

Aging, self-referencing, and medial prefrontal cortex

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The lateral prefrontal cortex undergoes both structural and functional changes with healthy aging. In contrast, there is little structural change in the medial prefrontal cortex, but relatively little is known about the functional changes to this region with age. Using an event-related fMRI design, we investigated the response of medial prefrontal cortex during self-referencing in order to compare age groups on a task that young and elderly perform similarly and that is known to actively engage the region in young adults. Nineteen young (M age = 23) and seventeen elderly (M age = 72) judged whether adjectives described themselves, another person, or were presented in upper case. We assessed the overlap in activations between young and elderly for the self-reference effect (self vs. other person), and found that both groups engage medial prefrontal cortex and mid-cingulate during self-referencing. The only cerebral differences between the groups in self versus other personality assessment were found in somatosensory and motor-related areas. In contrast, age-related modulations were found in the cerebral network recruited for emotional valence processing. Elderly (but not young) showed increased activity in the dorsal prefrontal cortex for positive relative to negative items, which could reflect an increase in controlled processing of positive information for elderly adults.

Aging is associated with declines in cognitive performance in a number of domains. Recent neuroimaging data suggest that changes to the prefrontal cortex may contribute to impaired memory and cognition with age. Structurally, the prefrontal cortex shows pronounced shrinkage with age (Raz, 2000). Functionally, the engagement of frontal mnemonic processes appears to differ in young and elderly adults: Older adults show reduced activation of left inferior frontal

cortex (e.g., Logan, Sanders, Snyder, Morgan, & Buckner, 2002; Stebbins et al., 2002) and increased activation of homologous regions in the right hemisphere or of distinct subregions of prefrontal cortex (e.g., Cabeza, 2002; Cabeza et al., 1997; Gutchess et al., 2005; Reuter-Lorenz & Lustig, 2005), relative to young adults. While much of the literature thus far focuses on age-related changes to prefrontal cortex, the predominant focus has been on lateral regions, such as

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inferior frontal gyrus. Given the number of structurally and functionally distinct regions of prefrontal cortex, it is unknown whether the age-related changes identified in lateral prefrontal cortex characterize other regions, such as medial prefrontal cortex.

Medial prefrontal cortex may exhibit a different trajectory with age than inferior frontal regions. Structurally, volumetric measures suggest that medial prefrontal cortex may actually enlarge with age, in contrast to inferior frontal regions that shrink with age (Salat et al., 2004). Given the intact structure of medial prefrontal cortex with age, we might expect the region to respond similarly in younger and older adults for relevant tasks. An intact medial prefrontal response with age would contrast with the typical findings of dysfunctional or compensatory activity within lateral prefrontal regions.

To date, the vast majority of studies examining age-related changes in medial prefrontal activity have focused on the region's role as part of a "default network" that is engaged during baseline rest periods when participants are not focused on task-directed thought and is suppressed during attention-demanding tasks (Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005; Gusnard, Akbudak, Shulman, & Raichle, 2001; Gusnard & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). Although most studies that identify changes to the default network focus on Alzheimer's disease (Buckner et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004; Lustig et al., 2003; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005), changes in the activity of default regions also occur in healthy aging. Whereas young adults deactivate both medial prefrontal and medial parietal/posterior cingulate regions, Lustig et al. (2003) found that activity in these regions increases to approach baseline, or even surpass it, for nondemented elderly during a semantic classification task. Across a number of memory tasks, medial prefrontal and parietal regions that are deactivated by young adults exhibit linear increases in activity with age (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006). Grady and colleagues interpreted this finding as evidence for age-related impairments in suppressing irrelevant processes, but a study testing age differences in default network activity as a function of task difficulty did not support such an interpretation (Gould, Brown, Owen, Bullmore, & Howard, 2006). Thus, currently it is not clear whether age-related changes

in medial prefrontal deactivations reflect age-related impairments in suppressing activity irrelevant to attention-demanding externally focused tasks, or a general age-related impairment in the recruitment of the region across all tasks.

One way to clarify whether medial prefrontal cortex can be engaged normally by older adults is to examine its activity during a task that requires its active recruitment (rather than its disengagement). The one study that has examined this issue found that, during processing of emotional facial expressions, older adults recruit less medial prefrontal cortex when viewing happy faces and more when viewing angry faces, compared to younger adults (Williams et al., 2006). Because emotion regulation ability is known to improve with aging (Gross et al., 1997) it is perhaps unsurprising that older adults would show differential medial prefrontal recruitment.

In the present study, we sought to explore whether medial prefrontal cortex could be engaged similarly by both young and elderly adults under appropriate task demands (i.e., with a task that should not show large age differences in the cognitive processes recruited to perform it). We selected a self-reference task in order to compare age groups on a task known to engage the region in young adults that requires cognitive functions thought to be spared with aging. Default network regions such as medial prefrontal cortex and posterior cingulate gyrus are implicated in the processing of social information for young adults (e.g., Harvey, Fossati, & Lepage, 2007; Mitchell, Macrae, & Banaji, 2005), particularly when the information is self-relevant (D'Argembeau et al., 2005; Kelley et al., 2002; Macrae, Moran, Heatherton, Banfield, & Kelly, 2004). The involvement of these regions in self-relevant cognitive processes has been replicated across a number of conditions (see Northoff et al., 2006, for a meta-analysis), and the regions respond most strongly when information is self-descriptive (Macrae et al., 2004; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006). Medial prefrontal cortex is critical to the processing of self-relevant information in that increased engagement of the region during encoding distinguishes items later remembered from those later forgotten (Macrae et al., 2004). Furthermore, self-referencing improves memory to the same extent for both young and elderly, which suggests that self-referencing operates similarly in both age groups (Gutchess, Kensinger, Yoon, & Schacter, 2007c; Mueller, Wonderlich, & Dugan, 1986). In

contrast to the default state literature, these regions are engaged, rather than suppressed or deactivated, during judgments of self-relevance. Medial prefrontal cortex can be activated during judgments of self-relevance (D'Argembeau et al., 2005; Heatherton et al., 2006), or at least approach baseline relative to conditions that deactivate well below baseline (Kelley et al., 2002).

