Functional Changes in Brain Activity During Priming in Alzheimer's Disease

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Abstract

■ Patients with Alzheimer's disease (AD) are often impaired on certain forms of implicit memory, such as word-stem completion priming (WSCP). Lesion data suggest that deficient WSCP may be associated with abnormal functioning in the posterior neocortex. Using positron emission tomography (PET), we here provide direct support for this view. Compared with normal old adults, AD patients showed reduced priming on a word-stem completion task. The normal old showed decreased activity in right occipital cortex (area 19), whereas the AD patients showed increased activity in this region during priming. To the extent that decreased activity during priming reflects an experience-dependent reduction of the neuronal population involved, these results indicate that shaping of the relevant neurons is slower in AD, possibly as a result of inadequate initial-stimulus processing. ■

INTRODUCTION

Perceptual priming refers to the unconscious facilitation of performance following prior exposure to a target item or a related stimulus (for example, Schacter, 1987). Several different measures can be used to assess perceptual priming, such as word identification, lexical decision, and word-fragment completion. Here, we are concerned with a measure involving completion of word stems. In the word-stem completion task, subjects are required to complete a word stem (for example, Pre_____) with the first word that comes to mind (Warrington & Weiskrantz, 1974). The stems are generally selected to have several possible completions, and of interest is whether prior presentation of an appropriate completion of a stem (for example, President) increases the probability of its generation. This is assessed by comparing the probability of completing stems with specific completions (targets), when these have (primed condition) or have not (unprimed/baseline condition) been presented in the experimental setting prior to the completion task (for overviews, see Roediger, 1990; Schacter, Chiu, & Ochsner, 1993).

Memory retrieval, as revealed by word-stem completion priming (WSCP), has been referred to as "implicit," because the test instructions do not inform the participants to actively think back at a previous study episode. Implicit retrieval is often contrasted with "explicit" retrieval, as measured by standard episodic memory tasks in which subjects are told to recollect information from the study session (for example, Graf & Mandler, 1984; Tulving, Schacter, & Stark, 1982).

To be sure, there is no guarantee that participants engaged in an implicit retrieval test do not realize that cues map on to previously studied items and attempt to make use of explicit retrieval strategies. Indeed, much effort in cognitive psychology has been devoted to the issue of measurement properties of different retrieval tasks, and it is generally agreed that tasks are rarely "pure" in the sense that they only reflect a single underlying process or memory system (for example, Jacoby, Toth, & Yonelinas, 1993). However, there is evidence that explicit retrieval strategies are not necessarily preferred over implicit retrieval operations in priming tasks (for example, Nyberg, Olofsson, Gardiner, & Nilsson, 1997), and work with brain-damaged pa-

tients shows that normal levels of priming may not depend on explicit retrieval. For example, despite their profound episodic memory deficits, amnesic patients of varying etiologies exhibit relatively normal priming effects, suggesting that the brain systems that subserve episodic remembering are of limited importance to priming (for example, Cermak, Talbot, Chandler, & Wolbarst, 1985; Graf, Squire, & Mandler, 1984; Tulving & Schacter, 1990).

It is well documented from lesion research that episodic remembering draws on a widespread network of brain regions, including medial-temporal, diencephalic, and frontal structures (for example, Squire, 1987; Wheeler, Stuss, & Tulving, 1995). By inference, then, these regions should play a relatively limited role in perceptual priming. Rather, at least for the form of perceptual priming indexed by the word-stem completion task, regions in posterior occipital cortex seem to be critically involved (for example, Fleischman et al., 1995; Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995). In line with this conclusion from lesion studies, activation research with positron emission tomography (PET) indicates that WSCP is associated with *decreased* activity in right or bilateral posterior cortex (area 19) for both young (Buckner et al., 1995; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1992) and normal old (Bäckman et al., 1997) adults. This may be contrasted against the patterns of brain activation observed during episodic retrieval in which a variety of brain structures (for example, prefrontal cortex, medial-temporal regions, anterior cingulate, precuneus, cerebellum) typically show *increased* activity (for overviews, see Cabeza & Nyberg, 1997; Fletcher, Frith, & Rugg, 1997).

The decreased neural activity in occipital cortex during WSCP suggests that this form of memory retrieval reflects changes in posterior processing areas, such that processing of a particular stimulus is faster or more efficient when it is presented a second time (Bäckman et al., 1997; Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992). Note here that word-stem completion performance in general relies on the operation of a network of brain regions, including left prefrontal areas (Buckner et al., 1995; Desmond, Gabrieli, & Glover, 1998), but what primarily seems to differentiate primed and unprimed stem completion is that primed stem completion is associated with decreased occipital activity.

