modified gPPI analyses to examine functional connectivity within and between regions of domain-general networks. We were interested in age-related effects on functional connectivity patterns and how within- and between-network functional connectivity relate to behavioral performance for both age groups. We expected a language-specific left-lateralized network for semantic fluency. We further hypothesized that increased task demand (reflected by the contrast of semantic fluency with counting, as well as by the modulation of difficulty within the semantic fluency task) would affect task performance and should be accompanied by an increased recruitment of domain-general systems. With respect to task-related functional connectivity, we reasoned that older adults should demonstrate a stronger involvement of the DMN for the semantic fluency task based on their increased semantic knowledge. Moreover, a higher task load associated with general cognitive decline might further result in a stronger recruitment of the MDN in older adults. However, in line with neurocognitive theories of aging, the increased recruitment of domain-general systems might be associated with reduced specificity and efficiency; thus, overall leading to a poorer performance in the older adults.

Methods

Participants

Twenty-eight healthy older adults (mean age: 65.2 years, range: 60-69 years) and thirty healthy younger adults (mean age: 27.6 years, range: 21-34 years) completed our study. The data of three additional participants in the older group were excluded due to excessive head movement during fMRI (> 1 voxel size). Groups were matched for gender. Participants in the younger group had significantly more years of education ($t = 5.2$, $p < .001$). All participants were native German speakers and right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). They had normal hearing, normal or corrected-to-normal vision, and no history of neurological or psychiatric conditions or contraindication to MR-scanning. Older adults were additionally screened for cognitive impairments using the Mini-Mental State Examination (Folstein et al., 1975; all ≥26/30 points) and for depression with the Beck Depression Inventory (Beck et al., 1996; all ≤14/ points). The study was approved by the local ethics committee of the University of Leipzig and conducted in accordance with the Declaration of Helsinki. Participants gave written informed consent prior to the experiment. They received 10 Euro per hour for their participation.

Neuropsychological Assessment

A battery of neuropsychological tests was administered to all participants to assess cognitive functioning. Verbal knowledge and executive language functions were measured with the German version of the spot-the-word test (Wortschatztest; Schmidt & Metzler, 1992; Baddeley et al., 1993), a German version of the reading span test (Daneman & Carpenter, 1980), and the semantic subtest of a verbal fluency test (Regensburger Wortflüssigkeitstest; Aschenbrenner et al., 2000). The latter comprised two 1-minute trials of semantic categories (surnames and hobbies) that were not part of the fMRI task. Additionally, executive functions were assessed with the Digit Symbol Substitution Test (Wechsler, 1944) and the Trail Making Test A/B (Reitan, 1958).

Group comparisons showed that older participants only performed better than the younger group on the spot-the-word test (see Table 1; Supplementary information (SI) Fig. S1), which is considered a measure of lexical semantic knowledge and vocabulary. Consistent with our results, it has been shown to be robust to aging and cognitive decline (Baddeley et al., 1993; Law & O'Carroll, 1998; Cohen-Shikora & Balota, 2016). Our results confirm the maintenance of semantic memory across age (Grady, 2012) and an increase in size of vocabulary with age (Verhaegen, 2003). All other tests showed better performance for younger participants, which is in line with the assumption of a general decline in executive functions like working memory and processing speed

with age (e.g., Balota et al., 2000; Zacks et al., 2000). However, when considering age-corrected norms, the older participants performed within normal ranges on all neuropsychological tests.

Table 1. Demographic and neuropsychological characteristics of participants

	Younger adults (n = 30)	Older adults (n = 28)
Demographics		
Age (years)	27.6 (4.4)	65.2 (2.8)
Gender (F:M)	16:14	14:14
Education (years)	18.7 (2.6)	15.2 (2.5)*
Beck Depression Inventory (cut-off 18 points)	–	4.7 (4.1)
Neuropsychological		
Spot-the-word test (max. 40)	29.1 (3.2)	31.5 (2.5)*
Semantic fluency (sum surnames, hobbies)	51.2 (8.4)	40.7 (6.7)*
Reading span test (max. 6)	3.5 (1)	2.9 (0.7)*
Digit symbol substitution test (max. 90 in 90 s)	72.1 (11.4)	50.2 (10.4)*
Trail Making Test A (time in s)	17.3 (5.8)	25.4 (6.4)*
Trail Making Test B (time in s)	36.1 (11.9)	61.8 (29.4)*
Mini-Mental State Examination (max. 30 points)	–	28.36 (1.2)

Mean values of raw scores with standard deviations. * Significant differences between age groups at $p < 0.01$.

Experimental Design

All participants completed one fMRI session which was divided into two runs. Tasks consisted of a paced overt semantic fluency task and a control task of paced counting which were implemented in a block design in the scanner. We chose a paced design for our tasks since it has been shown to be less sensitive to motion artifacts and to yield robust brain activation patterns (Basho et al., 2007). Task blocks were 43 s long and separated by rest blocks of 16 s (Fig. 1A). Each block started with a 2 s visual word cue indicating whether participants were expected to generate category exemplars or count forward (1 to 9) or backward (9 to 1). This was followed by 9 consecutive trials of the same category or counting task, respectively. Trials within one block were separated by inter-stimulus intervals of 2-4 s. Participants were instructed to generate one exemplar for a category or one number per trial, which was indicated through a green cross on the screen, and to pause when the cross turned red (Fig. 1B & C). They were told not to repeat items and to say “next” if they could not think of an exemplar for the respective category. Each run contained 10 semantic fluency

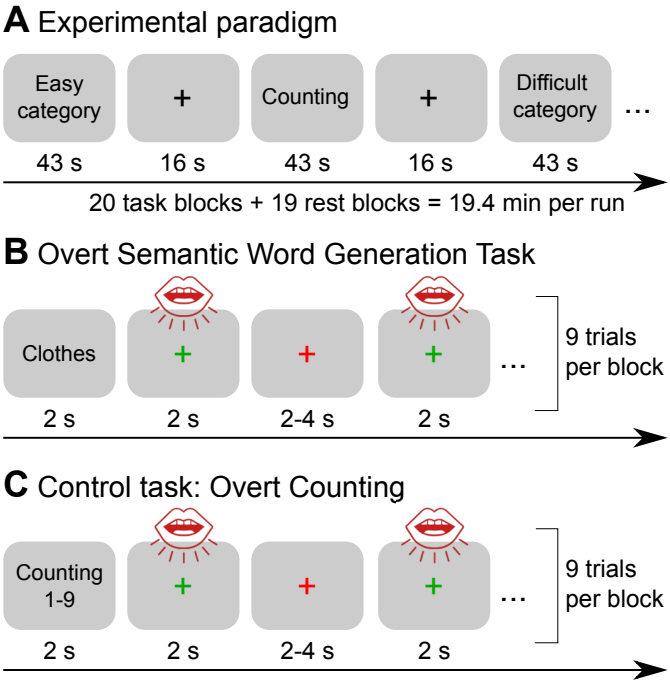

Figure 1. Experimental design. (A) fMRI experiment consisting of alternating blocks of a semantic fluency and a counting task separated by 16-s rest periods. (B) and (C) demonstrate the implementation of the paced design in both tasks. Procedures were identical for both tasks. Participants were instructed to produce one exemplar for a category or to say one number per green cross, respectively, and to pause when the cross turned red. Each block contained 9 trials which were separated by jittered inter-stimulus intervals.

blocks, divided in easy and difficult categories, and 10 counting blocks, consisting of forward and backward counting, thus resulting in a total duration of 19.4 min per run. The order of blocks was counter-balanced and pseudo-randomized across participants. Before the fMRI experiment, participants received instructions and practiced the task with a separate set of categories outside the scanner. Stimuli were presented using the software Presentation (Neurobehavioral Systems, Berkeley, USA; version 18.0). Answers were recorded via a FOMRI III microphone (Optoacoustics, Yehuda, Israel).

Stimuli

Stimuli consisted of 20 semantic categories which were divided in 10 easy and 10 difficult categories. Difficulty was assessed in a separate pilot study with 24 older adults (10 male, mean age: 65 years, range: 60-69 years). Participants were recruited and screened using similar criteria as in the fMRI study. They generated as many exemplars as possible during 1-minute trials for 30 semantic categories which were taken from German category-production norm studies (Mannhaupt, 1983; Glauer et al., 2007). Responses were recorded and subsequently transcribed and analyzed. Based on the total number of correct exemplars produced for each category, the 10 categories with the largest number of produced items (colors, body parts, clothing, types of sport, animals, car parts, professions, trees, food, and musical instruments) and the 10 categories with the fewest items (flowers, insects, metals, kitchen devices, tools, gardening tools, fishes, cosmetics, toys, and sweets) were chosen for the easy and difficult conditions of the semantic fluency task in the fMRI experiment, respectively. Easy (M = 16.8, SD = 2.5) and difficult categories (M = 10.4, SD = 2.0) differed significantly in the mean number of generated exemplars ($t(38.9) = 9.2$, $p < .001$) during piloting.

Data Acquisition and Preprocessing

MR images were collected at a 3-Tesla Prisma Scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. For the acquisition of fMRI data, a dual gradient echo-planar imaging multiband sequence (Feinberg et al., 2010) was used for optimal BOLD sensitivity across the whole brain (Poser et al., 2006; Halai et al., 2014). The following scanning parameters were applied: TR = 2,000 ms; TE = 12 ms, 33 ms; flip angle = 90°; voxel size = 2.5 x 2.5 x 2.5 mm with an inter-slice gap of 0.25 mm; FOV = 204 mm; multiband acceleration factor = 2. To increase coverage of ATL regions, slices were tilted by 10° of the AC-PC line. 616 images consisting of 60 axial slices in interleaved order covering the whole brain were continuously acquired per run. Additionally, field maps were obtained for later distortion correction (TR = 8000 ms; TE = 50 ms). This study analyzed the data from echo 2 (TE = 33 ms) since preprocessing was performed using the software fMRIPrep (Esteban et al., 2019), which currently does not support the combination of images acquired at different echo times. However, after double-checking with an SPM preprocessing pipeline of both echoes, our activation analyses did not appear to be affected by reduced sensitivity in regions that are especially susceptible to signal loss like the ATL. A high-resolution, T1-weighted 3D volume was obtained from our in-house database (if it was not older than 2 years) or collected after the functional scans using an MPRAGE sequence (176 slices in sagittal orientation; TR = 2300 ms; TE = 2.98 ms; flip angle = 9°; voxel size = 1 x 1 x 1 mm; no slice gap; FOV = 256 mm).

Results included in this manuscript come from preprocessing performed using fMRIPprep 1.2.6 (Esteban et al., 2019), which is based on Nipype 1.1.7 (Gorgolewski et al., 2017). In short, within the pipeline, anatomical images were processed using the software ANTs (Tustison et al., 2010) for bias field correction, skull stripping, coregistration, and normalization to the skull-stripped ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al. 2009). FreeSurfer (Dale, Fischl, and Sereno 1999) was used for brain surface reconstruction and FSL (Jenkinson et al. 2012) for segmentation. Functional data of each run were skull stripped, distortion corrected, slice-time corrected, coregistered to the corresponding T1 weighted volume, and resampled to MNI152NLin2009cAsym standard space. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using FSL. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation (https://fmriprep.org/en/1.2.6/workflows.html). After preprocessing, 29 volumes from the beginning of each run were discarded since they were collected for the combination of the short and long TE images via an estimation of the temporal signal-to-noise-ratio (Poser et al., 2006). This yielded 587 normalized images per run which were included in further analyses. The images were smoothed

with a 5 mm^3 FWHM Gaussian kernel using Statistical Parametrical Mapping software (SPM12; Wellcome Trust Centre for Neuroimaging), implemented in MATLAB (version 9.3/2017b).

Data Analysis

Behavioral data

Response recordings during the semantic fluency task were cleaned from scanner noise using Audacity (version 2.3.2, https://www.audacityteam.org/) and verbal answers and onset times were transcribed by 3 independent raters. Repetitions of words within a category were counted as incorrect, incomplete answers and null reactions were marked separately, and full categories that had been missed by participants (in total 10 categories) were excluded from the analyses. Statistical analyses were performed with R via RStudio (R Core Team, 2018) and the packages lme4 (Bates et al., 2015) and afex (Singmann et al., 2020) for mixed models and ggplot2 (Wickham, 2016) for visualizations. We used sum encoding (ANOVA-style encoding) for all categorical predictors. In this way, the intercept represents the mean across conditions (grand mean), and the model coefficients represent the difference between the grand mean and the mean of the respective condition. For the analysis of accuracy, a mixed-effects logistic regression was used accounting for the binary nature of the response variable (see SI Table S1, Equation 1). A linear mixed-effects model was fit to the log-transformed response time data (see SI Table S1, Equation 2). As fixed effects, we entered age, condition, and difficulty into the model. As random effects, we had intercepts for participants and categories. P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question. Post-hoc comparisons were applied using the package emmeans (Lenth et al., 2020).