Although we focus on the effects of aging during judgments of self-relevance compared to other person relevance, we also compare the age groups on judgments of positively and negatively valenced words and endorsements of items as self-relevant or not. In young adults, distinct but adjacent regions of medial prefrontal cortex respond to the degree of self-descriptiveness (i.e., medial prefrontal) and the valence of information (i.e., ventral anterior cingulate cortex; Moran et al., 2006). Because emotional information differentially captures the attention of young and elderly (Charles, Mather, & Carstensen, 2003; Kensinger, Piquet, Krendl, & Corkin, 2005; Mather & Carstensen, 2005), comparisons of valence allow us to assess the degree to which emotion contributes to self-referencing across the age groups.

METHODS

Participants. Nineteen young adults (ages 18–28, $M = 23$ years; 10 females) and seventeen elderly adults (ages 61–80, $M = 72$ years;

11 females) participated in the study in exchange for payment. Three additional elderly adult males were recruited but were unable to participate because they could not be positioned comfortably in the head-only scanner. Eligibility criteria for fMRI included right-handedness, English as a native language, good neurological, psychological, and physical health, and the absence of medications that affect the central nervous system or other contraindications for MRI scanning. The study was approved by the Harvard University and the Massachusetts General Hospital Institutional Review Boards, and participants provided written informed consent.

Materials and procedure. Materials consisted of 288 adjectives, drawn from the sets used by Craik et al. (1999). Half of the words were positive and half were negative, as determined by norms (Anderson, 1968; Bradley & Lang, 1999). The adjectives were encoded with one of three encoding conditions, each requiring a key press to indicate yes or no. Participants judged whether the adjective described them (Self trials), described Albert Einstein (Other trials), or was presented in upper case (Case trials). Albert Einstein was selected as an appropriate target person based on prior work (Gutchess et al., 2007c) that established that young and elderly did not differ in their familiarity with or attitude towards him. Figure 1 presents a schematic of the trial types.

After a brief practice session outside of the scanner, participants encoded 144 adjectives, 48

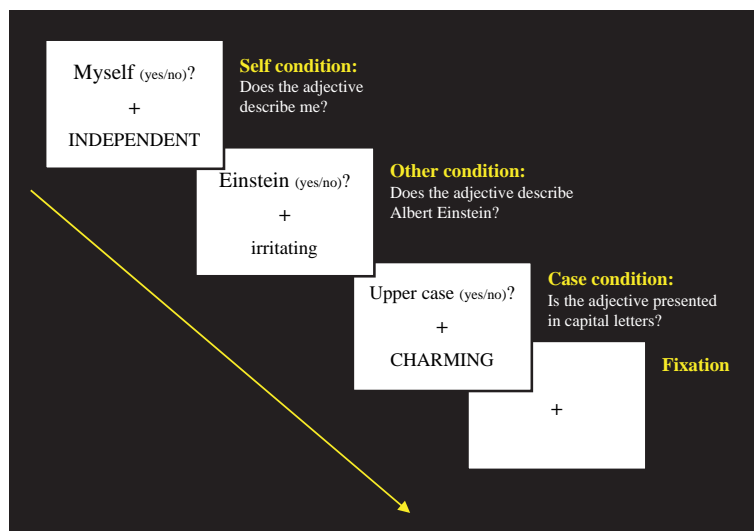


Figure 1. Design. Each of the three different trial types, as well as fixation, are depicted in this figure. Trials were presented for a fixed 4 s duration in a jittered event-related design.

for each of the three conditions, across two runs in the scanner in an event-related design. Three different counterbalanced lists allowed for the adjectives to be assigned to all three conditions across participants. Trials lasted for a fixed duration of four seconds each, and were pseudorandomly interspersed with fixation cross baseline trials to introduce jitter (Dale, 1999). Participants were instructed to make a yes or no decision for each trial and to respond quickly. The task was presented with E-Prime software (Psychology Software Tools, Pittsburgh, PA), which also recorded participants' yes/no responses from a button box. The scanning portion of the study lasted approximately 40 minutes. After a delay of approximately fifteen minutes, participants completed a self-paced recognition test outside of the scanner by making a yes/no recognition decision for each of the 144 adjectives studied previously and 144 novel lures. Analyses based on recognition data are not the focus of the present investigation, and will be presented separately in a forthcoming paper (Gutchess, Kensinger, & Schacter, 2007b).

Neuropsychological measures. To ensure that our population consisted of cognitively intact elderly we administered the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and basic measures of cognitive function. All elderly participants scored at least a 28 (out of 30) on the MMSE, indicating that the sample did not include demented participants. Young and elderly groups both completed speed of processing (Hedden et al., 2002) and vocabulary (Shipley, 1986) measures. Scores are presented in Table 1.

TABLE 1
Means and standard deviations for demographics and performance measures

	Young	Elderly	<i>p</i> -value
Age	23.11 (2.85)	71.71 (4.69)	.001*
Years of education	15.84 (1.81)	15.35 (2.29)	.48
Self-rated health [†]	3.72 (0.67)	4.18 (0.73)	.06
Digit comparison	81.95 (11.65)	52.76 (8.41)	.001*
Vocabulary	35.42 (2.50)	36.82 (3.25)	.15
MMSE	N/A	29.65 (0.70)	

Notes: [†]Self-rated health reflects a rating on a 5-point scale in comparison to others in one's age group. A rating of 3 denotes "average" and 4 denotes "better than average". *Significant at $p < .001$.

Image acquisition and data analysis. Data were acquired with a Siemens Allegra 3T scanner, using an echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, FOV = 200 mm, flip angle = 90°) to acquire 30 AC/PC oriented slices 3.2 mm thick with a 0.3 mm skip. Stimuli were back-projected onto a screen behind the scanner, and viewed by the participants using a mirror attached to the headcoil. High-resolution anatomical images were acquired using a multiplanar rapidly acquired gradient echo (MP-RAGE) sequence.

Pre-processing and data analysis were conducted with SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were slice-time corrected, realigned to the first image to correct for motion, normalized to the Montreal Neurological Institute template, resampled to 2 mm cubic voxels, and spatially smoothed using a 6 mm full-width half maximum isotropic Gaussian kernel.

