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Cerebral metabolic correlates of attention networks in Alzheimer's Disease: a study of the Stroop

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Abstract

Patients with Alzheimer's Disease (AD) show difficulties with attention. Cognitive neuroscience models posit that attention can be broken down into alerting, orienting, and executive networks. We used the Stroop Color-Word test to interrogate the neural correlates of attention deficits in AD. We hypothesized that the Word, Color, and Color-Word conditions of the Stroop would all tap into the alerting and orienting networks. The Color-Word condition would additionally tap into the executive network. A ratio of Color-Word to Color naming performance would isolate the executive network from the others. To identify the neural underpinnings of attention in AD we correlated performance on the Stroop with brain metabolic activity. Sixty-six patients with probable AD completed [^{18}F] fluorodeoxyglucose PET scanning and neuropsychological testing. **Analysis was conducted with SPM12 (p<.001 uncorrected, extent threshold 50 voxels)**. Performance on the Word, Color, and Color-Word conditions directly correlated with metabolic rate in right inferior parietal lobules/intraparietal sulci. The Color-Word/Color ratio revealed associations with metabolic rate in **right** medial prefrontal cortex and insula/operculum. Overall findings were largely consistent with the hypothesized neuroanatomical substrates of the alerting, orienting, and executive networks. As such, attention deficits in AD reflect compromise to multiple large-scale networks.

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Alzheimer's Disease; attention; Stroop; prefrontal cortex

1. Introduction

Alzheimer's disease (AD) is characterized by profound memory impairment, as well as deficits in other cognitive domains including attention. One of the dominant models of attention processing in cognitive neuroscience was introduced by Posner & Petersen (Petersen & Posner, 2012; Posner & Petersen, 1990). In brief, this model proposes there are three distinct, yet interactive attention networks that work to support vigilance, focus, and the ability to maintain attention in the face of distractions or interference. The model also proposes that each of these networks has specific neuroanatomical substrates, that while overlapping in some regions (e.g. parietal cortex), are largely independent from one another (Petersen & Posner, 2012). One of the most common measures used to study attention is the Stroop task, in part because of its elegance in isolating the process of distraction or interference. Thus the goal of the study is to understand attention dysfunction in AD by exploring the neuroanatomical correlates of the Stroop task in AD using Petersen and Posner's framework (Petersen & Posner, 2012).

1.1 Attention Networks

Traditionally, three neural networks supporting various aspects of attentional control have been identified in the visual domain (Petersen & Posner, 2012; Posner & Rothbart, 2007). More recently, the model has been broadened to include five networks (Petersen & Posner, 2012). The alerting network, predominately dependent upon brainstem and right frontoparietal regions, allows for the ability to maintain a focused and vigilant state when engaging in a task, and is primarily reliant on norepinephrine. The orienting network allows for selective attention to external stimuli and depends on acetylcholine. In the elaborated (five-network) framework, this network is subdivided into two sub-systems: 1) the dorsal sub-system, which involves the frontal eye fields (FEF) and intraparietal sulcus (IPS), enables top-down selection of relevant external stimuli, and 2) the ventral sub-system, including the temporoparietal junction (TPJ) and ventral frontal regions, underlies bottom-up responsiveness to external stimuli, which facilitates detection of and attentional switches to unexpected stimuli. The final network, termed the executive network, allows for higher-order cognitive control via top-down mechanisms, and has also been expanded to include two sub-networks in the elaborated model: 1) the cinguloopercular sub-system, which consists of temporal, parietal, and insular regions, allows for monitoring of behavior, and 2) the frontoparietal/dorsolateral prefrontal cortex (DLPFC) subsystem allows for transient control (i.e., task-switching/rule-shifting) within a given task.

