Neural Signatures of Semantic and Phonemic Fluency in Young and Old Adults

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Abstract

■ As we age, our ability to select and to produce words changes, yet we know little about the underlying neural substrate of word-finding difficulties in old adults. This study was designed to elucidate changes in specific frontally mediated retrieval processes involved in word-finding difficulties associated with advanced age. We implemented two overt verbal (semantic and phonemic) fluency tasks during fMRI and compared brain activity patterns of old and young adults. Performance during the phonemic task was comparable for both age groups and mirrored by strongly left-lateralized (frontal) activity patterns. On the other hand, a significant drop of performance during the semantic task in the older group was accompanied by additional right (inferior and middle) frontal activity, which was negatively correlated with performance. Moreover, the younger group recruited different subportions of the left inferior frontal gyrus for both fluency tasks, whereas the older participants failed to show this distinction. Thus, functional integrity and efficient recruitment of left frontal language areas seems to be critical for successful word retrieval in old age. ■

INTRODUCTION

A growing segment of the population is entering old age and is likely to suffer some degree of age-related cognitive decline, including the most severe cases of dementias such as Alzheimer disease (AD). Recently, considerable attention has been devoted to elucidate the underlying neural substrates of age-related cognitive decline. Still, research concerning cognitive decline in normal and pathological aging has mainly focused on memory, cognition, and perception (Cabeza, Anderson, Locantore, & McIntosh, 2002). On the other hand, age-related changes in language functions and their underlying neuronal causes have widely been neglected, although word-retrieval difficulties are frequently observed in old age (Burke & Shafto, 2008) and are among the earliest signs of pathological aging (e.g., Henry, Crawford, & Phillips, 2004). In particular, whereas certain aspects of language, like semantic knowledge, increases across the lifespan with little decline even in very old age (Burke & Shafto, 2008; Verhaeghen, 2003), others have been found to be heavily affected by aging. For example, access to and integration of information at multiple levels during real-time language processing seem to be affected, especially when processing resources are taxed (e.g., by increased cognitive load) and older adults may be less able to inhibit competing or irrelevant information. Even during nonchallenging language comprehension tasks where older and younger adults perform similarly, changes in brain activity patterns have recently been confirmed (for a review, see Federmeier, 2007). Moreover, during language production tasks, the retrieval of lexical-semantic knowledge from memory stores may be impaired (Ivnik, Malek, Smith, Tangolos, & Petersen, 1996), and errors accessing phonological word forms, like tip-of-the tongue phenomena, occur more frequently in old than in young persons (Shafto, Burke, Stamatakis, Tam, & Tyler, 2007). These findings may point to a specific compromise of executive language functions.

Such a conclusion is in line with current theories of cognitive aging that focus on the frontal and the medial-temporal lobes as a major source of age-related disruptions in cognitive performance (Craik & Bialystok, 2006; Raz et al., 2004; West, 1996). For example, recent research in animals and humans revealed subtle region-specific alterations in dendritic morphology, cellular connectivity, gene expression, and other factors that affect plasticity and ultimately alter the network dynamics of neuronal ensembles that support cognition (Burke & Barnes, 2006). Moreover, functional imaging studies of aging have consistently confirmed that older adults tend to recruit regions in the contralateral non-task-dominant (prefrontal) cortex when performing various cognitive tasks (e.g., episodic memory, semantic memory retrieval, working memory, perception, and inhibitory control). This has been described as the hemispheric asymmetry reduction in older adults (Cabeza et al., 2002). The functional relevance of this reduced asymmetry for cognition in old age has been controversial; for example, a beneficial role has been

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suggested by studies that found additional (bilateral) activity in high- but not in low-performing old adults during a variety of cognitive tasks (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003; Cabeza et al., 2002; Reuter-Lorenz, 2002; Rosen et al., 2002; Reuter-Lorenz et al., 2000). Still, others have suggested that the more bilateral activity pattern observed in older individuals may only reflect increased task demands in older adults as young adults tend to recruit the non-task-dominant hemisphere more when difficulty levels are raised (e.g., Braver et al., 2001; Grady et al., 1998). The more bilateral pattern found in older adults may also be explained by inefficient recruitment of specialized brain regions in the dominant hemisphere, disinhibition of nonspecialized networks, or dedifferentiation of function (Rajah & D'Esposito, 2005; Li & Lindenberger, 1999).

So far, little is known about word retrieval difficulties in healthy old adults, and only one study has directly compared the neural substrates of word retrieval in healthy younger and older adults during an overt picture-naming task (Wierenga et al., 2008). Although naming accuracy was comparable between younger and older participants (age range = 68–84 years), on average, fMRI in the old participants revealed not only larger frontal network during word retrieval in left hemisphere areas but also less lateralization compared with younger adults as evident by increased right frontal activation (homologue of Broca's area, BA 45; anterior inferior frontal gyrus, IFG; anterior cingulate). Notably, frontal brain regions that showed a correlation with performance in older adults were not similar compared with the group of younger adults with one exception: In young adults and low-performing old adults, activity in the right IFG was negatively correlated with performance. Moreover, the older group scored significantly worse in tests that placed demands on executive language functions as assessed outside the scanner (i.e., selection, retrieval, and manipulation of semantic information). In sum, although naming performance in (healthy) older adults activated a larger bilateral frontal network, including additional right inferior frontal areas not activated by younger participants, this activation pattern was not beneficial for performance in all of the participants. Taking into account the abovementioned results, further research is needed to elucidate the specific frontally mediated retrieval processes involved in word-finding difficulties in older adults.