In an event-related analysis, events were convolved with a canonical hemodynamic response function. The first model included regressors for Self, Other, and Case, focusing exclusively on the conditions and excluding the contribution of valence in order to maximize power. The second model included regressors for the combinations of condition and valence: Self-positive, Self-negative, Other-positive, Other-negative, Case-positive, Case-negative.¹ In both models, session regressors were included for each of the two runs. For the conditions of interest, we estimated contrasts, and smoothed these with an 8 mm full-width half maximum isotropic Gaussian kernel, which provided a total effective smoothing of 10 mm. Data were not proportionally scaled. These smoothed contrasts were taken to the second level in a random effects group analysis. Age differences between young and elderly were assessed using two-sample *t*-tests thresholded at $p < .001$ (uncorrected). Note that age differences in a single comparison can result

¹ We also tested a third model to assess age differences and commonalities in "yes" versus "no" judgments of adjectives. This model included regressors for self-yes, self-no, other-yes, other-no, case-yes, case-no. For the yes versus no comparisons of commonalities and differences with age, few voxels survived the threshold for significance. These voxels were not located in regions of interest, such as medial prefrontal cortex and cingulate, so we do not present the data in more detail. There were not sufficient numbers of trials in the relevant bins to allow us to cross the yes/no variable with the positive/negative variable.

from one of two different patterns. For example, a region can respond because young activate more than elderly for the self condition minus the other person condition, or the region can respond because elderly activate more than the young in the comparison of other minus self. Our tables report age differences in the direction of Self > Other or Positive > Negative. Commonalities across the two groups were identified using masking procedures, in which each group's mask consisted of voxels significant at $p < .01$, allowing for a conjoint probability of $p < .001$ using Fisher's method (Fisher, 1950; Lazar, Luna, Sweeney, & Eddy, 2002).

To characterize the response of regions across the conditions in each group, we used MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) to extract the percent signal change from spheres with a radius of 6 mm around the activation peaks.

RESULTS

Behavioral results

Neuropsychological measures. In the direct comparison of young and elderly on the speed of processing and vocabulary measures (Table 1), younger adults completed significantly more digit comparisons, $t(34) = 8.52$, $p < .001$, and elderly correctly completed more vocabulary items, although the difference was not significant, $t(34) = 1.46$, $p = .15$. These are the typical patterns for speed and vocabulary performance reported in much of the cognitive aging literature.

Reaction times. To compare the response times for young and elderly, we removed responses

under 400 ms due to their high likelihood of indicating erroneous button presses, and then computed median reaction times for each of the three conditions for each participant (see Figure 2A). Reaction times were compared in a mixed ANOVA with Condition as a within-groups variable and Age as a between-groups variable. There was a main effect of Condition, $F(2, 68) = 80.82$, $MSE = 27870.33$, $p < .001$, with case judgments faster than self, $F(1, 34) = 74.76$, $MSE = 33475.41$, $p < .001$, and other, $F(1, 34) = 109.54$, $MSE = 37121.17$, $p < .001$, judgments. Other-person judgments were also significantly slower than self judgments, $F(1, 34) = 14.51$, $MSE = 13014.40$, $p < .002$. Not surprisingly, there was a main effect of age, $F(1, 34) = 42.24$, $MSE = 150835.30$, $p < .001$, with younger adults ($M = 1650$ ms) faster than older adults ($M = 2136$ ms). The interaction of Condition \times Age group did not reach significance, $F(2, 68) = 2.33$, $MSE = 27870.33$, $p < .11$. The results suggest that even though young adults are faster than older adults, the relative difference across conditions is comparable for both age groups. This pattern in both age groups of the slowest RTs for other-person judgments and the fastest RTs for case judgments is consistent with the pattern reported by Kelley et al. (2002). To verify that reaction time patterns did not vary substantially across young and elderly, we conducted an additional ANOVA that included Valence (positive/negative) as a variable. We found no main effects or interactions involving valence, suggesting that any interactions in the functional data between age and valence do not result from reaction time differences.

Proportion "yes" responses by condition. In order to compare the frequency with which items were endorsed in each condition across the age

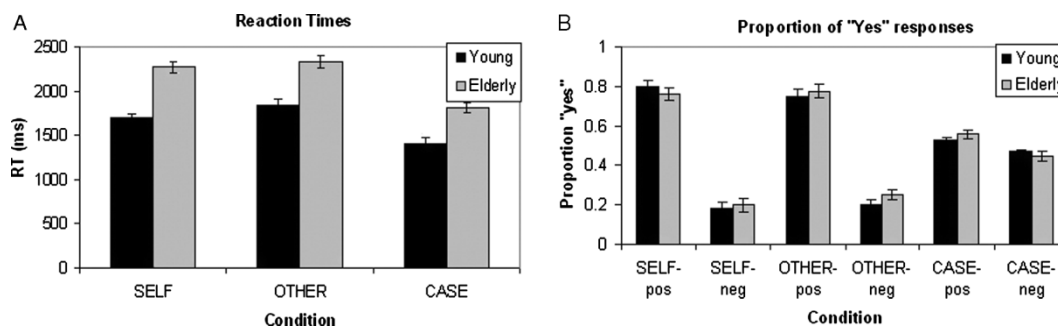


Figure 2. Reaction times and behavioral responses. (A) Reaction times for young and elderly across the three conditions. Although the elderly respond slower than the young, there is no interaction with condition. (B) Proportion of "yes" responses to each of the trial types. Participants respond "yes" to positive items more than negative items for the self and other conditions, but this tendency does not differ with age.

groups, we conducted a mixed $2 \times 2 \times 3$ ANOVA on the proportion of “yes” responses, with Age (young/elderly) as a between-subjects variable and Valence (positive/negative) and Condition (self/other/case) as within-subject variables. Although none of the interactions or main effects involving Age reached significance, there was a main effect of Valence such that positive items received more “yes” endorsements than negative items, $F(1, 34) = 374.10, p < .001$, and a significant interaction of Condition \times Valence, $F(2, 68) = 108.18, p < .001$, such that participants overwhelmingly made “yes” responses for positive items and “no” responses for negative items in the self-reference condition and, to a slightly reduced extent, in the other person condition. In contrast, there were roughly equivalent proportions of yes and no responses to positive and negative adjectives in the case condition, consistent with generally correct responses in this condition. See Figure 2B for an illustration. This pattern is consistent with previous reports that people tend to endorse more positive than negative traits, particularly for the self, but also for judgments about others (Ferguson, Rule, & Carlson, 1983). Importantly, this pattern is true for both younger and older adults, suggesting that

similar judgments are made across the age groups for each condition.