Functional MRI data

Functional MRI data were modelled in SPM using the two-level approach. On the first level, a general linear model (GLM) was implemented for each participant. The GLM included regressors for the task blocks of the 4 experimental conditions (easy categories, difficult categories, counting forward, and counting backward) and nuisance regressors consisting of the six motion parameters and individual regressors for strong volume-to-volume movement as indicated by values of framewise displacement > 0.9 (Siegel et al., 2014). Additionally, an individual regressor of no interest was included if a participant had missed a whole task block during the experiment. Before model estimation, a high-pass filter with a cut-off at 128 s was applied to the data. Statistical parametric maps were generated by estimating the contrast for each condition against rest as well as the direct contrasts between conditions. At the second level, contrast images were entered into a random effects model. For each participant, an averaged mean-centered value of response time was

entered as covariate of no interest in the design matrix. For within-group comparisons, one-sample *t* tests were calculated for the main task-related contrasts Semantic fluency > Counting and Counting > Semantic fluency. To evaluate the modulation of task difficulty within the semantic fluency task, the contrasts Easy > Difficult categories and Difficult > Easy categories were computed.

To investigate the effect of age on task-related activity, we conducted between-group comparisons for Semantic Fluency > Rest and the interaction contrast $c_{Age\ x\ Condition}$. Two-sample *t* tests were carried out using the individual contrast images from the first-level analysis. To ensure that potential areas were indeed active in the respective group, all interactions were characterized by inclusively masking each contrast with significant voxels of the minuend (cf. Noppeney et al., 2006, Meinzer et al., 2012b). A gray matter mask which restricted statistical tests to voxels with a gray matter probability > 0.3 (SPM12 tissue probability map) was applied to all second-level analyses. All results except for the interaction contrasts were corrected for multiple comparisons applying a peak-level threshold at $p < 0.05$ with the family-wise error (FWE) method and a cluster-extent threshold of 20 voxels. Interaction results were thresholded at $p < 0.05$ at the cluster-level with FWE correction and a voxel-wise threshold at $p < 0.001$. Anatomical locations were identified with the SPM Anatomy Toolbox (Eickhoff et al., 2005, version 2.2c) and the Harvard-Oxford cortical structural atlases distributed with FSL (https://fsl.fmrib.ox.ac.uk). Brain results were rendered by means of BrainNet Viewer (Xia et al., 2013, version 1.7) and MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/, version 1.2.20200331).

Since the strongest activation peaks for both tasks were found in the domain-general systems MDN and DMN, we decided to examine the amount of activation for each condition and age group. We applied binary masks of both networks to within-group analyses to identify clusters that fell within the respective network. The MDN mask was based on the anatomical parcels of the MD system defined by Fedorenko et al. (2013; available at https://evlab.mit.edu/funcloc/). For the DMN, a mask was created from the 7 networks parcellation by Schaefer et al. (2018). For the contrast Semantic fluency > Counting, peak global maxima were found in the MDN, whereas the reverse contrast identified maxima in the DMN. In total, we found 9 peak maxima for older adults and 5 peak maxima for younger adults in the MDN, and 2 and 3 peak maxima in the DMN, respectively (Table 2). Regions of interest (ROIs) for these maxima were created using the MarsBar toolbox (Brett et al., 2002; version 0.44). To this end, identified clusters were extracted from contrast images, spheres of 5 mm from each maxima coordinate were created, and, in a last step, both images were combined. Subsequently, we extracted parameter estimates for these ROIs from the individual contrast images for Semantic fluency > Rest and Counting > Rest. The data were

then entered into a linear mixed-effects model with network, age, and condition as fixed effects. A random intercept was included for participants (see SI Table S1, Equation 3). Categorical predictors were effect-coded. Significance values were obtained through likelihood ratio tests using the packages lme4 (Bates et al., 2015) and afex (Singmann et al., 2020). Post-hoc comparisons were applied using the package emmeans (Lenth et al., 2020).

Connectivity analyses

We conducted psychophysiological interaction (PPI) analyses using the gPPI toolbox for SPM12 (McLaren et al., 2012) to investigate task-related modulation of functional connectivity associated with the semantic fluency and the counting task. Furthermore, we applied a modified version of gPPI methods to examine functional connections between individual ROIs during the semantic fluency task (Pongpipat et al., 2020). Seed regions were defined for all previously identified global maxima that were located within the MDN and the DMN (Table 2). For each participant, ROIs were created by searching for the individual peaks within a bounding region of 10 mm relative to the group peak and then drawing a sphere mask (5 mm in diameter) around the individual peak of a given contrast at a threshold of $p < 0.01$. Regression models were set up for each ROI in each participant containing the deconvolved time series of the first eigenvariate of the BOLD signal from the respective ROI as the physiological variable, the four task conditions convolved with the HRF as the psychological variable, and the interaction of both variables as the PPI term. Subsequently, first-level GLMs were calculated. For the gPPI proper methods, contrast images were then entered into a random effects model for group analyses in SPM. We restricted this analysis to the strongest peaks of both contrasts (Semantic fluency > Counting and Counting > Semantic fluency) that fell within the MDN and DMN, respectively, and were present in both age groups. This included the left pre-SMA, bilateral insulae, the right temporal pole and the right precuneus. Our main contrast of interest Semantic fluency > Counting was examined in within-group as well as between-group comparisons by conducting one-sample *t* tests and a two-sample *t* test, respectively. Multiple comparison correction was performed with the FWE method at $p < 0.05$ at peak-level and a cluster-extent value of 20 voxels. A gray matter mask was applied to all group analyses as described for the task-based fMRI data analysis.

For the modified gPPI, we used the individual first-level GLMs to retrieve parameter estimates (mean regression coefficients). Estimates were extracted for the PPI variable Semantic fluency > Counting for each seed-to-target ROI (Older adults: 1 regression coefficient [PPI] * 11 seed ROIs * 10 target ROIs = 110 parameter estimates per participant; Young adults: 1 regression coefficient [PPI] * 8 seed ROIs * 7 target ROIs = 56 parameter estimates per participant).

Table 2. Regions of interest (ROIs) within domain-general networks.

ROI	Hemi	*x*	*y*	*z*	Region
Older adults					
MDN (from contrast Semantic fluency > Counting)					
1	L	-9	15	51	Pre-SMA
2	L	-31	25	4	Insula
3	R	31	27	2	Insula
4	L	-34	0	57	MFGd
5	L	-44	5	35	MFGv
6	R	43	35	32	MFG
7	L	-14	-65	51	SPL
8	L	-11	-72	10	IntraCAL
9	R	18	-80	7	IntraCAL
DMN (from contrast Counting > Semantic fluency)					
10	R	6	-52	38	Precuneus
11	R	51	12	-31	TP
Young adults					
MDN (from contrast Semantic fluency > Counting)					
1	L	-4	2	29	dACC
2	L	-31	25	2	Insula
3	R	31	27	2	Insula
4	R	36	42	32	MFG
5	L	-29	-65	51	SPL
DMN (from contrast Counting > Semantic fluency)					
6	L	-56	2	-20	MTG
7	R	8	-65	29	Precuneus
8	R	51	10	-31	TP

Coordinates are given in MNI standard space. Abbreviations: Hemi Hemisphere; Pre-SMA Pre-supplementary motor area; MFG/MFGd/MFGv Middle frontal gyrus dorsal/ventral; SPL Superior parietal lobe; IntraCAL Intracalcarine gyrus; TP Temporal pole; dACC Dorsal anterior cingulate cortex; MTG Middle temporal gyrus; MDN Multiple-demand network; DMN Default mode network.

Subsequent group analyses were performed in RStudio (R Core Team, 2018) with the packages lme4 (Bates et al., 2015) and afex (Singmann et al., 2020), and visualized using the ggplot2 (Wickham, 2016) and the ggeffects (Lüdecke, 2018) packages. Categorical predictors were sum-encoded. We were interested in the functional connectivity within and between MDN and DMN regions for each age group. To this end, we calculated intercept-only GLMs where each parameter estimate of each seed and target combination was entered into the model except when seed and target were identical (SI Table S1, equation 4). The α-level (Type I error) for post-hoc comparisons was adjusted using the *Meff* correction (Derringer, 2018). This method estimates the effective number of tests (*Meff*) from the correlations among tested variables and thereby allows for adjusting statistical significance thresholds for multiple comparisons without assuming independence of all tests (Derringer, 2018). The *Meff* value for MDN and MDN variables was calculated to be 7.46 for the young adults and 10.00 for the older adults. By dividing this value by the overall α of 0.05, we obtained a Meff-corrected α of 0.007 for the young and a Meff-corrected α of 0.005 for the older adults, respectively. For subsequent analyses, the individual parameter estimates of each seed-to-target combination were averaged to create one value per participant for within-MDN, within-DMN, and between-network functional connectivity (3 parameter estimates per participant). To test for an effect of age on

functional connectivity, the parameter estimates were then entered into a GLM with age as independent variable (SI Table S1, equation 5). We used Meff-correction to adjust for multiple comparisons. A *Meff* value of 2.76 yielded a Meff-corrected α of 0.018.

Finally, we were interested in the effect of within- and between-network functional connectivity on participants' behavioral performance during the in-scanner task. To this end, we calculated generalized mixed-effects logistic regressions for the accuracy data (SI Table S1, equation 6) and linear mixed-effects models for the log-transformed response time data (SI Table S1, equation 7). The mean-centered $PPI_{network}$ variable, age, and condition as well as their interaction terms were entered as fixed effects. Random intercepts were included for participants and semantic categories.

Results

Behavioral Results

For response accuracy, we fitted a generalized linear mixed-effects model (SI Table S1). Likelihood ratio tests indicated main effects of condition ($\chi^2 = 21.55$, $p < 0.001$) and task difficulty ($\chi^2 = 27.43$, $p < 0.001$) but not of age group ($\chi^2 = 0.19$, $p = 0.66$). Post-hoc tests applying Bonferroni-corrected pairwise comparisons showed that both age groups produced more correct items in the counting than in the semantic fluency task. For the main effect of task difficulty, post-hoc tests indicated a significant difference for the difficulty modulation within the semantic fluency task (easy vs. difficult categories) and the counting task (counting forward vs. counting backward) (Fig. 2A; SI Table S2).

Response time data were analyzed fitting a linear mixed-effects model. Likelihood ratio tests revealed main effects of age group ($\chi^2 = 17.02$, $p < 0.001$), condition ($\chi^2 = 1404.94$, $p < 0.001$), and difficulty ($\chi^2 = 167.62$, $p < 0.001$). There was a significant interaction between age and condition ($\chi^2 = 68.37$, $p < 0.001$), and between condition and difficulty ($\chi^2 = 118.43$, $p < 0.001$). Post-hoc tests using Bonferroni-corrected pairwise comparisons showed that both age groups responded significantly slower during the semantic fluency task than the counting task and during the difficult than the easy condition. Furthermore, young adults responded generally faster than older adults during the semantic fluency task, independent of the level of difficulty, but not during the counting task (Fig. 2B; SI Table S3).