Hence, in this study, we used fMRI and two different overt verbal fluency paradigms to investigate frontally mediated language functions in healthy young and old participants. In particular, we assessed brain activity patterns during semantic (category based) and phonemic (letter based) fluency tasks. Several previous functional imaging studies have demonstrated that both tasks draw heavily on frontally mediated processes and mainly activate dorsolateral frontal cortices. Activity patterns have been found to be strongly left lateralized in younger participants, and it has been suggested that different subportions in the left IFG are differentially activated during both tasks (i.e., more dorsal peak of activity for phonemic fluency; for a recent review of functional imaging during verbal fluency tasks, see Costafreda et al., 2006). Moreover, semantic fluency has been shown to be affected by age more strongly than phonemic fluency (e.g., Brickman et al., 2005), replicating findings in mild cognitive impairment (Murphy, Rich, & Troyer, 2006) and in AD (Monsch et al., 1992), although in pathological aging, this pattern is relatively more pronounced. Therefore, both tasks are well suited to compare neural activity in young and old participants to assess (a) the potentially different patterns of activity in either left or right frontal regions, (b) the impact of different performance levels on brain activity, and (c) the differential contribution of different subportions of the IFG in each group. Moreover, by implementing an overt language design, we were able to relate the respective differential activity pattern to the actual behavioral performance during scanning.

METHODS

Participants

Sixteen healthy older participants (age: M = 69.3 years, SD = 5.6 years, range = 64–88 years, 8 women) were recruited for the study. Another 16 younger participants (age: M = 26.1 years, SD = 3.7 years, range = 20–33 years, 8 women) served as a control group and were matched to the older participants for sex and education (years of education: old group, M = 13.3 years, SD = 3.0 years, range = 8–19 years; young group, M = 14.8 years, SD = 2.6 years, range = 10–19 years), $F(1, 30) = 2.4$, $p = .12$. All participants were native speakers of the German language. Written informed consent was obtained from the participants. Before the fMRI scanning, participants were briefed on scanner security and paid a compensation of 20 euros for participation. The ethics committee of the University of Konstanz had approved the study protocol, and the study was conducted in accordance with the Helsinki Declaration.

Psychometric Assessment

Dementia Screening

Before the fMRI session, each old subject completed a standard health questionnaire to exclude any previous or current neurological or psychiatric condition, the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and the neuropsychological test battery established by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus; www.memoryclinic.ch). The CERAD-Plus is a well-established screening tool that comes along with an on-line database, including age- and sex-adjusted norms (z-scores), to differentiate normal aging from dementia and its precursors (i.e., amnestic mild cognitive impairment; Petersen, 2004). The CERAD is comprised of several subtests to assess semantic (animals) and phonemic fluency (words beginning with S), naming (short version of the Boston Naming Test), constructional praxis, verbal memory (three immediate recall trials of a 10 word list, delayed recall, and discrimination), and executive functioning (Trail Making Test A/B). In particular, the word list test has been shown to be sensitive to MCI (cf. Shankle et al., 2005). Although the CERAD does not provide norms for younger participants, the younger group completed the test to assure similar testing conditions.

In addition, all participants were screened for depression by using the Beck Depression Inventory (Beck, Steer, & Garbin, 1988) and found to score within normal ranges. None of the old participants reported subjective memory complaints in everyday life or had a Mini-Mental Status Examination score below 27 ($M = 29.1$, $SD = 1.8$). All participants scored within ± 1.5 *SD* of the mean for the CERAD normative sample in all subtests. In particular, none was more than 1 *SD* below age norms in the word list test. Average scores for all CERAD subtests are provided in Table 1.

Additional Neuropsychological Language Tests

To assess executive language functions outside the scanner, old and young participants completed the Regensburger verbal fluency test [Regensburger Wortflüssigkeitstest (RWT); Aschenbrenner, Tucha, & Lange, 2000]. The RWT comprises semantic and phonemic fluency trials. Two 1-min trials of semantic fluency (food and surnames) and phonemic fluency (letters M and B) were administered. Two additional language tests were completed before scanning to assess semantic processing: a synonym test, the Synonym–Antonym Selection–Classification Test (Riegel, 1967), and a standardized German vocabulary test, the Wortschatztest (Schmidt & Metzler, 1992).

Functional Magnetic Resonance Imaging

Experimental Task and Stimulus Characteristics

We implemented an overt verbal fluency task, and participants were instructed that they would see different categories and initial letters at the center of a video screen. The participants' task was to generate different exemplars of the respective category (semantic fluency) or words beginning with a particular letter (phonemic fluency). During the phonemic fluency task, production of words from all word classes was allowed (with the exception of names, brand names, and repeated use of composita that share the same stem; e.g., tennis court, tennis player).

The fMRI tasks consisted of two blocked conditions of category or phonemic generation, which alternated with a control condition [reading the German word "Pause" (English "rest") aloud]. A complex baseline condition was chosen to control for activity associated with (a) basic visual processing, (b) articulation, and (c) hearing of the subject's own voice. Each category/letter or rest condition was preceded by a speech bubble (5.5 sec), introducing the respective condition, afterward the first category/initial letter or the word "Pause" was displayed.