In contrast to what is true for patients with amnesia, and many other groups of individuals with memory disturbances, the empirical picture is rather mixed with regard to the effects of Alzheimer's disease (AD) on tasks assessing perceptual priming. Although AD patients show intact performance on some perceptual priming tasks, such as word identification and lexical decision, in WSCP, the size of the priming effect is typically, but not always, reduced in AD (for overviews, see Fleischman & Gabrieli, 1998; Meiran & Jelicic, 1995). Our understanding of when AD-related deficits in WSCP do and do not occur is still incomplete, and likely requires consideration of multiple interactions between subject-related and task-related factors (Fleischman & Gabrieli, 1998). Yet, there is partial evidence that AD patients may perform normally in WSCP tasks when directed to process the target information in an elaborated manner during study (for example, Christensen, Maltby, Jorm, Creasy, & Bore, 1992; Grosse, Wilson, & Fox, 1990; Partridge, Knight, & Feehan, 1990), but not under less supportive standard conditions (for example, Downes et al., 1996; Heindel, Salmon, Shults, Walicke, & Butters, 1989; Salmon, Shimamura, Butters, & Smith, 1988; Shimamura, Salmon, Squire, & Butters, 1987).

The fact that deficits in WSCP are often seen in AD suggests that these patients constitute a particularly interesting group to study in order to further advance our understanding of the neural mechanisms that support implicit memory processes. The purpose of this study was to provide direct evidence that AD-related deficits in WSCP are associated with changes in brain activity during task performance. Behavioral evidence suggests that perceptual priming, in part, reflects attentional encoding processes facilitating lexical access to target information (Crabb & Dark, 1999; Hawley & Johnston, 1991; Weldon, 1991). Indeed, the deactivation in posterior brain regions observed during priming would seem to require adequate processing of the target items at study. Thus, to the extent that failure to process target information initially contributes to AD-related priming deficits, functional changes in posterior brain regions may be expected during priming in these patients when no specific guidance is provided during study.

To achieve the study objective, normal old adults and mildly demented AD patients were scanned in a baseline and a priming condition following a procedure devised by Squire et al. (1992). Based on previous findings (Bäckman et al., 1997), we expected that WSCP would be associated with decreased activity in occipital cortex for normal old adults, and of chief interest was whether AD patients would deviate from that pattern of brain deactivation. Importantly, however, whole-brain activity was monitored during task performance, which allowed testing the possibility that impaired priming in AD is associated with abnormal responses in brain regions other than visual association cortex.

RESULTS

Behavioral Data

Baseline data was derived from two sources: all items in the baseline condition and unprimed items in the priming condition. There were no differences between these two sources of baseline data in terms of "correct" completions (p's>.50); hence, in computing

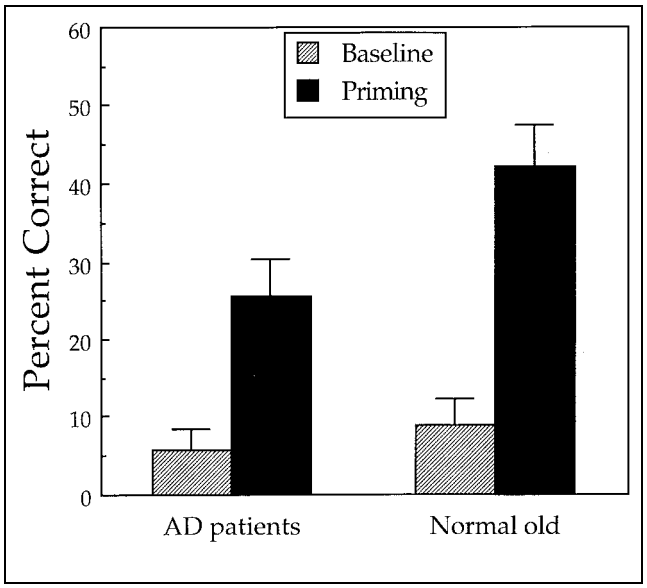

Figure 1. Mean percent correctly completed word stems in baseline and priming for normal old adults and AD patients. The bars represent standard errors around the means.

baseline data, we averaged the results from these two sources.