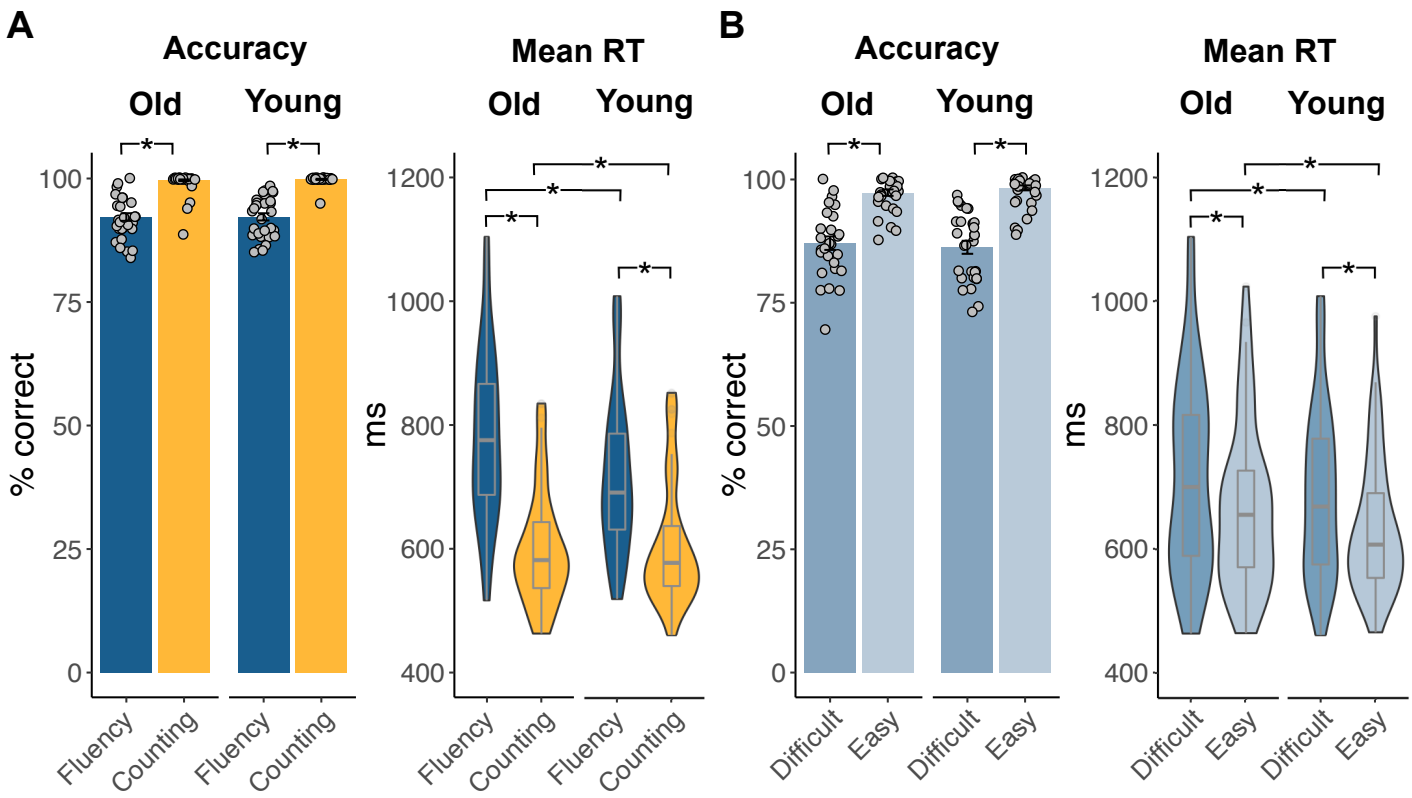

Figure 2. Behavioral results for both age groups. Bar graphs overlaid with mean individual data points for accuracy and violin plots with box plots for mean response times for (A) both tasks (semantic fluency and counting) and (B) difficulty levels (easy and difficult) within semantic fluency. Old: Older adults, Young: young adults. * $p < 0.001$ (Bonferroni-corrected for pairwise comparisons).

Functional MRI Data

The effect of task within groups

Both age groups showed similar activation patterns for the main effects of our tasks compared to rest. For semantic fluency, we found a left-lateralized fronto-temporo-parietal network with additional clusters in right frontal and temporal areas, bilateral caudate nuclei, and the cerebellum (SI Fig. S2A; Tables S4 & S5). The main effect of the less demanding task counting was evident in bilateral activation of sensorimotor cortices and the cerebellum (SI Fig. S2B; Tables S6 & S7). Within each age group, we were interested in the difference in brain activation between the more demanding semantic fluency task and the automatic speech counting task as well as in the impact of the modulation of task difficulty in the semantic fluency task. For the older adults, the contrast Semantic fluency > Counting revealed a bilateral frontal network with its strongest activation peaks in middle frontal gyri, bilateral insulae extending into inferior frontal gyri, and midline structures comprising superior and medial frontal gyri. Activation in the left hemisphere was further observed in the angular gyrus and superior parietal lobe. Additional bilateral activation peaks were found in the cerebellum, caudate nuclei, calcarine gyri, and thalami (Fig. 3A; SI Table S8). Younger adults demonstrated a similar pattern of activation for the contrast Semantic fluency > Counting, albeit

with generally larger clusters in the frontal network (Fig. 3A; SI Table S9). Analyses further yielded separate clusters in the dorsal anterior cingulate cortex (dACC) and the left superior temporal gyrus for the younger group which were not present in the older participants. The reverse contrast (Counting > Semantic fluency) revealed stronger activation in the right hemisphere for both groups. Results showed clusters in the right temporal pole and bilateral precunei (Fig. 3B; SI Tables S10 & S11). In the younger group, additional clusters were observed in bilateral insulae and the middle temporal gyrus.

A linear mixed-effects model was fit for the mean value of parameter estimates for all peak clusters in the MDN and DMN (Table 2), respectively. Likelihood ratio tests indicated that the model including explanatory variables for network ($\chi^2 = 164$, $p < 0.001$), age ($\chi^2 = 5.68$, $p = 0.017$), and condition ($\chi^2 = 22.44$, $p < 0.001$) provided a better fit for the data than a model without these effects (Fig. 3C; SI Table S12). We further found a significant interaction between network and condition ($\chi^2 = 206.16$, $p < 0.001$). Post-hoc comparisons applying Bonferroni correction showed that the MDN was stronger activated for the semantic fluency task in both age groups, whereas the DMN showed stronger deactivation for this task. For the counting task, there was no difference in activation between both networks.

The effect of task difficulty within groups

To investigate the effect of task difficulty on functional brain activation, we contrasted easy and difficult categories from the semantic fluency task in both age groups. We found a significant result only for young adults for the contrast Easy > Difficult categories in the right middle frontal gyrus (SI Table S13).

Between-group comparisons

We were interested in the effect of age on task-related activations. For the interaction of both tasks compared to baseline, we found a group difference only during the semantic fluency task for older adults. We detected stronger activity in right frontal regions including superior frontal gyrus and inferior frontal gyrus as well as bilateral parietal lobes (Fig. 4A; Table 3). We were further interested in the interaction of age and condition. The contrast Semantic fluency > Counting revealed a significant interaction with age only for young adults. Stronger activity was observed in regions related to the MDN, including the paracingulate gyrus, pre-SMA, and the dACC (Fig. 4B; Table 3). The interaction of age with task difficulty (easy and difficult semantic categories) did not yield any significant results.

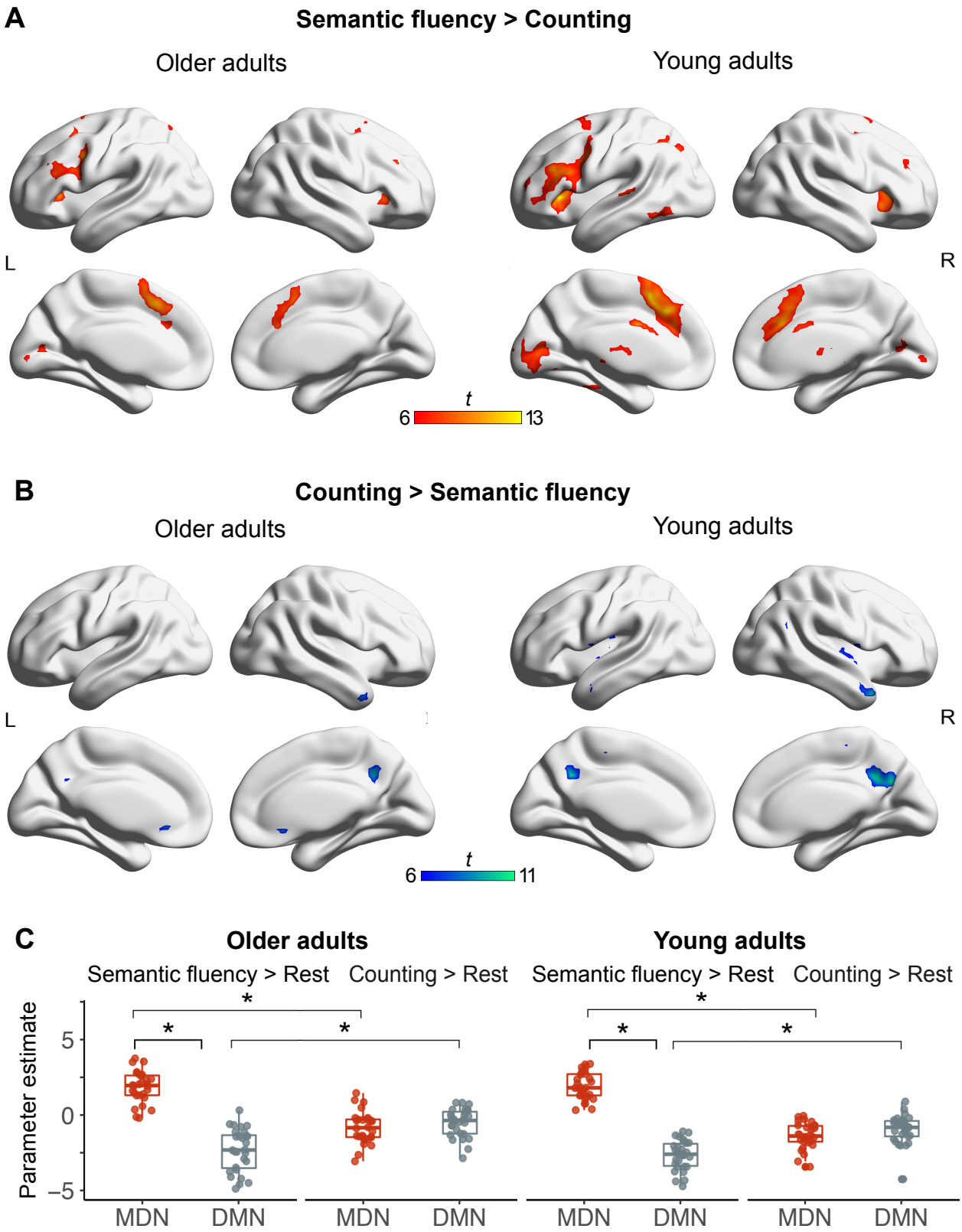

Figure 3. Functional MRI results from univariate analyses for each age group and parameter estimates for peak global maxima identified within the MDN and the DMN. (A & B) Results are FWE-corrected at $p < 0.05$ at peak-level with a minimum cluster size = 20 voxel. (C) * Significant effects are Bonferroni-corrected. Abbreviations: MDN Multiple-demand network; DMN Default mode network.

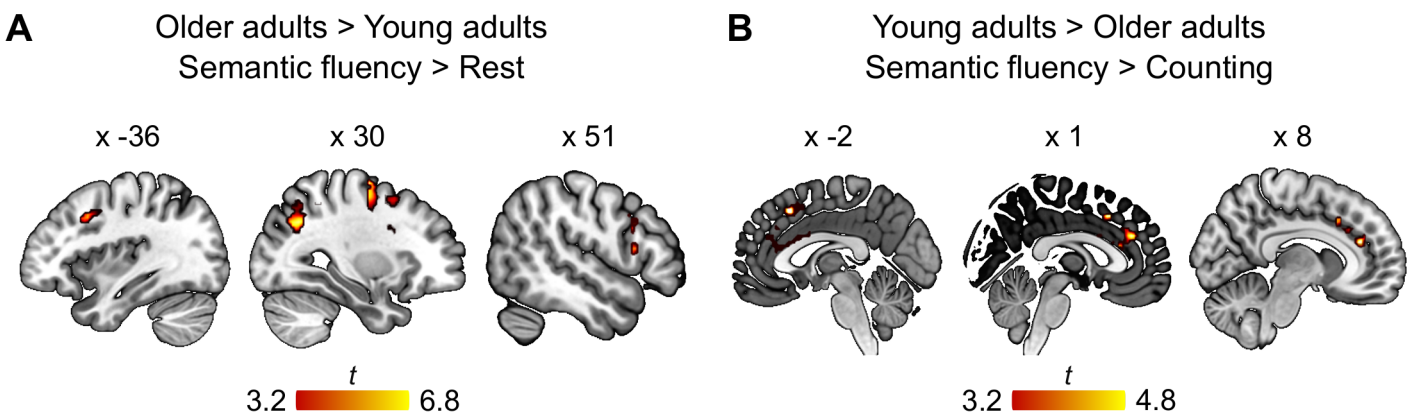

Figure 4. Functional MRI results for interaction effects. Cluster corrected at FWE $p < 0.05$ with a voxel-wise threshold at $p < 0.001$. (A) Restricted to voxels that showed a significant effect of semantic fluency in older adults and (B) restricted to voxels that showed a significant effect of semantic fluency in young adults.

Generalized psychophysiological interactions

Based on the activation patterns from our univariate within-group analyses, we conducted traditional gPPI analyses for the 5 strongest activation peaks that fell within the MDN or DMN and were present in both age groups.

Whole-brain functional connectivity for semantic fluency

For the contrast Semantic fluency > Counting, the seeds included the left pre-SMA and bilateral insulae. We asked whether and how increased semantic task demands modulate connectivity of our ROIs. For the seeds in the left pre-SMA and left insula, analyses revealed only significant clusters in the group of younger adults, whereas the seed in the right insula yielded only significant results for the older adults. The left pre-SMA showed increased connectivity with subcortical structures (bilateral caudate nuclei and thalami) as well as with the left precuneus and PCC in the parietal lobe (Fig. 5A; SI Table S14). For the seed in the left insula, we found a similar connectivity pattern. Significant coupling was observed with bilateral caudate nuclei and the left precuneus (Fig. 5B; SI Table S15). For the older adults, the right insula showed significant coupling with the precuneus and pars orbitalis in left inferior frontal gyrus (Fig. 5C; SI Table S16).