The same four different categories and initial letters were used for all participants with order of presentation

Table 1. Results of the Young and the Old Group in the CERAD Test Battery (Raw Scores)

	Older Group	*Younger Group*
Test (Maximum Score)	*M (SD)*	*M (SD)*
Semantic fluency	20.2 (2.9)	29.0 (5.5)
Boston Naming Test (15)	14.8 (0.6)	14.9 (0.3)
Word list learning total (30)	20.6 (3.8)	24.9 (1.2)
Word list recall (10)	7.6 (1.6)	8.8 (1.5)
Word list discrimination (10)	9.9 (0.3)	9.8 (0.4)
Constructional praxis (11)	10.1 (1.4)	11.0 (0.0)
Phonemic fluency	15.9 (3.7)	18.4 (4.3)
Trail Making Test A[a]	39.5 (10.7)	26.3 (4.0)
Trail Making Test B[a]	89.9 (20.0)	49.6 (9.1)
Mini-Mental Status Examination (30)	29.1 (1.8)	29.6 (0.8)

The CERAD test battery was used as a screening device for dementia in the older group. Because the test does not provide normative data for younger adults, we did not statistically compare the results of young and old adults in the CERAD and listed the average raw scores and *SD* of each group.

[a]Time to completion in seconds.

randomized across subjects. For half of the participants, the stimulation started with category fluency condition, for the other half with a letter fluency trial. Categories were selected to comprise a large range of category exemplars (sports/fruits/body parts/musical instruments) according to a German norming study (Mannhaupt, 1983). Initial letters (H, F, N, and A) were chosen because of the large number of legal German words beginning with these letters according to the Simplex Celex Database (http://iona.sprachwiss.uni-konstanz.de/simplex.html).

A total of four blocks for each condition were collected (i.e., 40 trials for category and phonemic fluency). Both experimental conditions (category and phonemic fluency) were presented in blocks of 10 consecutive trials (block duration 55 sec, the same category/letter was repeated 10 times within each block). The baseline blocks (five consecutive trials) were interspersed between category and letter fluency trials (block length 27.5 sec, eight blocks), therefore resulting in a balanced number of trials for each fluency condition and the baseline condition.

fMRI Setup and Acquisition Parameters

The fMRI paradigm used a temporal sparse-sampling design (Hall et al., 1999), in which the overt verbal response is assessed in the scanner during an off phase and the hemodynamic response is acquired after a short time delay; thereby, movement artifacts due to the articulation process are avoided. Scanning was conducted using a 1.5 Tesla Philips Intera MR-System equipped with Power Gradients. For functional scanning, a T2*-weighted fast-field echo, echo-planar-imaging sequence using a parallel scanning technique (SENSE factor 2; Pruessmann, Weiger, Scheidegger, & Boesiger, 1999) was used. Stimuli were presented by a visor (VisuaStim, Resonance Technology, Inc., Northridge, CA) for 3 sec, and overt responding was required during this interval. After a delay of 0.27 sec, a whole-brain fMRI volume was acquired (temporal sparse sampling). fMRI was performed with the following acquisition parameters: repetition time TR = 5.5 sec; acquisition time TA = 2.23 sec; TE = 40 msec; 34 transversal slices, slice thickness = 3 mm; in-plane resolution = 3 × 3 mm; interslice gap = 0.5 mm; field of view = 192; acquisition matrix = 64 × 64. A total of 120 functional whole-brain volumes were acquired, and the entire experiment had a duration of 12.5 min. Verbal responses were transmitted from the scanner to a microphone and transcribed. Before the first scan, a training session outside the scanner was performed to familiarize the participants with the experimental design. A different set of categories and letters was used for this training session.

fMRI Preprocessing

fMRI postprocessing was performed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included correction for slice-time differences and spatial alignment to the first volume in the image series to adjust for head movements during the course of the experiment. Afterward, functional volumes were normalized to the Montreal Neurological Institute standard stereotactic space and smoothed with a Gaussian Kernel of 9 × 9 × 11 mm FWHM. Data were modeled using a finite impulse response function (Gaab, Gabrieli, & Glover, 2007).

After preprocessing, the data were submitted to statistical analysis implementing the general linear model. The corresponding design matrix was comprised by the three covariates of interest representing the experimental conditions' onsets as well as covariates of no interest (the six movement parameters obtained during realignment). The covariates of no interest were included to improve overall model fit to the empirical data and to reduce residual error variance. Before estimating the modeled regressors, a high-pass filter with a cutoff period of 128 sec was applied to the data. Following estimation of the overall model, planned contrasts of interest were calculated for each subject. These included separate comparisons of category and phonemic fluency runs with the baseline condition for both age groups. Additional contrasts included the direct comparison of (a) category and phonemic fluency trials between the two age groups and (b) within-group comparison of activity patterns associated with category and phonemic fluency trials.

For the group analysis, a random effect model was calculated that included the abovementioned contrasts of all participants for each age group. Maximally activated voxels within significant clusters for the comparison of both fluency conditions with the baseline are reported at a vixen threshold of $p < .01$, false discovery rate (FDR) corrected (Genovese, Lazar, & Nichols, 2002), and a cluster extent of $k \geqq 20$ voxels. Comparison of activity patterns within each age group (category vs. phonemic fluency) and between groups (category/phonemic fluency old vs. young) are thresholded with $p < .05$, FDR corrected, $k \geqq 10$. Anatomic localization of significant voxels within clusters was conducted using the Talairach Daemon software (Lancaster et al., 2000), with the nearest gray matter option enabled. For presentation of the results, the data are superimposed on a standard brain template (Montreal Brain).

To explore the functional relevance of increased activity in brain regions that were more strongly activated by old than young adults, an ROI analysis was performed that correlated the averaged z-transformed activity in differentially activated clusters with the individual behavioral performance in the scanner. (Note that younger participants did not evidence increased activity compared with older participants in both fluency tasks; see Results.) Due to the limited behavioral variance during both word generation tasks, a correlation analysis between activity patterns and performance was not feasible in the younger participants.