1.2. The Stroop task

The Stroop Color and Word test is one of the most commonly-utilized measures of assessing attention. In the Golden version of the Stroop test (Golden, 1978), there are three separate conditions: Word, Color, and Color-Word. In the Word condition (WORD), patients are

instructed to read words of colors (red, green, or blue). In the Color condition (COLOR), patients are asked to name the color that a string of "X"s are printed in (printed in red, green, or blue ink). In the Color-Word (CW) condition, patients are told to name the color of the ink the word is printed in, and ignore the word itself (e.g., the word "blue" is printed in green ink). The dominant/automatic response for native English readers is to read the word, thus producing a conflict between the natural response and the correct response. On each of the conditions, patients receive a raw score that reflects the total correct responses made within 45 seconds. In addition, an interference score (INT) can be generated for the CW condition in order to isolate the effect of inhibitory control from processing speed during this task (i.e., the Stroop effect).

Through the three separate conditions of the Stroop aspects of the five networks proposed by Petersen and Posner (2012) can be distinguished. We hypothesize that the following networks will become engaged. During all three conditions (WORD, COLOR, and CW) the patient is required to focus on the presented stimuli for a sustained amount of time, thus tapping into both the alerting and orienting networks. Specifically, the patient must remain attentive and vigilant throughout the task (alerting network). Additionally, the orienting network, and more specifically the dorsal attention network, is engaged to enable selective attention to the task stimuli. As such, performance on all of these conditions should involve frontoparietal regions (alerting network), including the FEF and the IPS (dorsal orienting network). During the CW condition, the patient is required to persistently inhibit a natural response over the duration of the condition (i.e., say the color the word is printed in and ignore the word itself). This will require sustained monitoring of responses over time, which will involve the cingulo-opercular executive network. The frontoparietal/DLPFC executive network would be recruited to make in-time adjustments to produce correct responses rather than the more natural response of reading the word. Examining INT will control for the activity of the alerting and orienting networks that is common to all three conditions, and will isolate frontoparietal regions unique to the executive attention network.

1.3. Attention in AD

Attention is one of the first non-memory cognitive domains to be affected in AD (Parasuraman, 1993; Perry & Hodges, 1999; Perry, Watson, & Hodges, 2000). Deficits in attention, especially complex attention, can give rise to impairments in daily functioning, consequently increasing caregiver dependence (Miloyan, Razani, Larco, Avila, & Chung, 2013). Research indicates that deficits of attention are tied to dysfunction of the parietal and frontal lobes, their connectivity, as well as disruptions to cholinergic pathways implicated early in the AD process (Perry & Hodges, 1999). Neuropsychological measures of attention are commonly administered to patients with AD in order to characterize the nature of attentional deficits associated with the disease process. Research reveals impaired selective attention and divided attention, but relatively spared sustained attention (Perry & Hodges, 1999). Although terminology diverges with the Petersen & Posner model described above, sustained attention refers to maintained or focused attention (Lezak, 2012) and, in its simplest form, likely reflects the alerting network. Divided attention refers to the ability to focus on multiple stimuli simultaneously and selective attention refers to focusing on

relevant stimuli while ignoring distractors (Lezak, 2012), both of which likely recruit aspects of orienting and executive networks.

Prior research studies have investigated the neuroanatomy of attention in AD using the Stroop task. Most have focused on the Color-Word condition. Bracco and colleagues (2007) investigated patients with mild AD and found correlations between CW and metabolism of right middle frontal gyrus and right hippocampus (Bracco et al., 2007). In a mixed sample of AD, FTD, and MCI patients, CW correlated with metabolism of the left inferior frontal junction (junction of the inferior frontal sulcus and the inferior precentral sulcus) and superior and middle frontal gyri (Schroeter et al., 2012). To more specifically isolate the interference effect, some studies have examined CW controlling for speed of processing. For example, Helfin and colleagues (Heflin, 2011) examined associations between brain volume regions-of-interest and CW performance after controlling for Color naming in a mixed sample of MCI and dementia patients, finding associations with bilateral MFG and parietal cortex. In multiple regression models, there was a counterintuitive association between larger ACC volume predicting worse performance, after controlling for other significant parietal, temporal, and/or frontal regions. Yun and colleagues (2011) investigated the relationship between cerebral metabolism and the Stroop effect in individuals with AD by applying several different equations to isolate the interference effect during the Color-Word condition. The authors investigated six methods of scoring interference, two of which yielded scores that significantly correlated with pre-hypothesized regions of interest, namely the bilateral DLPFC and bilateral ACC (Yun, 2011). Furthermore, neurofibrillary counts in the hippocampus, inferior parietal, middle frontal, and superior temporal cortices were found to correlate with severity of CW deficits in AD (Bondi et al., 2002). While the specific regions identified across studies vary, it appears clear that the frontal cortex is necessary for successful Color-Word performance. Methodological differences across studies, as well as the use of ROI approaches likely contribute to the mixed findings in AD. Studies in other psychiatric populations, including patients with schizophrenia, obsessive-compulsive disorder, and bipolar disorder also point to a role for the ACC and DLPFC in inhibition (for a review see Melcher, Falkai, & Gruber, 2008) suggesting stability of these networks across diseases.