A 2 (group: normal old, AD patients)×2 (condition: baseline, priming)×2 (trial: 1, 2) mixed analysis of variance (ANOVA), with repeated measures on the last two factors was conducted on the word-stem completion data. There were no effects involving trial (p's>.50), and the data were collapsed across this variable. The normal old (M=25.6%) produced more completions to targets than the AD patients (M=15.7%), $F(1, 14)=9.61$, $p<.01$. Performance was generally higher in priming (M=33.8%) than in baseline (M=7.3%), $F(1, 14)=80.21$, $p<.001$. Most interestingly, a reliable group×condition interaction, $F(1, 14)=5.21$, $p<.05$, reflected the fact that there was no group difference in baseline (M_{NO}=8.8%; M_{AD}=5.8%, $p>.50$), although the normal old (M=42.1%) outperformed the AD patients (M=25.6%) in priming ($p<.001$). These data are shown in Figure 1.

The priming scores may be compared with the corresponding cued recall scores derived from the same experimental setting (reported in Bäckman et al., 1999). These were 58.8% for the normal old adults and 34.2% for the AD patients, indicating substantially higher performance in cued recall than in priming.

PET Data

A multivariate analysis of variance (MANOVA) on the blood flow data showed significant omnibus effects for condition (Wilks's Λ= 0.01, df=14, 183, $p<.001$), and for the group×condition interaction (Wilks's Λ=0.24, df=14, 183, $p<.001$). However, no local main or interaction effects were reliable, using $z>2.60$ (corrected for multiple comparisons) as the threshold for determining statistical significance (p's>.20). Further, there were no reliable effects involving trial (p's>.20).

A directed search in right area 19 revealed a significant group×condition interaction (p=.001, uncorrected), reflecting the fact that the normal old showed decreased activity ($p<.05$), whereas the AD patients showed increased activity ($p<.05$) in this area during priming relative to baseline (see Figure 2).

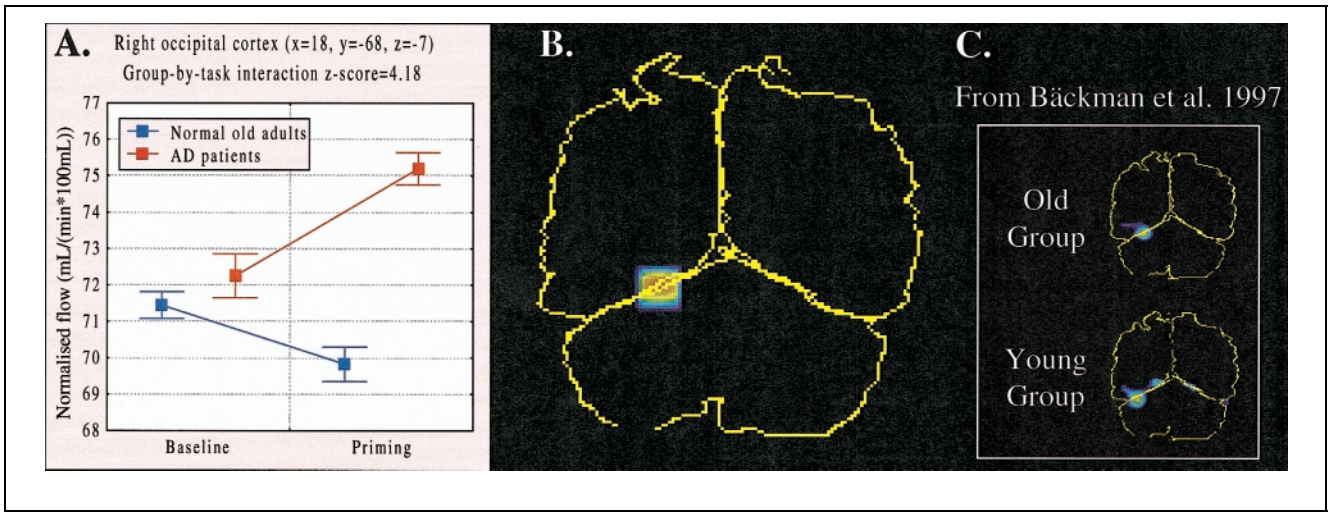

Figure 2. (a) Regional cerebral blood flow for normal old adults and AD patients in baseline and priming in the voxel in right area 19 showing a significant group×condition interaction. Six of the eight normal old subjects showed decreased activity, whereas seven of the eight AD patients showed increased activity in this area during priming. The bars represent standard errors around the means. (b) z-score map with a coronal slice through the point of maximum interaction between group and condition in right area 19. The image has been thresholded such that z scores below 3.09 are shown in black. (c) To demonstrate the close regional match between the present data and previous findings, the rightmost column shows deactivation during WSCP in right occipital cortex for normal old adults (24, −63, −13) and young adults (31, −67, −17) from an earlier study using the same experimental paradigm (Bäckman et al., 1997).