RESULTS

Behavioral Language Testing

Participants of the young group outperformed the old group during both semantic fluency trials outside the scanner, sum of words produced during the two 1-min trials, young = 59.1 ± 9.9, old = 46.1 ± 6.7, $F(1, 30) = 18.6$, $p = .0002$, same scores expressed as a function of the maximum number of correct responses attained (N/73), young = 0.40 ± 07, old = 0.31 ± 0.04, whereas performance in the two phonemic trials was comparable in both groups, young = 22.6 ± 6.1, old = 29.8 ± 7.0, $F(1, 30) = 1.7$, $p = .2$, N/73, young = 0.22 ± 0.04, old = 0.20 ± 0.04. Although both groups generated significantly more words during the semantic compared with the phonemic fluency task, young, $F(1, 30) = 83.4$, $p < .0001$, old, $F(1, 30) = 45.5$, $p < .0001$, this difference was more pronounced in the younger participants, Group × Condition interaction, $F(1, 30) = 6.1$, $p = .02$. Comparison of the old subjects with their respective norm group (age-corrected z-scores are provided for the RWT) revealed that they performed within the 78th–94th percentile for all subtests, that is, 1.0–1.7 z-scores above age norms. The younger subjects scored between the 56th and the 78th percentile of their age group, 0.2–1.1 z-scores. Therefore, although absolute performance levels of the old group were lower compared with the young participants in the semantic task, the old participants were indeed rather high functioning for their age. (Note that at least with respect to age-corrected scores, the older participants performed better than the younger participants. Therefore, differences between the two groups during functional imaging (see below) might even have been more pronounced if the subjects had been more closely matched with regard to age-corrected scores.)

No differences were found in the synonym and the vocabulary tasks [synonym test (Synonym–Antonym Selection–Classification Test), young = 48.1 ± 3.8, old = 50.7 ± 6.4, $p = .2$; vocabulary test (Wortschatztest), young = 35.8 ± 1.3, old = 34.9 ± 4.9, $p = .5$].

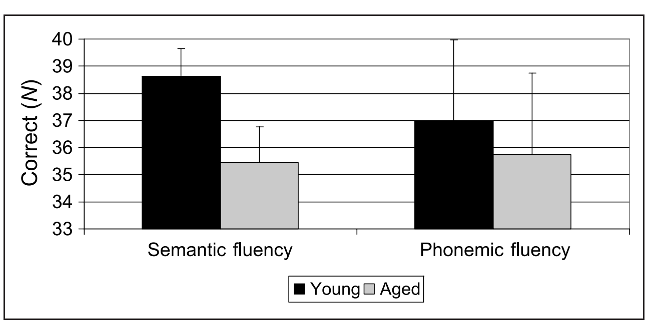

Figure 1. Number of correct responses during the semantic and the phonemic fluency task for young and old subjects as obtained in the scanner (maximum score 40).

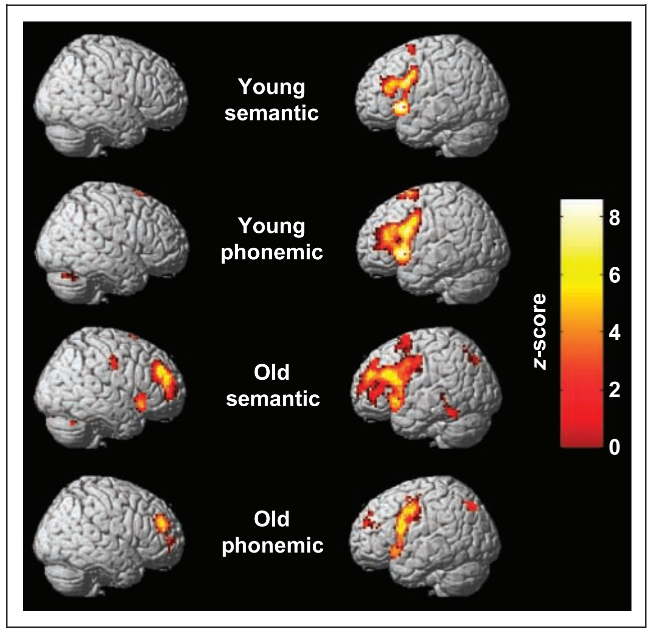

Figure 2. Activity pattern elicited during the semantic and the phonemic fluency tasks during fMRI for young and old participants compared with the baseline condition ($p < .01$, FDR corrected; $k \geqq 20$). Right column = left hemisphere, left column = right hemisphere.

Functional Magnetic Resonance Imaging

Fluency Scores in the Scanner

During scanning, the younger participants generated significantly more words during the semantic fluency task than the old participants (see Figure 1), scores expressed as a function of the maximum number of correct responses (N/40), young = 0.96 ± 0.02, old = 0.88 ± 0.03, $F(1, 30) = 9.1$, $p = .005$, whereas no differences were found during the phonemic fluency task, N/40, young = 0.92 ± 0.07, old = 0.89 ± 0.07, $F(1, 30) = 1.3$, $p = .3$. Only the younger participants generated more exemplars during the semantic fluency task than that in the phonemic task, young, $F(1, 30) = 4.3$, $p = .04$, old, $F(1, 30) = 0.2$, $p = .6$. For the performance obtained in the scanner, the Group × Condition interaction only approached significance, $F(1, 30) = 3.6$, $p = .069$.

Activity Patterns (Young Group)

Figure 2 shows the activity pattern elicited during semantic and phonemic fluency trials for the younger participants. Notably, for both fluency tasks, activity was strongly left lateralized.