1.4. Goal of study

This study aims to correlate behavioral performance on the Golden Stroop test with cerebral metabolism through fluorodeoxyglucose positron emission tomography (FDG-PET) in order to elucidate the neuroanatomical correlates of attentional networks in AD. In contrast to prior work, we aimed to examine performance in all three conditions, in order to compare and contrast networks involved in each. We used a voxel-based approach, allowing for identification of small but functionally important regions that may be missed in region-of-interest approaches that use large ROIs. Importantly, we aimed to isolate neural structures associated with the executive attention network. To this end, we created an interference score (INT) by calculating the ratio of correctly-stated CW to COLOR items, based on a method previously utilized (Bondi et al., 2002). This method is thought to represent an accurate measure of interference because it controls for color-processing, retrieval of color words, and articulatory processes inherent in the CW condition (Bondi et al., 2002; Taylor,

Kornblum, Lauber, Minoshima, & Koeppe, 1997). We hypothesized that WORD, COLOR, and CW would all show associations with frontoparietal regions common to the alerting and orienting networks, as described previously in Section 1.2. We hypothesized that CW would additionally show associations with DLPFC and cingulo-insular, regions related to executive attention. Finally, we hypothesized that relations between cerebral metabolism and INT would occur only in these latter structures, effectively isolating the executive attention networks in AD.

2. MATERIAL AND METHODS

2.1. Participants

A total of 66 patients with probable AD were included in this study. Patients were selected from a larger database of AD subjects with available FDG-PET data. Participants were recruited from the VA Greater Los Angeles Healthcare System Geropsychiatry Outpatient Program and from the University of California, Los Angeles Alzheimer's disease clinics. Each patient completed a clinical evaluation, neuropsychological testing, psychiatric assessment, and structural imaging with CT or MRI. All available clinical information was reviewed by a board-certified geriatric psychiatrist (D.L.S.) who confirmed the research diagnosis in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association criteria (McKhann et al., 1984), which is consistent with 2011 criteria (McKhann et al., 2011). Exclusion criteria included history of psychotic disorder prior to the onset of dementia, history of head trauma resulting in a loss of consciousness, presence of a current psychoactive substance use disorder, or presence of other neurological or medical illnesses that could account for cognitive decline. Of the included participants, 25 were taking a stable dose of cholinesterase inhibitor (23 taking donepezil, 2 taking galantamine). Fourteen were taking an antidepressant medication (bupropion, citalopram, escitalopram, fluoxetine, paroxetine, mirtazapine, sertraline, valproic acid). Patients taking other psychotropic medications were excluded.

The study was approved by the local IRB, and consent to participate was documented according to IRB guidelines.