Whole-brain functional connectivity for counting

For the contrast Counting > Semantic fluency, we conducted traditional gPPI analyses for two seeds that were located in the DMN and were present in univariate within-group results in both age groups, the right temporal pole and the right precuneus. Seeding in the right temporal pole showed increased functional connectivity exclusively in the ipsilateral hemisphere. For the older adults, we found a significant cluster in inferior frontal gyrus (pars orbitalis) which extended into the insula (Fig. 6A; SI Table S17). For the young adults, results revealed significant clusters in the inferior frontal gyrus (pars opercularis), superior frontal gyrus, insula, and supramarginal gyrus (Fig. 6B,

Table 3. Results for age-dependent differences in task-related activity.

Anatomical structure	Hemi	*k*	*t*	*x*	*y*	*z*
Interaction older > young adults for semantic fluency > rest (inclusively masked with [older adults: semantic fluency > rest])						
Superior frontal gyrus	**R**	**110**	**6.84**	**28**	**-8**	**65**
Precentral gyrus	R		5.53	28	-8	54
Superior parietal lobe	**R**	**263**	**6.82**	**18**	**-60**	**60**
Middle occipital gyrus	R		6.04	31	-62	35
Precuneus	R		5.93	11	-55	60
Precuneus	R		5.39	13	-67	62
Middle frontal gyrus	**L**	**74**	**5.38**	**-36**	**15**	**38**
Middle frontal gyrus	L		4.05	-46	17	38
Precentral gyrus	L		3.76	-41	2	48
Inferior parietal lobe	**L**	**109**	**5.12**	**-31**	**-45**	**54**
Superior parietal lobe	L		4.32	-19	-60	46
Precuneus	L		4.28	-11	-70	48
Superior parietal lobe	L		4.19	-16	-62	60
Middle frontal gyrus	**R**	**132**	**4.96**	**36**	**5**	**38**
Inferior frontal gyrus, p.tr.	R		4.53	36	17	24
Inferior frontal gyrus, p.op.	R		4.07	48	17	13
Inferior frontal gyrus, p.op.	R		3.73	51	15	26
Middle frontal gyrus	**R**	**74**	**4.47**	**26**	**12**	**51**
Interaction young > older adults for semantic fluency > counting (inclusively masked with [young adults: semantic fluency > counting])						
Pre-SMA	**L**	**79**	**4.84**	**-1**	**20**	**46**
Pre-SMA	R		3.81	11	27	32
Pre-SMA	L		3.55	-1	10	48
Anterior cingulate cortex	**R**	**114**	**4.58**	**8**	**37**	**21**
Pre-SMA	R		4.36	1	37	26
Anterior cingulate cortex	L		4.13	-1	20	21
Anterior cingulate cortex	L		3.58	-4	5	29

Cluster corrected at FWE $p < 0.05$ with a voxel-wise threshold at $p < 0.001$. Coordinates are given in MNI standard space, cluster size (k) is given in mm^3. Note that no significant differences above cluster correction threshold were found for (i) interaction young > older adults for semantic fluency > rest, (ii) interaction older > young adults for semantic fluency > counting. Abbreviations: Hemi Hemisphere; p. tr. pars triangularis; p.op. pars opercularis; pre-SMA pre-supplementary motor area.

SI Table S17). The seed in the right precuneus revealed extensive bilateral functional coupling in both age groups. For the older adults, the right precuneus showed prominent connectivity with frontal and parietal areas in both hemispheres (Fig. 6C; SI Table S18). A similar pattern emerged for the group of younger adults, albeit with a greater number of significant clusters. Moreover, clusters were also found in the temporal lobe, occipital cortex, and cerebellum (Fig. 6D; SI Table S18). Two-sample *t* tests did not show significant differences between groups in the PPI results for either task.

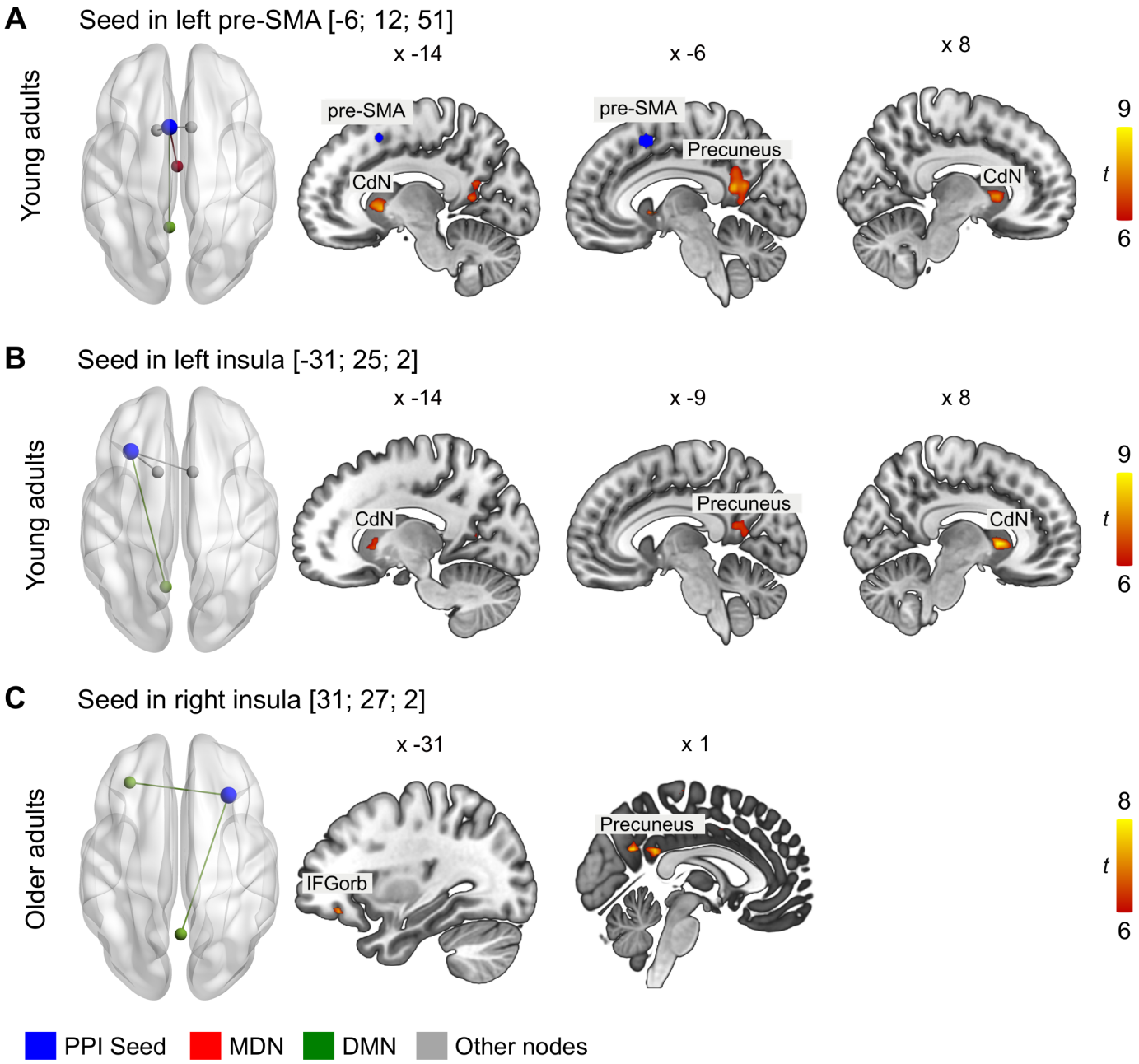

Figure 5. Functional connectivity for Semantic fluency. gPPI within-group results for the different seeds in the contrast Semantic fluency > Counting. All results are FWE-corrected at $p < 0.05$ at peak-level with a minimum cluster size = 20 voxel. Abbreviations: Pre-SMA Presupplementary motor area; CdN Caudate nucleus; IFGorb Inferior frontal gyrus, pars orbitalis.

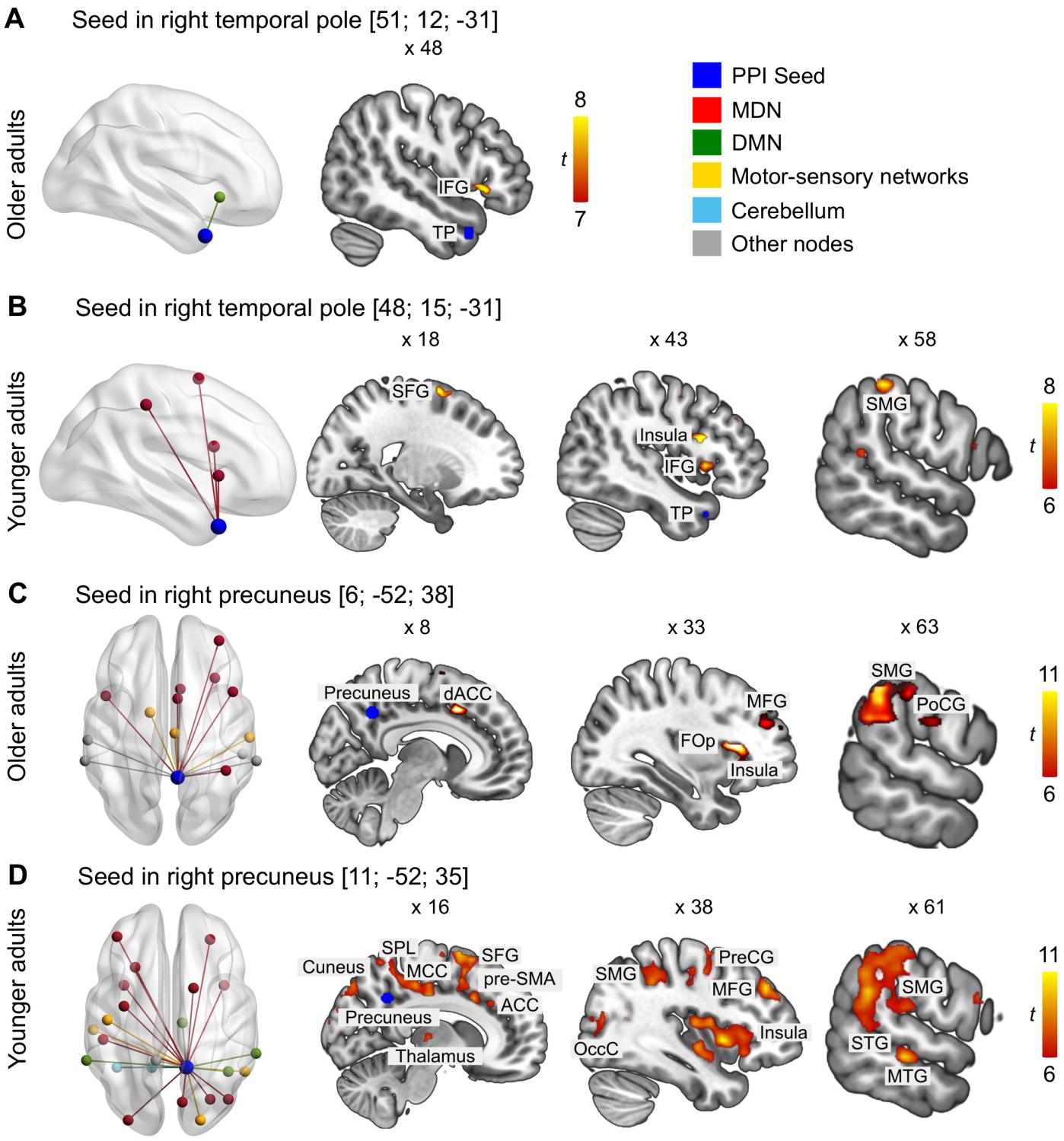

Figure 6. Functional connectivity for Counting. gPPI within-group results for the different seeds in the contrast Semantic fluency > Counting. All results are FWE-corrected at $p < 0.05$ at peak-level with a minimum cluster size = 20 voxel. Abbreviations: IFG Inferior frontal gyrus; TP Temporal pole; SFG Superior frontal gyrus; SMG Supramarginal gyrus; dACC dorsal anterior cingulate cortex; FOp Frontal operculum; PoCG Posterior central gyrus; SPL Superior parietal lobe; MCC Middle cingulate cortex; pre-SMA Presupplementary motor area; ACC Anterior cingulate cortex; PreCG Precentral gyrus; MFG Middle frontal gyrus; OccC Occipital cortex; STG Superior temporal gyrus; MTG Middle temporal gyrus.