When comparing the semantic fluency task with the complex baseline in the younger group, peak activity was centered at the junction of the left anterior superior temporal gyrus (STG; BA 22) and the IFG (BA 9). Additional activity was found in the left cuneate gyrus (BA 17) and in the medial and middle frontal gyri (BA 6). Activity in the right hemisphere was confined to the caudate nucleus. In general, a very similar pattern of activity was observed during the phonemic fluency task, although a larger network of brain regions appeared to be activated and peak activity in several regions was more pronounced. In particular, a large anterior cluster was activated in the left hemisphere that included the left STG and the IFG (BAs 22/9) and also encompassed pars triangularis (BA 45). In addition, the superior frontal gyrus (BA 6), the cuneate gyrus, and the caudate nucleus were activated. As for the category fluency condition, right hemispheric activity was found only in the caudate nucleus (for details, see Table 2).

The direct comparison of the two fluency tasks yielded two significant clusters with peak activity in BA 45 (k = 47, Z = 5.5, −56/24/4) and BAs 9/44 (k = 39, Z = 4.3, −56/13/24 and −50/13/19, respectively) of the left IFG that were more strongly activated for the phonemic task. Naming of category exemplars resulted in more pronounced activity in medial frontal structures only (right medial frontal gyrus, BA 11, k = 17, Z = 4.6, 3/37/−17; left anterior rostral cingulate zone, BA 32, Z = 4.3, −9/31/−12).

Activity Patterns (Old Group)

As can be seen in Figure 2, when compared with the younger group, a more extensive pattern of activity was observed in the old participants for the semantic fluency task. The generation of category exemplars yielded significant activity in a large left hemisphere cluster with peak activity being located in superior temporal and superior/middle/inferior frontal areas (BAs 22/46/10/6). Additional left hemisphere regions included medial frontal areas, the precuneus (BA 7), the inferior and middle temporal gyri (BAs 20/21), and the thalamus. Right hemisphere activity was located in the middle frontal gyrus and IFG (BAs 47/10/9), the lingual gyrus (BA 18), and the premotor cortex (BA 6). Phonemic generation yielded only one significant cluster in the right hemisphere (middle frontal gyrus, BA 10). Significantly activated clusters in the left hemisphere for this condition were located in the inferior (BA 44) and medial frontal (BAs 9/32) gyrus and in posterior parietal regions (for details, see Table 2).

Although the activity patterns of the two fluency tasks against the baseline suggested more pronounced differences between the two conditions, only one small cluster was significantly more activated for the category fluency than the phonemic fluency task and was located in the right medial frontal cortex (BA 11, Z = 5.5, k = 26, 6/39/−14). Inspection of the activity pattern elicited during phonemic fluency compared with the baseline at a lower threshold ($p < .05$, FDR corrected) revealed a very similar pattern of activity compared with the category fluency task, in particular in the right IFG, which explains the minimal differences between the tasks.

Differences between Groups for Both Fluency Tasks

The comparison of activity patterns of the two age groups revealed more pronounced activity in the old participants only for the category fluency condition. Significant clusters were found in the left paracentral lobe (BA 31, k = 30, Z = 5.2, −3/−30/43) and the cingulate gyrus (BA 23, k = 13, Z = 4.5, 0/−28/26). In the right hemisphere, the pars triangularis in the IFG (BA 45, k = 16, 4.7, 59/21/4), the anterior- and inferior-most portion of the middle frontal gyrus (BA 47, k = 15, Z = 4.6, 36/43/−5), and the STG (BA 42, k = 11, Z = 4.0, 68/−17/9) were more strongly activated in the old group.

Correlation Analysis between Activity in Differentially Activated Clusters in the Old Subgroup and Performance

To explore the functional relevance of clusters that were more strongly activated in the old participants during the category fluency task, we correlated individual performance and activity within these clusters. There was a strong negative correlation between behavioral performance and activity in the right IFG ROI (r = −.63, p = .01) and the right middle frontal gyrus ROI (r = −.62, p = .009; see Figure 3A and B). Activity in the left paracentral and cingulate gyrus and the right STG was not correlated with behavioral performance.

To further qualify the role of left frontal activity patterns in the older participants, we performed two additional analyses: (1) For the semantic fluency condition, correlation coefficients were calculated between performance and left hemisphere areas of activity homologous to the active right IFG and MFG ROIs. The correlation for the left IFG ROI was not significant (r = −.3, p = .2). A marginally significant (negative) correlation in the left MFG was driven by one participant (r = −.4, p = .1, 33 correct responses, z = 2.97), when we removed this outlier, the correlation dropped to r = −.05 (p = .9). (2) To assess the functional significance of left frontal activity during the phonemic task, we calculated correlation coefficients between the performance and the left frontal cluster that was activated by the older participants when compared with the baseline condition (see Table 2). Activity in this cluster (BA 44, left IFG) was positively correlated with the behavioral performance in the scanner (r = .56, p = .02). A similar analysis that included the large left fronto-temporal cluster obtained during the semantic fluency task (see Table 2) confirmed the previous ROI analysis (which only included the homologous area of the right IFG) and yielded a nonsignificant correlation (r = −.03, p = .2).