2.2. Neuropsychological testing

All patients were administered a battery of neuropsychological measures. Global cognition was assessed via the Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975) and the Dementia Rating Scale (DRS; (Mattis, 1988). All patients were administered the Golden (1978) version of the Stroop. In this version, patients have 45 seconds to complete each condition. In the WORD condition, participants are instructed to read as many words as quickly as possible. The words include "red," "green," and "blue." In the COLOR condition, participants are instructed to name the color of printed "X"s as quickly as possible. The colors of ink included red, green, and blue. In the CW condition (or interference condition), participants are instructed to name the color of ink as quickly as they can. The written words are "red," "green," and "blue," as in previous conditions, but are printed in a different color ink. Each item is incongruous, meaning the word "red" is never

printed in red ink; it is always printed in either green or blue ink. For all conditions, when a participant makes a mistake, the examiner states this and prompts the patient to correct their error. The number of accurate responses was summed and normed using an age-corrected normative database (Smith, 1992).

2.3. FDG-PET image acquisition

[^{18}F] fluorodeoxyglucose (FDG) was synthesized at the Veterans Affairs Greater Los Angeles Healthcare System PET Imaging facility (Hamacher, Coenen, & Stocklin, 1986). Participants received 5–10 mCi of FDG intravenously and rested with their eyes open for a 40-minute uptake phase. Participants then underwent PET scanning, lasting 30 to 40 minutes. Patients were scanned using three different PET tomographs over the course of the study: 37 patients were scanned on a Siemens 953/31 tomographic scanner, 16 on a GE Advance PET-CT, and 13 on a Philips Gemini TF PET-CT. Each scanner had an in plane resolution of approximately 5 mm at full-width half maximum and axial slice thickness of 2–4 mm.

2.4. Analysis of clinical data

Statistical analyses were conducted using SPSS version 20. Normality of data was assessed via visual examination and evaluation of the skewness and excess kurtosis of the histograms (maximum absolute value of 2), and the Kolmogorov-Smirnov test ($p < 0.05$).

2.5. PET image analysis

SPM12 (Wellcome Trust Centre for Neuroimaging) was used to analyze PET data in Matlab R2012a (MathWorks). Images were normalized to Montreal Neurological Institute (MNI) space using trilinear interpolation and resampled to 2 × 2 × 2 mm voxels and smoothed using a 6-mm full width at half maximum (FWHM) smoothing kernel.

The associations between performance on the WORD, COLOR, and CW conditions and metabolic data were examined separately, using the regression procedure in SPM12. Raw scores, rather than normed scores were used for all analyses to avoid floor effects. To isolate the interference effect (INT), we calculated the ratio of CW/COLOR (Bondi et al., 2002; Saunders, 1980; Weir, Bruun, & Barber, 1997), as described in Section 1.4. Higher scores on INT reflect less interference. The smoothed PET images were normalized to the global mean using proportional scaling and threshold masking was used to remove signal from structures outside of grey matter (set to 0.8). The results map was set to $p < 0.001$ uncorrected with an extent threshold of 50 contiguous voxels. Results were considered significant at the voxel level (uncorrected) at this threshold. Regions were determined using *Human Brain Anatomy in Computerized Images* (Damasio, 2005) and MRIcro (Rorden & Brett, 2000) and Petrides & Pandya (1999) were used to approximate Brodmann's regions (Damasio, 2005; Petrides & Pandya, 1999). To understand the strength of the findings, parameter estimates from significant clusters were extracted using the VOI tool. These were then imported to SPSS. Correlations were run between the Stroop variable of interest and these scores. The correlation coefficient for each cluster is reported in the results tables.

3. Results

Participant characteristics and neuropsychological performance (Stroop, DRS, MMSE) are presented in Table 1. Mean age was 78.7 years (6.2 *SD*), mean education was 14.2 years (3.7 *SD*), and most participants were male (22.7% female, n= 15). Sixteen (24%) identified as African-American, four (6%) identified as Hispanic, 3 (4.5%) identified as Asian/Pacific Islander, and 42 (64%) identified as Caucasian. On average, participants had been diagnosed for 3 years (2.4 *SD*) prior to study participation. With regards to global cognition, mean performance on the MMSE was 20.5 (5.1 *SD*) out of 30 possible points, and mean performance on the DRS was 107.4 (15.3 *SD*) out of 144 possible points.