Within- and between-network functional connectivity during semantic fluency

To further examine the task-related connectivity within and between the domain-general systems MDN and DMN during the semantic fluency task compared to counting, we conducted modified gPPI analyses. For each seed-to-target combination of the ROIs in MDN and DMN (Table 2), we calculated intercept-only GLMs for each age group (Fig. 7A). For the older adults, the results showed significant positive functional connectivity for regions within the MDN but not for regions within the DMN. Further, the results revealed strong coupling for regions between MD and DM networks for the older adults. A similar pattern was observed for the young adults, albeit with overall stronger connectivity. Compared to the counting task, results showed strengthened functional connectivity within regions of the MDN and for regions between MD and DM networks during semantic fluency.

Effect of age on within- and between-network functional connectivity

We were interested whether there was an effect of age group on the within- and between network functional connectivity. To this end, each PPI network pair (within-MDN, within-DMN, and between MDN and DMN) was regressed on age (Fig. 7B; SI Table S19). Multiple-comparisons correction was performed using Meff-correction. The results did not show a significant effect of age on within- and between-network functional connectivity (p's > 0.2) suggesting that the strength of functional connectivity was age-invariant.

Effect of functional connectivity on task performance

To determine whether functional connectivity within and between regions of MDN and DMN predicted participant's in-scanner task performance, we fitted mixed-effects models for accuracy and response time as outcome variables and functional connectivity, age, condition, and their interaction terms as explanatory variables. For accuracy, we found significant effects for within-network and between-network functional connectivity pairs (Fig. S2). For within- network functional connectivity, results showed similar patterns for MDN and DMN (SI Fig. S2A & B, Table S20 & S21). We identified main effects of within-network functional connectivity (within-MDN: $\chi^2 = 11.89$, $p < 0.001$; within-DMN: n.s.) and condition (within- MDN: $\chi^2 = 10.40$, $p =$ 0.001; within-connectivity and age (within-MDN: $\chi^2 = 4.71$, $p = 0.30$; within-DMN: $\chi^2 = 10.85$, $p <$ 0.001), and within-network functional connectivity and condition (within-MDN: $\chi^2 = 17.98$, $p <$ 0.001; within-DMN: $\chi^2 = 3.98$, $p = 0.046$). Further, results revealed a significant three-way interaction between within-network functional connectivity, age, and condition for both networks (within-MDN: $\chi^2 = 5.56$, $p = 0.18$; within-DMN: $\chi^2 = 13.32$, $p < 0.001$). For both age groups,

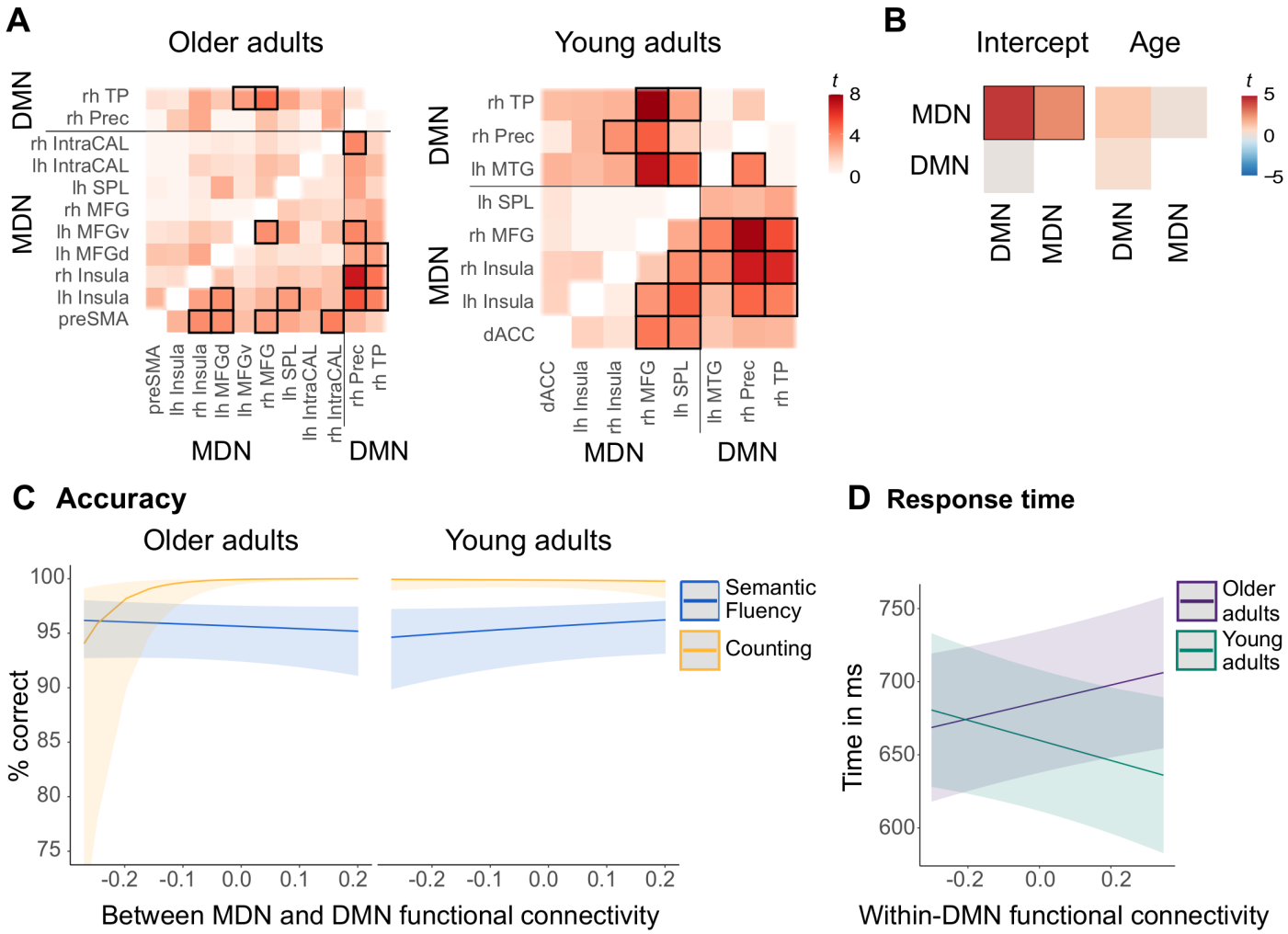

Figure 7. Functional connectivity of domain-general network regions during Semantic fluency. (A) Within- and between-network functional connectivity for each seed to target combination for each age group. Heatmaps show *t* values. Thresholded *t* values with Meff-corrected α of 0.005 (Older adults) and 0.007 (Young adults) are indicated with black boxes. (B) Effect of age on functional connectivity. There were no age differences in functional connectivity between or within networks. Heatmaps show t values with Meff-corrected α of 0.018. Significant effects are indicated with black boxes. (C) Significant three-way interaction between age, condition, and between-network functional connectivity for Accuracy. (D) Significant two-way interaction between age and within-DMN functional connectivity for Response time. Abbreviations: rh right hemisphere; lh left hemisphere; TP Temporal pole; Prec Precuneus; IntraCAL Intracalcarine gyrus; SPL Superior parietal lobe; MFGd/v Middle frontal gyrus dorsal/ventral; preSMA Presupplementary motor area; MTG Middle temporal gyrus; dACC Dorsal anterior cingulate cortex; MDN Multiple-demand network; DMN Default mode network.

strengthened within-network connectivity was associated with an increase in accuracy for counting and a decrease in accuracy for semantic fluency. Analyses for the between-network functional connectivity also showed main effects of functional connectivity ($\chi^2 = 8.05$, $p = 0.005$) and condition ($\chi^2 = 11.85$, $p < 0.001$), as well as two-way interactions between functional connectivity and age ($\chi^2 = 17.79$, $p < 0.001$) and functional connectivity and condition ($\chi^2 = 7.97$, $p = 0.005$), and a three-way interaction between functional connectivity, age, and condition ($\chi^2 = 24.95$, $p < 0.001$). Contrary to the results for within-network functional connectivity, the age groups showed

divergent effects for functional connectivity between MDN and DMN (SI Table S22). A strengthened functional connectivity between MD and DM network regions was associated with a decrease in performance for semantic fluency for the older adults and an increase in performance for the young adults (Fig. 7C).

Analyses further revealed significant effects of functional network connectivity on response time data (Fig. 7C; SI Fig. S3). Results for all 3 network pairs confirmed our findings for the behavioral data with main effects of age and condition as well as their significant interaction. For functional connectivity, we identified main effects of within-MDN ($\chi^2 = 53.15$, $p < 0.001$) and between MDN and DMN ($\chi^2 = 262.11$, $p < 0.001$) functional connectivity. Both main effects showed that an increase of connectivity led to a slower response time (Fig. 7C; SI Fig. S3A & C, Table S23 & S25). Moreover, a significant interaction between within-MDN functional connectivity and condition ($\chi^2 = 13.12$, $p < 0.001$) was found where participants responded slower for semantic fluency than for counting with increasing connectivity (Fig. S3A). For within-DMN functional connectivity, age moderated the effect on response time ($\chi^2 = 19.38$, $p < 0.001$). While response time increased with strengthened connectivity for older adults, the opposite pattern was observed for young adults who responded faster when within-DMN functional connectivity increased (Fig. 7D; SI Fig. S3B, Table S24).

Taken together, functional connectivity within- and between MD and DM network regions was associated with accuracy and response time of the experimental task. For accuracy, age had different effects on the connectivity pairs where a stronger within-network functional connectivity was associated with a decreasing performance in semantic fluency while a different picture emerged for between-network functional connectivity. Here, young adults profited from a strengthened connectivity whereas older adults showed the opposite pattern. For response time, we found that age only moderated the within-DMN functional connectivity. Again, young adults improved their performance with stronger connectivity while older adults responded slower when within-DMN functional connectivity strengthened.

Discussion

The current study set out to describe the effects of aging on the role of domain-specific and domain-general neural networks in semantic cognition. By contrasting a semantic fluency task with a low-level verbal control task in an fMRI experiment, we delineated two distinct task-related networks which displayed strong overlap with the domain-general MD and DM systems. Using task-based connectivity analyses, our findings point towards a strong interaction of these networks during verbal semantic processing across age groups and lend support to the notion that integration between usually anti-correlated functional networks increases for tasks that require cognitive control (Shine et al., 2016). Importantly, our results provide new insights into the impact of age on the functional coupling between MDN and DMN regions when semantic knowledge is retrieved in a goal-directed manner from memory. In line with a recent suggestion that additional recruitment of the prefrontal cortex in older adulthood might not reflect compensation but rather reduced efficiency or specificity (Morcom and Henson, 2018), we show here for the first time that the frequently reported pattern of strengthened between-network functional connectivity in older adults (Chan et al., 2014; Geerligs et al., 2015; Spreng et al., 2016) is associated with a decline in task efficiency in semantic cognition.

Our task paradigm revealed two distinct functional networks for semantic fluency and counting. The main effect of semantic fluency displayed a predominantly left lateralized fronto-temporo-parietal network for both age groups with additional activation peaks in right frontal and temporal areas, bilateral caudate nuclei, and the cerebellum. These results align well with previous investigations that applied a semantic fluency paradigm (Baciu et al., 2016; Birn et al., 2010; Marsolais et al., 2014; Meinzer et al., 2009, 2012a, 2012b; Nagels et al., 2012; Vitali et al., 2005; Wagner et al., 2014; Whitney et al., 2009). The main effect of the counting task was evident in both groups in bilateral activation of sensorimotor cortices and the cerebellum which is consistent with previous studies that used an automated speech task (e.g., Birn et al., 2010; Geranmayeh et al., 2014; Marsolais et al., 2014). Older adults showed additional recruitment of the pre-supplementary motor area which could reflect increased cognitive demands for this age group while keeping track of the numbers during counting. In the direct comparison of both tasks, semantic fluency elicited a network that resembled the main effect of the task minus activity in pre- and postcentral gyri in both age groups which corroborates the functional role of this network in spoken language beyond low-level sensorimotor aspects (Geranmayeh et al., 2014). Significant activation for the counting task compared to semantic fluency was evident in a mainly right lateralized network. Previous studies have suggested that neural networks for highly overlearned automated speech tasks are either right-lateralized in healthy participants (Sidtis et al., 2009; Vanlancker-Sidtis et al., 2003) or show less

left lateralization than semantically rich language production tasks (Bookheimer et al., 2000; Petrovich Brennan et al., 2007). Further evidence stems from the common observation that automated speech (e.g., counting) is often preserved in patients who suffer from aphasia after a left hemisphere stroke (Vanlancker-Sidtis et al., 2003).