Because fluency scores were at ceiling for most young participants, there was little variance in their fluency

Table 2. Activity Patterns of Young and Old Participants during Semantic and Phonemic Fluency Tasks

Anatomical Structure	*Hemi*	*BA*	*k*	*Z*	*x*	*y*	*z*
Young group							
Category fluency > baseline							
Superior temporal	L	22	695	6.44	−50	14	−3
Inferior frontal		9		5.67	−42	7	27
Cuneate gyrus	L	17	103	5.41	−21	−75	12
Medial frontal	L	6	76	4.95	−6	17	43
Cingulate gyrus		32		4.21	−6	28	32
Caudate nucleus	R		53	4.88	36	−35	−3
Middle frontal	L	6	41	4.34	−18	9	60
Phonemic fluency > baseline							
Superior temporal	L	22	1600	7.31	−50	14	−3
Inferior frontal		9/45		6.81	−53	10	30
Superior frontal	L	6	201	5.28	−18	9	63
Cuneate gyrus	L	17	740	5.23	−15	−78	12
Thalamus	L		83	4.84	0	−23	15
Caudate nucleus	L		28	4.59	−36	−41	2
Caudate nucleus	R		40	4.45	33	−38	7
Old group							
Category fluency > baseline							
Superior temporal	L	22	1525	5.91	−50	14	−3
Middle frontal		46		5.79	−45	27	24
Superior frontal		10		5.70	−30	51	20
Middle frontal	R	10/9	444	5.81	33	42	17
Inferior frontal	R	47	116	5.55	45	20	−9
Rostral cingulate zone	L	32	400	5.47	−3	20	40
Medial/superior frontal		6		5.21	−21	5	49
Lingual gyrus	R	18	103	3.69	18	−85	−13
Precuneus	L	7	98	4.77	−27	−65	39
Inferior temporal	L	20	57	4.42	−53	−47	−13
Middle temporal		20/21		4.09	−59	−41	−11
Precentral	R	6	57	4.41	48	−10	36
Thalamus	L		43	4.35	−15	−17	15
Phonemic fluency > baseline							
Inferior frontal	L	44	584	6.19	−48	10	16
Precentral		6		5.54	−39	2	33
Medial frontal	L	9	175	4.99	−21	39	20
Rostral cingulate zone		32		4.79	−6	25	37
Superior frontal		10		4.09	−30	54	22
Middle frontal	R	10	149	4.96	33	42	17
Superior parietal	L	7	67	4.85	−27	−68	45
Precuneus		7		3.96	−24	−59	50

L = left; R = right; Hemi = hemisphere; BA = Brodmann area; *k* = cluster extent; *x/y/z* = Talairach coordinates, *Z*-values for maximally activated voxels within significant clusters ($p < .01$, FDR corrected); voxel threshold, $p < .01$, FDR corrected, $k \geqq 20$. In **boldface**: peak voxel within significant cluster.

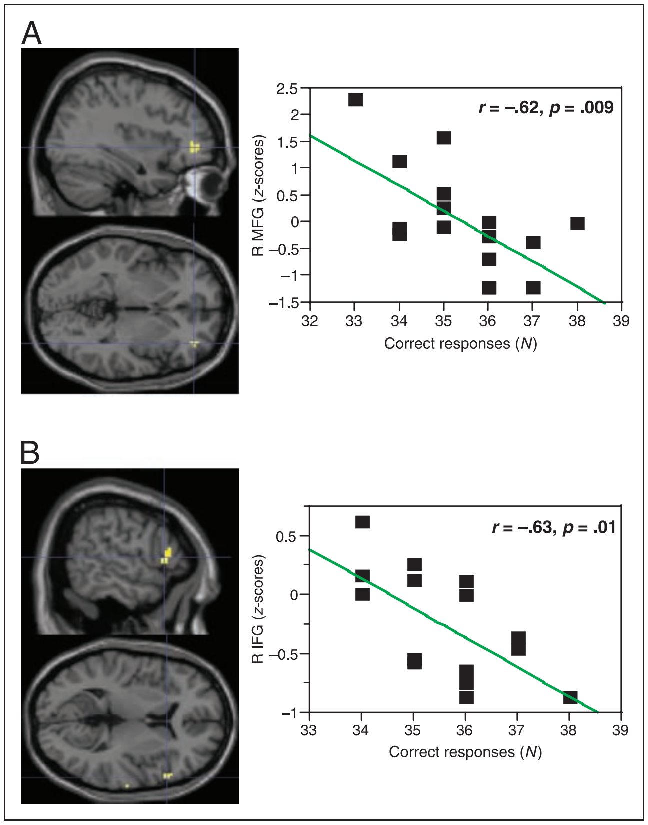

Figure 3. (A and B) Negative correlation between task performance during the semantic fluency task in the aged group (number of correct responses) and activity within (A) the right middle frontal gyrus (R MFG; 36/43/−5) and (B) the right inferior frontal gyrus (R IFG; *x*/*y*/*z*: 59/21/4). Note: For illustrative purposes, we excluded one outlier whose average *z*-score within the IFG-ROI was 3.18 (33 correct responses). The significant correlation was not affected by this participant ($N = 16$; $r = -.69$, $p = .003$).

scores; therefore, correlation analysis would not have yielded meaningful statistics for the young group.

DISCUSSION

In this study, we used fMRI to compare activity patterns elicited by two different verbal fluency tasks (semantic and phonemic fluency) in healthy young and old adults. The main findings of our study can be summarized as follows: (1) In the young adults, a strongly left-lateralized (frontal) pattern of activity was evident during both tasks. A more bilateral pattern was found in the old group during semantic fluency. Although performance during the phonemic fluency task was comparable between young and old participants, a selective drop of performance was observed in the old compared with the young group during the semantic task. The latter difference was accompanied by greater activity in the old than the young group mainly in right inferior and middle frontal regions. (2) This additional right frontal activity pattern was not beneficial to performance, as participants with more pronounced right frontal activity produced less correct words during the semantic task. (3) Only during the phonemic task, when performance levels were comparable between old and young adults, a positive correlation between left frontal activity and behavioral performance could be substantiated. (4) Although in the younger participants the activity pattern was larger and more pronounced for the phonemic compared with the semantic fluency task in anterior ventral (BA 45) and posterior dorsal (BA 44/9) portion of the IFG, the old participants' activity pattern failed to show this distinction. We will comment on these findings in more detail below.