Neuroimaging results

Self vs. other: Commonalities with age. We first tested for regions associated with self-referencing that were common across younger and older adults. In a conjunction analysis of self–other across both age groups, we identified regions associated with self-referencing in previous studies of young adults (see Table 2A). Chiefly, there was a large medial prefrontal activation that extended into the anterior cingulate and the middle orbital frontal gyrus, as well as a mid-cingulate activation. Figure 3 illustrates the response of these regions in each condition. For the mid-cingulate region, the direction of the response (i.e., activation vs. deactivation) differed across the age groups, but the relative comparison of self to other (i.e., more activation, or less deactivation, for the self condition than the other condition) was similar for young and elderly. The response of medial prefrontal cortex was not marked by differences in direction and showed a very similar pattern for young and elderly (i.e., self > other). It is interesting that the region was activated during the self judgments, despite some

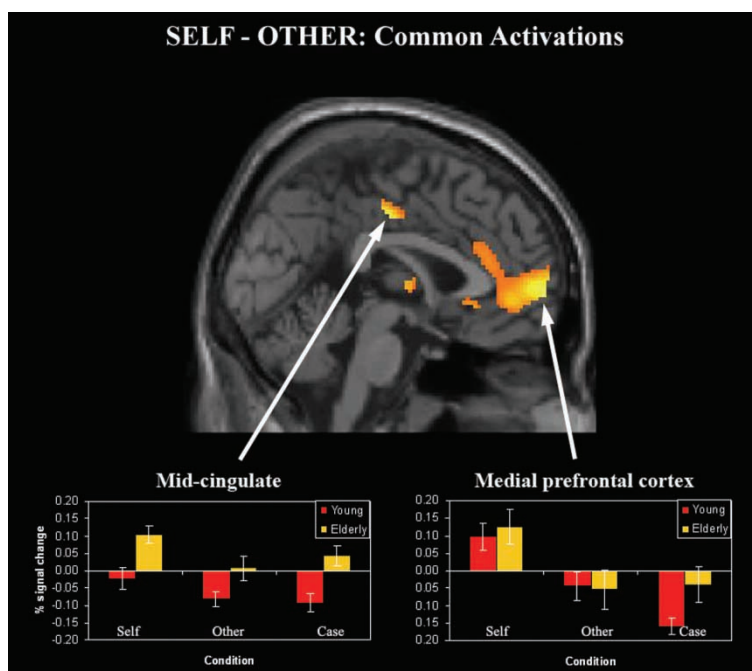


Figure 3. Common activations with age for self–other. Midline regions typically implicated in self referencing are engaged by young and elderly. The displayed slice corresponds to $x = 0$; the peaks of the depicted regions are located at $(-8, 60, 4)$ for the medial prefrontal activation and $(-2, -18, 42)$ for the mid-cingulate activation.

TABLE 2

Self versus other comparisons. MNI coordinates of neural activations that are common and distinct across age groups, and coordinates for young and elderly groups analyzed separately

Region	BA	Activation peak			No. of voxels	t-value
		x	y	z		
<i>A. Common (young and elderly)</i>						
<i>Self-other</i>						
L medial prefrontal	10/11	-8	60	4	1853	6.51
L anterior cingulate	25	-8	46	-2		4.80
L middle orbital frontal	32/24	-6	28	-6		3.81
L middle/superior frontal	46	-22	50	24	151	3.36
L mid-cingulate	23	-2	-18	42	63	4.67
L middle/superior temporal	21/22	-70	-40	22	105	3.76
		-60	-44	16		3.26
		-48	-44	8		3.10
Midline	N/A	-2	-8	4	36	3.49
<i>Other-self</i>						
R lingual	17/18	10	-76	-2	425	3.56
R calcarine	18	4	-88	12		3.53
L middle temporal	21	-68	-8	-18	31	3.75
<i>B. Age differences: self-other</i>						
<i>Young > elderly</i>						
No significant differences						
<i>Elderly > young</i>						
L supplementary motor	6	-6	2	66	89	4.37
L postcentral	3/4	-42	-14	38	116	4.33
R postcentral	3/4	42	-20	36	79	3.60
		50	-18	44		3.57
		40	-22	46		3.59
R cerebellum	30	18	-38	-22	10	3.67
<i>C. Young</i>						
<i>Self-other</i>						
L anterior cingulate	24	-4	34	14	2256	6.70
L anterior cingulate	11	-6	40	0		6.54
L caudate	25	-4	12	4		4.47
L superior temporal	22	-68	-48	22	200	4.94
L middle temporal	22	-56	-48	18		4.05
L superior frontal	46	-24	54	24	44	4.06
R superior frontal	9	28	52	42	15	4.05
L middle frontal	9	-26	38	42	12	3.78
<i>Other-self</i>						
R lingual	18	18	-80	0	2768	7.40
R lingual	18	12	-68	-6		6.10
L cuneus	18	-6	-88	20		5.80
L fusiform	20	-36	-10	-26	388	6.84
L middle temporal	20	-56	-16	-22		4.19
L rolandic operculum	48	-44	-22	22	242	5.46
L supramarginal	3	-48	-22	36		4.84
R postcentral	48	62	-12	20	23	4.31
L fusiform	37	-26	-32	-22	26	4.06
R rolandic operculum	48	56	-4	20	25	3.89

(Continued overleaf)

TABLE 2 (Continued)

Region	BA	Activation peak			No. of voxels	t-value
		x	y	z		
<i>D. Elderly</i>						
<i>Self–other</i>						
L medial prefrontal	10	–8	60	4	651	6.51
L anterior cingulate	10	–8	46	–2		4.80
L mid-cingulate	23	–2	–18	40	87	5.34
R cerebellum		18	–38	–24	27	4.42
L superior temporal	22	–70	–40	18	12	4.02
L caudate		–4	–4	14	14	3.97
L supplementary motor	6	–6	4	66	12	3.91
<i>Other–self</i>						
No significant effects						

Note: Data are thresholded at $p < .001$ (uncorrected) with a 10 voxel extent threshold. Up to three local maxima, separated by at least 8 mm, are displayed.

reports that self and other judgments result in deactivations relative to baseline (Kelley et al., 2002) or that resting states consist of self-referential thought (Wicker, Ruby, Royet, & Fonlupt, 2003). However, there is some precedence in the literature for activations for the self condition (e.g., D’Argembeau et al., 2005; Heatherton et al., 2006).

When we looked for regions in common across young and elderly adults for the reverse comparison (i.e., other–self), we noted that both groups recruited visual (i.e., lingual and calcarine gyri) and semantic regions (i.e., left middle temporal). Although this comparison is not of primary interest, the findings suggest that making judgments about another person, in this case, Albert Einstein, relied on visual imagery and semantic knowledge more than making judgments about oneself. For young adults, D’Argembeau et al. (2005) reported that subjects rated the highest amount of visual imagery as occurring in the “other person” condition; our results suggest that this may also be true for older adults.