The fact that the MANOVA yielded main and interaction effects, although such effects were not seen locally deserves comment. A probable reason for this discrepancy is that the omnibus and cluster tests represent different trade-offs between sensitivity and localizing power. The omnibus test is highly sensitive, but lacks localizing power. Therefore, it is not surprising to find significant overall effects using this test. When using the cluster test in order to achieve some localizing ability, sensitivity drops. This may result in failure to obtain significant effects at the local level, as was the case in the present study (for a detailed discussion of this issue, see Friston, Poline, Holmes, Price, & Frith, 1996).

DISCUSSION

Consistent with the bulk of previous research (Fleischman & Gabrieli, 1998; Meiran & Jelicic, 1995; Russo & Spinnler, 1994), both normal old and AD subjects showed significant priming, although the size of the priming effect was reduced in AD. Most importantly, we were able to document for the first time a functional difference in brain activity during priming between normal old adults and AD patients: Whereas the normal old exhibited decreased blood flow in right occipital cortex (area 19), the AD patients showed increased activity in this region during WSCP. The locus of this interaction effect was very close to where deactivations during WSCP have been observed in previous research with normal old adults (Bäckman et al., 1997; see Figure 2) as well as with young adults (Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992).

This suggests that the deactivation in posterior cortical areas during WSCP initially reported by Squire et al. (1992) generalizes to late life, and that AD-related deficits in WSCP may be associated with changes in brain activity in this specific region. Another striking observation that replicates and extends prior research is that neither the normal old nor the AD patients showed significant activation or deactivation in any other brain region during priming.

The right occipital deactivation observed during priming in the normal old suggestsa modality-specific locus of WSCP (for example, Schacter & Buckner, 1998), and indicates that less neural activity may be required for word processing at the time of a subsequent, compared with a previous, encounter for these subjects. The view that the right occipital cortex plays an important role in priming of visually presented verbal information receives further support from human lesion studies. Several studies have demonstrated impaired WSCP in a patient who, because of pharmacologically intractable epilepsy, underwent right-hemisphere occipital lobectomy involving areas 17, 18, and 19. This patient's priming deficit occurred despite the fact that his performance on various standard neuropsychological measures (including tests of episodic memory) was normal (Fleischman et al., 1995; Vaidya, Gabrieli, Verfaellie, Fleischman, & Askari, 1998).

A concern in studies addressing implicit retrieval operations is the potential contamination by explicit retrieval operations (for example, Bowers & Schacter, 1990; Java, 1994). The magnitude of the priming effects obtained for the normal old (33%) and AD patients (20%) in this study were somewhat higher than what is typically observed. This leaves open the possibility that test awareness may have affected the results. However, the fact that the pattern of brain activation obtained is highly consistent with related brain imaging research on WSCP (Bäckman et al., 1997; Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992), and completely different from what is routinely observed during explicit retrieval (Cabeza & Nyberg, 1997; Fletcher et al., 1997), suggests that explicit retrieval strategies played a limited role in the present experimental situation. Indeed, in a cued recall condition in this experiment (see Bäckman et al., 1999), there was no activation or deactivation in area 19. Rather, in agreement with the bulk of related research, increased activity was observed in a variety of brain regions (for example, prefrontal cortex, precuneus, cerebellum, hippocampus), whereas decreased activity was seen in other regions (for example, inferior temporal gyrus) during cued recall.

The major finding in this study was the abnormal pattern of brain activity shown by the AD patients during priming. In conjunction with the AD-related reduction in the size of the priming effect, this provides a neuroanatomical correlate of deficient WSCP in AD. A decrease in neural activity during priming is thought to reflect a reduction of the number of activated neurons (Ungerleider, 1995). Thus, the pattern of brain activity observed in AD suggests that this disease results in a slower shaping of the relevant neuronal population.