Remarkably, we found that the strongest activation clusters for semantic fluency were located in the domain-general MD system in both age groups. There is emerging evidence on the overlap of language-specific regions like the left inferior frontal gyrus with networks that are implicated in domain-general executive processing (Fedorenko et al., 2012) and semantic control processes (Noonan et al., 2013; Thompson-Schill et al., 1997; Wagner et al., 2001). Here, we observed strong activation in cognitive control regions like the midline dorsal frontal cortex, including dACC and the pre-SMA in superior frontal gyrus, and bilateral anterior insulae, that have been repeatedly associated with language production (Eickhoff et al., 2009; Geranmayeh et al., 2012; Tremblay and Gracco, 2009) but also with domain-general cognitive control across a variety of tasks (Fedorenko et al., 2013; Kennedy et al. 2015; Kerns et al., 2004). Hence, these regions may not be language-specific but appear to strongly contribute to a task that requires goal-directed controlled access to semantic memory while monitoring the verbal articulation of words that match the semantic categories. Further support for the contribution of executive functions to semantic fluency stems from behavioral studies that associated cognitive flexibility, inhibition, working memory, and attention with a successful performance (Aita et al., 2018; Amunts et al., 2020; Gordon et al., 2018). Although activations in regions of the MDN have been reported by studies on semantic fluency repeatedly (Heinzel et al., 2013; Nagels et al., 2012; Whitney et al., 2009), to our knowledge, this is the first investigation that related them to a cognitive control network in an integrative manner (in the direct comparison of language and cognitive control networks). For both age groups, peak clusters of counting were found to be located in the posterior DMN which is in line with our expectation of a low-level language production task in comparison to the more demanding semantic fluency task.

Our whole-brain functional connectivity results based on traditional gPPI analyses showed that regions in the domain-general MD and DM systems strongly interact during a semantic word retrieval task compared to counting across both age groups. This was true for seeds coming from the MDN as well as the DMN. This finding is in line with previous studies that reported task-specific functional coupling of cognitive control regions with the DMN, most notably the posterior cingulate cortex (PCC)/precuneus, especially in tasks requiring controlled access to semantic memory (Krieger-Redwood et al., 2016; Smith et al., 2016). Remarkably, the PCC/precuneus was

the only region in our study that showed functional connectivity with all seeds from the MDN and also displayed extensive functional coupling with multiple nodes in the MDN as well as other neural networks in both age groups. This finding stresses its role as a cortical hub connecting networks to support complex behavior (Leech et al., 2012). The functional coupling of MDN and DMN is especially interesting in light of our functional results where we observed significant deactivation in regions of the DMN during semantic fluency in both age groups. It corroborates the notion that networks that are anti-correlated during task can still show functional integration in contextually relevant situations to facilitate goal-directed behavior (Krieger-Redwood et al., 2016; Spreng et al., 2014).

We gained further insight into the task-related functional integration of MD and DM network regions by our analyses of phase synchronization within and between both domain-general systems. Our results show that functional coupling within the MDN and between the MDN and the DMN strengthened with an increase of task load, which was independent of age. First, the positive coupling within regions of the MDN is in line with our univariate results for semantic fluency: here, we found that the strongest activation clusters were located in the MDN in both age groups, thus confirming the necessary engagement of this network for successful task performance. Second, the strong in-phase synchronicity between regions of the MD and DM network for semantic fluency compared to the control task complement our PPI results which showed a strong interaction of both domain-general systems. This is line with the notion that the integration of the DMN is relevant for successful task processing in memory-guided cognition (Smith et al., 2016; Vatansever et al., 2015), especially when access to semantic memory is required (Wirth et al., 2011; Krieger-Redwood et al., 2019).

Interestingly, our results on whole-brain as well as within- and between-network functional connectivity did not reveal an effect of age. There is an extant literature describing age-related changes in connectivity in resting state networks with the most common observation of decreased within- and increased between-network functional connectivity (Chan et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015; Grady et al., 2016; Ng et al., 2016; Zonneveld et al., 2019). However, results are more inconsistent for task-related changes in functional connectivity with age. Across a range of cognitive tasks, studies reported a similar pattern as for resting state investigations (Geerligs et al., 2014; Spreng et al., 2016), no changes for within- but only for between-network connectivity (Gallen et al., 2016; Grady et al., 2016), as well as age invariance (Pongpipat et al., 2020; Trelle et al., 2019). In the domain of semantic cognition, findings are sparse with one study observing reduced within-network integration for a semantic fluency task which was not associated

with a poorer performance in older adults (Marsolais et al., 2014). There are two possible explanations for the present age invariance in functional connectivity. First, the group of older adults in our study might have been too young to detect changes in functional connectivity. Longitudinal studies on cognitive aging showed that a turning point in functional coupling takes place around the age of 65-70 years (Ng et al., 2016; Zonneveld et al., 2019). Thus, although the young adults in our study displayed numerically greater and stronger functional coupling than the older adults, the overall pattern was too similar in both groups. Second, the lack of an age effect on functional connectivity might be related to the semantic nature of our fluency paradigm. Semantic tasks have been shown to require functional coupling between cognitive control as well as DM regions like the PCC/precuneus which has been implicated in semantic cognition even in young adults (Krieger-Redwood et al., 2016). Hence, this might have aggravated the possibility of observing the frequently reported increase of between-network functional connectivity in older adults and underlines the necessity for more task-based investigations in the future to better understand the picture of neurocognitive aging.

Intriguingly, despite the observed age invariance, functional connectivity had different effects on task performance in both age groups. Our results show that older adults did not capitalize on strengthened functional connectivity in the same way as young adults. This was the case for functional connectivity within the DMN and for between MD and DM network regions where an increase of connectivity was associated with poorer and slower performance in the semantic fluency task in older adults but with better performance in young adults (Fig. 8). These findings are in line with theories of neurocognitive aging that suggest a reduced efficiency of neural networks as a result of increased dedifferentiation with age (Davis et al., 2012; Geerligs et al., 2014). Our results provide new insights into the behavioral relevance of the frequently observed pattern of neural dedifferentiation (Baltes & Lindenberger, 1997; Grady, 2012; Park et al., 2004) showing that older adults do not engage task-relevant networks in the same beneficial way as young adults. This is especially relevant in the context of semantic cognition where, according to the DECHA framework, increased semantic knowledge with age could lead to a performance advantage (Spreng and Turner, 2019). Here, we show that this is not the case in a task that requires an efficient use of control systems while accessing semantic memory; thus, lending support to the notion that older adults are less flexible in the goal-directed functional coupling between executive and default resources (Spreng and Turner, 2019).

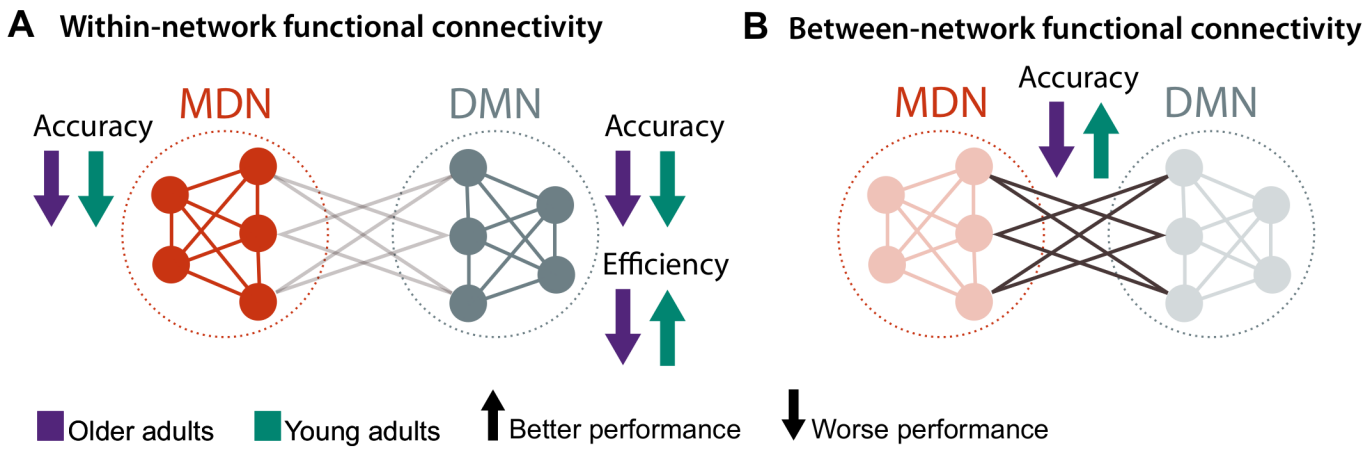

Figure 8. The different effects of within- and between network functional connectivity on task performance in each age group. (A) Both age groups showed a reduced accuracy when within-network functional connectivity in the MDN or DMN strengthened. However, young adults improved their efficiency in the form of faster response times when within-DMN connectivity increased whereas older adults performed slower in this case. (B) A similar pattern was observed for strengthening between-network connectivity: Young adults improved in their accuracy while older adults performed worse. Abbrev.: MDN Multiple-demand network; DMN Default mode network.

Our findings on age-related differences in cortical activation for both tasks further underline the observed reduced efficiency of neural networks in older adults. The comparison of age groups for the semantic fluency task compared to rest revealed stronger activation only for the older adults. Significant clusters comprised hubs of the MDN as well as the right inferior frontal gyrus which has been emphasized in studies on semantic fluency in aging before (Meinzer et al., 2009; Meinzer et al., 2012a; Meinzer et al., 2012b; Nagels et al., 2012). Remarkably, the interaction between both tasks and age revealed significant effects only for the young adults who displayed stronger activation of frontal key regions of the MDN including the pre-SMA and dACC for semantic fluency. This finding suggests a pattern of increased processing efficiency which was reflected by faster response times compared to the older group. It converges with previous studies on language production and comprehension that associated greater activation in the prefrontal cortex with an increased task demand in young adults (Fu et al., 2002; Thompson-Schill et al., 1997; Whitney et al., 2009). The supplementary activation of MDN regions in older adults for the semantic fluency task compared to rest aligns with a meta-analysis on semantic cognition that found greater activity in areas of the MDN with older age (Hoffman and Morcom, 2018). The nature of this upregulation in brain activity in older adults has been subject of some debate (Cabeza et al., 2018; Morcom and Johnson, 2015). Here, we observed additional activation in the older adults while they performed poorer than the young adults during the more demanding semantic fluency task. In light of the additional beneficial activation of frontal MDN regions in the young adults, the observed upregulation in the older adults seems to support the idea of age-related reduced efficiency of neural responses (Nyberg et al., 2014) leading to a stronger involvement of executive control at a lower level of task demand (Gallen et al, 2016; Hakun et al., 2015). In line with our functional

connectivity results, older adults recruit similar neural resources as young adults, albeit at a lower level of processing efficiency which lends additional support to the hypothesis of dedifferentiation (Morcom and Henson, 2018; Park et al., 2004).

It should be noted that our results did not show a consistent effect of the intended modulation of task difficulty within the semantic fluency task on neural activation patterns. This could be related to the limited number of items participants had to produce for each category. A recent behavioral investigation on semantic fluency showed that the amount of correct responses continuously decreases with time (Gordon et al., 2018). Thus, although the effect of difficulty was present in the behavioral results in the form of reduced accuracy and slower responses, we assume that 9 trials per category were not enough to establish this effect on the neural level.

Conclusion

In conclusion, our results provide evidence for the concept of age-related reduced efficiency, due to neural dedifferentiation, in the domain of semantic cognition. Although young and older both adults relied on the interaction of the domain-general MD and DM systems during processing of a verbal semantic fluency task, only the group of young adults engaged these task-relevant networks in a beneficial way. Further, we showed for the first time that the frequently reported pattern of increased between-network functional connectivity with aging leads to a decline in task efficiency in semantic cognition. Our findings are in line with the DECHA framework by lending support to the notion that older adults are less flexible in the goal-directed functional coupling between executive and default resources.

Acknowledgements

The authors would like to thank the medical technical assistants of MPI CBS for their support with data acquisition, and Annika Dunau, Caroline Duchow, and Rebekka Luckner for their support with transcriptions of recordings.

Funding

SM held a stipend by the German Academic Scholarship Foundation. DS was supported by the Deutsche Forschungsgemeinschaft (SA 1723/5-1) and the James S. McDonnell Foundation (Understanding Human Cognition, #220020292). GH was supported by the Lise Meitner excellence program of the Max Planck Society.

Code and Data Availability

All self-written code used for data analysis is made publicly available:
https://gitlab.gwdg.de/functionalconnectivityaging/mdn_lang
Data is made available from the authors upon reasonable request. Restrictions might apply due to the General Data Protection Regulation (EU).

Competing Interests

The authors declare that no competing interests exist.