Self vs. other: Age differences. As shown in Table 2B, few differences occur across young and elderly in the comparison of self vs. other. The contrasts of self–other and other–self are displayed separately for young (Table 2C) and elderly (Table 2D) for comparison. Those regions that differ (i.e., postcentral and supplementary motor gyri, cerebellum) likely reflect age differences in planning and executing the button press for the task. Given that age does not interact with condition in the reaction time data, the age

differences in activations are not straightforward to interpret; they could reflect older adults’ apraxia and impaired motor skills, and the reorganization of the neural substrates for motor function with age (e.g., Mattay et al., 2002).

Positive/negative valence. Previous research reveals that regions adjacent to the self network can respond to valence (Moran et al., 2006). To assess age differences in the contribution of valence to self-referential activity, we first compared the main effects of valence across all trial types for both age groups. As shown in Table 3A, the only region in which young and elderly distinguish positive from negative items is left inferior temporal cortex. Kensinger and Schacter (2006) identified a nearby peak in which activity was higher for positive than negative items. The activity likely reflects semantic knowledge of word valence across all conditions.

In terms of age differences, young and elderly differ in their response to valence in a number of regions, with several foci occurring in visual and frontal regions (see Table 3B). Although frontal regions include superior, middle, and inferior frontal gyri, the activations do not overlap with the medial prefrontal and mid-cingulate activations identified in the contrast of self–other. Thus, the main effect of valence and its interaction with age appear to be distinct from the regions that respond to referencing information to oneself compared to referencing another person. The region most similar to the ones that emerge from the comparison of self > other is the superior frontal activation extending from BA 10 into

TABLE 3
Valence comparisons. MNI coordinates of common and distinct neural activations in younger and older adults

Region	BA	Activation peak			No. of voxels	t-value
		x	y	z		
<i>A. Common (young and elderly)</i>						
<i>Positive–negative</i>						
L inferior/middle temporal	20	–60	–18	–24	95	3.76
<i>Negative–positive</i>						
No significant effects						
<i>B. Age differences: positive–negative</i>						
<i>Young > elderly</i>						
No significant differences						
<i>Elderly > young</i>						
R superior frontal	10	22	56	16	509	4.32
R middle frontal	46	34	36	28		4.17
R middle frontal	46	32	42	22		3.85
R inferior frontal	48	58	12	–2	321	3.80
R insula	48	48	12	–8		3.79
R inferior frontal	45	58	22	18		3.63
R inferior frontal	45	54	36	–2	47	3.75
R superior frontal	6	34	6	70	71	3.93
L precentral	6	–42	0	42	162	3.73
R precentral	6	48	6	36	50	3.66
L calcarine	18	–16	–74	6	433	4.58
L cuneus	18	–6	–80	24		3.91
R lingual	18	12	–80	–4	199	3.95
R calcarine	18	8	–86	10		3.47
R lingual	19	22	–58	4	10	3.47
R middle occipital	19	30	–76	38	723	4.19
L middle occipital	19	–34	–76	8	109	3.86
R cuneus	7	22	–76	46		4.04
R angular	7	34	–58	46		4.03
L precuneus	7	–6	–70	50	331	4.03
R precuneus	7	6	–68	54		3.54
R precuneus	7	4	–56	62		3.47
L superior parietal	7	–30	–62	48	229	3.96
L superior parietal	7	–22	–58	48		3.84
R middle temporal	21	54	–26	–2	78	3.95
L inferior temporal	20	–44	–40	–22	64	4.15
L inferior temporal	37	–46	–66	–8		3.55
R middle temporal	21	62	–50	4	13	3.48
R cerebellum		30	–52	–40	139	3.91
R cerebellum		16	–56	–40		3.71
R cerebellum		24	–36	–44	14	3.81
L cerebellum		–20	–78	–36	27	3.71

Note: The data are thresholded at $p < .001$ (uncorrected) with an extent threshold of 10 voxels. Up to three local maxima, separated by at least 8 mm, are displayed.

BA 46 (see Figure 4A). Although it is more superior and right lateralized than the predominantly left lateralized medial prefrontal BA 10 activation that responds to self-referencing (see Panel B), the activation extends posteriorly into BA 46 (see Panel C) and appears to be a right-hemisphere homologue of the left BA 46

activation in the self–other contrast. The pattern of the response in these two peaks varies across the age groups, as seen in the graphs in Figure 4. For example, the top graph, selected from the anterior BA 10 peak (Panel A), shows that young adults activate similarly to the positive and negative adjectives, whereas elderly adults exhibit