However, the fact that the AD patients showed reliable, albeit reduced, priming suggests that increased neural response can be associated with priming (Schacter et al., 1996). It is conceivable that repeated or more extensive exposure to the target information for AD patients would result in a reduced neural response typical for normal adults. This hypothesis is consistent with findings demonstrating that poor elaboration of target items at encoding may contribute to AD-related priming deficits. As noted, although such deficits are legion under standard encoding conditions (Downes et al., 1996; Heindel et al., 1989; Salmon et al., 1988; Shimamura et al., 1987), they may be eliminated when subjects are explicitly instructed to engage in elaborative processing of the target information during study (Christensen et al., 1992; Grosse et al., 1990; Partridge et al., 1990).

Thus, in addition to representing perceptual information, as evidenced by our findings of decreased neural activity in normal old adults as well as by other research (for example, Bäckman et al., 1997; Buckner et al., 1995;

Fleischman et al., 1995; Schacter et al., 1996; Squire et al., 1992; Vaidya et al., 1998), area 19 may represent associations between semantic and perceptual information. The latter proposition is supported by PET research on reading of words (Menard, Kosslyn, Thompson, Alpert, & Rauch, 1996) and word-name associations (Kosslyn et al., 1993), indicating that area 19 is involved in semantic processing of visually presented information. On this view, the AD-related priming deficit stems from a weakened link between the target word and the perceptual cue, because of inadequate activation during study.

METHOD

Subjects

Five women and three men with AD, and four male and four female control subjects, participated. All subjects were right-handed. The groups were matched on age (M_{AD}=62.7 years; M_C=60.2 years) and education (M_{AD}=10.9 years; M_C=11.2 years). The diagnosis of AD was based on the NINCDS-ADRDA criteria (McKhann et al., 1984). The evaluation included medical, neurological, psychiatric, and neuropsychological examinations; interview with a close informant; laboratory testing (that is, blood status, vitamin B_{12} and folate levels, electrolytes, renal function, thyroid function, and syphilis serology); electroecephalogram (EEG) and electrocardio-gram (ECG) investigations; and computerized axial tomography (CT) or magnetic response (MR) imaging of the brain. The structural imaging showed widening of the sulci and ventricular enlargement in most patients. In addition, some patients exhibited minor white matter changes. As assessed by the Mini-Mental State Examination or MMSE (Folstein, Folstein, & McHugh, 1975), all AD patients were classified as mildly demented (MMSE>24).

The normal old adults were recruited through advertisements in local newspapers. They were all classified as healthy based on the same diagnostic procedure as used for the AD patients. Exclusion criteria were: a history of brain trauma, brain disease, or psychiatric disease; signs of arteriosclerosis; and intake of medication that may affect cognitive functioning.

The neuropsychological examination involved a series of standardized instruments. The results from this examination are shown in Table 1. As can be seen from this table, the performance profile of the AD patients is highly typical for persons in a very early phase of the disease, with deficits occurring in tasks assessing episodic memory and cognitive speed along with relative preservation in tasks assessing verbal skill (for example, Morris, 1996; Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997)

Materials and Procedure

Word-Stem Completion

Subjects were assessed in a word-stem completion task involving baseline, priming, and memory conditions, following a procedure devised by Squire et al. (1992). The memory data were presented in another report

Table 1. Neuropsychological Test Results

	Normal Old Adults	*AD Patients*
MMSE[a]	29.12±0.99	26.13±1.77*
Similarities[b]	22.62±2.50	19.48±4.71
Object Naming[c]	56.12±2.23	55.25±3.30
Verbal Fluency[d]	47.75±6.23	42.83±7.33
Digit Symbol[b]	44.00±9.65	32.14±9.77*
Block Design[b]	33.62±5.07	22.42±10.13*
R-OCF[e](copy)	35.25±0.89	32.85±3.23
R-OCF[e] (memory)	23.44±5.56	10.50±6.00*
RAVLT[f]	49.38±12.86	33.25±14.35*

[a]MMSE=Mini-Mental State Examination (Folstein et al., 1975).

[b]From the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981).

[c]Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983).

[d]Controlled Oral Word Association Test (Benton & Hamsher, 1989).

[e]R-OCF=Rey-Osterrieth's Complex Figure (Rey, 1941).

[f]RAVLT=Rey Auditory Verbal Learning Test (Rey, 1964).

*$p<0.05$.

(Bäckman et al., 1999). Four separate perfusion scans were acquired for each subject in the baseline and priming conditions (two baseline trials and two priming trials). These were presented in fixed order, with the baseline trials preceding the priming trials. Prior to each scan, subjects were exposed to a series of 12 words presented consecutively on a computer screen (Times, 72 point) at a rate of 5 sec per word. The words varied in length between 6 and 10 letters. The four word lists were equal with respect to mean-word frequency, as determined from a Swedish normative study (Molander, 1984). The lists were counterbalanced across subject group and condition. To ensure that the words were attended to, subjects made likability judgments for each word on a five-point scale ranging from very low (1) to very high (5).