References

Aita, S. L., Beach, J. D., Taylor, S. E., Borgogna, N. C., Harrell, M. N., & Hill, B. D. (2018). Executive, language, or both? An examination of the construct validity of verbal fluency measures. *Applied Neuropsychology: Adult*, 1–11. https://doi.org/10.1080/23279095.2018.1439830

Amunts, J., Camilleri, J. A., Eickhoff, S. B., Heim, S., & Weis, S. (2020). Executive functions predict verbal fluency scores in healthy participants. *Scientific Reports*, *10*(1), 11141. https://doi.org/10.1038/s41598-020-65525-9

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of Large-Scale Brain Systems in Advanced Aging. *Neuron*, *56*(5), 924–935. https://doi.org/10.1016/j.neuron.2007.10.038

Aschenbrenner, S., Tucha, O., & Lange, K. W. (2000). *Regensburger Wortflüssigkeits-Test*. Hogrefe.

Baciu, M., Boudiaf, N., Cousin, E., Perrone-Bertolotti, M., Pichat, C., Fournet, N., Chainay, H., Lamalle, L., & Krainik, A. (2016). Functional MRI evidence for the decline of word retrieval and generation during normal aging. *AGE*, *38*(1), 3. https://doi.org/10.1007/s11357-015-9857-y

Baddeley, A., Emslie, H., & Nimmo-Smith, I. (1993). The Spot-the-Word test: A robust estimate of verbal intelligence based on lexical decision. *The British Journal of Clinical Psychology*, *32*(1), 55–65. https://doi.org/10.1111/j.2044-8260.1993.tb01027.x

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). Memory changes in healthy older adults. In *The Oxford handbook of memory.* (pp. 395–409). Oxford University Press.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12–21. https://doi.org/10.1037//0882-7974.12.1.12

Basho, S., Palmer, E. D., Rubio, M. A., Wulfeck, B., & Müller, R.-A. (2007). Effects of generation mode in fMRI adaptations of semantic fluency: Paced production and overt speech. *Neuropsychologia*, *45*(8), 1697–1706. https://doi.org/10.1016/j.neuropsychologia.2007.01.007

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*(3), 588–597. https://doi.org/10.1207/s15327752jpa6703_13

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: A

self-paced overt response fMRI study of verbal fluency. *NeuroImage*, *49*(1), 1099–1107. https://doi.org/10.1016/j.neuroimage.2009.07.036

Bookheimer, S. Y., Zeffiro, T. A., Blaxton, T. A., Gaillard, W., & Theodore, W. H. (2000). Activation of language cortex with automatic speech tasks. *Neurology*, *55*(8), 1151–1157. https://doi.org/10.1212/WNL.55.8.1151

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of Interest Analysis Using an SPM Toolbox. *Neuroimage*, *16*. https://doi.org/10.1016/S1053-8119(02)90013-3

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. https://doi.org/10.1037/0882-7974.17.1.85

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*(11), 701–710. https://doi.org/10.1038/s41583-018-0068-2

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences*, *111*(46), E4997–E5006. https://doi.org/10.1073/pnas.1415122111

Cohen-Shikora, E. R., & Balota, D. A. (2016). Visual word recognition across the adult lifespan. *Psychology and Aging*, *31*(5), 488–502. https://doi.org/10.1037/pag0000100

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Rombouts, S. a. R. B. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex*, *18*(8), 1856–1864. https://doi.org/10.1093/cercor/bhm207

Damoiseaux, Jessica S. (2017). Effects of aging on functional and structural brain connectivity. *NeuroImage*, *160*, 32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077

Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior*, *19*(4), 450–466. https://doi.org/10.1016/S0022-5371(80)90312-6

Derringer, J. (2018). *A simple correction for non-independent tests* [Preprint]. PsyArXiv. https://doi.org/10.31234/osf.io/f2tyw

Eickhoff, S. B., Heim, S., Zilles, K., & Amunts, K. (2009). A systems perspective on the effective connectivity of overt speech production. *Philosophical Transactions of the Royal Society A:*

Mathematical, Physical and Engineering Sciences, *367*(1896), 2399–2421. https://doi.org/10.1098/rsta.2008.0287

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, *25*(4), 1325–1335. https://doi.org/10.1016/j.neuroimage.2004.12.034

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: A robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, *110*(41), 16616–16621. https://doi.org/10.1073/pnas.1315235110

Fedorenko, Evelina, Duncan, J., & Kanwisher, N. (2012). Language-Selective and Domain-General Regions Lie Side by Side within Broca's Area. *Current Biology*, *22*(21), 2059–2062. https://doi.org/10.1016/j.cub.2012.09.011

Feinberg, D. A., Moeller, S., Smith, S. M., Auerbach, E., Ramanna, S., Glasser, M. F., Miller, K. L., Ugurbil, K., & Yacoub, E. (2010). Multiplexed Echo Planar Imaging for Sub-Second Whole Brain FMRI and Fast Diffusion Imaging. *PLOS ONE*, *5*(12), e15710. https://doi.org/10.1371/journal.pone.0015710

Ferreira, L. K., Regina, A. C. B., Kovacevic, N., Martin, M. da G. M., Santos, P. P., Carneiro, C. de G., Kerr, D. S., Amaro, E., McIntosh, A. R., & Busatto, G. F. (2016). Aging Effects on Whole-Brain Functional Connectivity in Adults Free of Cognitive and Psychiatric Disorders. *Cerebral Cortex*, *26*(9), 3851–3865. https://doi.org/10.1093/cercor/bhv190

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fonov, V., Evans, A., McKinstry, R., Almli, C., & Collins, D. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*, *47*, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Fu, C. H. Y., Morgan, K., Suckling, J., Williams, S. C. R., Andrew, C., Vythelingum, G. N., & McGuire, P. K. (2002). A Functional Magnetic Resonance Imaging Study of Overt Letter Verbal Fluency Using a Clustered Acquisition Sequence: Greater Anterior Cingulate Activation with Increased Task Demand. *NeuroImage*, *17*(2), 871–879. https://doi.org/10.1006/nimg.2002.1189

Gallen, C. L., Turner, G. R., Adnan, A., & D'Esposito, M. (2016). Reconfiguration of brain network architecture to support executive control in aging. *Neurobiology of Aging*, *44*, 42–52. https://doi.org/10.1016/j.neurobiolaging.2016.04.003

Geerligs, L., Maurits, N. M., Renken, R. J., & Lorist, M. M. (2014). Reduced specificity of functional connectivity in the aging brain during task performance: Functional Connectivity in the Aging Brain. *Human Brain Mapping*, *35*(1), 319–330. https://doi.org/10.1002/hbm.22175

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2015). A Brain-Wide Study of Age-Related Changes in Functional Connectivity. *Cerebral Cortex*, *25*(7), 1987–1999. https://doi.org/10.1093/cercor/bhu012

Geranmayeh, F., Wise, R. J. S., Mehta, A., & Leech, R. (2014). Overlapping Networks Engaged during Spoken Language Production and Its Cognitive Control. *Journal of Neuroscience*, *34*(26), 8728–8740. https://doi.org/10.1523/JNEUROSCI.0428-14.2014

Geranmayeh, Fatemeh, Brownsett, S. L. E., Leech, R., Beckmann, C. F., Woodhead, Z., & Wise, R. J. S. (2012). The contribution of the inferior parietal cortex to spoken language production. *Brain and Language*, *121*(1), 47–57. https://doi.org/10.1016/j.bandl.2012.02.005

Glauer, M., Häusig, S., Krüger, M., Betsch, T., Renkewitz, F., Sedlmeier, P., & Winkler, I. (2007). Typizitätsnormen für Vertreter von 30 Kategorien. *Neurolinguistik*, 12.

Gordon, J. K., Young, M., & Garcia, C. (2018). Why do older adults have difficulty with semantic fluency? *Aging, Neuropsychology, and Cognition*, *25*(6), 803–828. https://doi.org/10.1080/13825585.2017.1374328

Gorgolewski, K. J., Esteban, O., Ellis, D. G., Notter, M. P., Ziegler, E., Johnson, H., Hamalainen, C., Yvernault, B., Burns, C., Manhães-Savio, A., Jarecka, D., Markiewicz, C. J., Salo, T., Clark, D., Waskom, M., Wong, J., Modat, M., Dewey, B. E., Clark, M. G., … Ghosh, S. (2017). *Nipype: A Flexible, Lightweight And Extensible Neuroimaging Data Processing Framework In Python. 0.13.1*. Zenodo. https://doi.org/10.5281/ZENODO.581704

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. https://doi.org/10.1038/nrn3256

Grady, C., Sarraf, S., Saverino, C., & Campbell, K. (2016). Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiology of Aging*, *41*, 159–172. https://doi.org/10.1016/j.neurobiolaging.2016.02.020

Hakun, J. G., Zhu, Z., Brown, C. A., Johnson, N. F., & Gold, B. T. (2015). Longitudinal alterations to brain function, structure, and cognitive performance in healthy older adults: A fMRI-DTI study. *Neuropsychologia*, *71*, 225–235. https://doi.org/10.1016/j.neuropsychologia.2015.04.008

Halai, A. D., Welbourne, S. R., Embleton, K., & Parkes, L. M. (2014). A comparison of dual gradient-echo and spin-echo fMRI of the inferior temporal lobe. *Human Brain Mapping*, *35*(8), 4118–4128. https://doi.org/10.1002/hbm.22463

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87–96. https://doi.org/10.1038/nrn1323

Heinzel, S., Metzger, F. G., Ehlis, A.-C., Korell, R., Alboji, A., Haeussinger, F. B., Hagen, K., Maetzler, W., Eschweiler, G. W., Berg, D., & Fallgatter, A. J. (2013). Aging-related cortical reorganization of verbal fluency processing: A functional near-infrared spectroscopy study. *Neurobiology of Aging*, *34*(2), 439–450. https://doi.org/10.1016/j.neurobiolaging.2012.05.021

Hoffman, P., & Morcom, A. M. (2018). Age-related changes in the neural networks supporting semantic cognition: A meta-analysis of 47 functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *84*, 134–150. https://doi.org/10.1016/j.neubiorev.2017.11.010

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Kavé, G., & Knafo-Noam, A. (2015). Lifespan development of phonemic and semantic fluency: Universal increase, differential decrease. *Journal of Clinical and Experimental Neuropsychology*, *37*(7), 751–763. https://doi.org/10.1080/13803395.2015.1065958

Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Hebrank, A. C., Reuter-Lorenz, P. A., & Park, D. C. (2015). Age trajectories of functional activation under conditions of low and high processing demands: An adult lifespan fMRI study of the aging brain. *NeuroImage*, *104*, 21–34. https://doi.org/10.1016/j.neuroimage.2014.09.056

Kerns, J. G., Cohen, J. D., MacDonald, A. W., Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science (New York, N.Y.)*, *303*(5660), 1023–1026. https://doi.org/10.1126/science.1089910

Krieger-Redwood, K., Jefferies, E., Karapanagiotidis, T., Seymour, R., Nunes, A., Ang, J. W. A., Majernikova, V., Mollo, G., & Smallwood, J. (2016). Down but not out in posterior cingulate cortex: Deactivation yet functional coupling with prefrontal cortex during demanding semantic cognition. *NeuroImage*, *141*, 366–377. https://doi.org/10.1016/j.neuroimage.2016.07.060

Krieger-Redwood, K., Wang, H.-T., Poerio, G., Martinon, L. M., Riby, L. M., Smallwood, J., & Jefferies, E. (2019). Reduced semantic control in older adults is linked to intrinsic DMN connectivity. *Neuropsychologia*, *132*, 107133. https://doi.org/10.1016/j.neuropsychologia.2019.107133

Law, R., & O'Carroll, R. E. (1998). A comparison of three measures of estimating premorbid intellectual level in dementia of the Alzheimer type. *International Journal of Geriatric*

Psychiatry, *13*(10), 727–730. https://doi.org/10.1002/(sici)1099-1166(1998100)13:10<727::aid-gps851>3.0.co;2-2

Leech, R., Braga, R., & Sharp, D. J. (2012). Echoes of the Brain within the Posterior Cingulate Cortex. *Journal of Neuroscience*, *32*(1), 215–222. https://doi.org/10.1523/JNEUROSCI.3689-11.2012

Lenth, R. (2020). *Emmeans: Estimated Marginal Means, aka Least-Squares Means. R package version 1.4.8.* https://CRAN.R-project.org/package=emmeans

Li, H.-J., Hou, X.-H., Liu, H.-H., Yue, C.-L., Lu, G.-M., & Zuo, X.-N. (2015). Putting age-related task activation into large-scale brain networks: A meta-analysis of 114 fMRI studies on healthy aging. *Neuroscience & Biobehavioral Reviews*, *57*, 156–174. https://doi.org/10.1016/j.neubiorev.2015.08.013

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: From neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479–486. https://doi.org/10.1016/S1364-6613(00)01769-1

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin*, *136*(4), 659–676. https://doi.org/10.1037/a0020080

Lüdecke, D. (2018). ggeffects: Tidy Data Frames of Marginal Effects from Regression Models. *Journal of Open Source Software*, *3*(26), 772. https://doi.org/10.21105/joss.00772

Mannhaupt, Hans-Rainer. (1983). Produktionsnormen für verbale Reaktionen zu 40 geläufigen Kategorien. *Sprache & Kognition*.