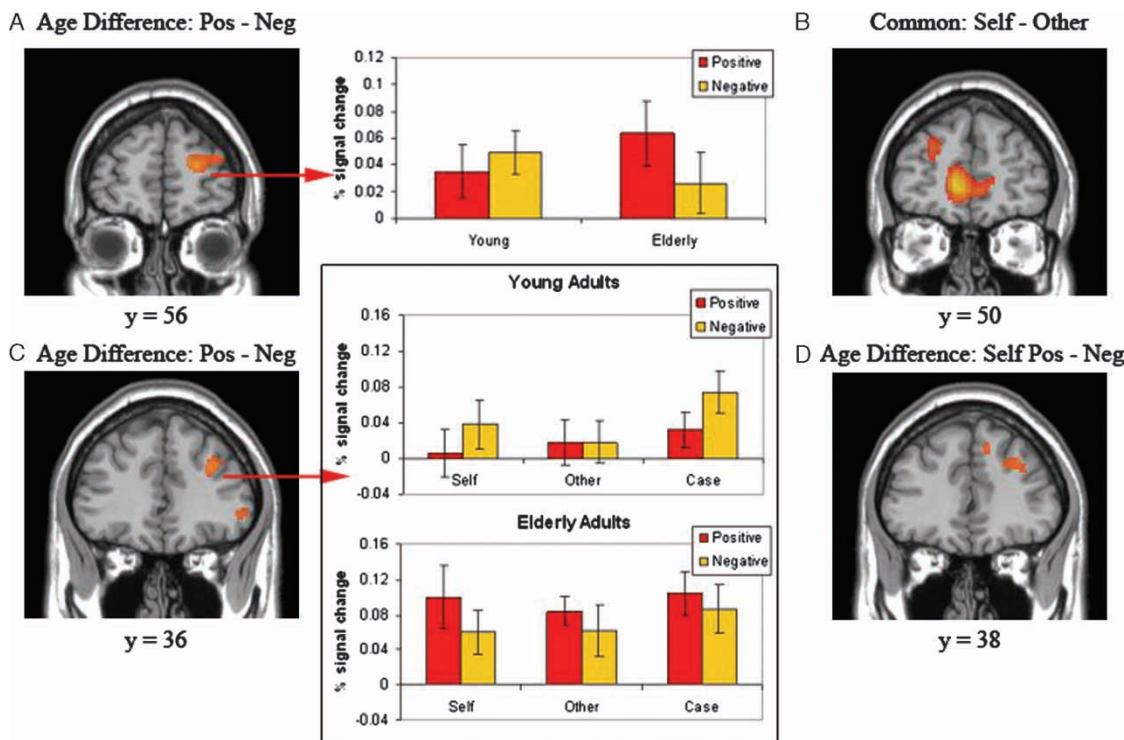


Figure 4. Positive versus negative prefrontal differences. Medial and middle prefrontal regions are displayed across the different contrasts. The valence comparison differs across the age groups in the engagement of a region of superior prefrontal cortex (Panel A: BA 10; peak = 22, 56, 16) that elderly, but not young, activate for positive more than negative adjectives (top graph). The age difference across positive and negative valence extends into right middle prefrontal cortex (Panel C: BA 46; peak = 34, 36, 28), a region that also shows age differences in the comparison of valence for the self trials only (Panel D: peak = 28, 38, 30). While elderly consistently engage the region more for positive than negative trials across all conditions, young show the reverse pattern (bottom graphs). For comparison, Panel B (peak = -22, 50, 24) illustrates the medial and left middle prefrontal regions activated in the contrast of self–other, and the regions do not overlap with any of the valence comparisons.

a larger difference in activity, with more activation to positive than negative adjectives. The bottom two graphs plot activity in the posterior prefrontal peak in BA 46 (Panel C). Collapsing across the conditions reveals that young adults activate the region more for negative than positive adjectives whereas older adults show a difference in the opposite direction, with greater activation for positive than negative adjectives. These two regions show an enhanced response for positive items for older adults compared to younger adults, offering tantalizing support for a positivity shift in the processing of valenced information with age by which elderly attend to positive information more than negative, and young show the reverse pattern (Mather & Carstensen, 2005).

Our finding that the regions that respond to valence are distinct from those implicated in self-referencing is consistent with previous research (Fossati et al., 2003, 2004; Moran et al., 2006). However, previous studies assessed the effect of

valence under self-referencing conditions; we might expect age differences in the effects of valence under self-referencing conditions to differ from those effects of valence that are present across all conditions. To address this possibility, we focus on the contribution of valence to the self condition in the remaining analyses.

Interaction of self-referencing and valence. To compare the influence of valence on judgments of self-relevance across age groups, we contrasted the positive and negative trials across age groups for only the self-reference condition. As shown in Table 4A, a region of left middle temporal cortex responds more for both young and elderly when self-referenced adjectives are positive, rather than negative. This region is virtually identical to the one that responds to the main effect of valence, suggesting that the semantic processes employed by positive versus negative items are consistent across self-relevant and other types of adjective judgments.

TABLE 4

Self-reference \times valence comparisons. MNI coordinates of common and distinct neural activations in younger and older adults

Region	BA	Activation peak			No. of voxels	t-value
		x	y	z		
<i>A. Common (young and elderly): positive versus negative self</i>						
<i>Positive self–negative self</i>						
L middle/inferior temporal	21/20	–64	–14	–22	100	3.40
<i>Negative self–positive self</i>						
No significant effects						
<i>B. Age differences: positive–negative self</i>						
<i>Young–elderly</i>						
No significant differences						
<i>Elderly–young</i>						
R inferior parietal	7	24	–48	48	513	5.02
R precuneus	5	10	–58	64		4.19
R angular gyrus	7	30	–54	42		3.74
R superior occipital	19	30	–82	40	81	3.97
R middle frontal	46	28	38	30	82	3.78
R superior medial frontal	32	12	36	42	25	3.65
R precentral	6	54	6	48	38	3.87
L precentral	4	–54	0	36	150	4.29
L precentral	6	–44	2	44		3.57
L middle frontal	6	–36	4	54		3.56
<i>C. Common (young and elderly): self/other \times positive/negative</i>						
No significant effects						
<i>D. Age differences: (self positive – other positive) > (self negative – other negative)</i>						
<i>Young–elderly</i>						
No significant differences						
<i>Elderly–young</i>						
L middle frontal	8	–28	12	54	20	3.85
R middle frontal	45	50	46	6	13	3.54
R superior medial frontal	32	12	38	40	23	3.79
R supplementary motor	6	12	–2	62	11	3.56
R temporal pole	38	38	22	–34	11	3.53

Note: The data are thresholded at $p < .001$ (uncorrected) with an extent threshold of 10 voxels. Up to three local maxima, separated by at least 8 mm, are displayed.

Even though this analysis is comparable to previous studies that compared valence during self-referencing (Fossati et al., 2003, 2004; Moran et al., 2006), the regions reported in previous studies generally do not emerge in our data as equivalent (Table 4A) or different (Table 4B) with age. The BA 46 prefrontal region that distinguished the age groups for the main effect of valence (Figure 4C) also shows an effect of valence in the comparison of positive and negative valenced items in the self-reference condition (Figure 4D). Graphing the activity across the different conditions shows that the pattern for the self condition (negative > positive for the young and positive > negative for the elderly)

also generally holds for the other conditions, but more so for the old than young.

In a final analysis of the influence of valence on self-referencing, we compared the interaction of judgments about self or other with positive and negative valenced items. Young and elderly had no regions in common (Table 4C) in either direction, i.e., (self positive–other positive) > (self negative–other negative) or (self negative–other negative) > (self positive–other positive). Age differences (Table 4D) occurred in predominantly frontal cortex, such as left (BA 8) and right (BA 45) middle frontal cortex, and right superior medial prefrontal cortex (BA 32), as well as right superior temporal cortex (BA 22).