Previous studies have suggested a positive effect of additional activity in the non-task-dominant hemisphere in particular for high-functioning healthy old adults across a variety of cognitive tasks (for a review, see Cabeza, 2002). Moreover, recently Davis et al. (2008) compared fMRI activity patterns in old and young participants during an episodic retrieval and visual perceptual task. These authors convincingly demonstrated that this pattern may not solely be explained by increased task demands in the older subjects as they controlled for task difficulty and matched their young and old subjects according to performance levels and confidence to master the task. Concerning language functions, little is known about the neural concomitants of word-retrieval processes in older adults, and only one study used a language production task to scrutinize the neural concomitants word-retrieval processes in old age (Wierenga et al., 2008). In this latter study, compared with previous nonlanguage tasks, a slightly different picture emerged: Not only did older adults recruit a larger network in left frontal brain regions, it was also suggested that during language tasks, right hemisphere activity might not be universally beneficial to performance. In particular, although across the group naming accuracy was similar in old and young adults, when the authors only considered the lower functioning old participants, a negative correlation with performance was found in the posterior ventral portion of the right IFG (BA 45). This result is in line with our findings. As suggested by previous reports (e.g., Brickman et al., 2005), during the semantic task, performance levels of our old participants were reduced compared with the young group inside and outside (RWT) of the scanner. Moreover, only during the semantic task, the older adults (a) recruited additional right (inferior and middle) frontal areas, and (b) this activity pattern was negatively correlated with performance. These findings contrast with those of Wierenga et al. (2008), who found a positive correlation in the right IFG (BAs 47) with picture-naming performance in neurologically normal old adults. However, a closer inspection of the positive correlation between performance of old adults and activity in the right IFG as reported by Wierenga et al. reveals that it was largely driven by three of 20 participants who had both low performance on picture naming and reduced activity in the IFG.

It also is worth noting that in the picture-naming task of Wierenga et al. (2008), performance was strongly determined by an external stimulus (i.e., the picture). Crosson et al. (2001) demonstrated differences in extent of activity in the IFG for externally driven versus internally driven tasks like the verbal fluency task we used. Thus, this difference between tasks in the two studies may be of some importance in correlations between performance and IFG activity.

For the phonemic fluency task, the older participants performed on the same level as their younger counterparts, and the direct comparison of the activity patterns of young and old adults revealed no statistically significant differences in the left or the right hemisphere. Moreover, a positive correlation between activity in the task-dominant left hemisphere and performance in the older adults was found only during the phonemic task. These results are similar to previous reports that investigated other types of language tasks (nonexpressive). For example, in a study by Rotte (2005), old and young subjects performed simple synonym or letter identity judgments. Here, similar performance of both groups was accompanied by a strongly left-lateralized activity pattern in old and young participants. Moreover, Daselaar, Veltman, Rombouts, Raaijmakers, and Jonker (2005) investigated priming effects during a word-stem completion task using event-related fMRI and observed similar priming-related activity reductions in the left IFG. It was noteworthy that no differences were found in the right IFG but rather confined to areas in the left hemisphere (e.g., the anterior superior temporal lobe).

Moreover, two recent studies investigated the influence of difficulty levels on phonemic word-retrieval tasks in younger subjects (to mimic word-retrieval difficulties in aphasia) by means of fMRI (Drager et al., 2004) and functional transcranial Doppler sonography (Drager & Knecht, 2002). In both studies, the subjects' task was to generate words beginning with a single letter (T…; simple condition) or up to three letters (TEN…; difficult condition due to the limited search volume). Therefore, the difficulty levels were increased, but the fundamental phonological nature of the task was unaltered. (Such alterations could have lead to recruitment of different neural resources.) Both studies found no additional activity in right hemisphere regions or no increased blood flow in the right middle cerebral artery subserving homologous right hemisphere areas of the classical perisylvian language cortex of the dominant hemisphere.

The pattern of activity observed in semantic fluency task of our study is strongly reminiscent of that seen in patients with acquired language disorders after cerebrovascular stroke (i.e., aphasia). Although effective takeover of functions by the right hemisphere has convincingly been demonstrated for language comprehension tasks (e.g., Crinion & Price, 2005), this has not universally been shown for language production tasks. Rather, increased activity in the contralesional (right) hemisphere has usually been linked to a less favorable outcome in most studies (Winhuisen et al., 2007; Heiss & Thiel, 2006; Cao, Vikingstad, George, Johnson, & Welch, 1999) and seems to be related to larger lesions when less language eloquent cortex in the left hemisphere is preserved (Heiss et al., 1997). Further, it is important to note that right frontal lesions rarely cause aphasia in older adults, although older adults demonstrate right frontal activity during word-finding tasks such as in the current study or that of Wierenga et al. (2008). Given these facts, it cannot be assumed that right frontal activity in patients with aphasia necessarily represents language production (unless there is no left frontal activity to support production).