Marsolais, Y., Perlbarg, V., Benali, H., & Joanette, Y. (2014). Age-related changes in functional network connectivity associated with high levels of verbal fluency performance. *Cortex*, *58*, 123–138. https://doi.org/10.1016/j.cortex.2014.05.007

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI): A Comparison to Standard Approaches. *Neuroimage*, *61*(4), 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Meinzer, M., Flaisch, T., Seeds, L., Harnish, S., Antonenko, D., Witte, V., Lindenberg, R., & Crosson, B. (2012). Same Modulation but Different Starting Points: Performance Modulates Age Differences in Inferior Frontal Cortex Activity during Word-Retrieval. *PLoS ONE*, *7*(3), e33631. https://doi.org/10.1371/journal.pone.0033631

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., Gonzalez-Rothi, L., & Crosson, B. (2009). Neural Signatures of Semantic and Phonemic Fluency in Young and Old

Adults. *Journal of Cognitive Neuroscience*, *21*(10), 2007–2018. https://doi.org/10.1162/jocn.2009.21219

Meinzer, M., Seeds, L., Flaisch, T., Harnish, S., Cohen, M. L., McGregor, K., Conway, T., Benjamin, M., & Crosson, B. (2012). Impact of changed positive and negative task-related brain activity on word-retrieval in aging. *Neurobiology of Aging*, *33*(4), 656–669. https://doi.org/10.1016/j.neurobiolaging.2010.06.020

Morcom, A. M., & Henson, R. N. A. (2018). Increased Prefrontal Activity with Aging Reflects Nonspecific Neural Responses Rather than Compensation. *Journal of Neuroscience*, *38*(33), 7303–7313. https://doi.org/10.1523/JNEUROSCI.1701-17.2018

Morcom, A. M., & Johnson, W. (2015). Neural Reorganization and Compensation in Aging. *Journal of Cognitive Neuroscience*, *27*(7), 1275–1285. https://doi.org/10.1162/jocn_a_00783

Nagels, A., Kircher, T., Dietsche, B., Backes, H., Marquetand, J., & Krug, A. (2012). Neural processing of overt word generation in healthy individuals: The effect of age and word knowledge. *NeuroImage*, *61*(4), 832–840. https://doi.org/10.1016/j.neuroimage.2012.04.019

Ng, K. K., Lo, J. C., Lim, J. K. W., Chee, M. W. L., & Zhou, J. (2016). Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. *NeuroImage*, *133*, 321–330. https://doi.org/10.1016/j.neuroimage.2016.03.029

Noonan, K. A., Jefferies, E., Visser, M., & Lambon Ralph, M. A. (2013). Going beyond Inferior Prefrontal Involvement in Semantic Control: Evidence for the Additional Contribution of Dorsal Angular Gyrus and Posterior Middle Temporal Cortex. *Journal of Cognitive Neuroscience*, *25*(11), 1824–1850. https://doi.org/10.1162/jocn_a_00442

Noppeney, U., Price, C. J., Penny, W. D., & Friston, K. J. (2006). Two Distinct Neural Mechanisms for Category-selective Responses. *Cerebral Cortex*, *16*(3), 437–445. https://doi.org/10.1093/cercor/bhi123

Nyberg, L., Andersson, M., Kauppi, K., Lundquist, A., Persson, J., Pudas, S., & Nilsson, L.-G. (2014). Age-related and Genetic Modulation of Frontal Cortex Efficiency. *Journal of Cognitive Neuroscience*, *26*(4), 746–754. https://doi.org/10.1162/jocn_a_00521

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., Smith, M. R., & Smith, E. E. (2004). Aging Reduces Neural Specialization in Ventral Visual Cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age Differences in Deactivation: A Link to Cognitive Control? *Journal of Cognitive Neuroscience*, *19*(6), 1021–1032. https://doi.org/10.1162/jocn.2007.19.6.1021

Petrovich Brennan, N. M., Whalen, S., de Morales Branco, D., O'Shea, J. P., Norton, I. H., & Golby, A. J. (2007). Object naming is a more sensitive measure of speech localization than number counting: Converging evidence from direct cortical stimulation and fMRI. *NeuroImage*, *37*, S100–S108. https://doi.org/10.1016/j.neuroimage.2007.04.052

Pongpipat, E. E., Kennedy, K. M., Foster, C. M., Boylan, M. A., & Rodrigue, K. M. (2020). *Functional connectivity within and between n-back modulated regions: An adult lifespan PPI investigation* [Preprint]. Neuroscience. https://doi.org/10.1101/2020.06.11.145219

Poser, B. A., Versluis, M. J., Hoogduin, J. M., & Norris, D. G. (2006). BOLD contrast sensitivity enhancement and artifact reduction with multiecho EPI: Parallel-acquired inhomogeneity-desensitized fMRI. *Magnetic Resonance in Medicine*, *55*(6), 1227–1235. https://doi.org/10.1002/mrm.20900

R Core Team. (2018). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. http://www.r-project.org/

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*(7), 271. https://doi.org/10.2466/PMS.8.7.271-276

Schmidt, C. S. M., Schumacher, L. V., Römer, P., Leonhart, R., Beume, L., Martin, M., Dressing, A., Weiller, C., & Kaller, C. P. (2017). Are semantic and phonological fluency based on the same or distinct sets of cognitive processes? Insights from factor analyses in healthy adults and stroke patients. *Neuropsychologia*, *99*, 148–155. https://doi.org/10.1016/j.neuropsychologia.2017.02.019

Schmidt, K.-H., & Metzler, P. (1992). *WST-Wortschatztest*. Beltz Test.

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.00772

Shine, J. M., Bissett, P. G., Bell, P. T., Koyejo, O., Balsters, J. H., Gorgolewski, K. J., Moodie, C. A., & Poldrack, R. A. (2016). The Dynamics of Functional Brain Networks: Integrated Network States during Cognitive Task Performance. *Neuron*, *92*(2), 544–554. https://doi.org/10.1016/j.neuron.2016.09.018

Sidtis, D., Canterucci, G., & Katsnelson, D. (2009). Effects of neurological damage on production of formulaic language. *Clinical Linguistics & Phonetics*, *23*(4), 270–284. https://doi.org/10.1080/02699200802673242

Siegel, J. S., Power, J. D., Dubis, J. W., Vogel, A. C., Church, J. A., Schlaggar, B. L., & Petersen, S. E. (2014). Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. *Human Brain Mapping*, *35*(5), 1981–1996. https://doi.org/10.1002/hbm.22307

Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Schachar, M. S. (2020). *Afex: Analysis of Factorial Experiments. R package version 0.27-2*. https://CRAN.R-project.org/package=afex

Smith, D. V., Gseir, M., Speer, M. E., & Delgado, M. R. (2016). Toward a cumulative science of functional integration: A meta-analysis of psychophysiological interactions. *Human Brain Mapping*, *37*(8), 2904–2917. https://doi.org/10.1002/hbm.23216

Spreng, R. N., DuPre, E., Selarka, D., Garcia, J., Gojkovic, S., Mildner, J., Luh, W.-M., & Turner, G. R. (2014). Goal-Congruent Default Network Activity Facilitates Cognitive Control. *Journal of Neuroscience*, *34*(42), 14108–14114. https://doi.org/10.1523/JNEUROSCI.2815-14.2014

Spreng, R. Nathan, Stevens, W. D., Viviano, J. D., & Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: Evidence from task and rest. *Neurobiology of Aging*, *45*, 149–160. https://doi.org/10.1016/j.neurobiolaging.2016.05.020

Spreng, R Nathan, & Turner, G. R. (2019). *The Shifting Architecture of Cognition and Brain Function in Older Adulthood*. 20.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences*, *94*(26), 14792–14797. https://doi.org/10.1073/pnas.94.26.14792

Trelle, A. N., Henson, R. N., & Simons, J. S. (2019). Neural evidence for age-related differences in representational quality and strategic retrieval processes. *Neurobiology of Aging*, *84*, 50–60. https://doi.org/10.1016/j.neurobiolaging.2019.07.012

Tremblay, P., & Gracco, V. L. (2009). Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). *Brain Research*, *1268*, 112–124. https://doi.org/10.1016/j.brainres.2009.02.076

Troyer, A., Moscovitch, M., & Winocur, G. (1997). Clustering and Switching as Two Components of Verbal Fluency: Evidence From Younger and Older Healthy Adults. *Neuropsychology*, *11*(1), 138–146. https://doi.org/10.1037//0894-4105.11.1.138

Turner, G. R., & Spreng, R. N. (2015). Prefrontal Engagement and Reduced Default Network Suppression Co-occur and Are Dynamically Coupled in Older Adults: The Default–Executive Coupling Hypothesis of Aging. *Journal of Cognitive Neuroscience*, *27*(12), 2462–2476. https://doi.org/10.1162/jocn_a_00869

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 bias correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Vanlancker-Sidtis, D., McIntosh, A. R., & Grafton, S. (2003). PET activation studies comparing two speech tasks widely used in surgical mapping. *Brain and Language*, *85*(2), 245–261. https://doi.org/10.1016/S0093-934X(02)00596-5

Vatansever, D., Menon, D. K., Manktelow, A. E., Sahakian, B. J., & Stamatakis, E. A. (2015). Default Mode Dynamics for Global Functional Integration. *Journal of Neuroscience*, *35*(46), 15254–15262. https://doi.org/10.1523/JNEUROSCI.2135-15.2015

Verhaegen, P., Borchelt, M., & Smith, J. (2003). Relation Between Cardiovascular and Metabolic Disease and Cognition in Very Old Age: Cross-Sectional and Longitudinal Findings From the Berlin Aging Study. *Health Psychology*, *22*(6), 559–569. https://doi.org/10.1037/0278-6133.22.6.559

Vitali, P., Abutalebi, J., Tettamanti, M., Rowe, J., Scifo, P., Fazio, F., Cappa, S. F., & Perani, D. (2005). Generating animal and tool names: An fMRI study of effective connectivity. *Brain and Language*, *93*(1), 32–45. https://doi.org/10.1016/j.bandl.2004.08.005

Wagner, A. D., Paré-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering Meaning: Left Prefrontal Cortex Guides Controlled Semantic Retrieval. *Neuron*, *31*(2), 329–338. https://doi.org/10.1016/S0896-6273(01)00359-2

Wagner, S., Sebastian, A., Lieb, K., Tüscher, O., & Tadić, A. (2014). A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. *BMC Neuroscience*, *15*(1), 19. https://doi.org/10.1186/1471-2202-15-19

Wechsler, D. (1944). *The measurement of adult intelligence (3rd ed.).* Williams & Wilkins Co. https://doi.org/10.1037/11329-000

Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult*, *23*(1), 29–34. https://doi.org/10.1080/23279095.2015.1004574

Whitney, C., Weis, S., Krings, T., Huber, W., Grossman, M., & Kircher, T. (2009). Task-dependent Modulations of Prefrontal and Hippocampal Activity during Intrinsic Word Production. *Journal of Cognitive Neuroscience*, *21*(4), 697–712. https://doi.org/10.1162/jocn.2009.21056

Wickham, H. (2016). *ggplot2. Elegant Graphics for Data Analysis*. Springer International Publishing. https://doi.org/10.1007/978-3-319-24277-4

Wirth, M., Jann, K., Dierks, T., Federspiel, A., Wiest, R., & Horn, H. (2011). Semantic memory involvement in the default mode network: A functional neuroimaging study using independent

component analysis. *NeuroImage*, *54*(4), 3057–3066. https://doi.org/10.1016/j.neuroimage.2010.10.039

Xia, M., Wang, J., & He, Y. (2013). BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. *PLOS ONE*, *8*(7), e68910. https://doi.org/10.1371/journal.pone.0068910

Zacks, R. T., Hasher, L., & Li, K. Z. H. (2000). Human memory. In *The handbook of aging and cognition, 2nd ed.* (pp. 293–357). Lawrence Erlbaum Associates Publishers.

Zonneveld, H. I., Pruim, R. HR., Bos, D., Vrooman, H. A., Muetzel, R. L., Hofman, A., Rombouts, S. ARB., van der Lugt, A., Niessen, W. J., Ikram, M. A., & Vernooij, M. W. (2019). Patterns of functional connectivity in an aging population: The Rotterdam Study. *NeuroImage*, *189*, 432–444. https://doi.org/10.1016/j.neuroimage.2019.01.041