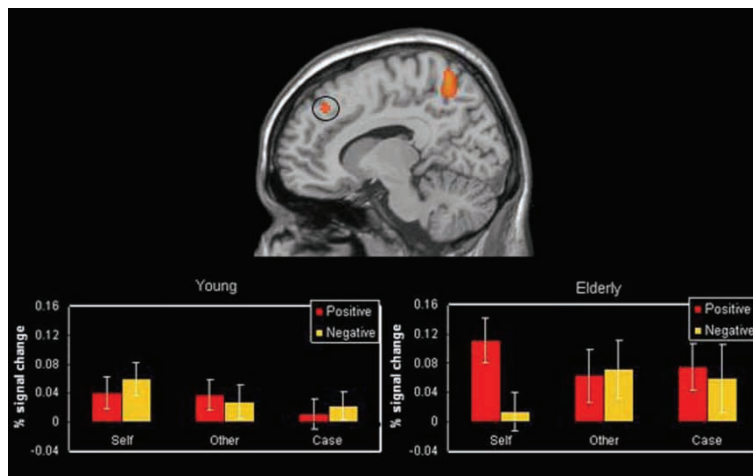


Figure 5. Age differences in self-referencing and valence. Graphs plot the activity of dorsal medial prefrontal cortex (BA 32) for positive and negative adjectives for young and elderly. The displayed slice is $x = 12$ with the peak dorsal medial prefrontal activation at MNI coordinate (12, 38, 40).

Unlike the comparisons of the main effect of valence, a midline region emerged in both comparisons of valence involving the self condition (Table 4B & D). As illustrated in Figure 5, the region of medial prefrontal cortex (BA 32) is superior to the self-reference activity displayed in Figure 3, but is consistent with previous reports of the involvement of dorsal medial prefrontal cortex in self-referential processes (Mitchell, Macrae, & Banaji, 2004; Mitchell et al., 2005). As displayed in Figure 5, the age groups differ in their response to items judged in reference to the self, with elderly activating strongly to positive but not negative items, while young activate somewhat more for negative than positive items. However, activity for positive and negative items differed little when making judgments about another person. Consistent with this pattern, the dorsal medial region overlapped with a region identified in the comparison of self-referencing of positively and negatively valenced items (Table 4B).

Discussion

In this study, we find that both young and elderly engage medial prefrontal and mid-cingulate cortex during self-referencing. Although previous studies (see Northoff et al., 2006, for a review) implicate these midline regions for young adults, this is the first study to establish the neural correlates of self-referencing for older adults. Except in somatosensory and motor regions, no

significant differences emerge across the age groups in the comparison of self–other. These results suggest that elderly accomplish self-referencing using a network similar to that employed by young. Additional recruitment of somatosensory and motor-related areas by elderly participants is likely related to modifications of motor skills rather than cognitive strategy. Because much of the aging literature highlights age-related changes and impairments to the structure and function of prefrontal cortex (Cabeza, 2002; Park & Gutches, 2004; Raz, 2000; Reuter-Lorenz & Lustig, 2005), the finding of intact function with aging is somewhat surprising. Moreover, the few studies to investigate functional changes in medial prefrontal cortex identify changes with age, such as reduced suppression when tasks require an external focus (Grady et al., 2006; Lustig et al., 2003), and for emotion regulation, increases or decreases with age, depending on the valence of the stimuli (Williams et al., 2006). While the response of the region may be impaired with age when tasks require suppression (Grady et al., 2006; Lustig et al., 2003) or controlled processing (Williams et al., 2006), our results suggest that the response of the medial prefrontal cortex is intact with age when the region is crucially engaged by the task.

Previous studies to investigate age differences in the response of medial prefrontal cortex use exceptionally large sample sizes; thus, it is possible that the age-equivalent response of medial prefrontal cortex in the present study is a result of limited power. Our sample, however, is larger

than many in which age differences have been identified across other regions of prefrontal cortex, suggesting at least that medial prefrontal engagement may be less susceptible to age-related decline than engagement of lateral prefrontal regions. Moreover, the self minus other differences appear to be relatively robust and, if anything, Figure 3 suggests a trend towards a larger differentiation between self and other for elderly, compared to young.

Some evidence for global changes with age in the ability to suppress baseline activity could be present in our data. The changing direction of the activity of the mid-cingulate, which young deactivate and elderly activate, could be related to age-related difficulty inhibiting attention to internal processes in order to focus on the external environment (see Grady et al., 2006, for a discussion). Although such a possibility is intriguing, age differences in the absolute level of baseline activity are best evaluated with a method such as PET rather than fMRI, which relies on relative differences between conditions.

One way in which the present data depart from previous studies is in the lack of a posterior cingulate contribution to self-referencing. The region does not emerge in our analysis of young alone or in comparisons of commonalities and differences across the age groups. It is possible that some key features of our task do not engage the posterior cingulate in the same manner as previous studies. Specifically, our 4 s trials are of longer duration than those used in prior studies with young adults. It is possible that the posterior cingulate response drops off quickly, leading to diminished signal across the 4 s window. Although it does not appear that the posterior cingulate response diminishes much faster than the medial prefrontal response in published time courses of the regions (e.g., Kelley et al., 2002; Lustig et al., 2003), it is unknown how the region responds to the relaxed response deadline. Another explanation for the failure to find posterior cingulate activations is that judgments about Albert Einstein and oneself both engage the region. Notably, Heatherton et al. (2006) and Schmitz, Kawahara-Baccus, and Johnson (2004) did not find that the posterior cingulate responded more for judgments about oneself compared to a close other, although the region responded in contrasts of self versus semantic judgments. This pattern is also true of our data; the posterior cingulate emerges as a common region activated by both young and elderly in the

comparison of self to case judgments. This suggests that the region responds to self judgments, but not significantly more than it responds to other person judgments. Perhaps our participants' views of Albert Einstein overlap with their self views in terms of positive regard or even personality traits more than is the case for the sometimes-polarizing public figures who have been used as the other person target in previous studies. The use of political figures such as George W. Bush (e.g., Kelley et al., 2002) also could emphasize the duties and obligations associated with elected offices, and this could induce a prevention focus for all personality judgments. Adopting a prevention focus has been associated with the activity of posterior cingulate cortex (Johnson et al., 2006).

Whether young and elderly engage the same neural substrates across a variety of self-referencing tasks remains to be seen. The task we selected was one for which we expected young and elderly to perform similarly due to the highly familiar process of referencing the self and the intact ability to process social information with age (e.g., Rahhal, May, & Hasher, 2002). Although young and elderly endorsed similar proportions of items as self-descriptive and showed similar patterns of reaction times across the conditions, it is possible that each age group adopted different strategies. For example, in making personality assessments, young adults could perhaps retrieve specific episodes from autobiographical memory whereas older adults could rely on semantic knowledge or more generalized schemas. We are unable to conclusively rule out possible differences in strategies in the present study but expect that larger age differences would emerge when particular strategies must be adopted in order to optimize self-referencing benefits.