Following presentation of each word list, subjects performed different masking tasks (generation of countries, lakes, fruits, and animals, respectively) during 60 sec in order to minimize the influence of primary memory. In all scanning conditions, subjects viewed 24 three-letter word stems for 4 sec each. All stems could form at least 10 Swedish words (Nyberg & Olofsson, 1991). In *baseline*, subjects were told to complete the word stems aloud with the first word to come to mind. No stem could be used to form words from the study list. In *priming*, subjects were also instructed to complete the word stems aloud with the first word that came to mind. Here, however, half of the stems could form words from the study list. All verbal responses were registered by means of a tape recorder. Word stems were completed in nearly every case by both normal old and AD subjects.

Scanning

We used a GEMS PC2048-15B scanner (Holte, Eriksson, & Dahlbom, 1989), producing 15 slices with a 6.5 mm slice spacing and a 6 mm axial and transaxial resolution. A venous catheter was inserted, and subjects were positioned in the scanner and fixated in a headholder using a fast hardening foam. For each emission scan, the injector started the scanning by pressing a pedal, while simultaneously injecting 600–800 MBq of ^{15}O-water. In order to obtain a scan with full axial coverage of the brain to aid in the stereotactical normalization, an additional scan was performed after the four perfusion scans. During the additional scan, the scanner couch was automatically translated back and forth between two positions 10 cm apart.

Image Reconstruction

Data from the first 100 sec after arrival of bolus to the brain were summed in a weighted fashion, such that data from the initial uptake phase were given a higher weight (Andersson & Schneider, 1997). Images were reconstructed from the weighted summation data following correction for attenuation and scatter and filtering with a 15 mm Hanning filter. The scan with couch translations was reconstructed to a 30-slice image set with a 20-cm coverage in axial direction, using contour finding for attenuation correction.

Image Registration

The scan with 20-cm axial coverage was automatically adapted to the computerized Greitz brain atlas (Andersson & Thurfjell, 1997), and each of the other emission scans were adapted to that scan. In order to facilitate communication of the results, the Talairach brain (Talairach & Tournoux, 1988) has been adapted to the Greitz brain, making it possible to derive Talairach coordinates for each point in the Greitz space.

Analysis of PET Data

The imaging data were normalized for global flow using linear scaling, and fitted to a statistical model described by:

$$\overline{\mathrm{GF}} \cdot \frac{\mathrm{LF}_{ijkl}}{\mathrm{GF}_{ijkl}} = u + \tau_i + \gamma_j + \beta_k$$

$$+e_{ijkl} \begin{cases} i = 1, 2, \ldots, 4 \text{(conditions)} \\ j = 1, 2, \ldots, 8 \text{(normal old adults)} \\ k = 1, 2, \ldots, 8 \text{(AD patients)} \\ l = 1, 2 \text{(trials)} \end{cases} \quad (1)$$

using multiple linear regression (Friston et al., 1995). The areas of the brain exhibiting a change in perfusion resulting from the experimental design were excluded from the estimation of global flow, thereby ensuring independence between local and global flow (Andersson, 1997). *t*-maps were created depicting priming effects and the interaction between group and condition, and converted to *z*-score maps. Significance was assessed locally using the spatial extent of connected clusters of voxels with a z score above 2.6 (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). In addition, a directed search was performed in right area 19, given that several studies have found decreased activity in this region during WSCP (Bäckman et al., 1997; Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992). This area was defined using the Greitz brain atlas (Greitz, Bohm, Holte, & Eriksson, 1991). A *z*-score level of 3.09 (p=.001, uncorrected) was chosen for the directed search.

The data were fitted to Equation 1, corrected for global activity and block effects, and used to create a voxel-by-voxel covariance matrix on which a Principal Component Analysis was performed. The scores from

the first 14 principal components (the maximum number of components which yielded a full rank of the design matrix) were entered into a three-way MANOVA (group×condition×subject), where subject was a random factor nested under group (Friston, Poline, Holmes, Frith, & Frackowiak, 1996). Note that the results obtained were independent of the number of principal components used in the MANOVA. Similar results were obtained using all numbers of principal components from 2 through 14.

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