On the basis of the presently available data on language (production) tasks in old age, it seems premature to exclude a potentially beneficial role of the right hemisphere in aging (i.e., the participants could even be more impaired without additional right hemisphere activity, which could be addressed in future studies by means of repetitive transcranial magnetic stimulation; rTMS). Still, as summarized above, previous studies in healthy subjects and aphasia patients pointed to a crucial role of the dominant left hemisphere. Although correlations between performance scores and increased right hemispheric (frontal) activity have been found in some studies involving patients with aphasia, which points to effective compensation of these areas, in general, re-recruitment of left hemispheric brain areas, when intact, usually leads to a better outcome in aphasia than compensatory right hemisphere involvement (for a review, see Heiss & Thiel, 2006). Moreover, suppression of additional activity in the pars triangularis of the right IFG by means of rTMS may improve word retrieval in stroke sufferers (Naeser et al., 2005). Notably, this is exactly the area that was negatively correlated with performance in our sample of old participants.

At present, we can only speculate about the mechanism that may be responsible for the additional right frontal activity pattern in old adults during the semantic task. For example, in aphasia, right hemispheric activity has been explained by decreased transcallosal inhibition that might even interfere with task performance in the dominant hemisphere (Heiss & Thiel, 2006). This might be related to inefficient recruitment of the left hemisphere during word retrieval (Li & Lindenberger, 1999), which would also be in line with the rather extended pattern that was evident during the semantic task in the left hemisphere in the old participants. In addition, in line with previous studies (Costafreda et al., 2006; Gourovitch et al., 2000; Mummery, Patterson, Hodges, & Wise, 1996) in the young participants, we observed more pronounced activity in the posterior dorsal part of the IFG (BAs 44/9) as well as in the more ventral and anterior portion (BA 45) for the phonemic task. This was not the case for the old group. Here, no statistically significant differences were found between the two tasks.

As mentioned earlier in the Introduction, recent electrophysiological studies indicated changed brain activity patterns during language comprehension tasks across the lifespan (e.g., changed amplitude and latency of the N400 component indicating processing of potentially relevant information like words or other meaningful stimuli; for a review, see Federmeier, 2007). In particular, older adults may be specifically compromised when they must use highly constrained contextual information to generate information about upcoming events (e.g., Federmeier, McLennon, DeOchoa, & Kutas, 2002). Moreover, in this study, a subset of the older participants continued to show a young like activity pattern that was best predicted by high working memory resources and verbal fluency scores. The latter was interpreted as reflecting a link between (internal or covert) language production processes and predictive processing during language comprehension tasks (Federmeier, 2007).

Tentatively, it might be speculated whether the more constrained character of the semantic fluency task (i.e., the limited number of category exemplars, although a larger number of items can be selected during the letter fluency task) might be an explanation for the selective impairment during the semantic task in our study. Moreover, it has been shown that (a) the use of contextual information and preactivation of likely upcoming events during language comprehension tasks (at least on a sentential level) might be most efficiently executed by the left hemisphere and (b) the left hemisphere is more tuned to make use of controlled processes to select word meaning (Federmeier, 2007). Integrity and effective use of this left (frontal-temporal) network may even be more important during language production tasks. Therefore, in line with our findings, additional activity in the right hemisphere in older adults may not be efficient or functionally compensatory at least with regard to selective cognitive processes, like in the context of the (more constrained) semantic fluency task.

A note of caution should be made concerning the task choice in our study: In this study, we chose to compare two different fluency tasks, as we expected a selective impairment of one task (the semantic) and a similar performance in the other (the phonemic task). Still, the direct comparison of the two tasks we used in this study is difficult to interpret as the two tasks may require different cognitive operations and involve different neural resources. For example, although both tasks require a strategic search and retrieval of information from semantic memory, previous studies found phonemic fluency to be more strongly affected by left frontal damage, whereas semantic fluency is affected by left frontal and (medial/inferior) temporal damage (e.g., Stuss et al., 1998). This pattern might be explained by the fact that semantic fluency requires a rather constrained search of exemplars from a superordinate category and strongly relies on semantic associations, whereas phonemic fluency can be accomplished within a relatively less constrained search volume (Murphy et al., 2006). Moreover, two previous studies (Gourovitch et al., 2000; Mummery et al., 1996) that used PET directly compared semantic and phonemic fluency tasks within the same (healthy young) subjects. Similar to our own study, both found increased activity in several subportions of the IFG for the phonemic task (including BAs 44/9). For the inverse contrast, increased activity was observed mainly in the inferior and middle temporal areas and the hippocampus. In our study, no difference between the two tasks was found in temporal areas, which may be related to greater sensitivity of PET for functional activity in temporal brain regions, the sparse sampling procedure that we used or/and the difference in baseline tasks (null baseline, Mummery et al., 1996; generation of days of the week or months of the year, Gourovitch et al., 2000). Therefore, to directly assess the impact of difficulty on the neural concomitants of verbal fluency measures in older and younger adults, future studies should also consider varying the level of difficulty within each task (e.g., by comparing activity elicited by superordinate categories that comprise a different number of possible exemplars).

Despite these potential differences between the two fluency tasks, the engagement of comparable brain regions in old and young participants during the phonemic task was consistent with the equal performance levels of the young and old groups, whereas reduced task performance in the semantic task for old adults resulted in an inefficient recruitment of homologous brain areas. Thus, functional integrity and recruitment of left frontal language areas in the task-dominant hemisphere seem to be crucial for successful word retrieval in old age. If the negative correlation found in our own study and in the subgroup of low-performing old adults of Wierenga et al. (2008) will be replicated, it might be worth exploring strategies to counteract these processes. Here, to confirm the nonbeneficial role of additional right hemisphere activity, two strategies are conceivable: the first might involve the active suppression of right frontal activity by means of rTMS, as has successfully been demonstrated in stroke patients suffering from aphasia (e.g., Naeser et al., 2005). A potentially complementary approach may involve facilitation of left-frontal activity by behavioral training as has been suggested for right frontal activity in aphasia treatment by Crosson et al. (2005, 2007).

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