Encoding processes may be one domain in which age differences in strategies and neural substrates could emerge. For young adults, successful encoding of self-referential words engages medial prefrontal cortex along with anterior prefrontal cortex and parahippocampal gyrus, with greater engagement for subsequently remembered adjectives compared to those later forgotten (Macrae et al., 2004). Across a variety of memory tasks, healthy aging is associated with reduced engagement of medial temporal regions and altered prefrontal activity (see Park & Gutchess, 2004, for a review), including some evidence for age-related changes in anterior

prefrontal activity (e.g., Morcom, Good, Frackowiak, & Rugg, 2003). In addition, compensatory recruitment of additional regions, often in prefrontal cortex, sometimes occurs to support task performance in healthy elderly (Grady, McIntosh, & Craik, 2003; Gutchess et al., 2005). Thus, under conditions of high cognitive processing demands, older adults' self-reference network could be expected to exhibit a combination of breakdowns in the activity of medial prefrontal cortex or other regions associated with self-referencing, as well as expansion to include additional regions in service of encoding.

The regions that respond more to thinking about oneself than to thinking about another person are distinct from those regions that respond to valence or the descriptiveness of an adjective. Both age groups rate adjectives similarly across conditions. These findings suggest that valence differences do not contribute to the activity of regions attributed to self-referencing. Our results are consistent with previous research (Fossati et al., 2003, 2004; Harvey et al., 2007; Moran et al., 2006) in finding that the regions that respond to valence are separate from those implicated in self-referencing or the encoding of social information, but there is considerable variability in the specific regions identified across studies. For example, Harvey et al. (2007) identify a dissociation between regions that respond to social information (medial prefrontal cortex) and regions that respond to emotional information (amygdala). Although broadly consistent with our findings (in the present study, medial prefrontal cortex responded in the comparisons of self-reference but not emotion), our activations do not overlap with the peaks from Harvey et al. (2007). Furthermore, the amygdala does not emerge in our comparisons involving emotion; only a lateral temporal region responded based upon emotional valence in a similar fashion in both age groups. Only one other self-referencing encoding study has collapsed valence across all conditions—self, social desirability, and letter identification—to compare valence, and they found no significant activity (Fossati et al., 2003). In our comparison of valence across all conditions (self, other, and case), we identified a number of regions that differed across age groups and a left middle temporal region that was involved for both young and elderly. A subset of the regions that differed with age in our study (i.e., cerebellum and insula) emerged in previous comparisons of valence during recognition

(Fossati et al., 2004), although the laterality can vary between encoding and retrieval. Most prior studies that assessed the effects of valence did so under self-referencing conditions, but the previously reported regions are not in the vicinity of our age differences. The minimal convergence of regions across studies may reflect power issues. The valence-specific ventral anterior cingulate cortex (BA 24 & 25) response was identified for a sample of 42 young adults who made self-relevance judgments exclusively (Moran et al., 2006), whereas trials were divided across multiple types of judgments in our study and that of Fossati et al. (2003). Strategy differences across studies could also contribute to different results. When participants make judgments about both self and other in a single paradigm, the self could be considered in a more relative and normative manner than when the task consists of self judgments only.

Interestingly, the regions that respond similarly or differently to valence across the age groups are not strongly implicated in emotional processing, aside from the insula. This observation may reflect the incidental nature of the emotional information in the task, and the use of nonarousing, common adjectives. Another possibility is that some of the regions, particularly in prefrontal cortex, respond to the *strategic* processing of emotional information, rather than to the perception and experience of emotion, as would be reflected by amygdala or orbitofrontal involvement. Age differences in the strategic processing of emotional information would be consistent with recent data suggesting that older adults recruit controlled processes to process positive emotional information (Mather & Knight, 2005). They administered a cognitive control individual differences battery and found that older adults with higher levels of cognitive control exhibited a larger positivity bias than older adults with lower levels of cognitive control. A number of prefrontal regions respond to cognitive control demands for both emotional (Ochsner & Gross, 2005) and nonemotional (Braver & Barch, 2002; Buckner, 2003) information. Even within older adults, individual differences in cognitive control are reflected in the activity of medial and middle prefrontal regions (Gutchess et al., 2007). Our finding that older adults increase activity for positive adjectives relative to negative, particularly in dorsal prefrontal cortex, could reflect increases in older adults' controlled processing of positive information. Such an interpretation

would offer a neural basis for the positivity bias with age (Mather & Carstensen, 2005), and support the theory that this bias results from controlled processing (Mather & Knight, 2005). However, the pattern of age-related changes varies across regions (e.g., a reversal in the valence response within the dorsolateral PFC vs. an enhanced activity for positive valence in older adults within the anterior PFC), suggesting functional subtleties in the mapping between age-related changes in prefrontal activity and in valence-specific processing. To fully understand the nature of age-related changes to emotion and cognition, further work is needed under conditions in which emotion is attended and experienced, as well as incidental to the task.

Valence contributes to self-referencing in some constrained ways, as evidenced by the disproportionate involvement of the dorsal medial prefrontal region for positive valence during self-referencing for older, but not younger, adults (Figure 5). Although we suggest that emotion generally is incidental to the task, previous studies identify dorsal medial prefrontal activation during impression formation (Mitchell et al., 2004; Mitchell et al., 2005). Taken together with our finding, the activity of the region may reflect evaluative components that are more salient for older adults, but only during self-referencing.

In conclusion, elderly adults recruit the same network as young when making personality assessments about the self as opposed to another person. The only cerebral age differences occurred in somatosensory and motor-related areas for this task. In addition, age differences in neural responses to valence occur in distinct regions from those that mediate the self-reference effect, and could reflect age differences in controlled, strategic processes underlying a positivity bias with age. Although highly specific neural responses characterize young adults in the domains of memory (Schacter, Gutchess, & Kensinger, 2006) and perception (see Kanwisher & Yovel, 2006, for a review), much of the aging literature reflects a loss of specificity with age: Bilateral regions respond in place of lateralized regions during encoding and retrieval (e.g., Cabeza, 2002) and object-specific regions of ventral visual cortex (e.g., fusiform face area) respond less discriminately to multiple classes of objects (Park et al., 2004). By contrast, our results suggest that cerebral specificity in the response to social information (i.e., self vs. other) is preserved with age.

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