3.1. Stroop Performance

On average, patients read 57.0 (20.6 *SD*) words during the WORD condition, named 32.8 (14.6 *SD*) colors during the COLOR condition, and named 12.0 (9.9 *SD*) colors during the CW condition (Table 1). Adjusted for age, the averaged scaled score across all three conditions was approximately five (Table 1), suggesting borderline impaired abilities across the group. The calculated mean INT score for the sample was 0.35 (0.21 *SD*).

An initial examination of WORD, COLOR, CW, and INT suggested an acceptable distribution for each of the conditions (skewness WORD, COLOR, and INT scores were normally distributed per all of our benchmarks; skewness and excess kurtosis < 2; K-S test, $D \leq 0.087$, $p > 0.20$). The CW score met our accepted cutoff for skewness of 1.3 and excess kurtosis of 1.5, but did not pass the Kolmogorov-Smirnov test (K-S, $D = 0.14$, $p = 0.002$). Examination of the scores revealed that fifteen percent of the sample ($n = 10$) produced a raw score that was 2 or below. Data were log transformed and imaging data were reanalyzed but findings did not change; thus imaging findings of the non-transformed dataset are presented here.

3.2. Imaging findings

3.2.1. WORD—Results of the SPM analysis (Table 2, Fig 1) revealed a relation between reduced cerebral metabolism and poorer WORD in three clusters. The clusters spanned the right inferior and middle temporal gyri, inferior occipital lobe, fusiform gyrus; and bilateral supramarginal gyri/IPS and superior parietal lobule.

3.2.2. COLOR—COLOR was directly associated with metabolism in five clusters spanning the bilateral angular gyri/IPS, right occipital lobe, posterior cingulate, and inferior/middle temporal gyri. Results are presented in Table 3, Fig 1.

3.2.3. CW—CW was directly associated with metabolism in four clusters. These regions included the right angular and supramarginal gyri/IPS, posterior cingulate cortex, superior parietal lobe, insular cortex, and middle/inferior frontal gyri. Results are presented in Table 4, Fig 1.

3.2.4. INT—The results of the correlation between the FDG-PET data and the INT yielded three clusters, all within the right hemisphere, including the insular cortex, medial aspect of

the superior frontal gyrus, the middle cingulate cortex, the supplementary motor area, and the middle frontal gyrus. Results are presented in Table 5, Fig 2.

4. Discussion

We sought to identify the neural correlates of the Stroop in AD. Following the Petersen & Posner model of attention (Petersen & Posner, 2012), all three Stroop conditions were conceptualized as requiring the alerting and orienting networks. Thus, we hypothesized that all three conditions would reveal associations with right parietal regions. The CW condition was additionally conceptualized as measuring the executive attention network, and thus we hypothesized that the DLPFC, insula/operculum, and anterior cingulate would relate to performance on CW. We also theorized that isolating the interference effect (INT) would elucidate neural correlates unique to the executive networks; thus, regions related to the alerting and orienting network would not arise, and only the regions associated with the executive network, namely the DLPFC, insula/operculum, and anterior cingulate, would be associated with INT scores. Our predictions were largely supported. We found that all three conditions correlated with metabolism in right inferior and superior parietal lobule surrounding the IPS. WORD showed unique associations with metabolism in right fusiform gyrus and COLOR showed unique associations with metabolism in more anterior right lateral temporal cortex. Both WORD and COLOR showed associations with left parietal regions. CW correlated with metabolism in the DLPFC and insula/operculum. The INT analysis revealed associations with metabolism of the medial PFC (cingulate and portions of the supplementary motor area) and insula/operculum. These results suggest that in AD, the Stroop test assesses anatomical regions associated with the different attention networks proposed by Petersen and Posner (2012). Furthermore, findings support a dissociation between the networks, suggesting that even in diseases such as AD that have widespread pathology, attentional dysfunction can be tied to the breakdown of specific networks.

4.1. Alerting & Orienting

The alerting network is believed to control alertness and sustained vigilance. Experimentally, the alerting network is often studied by examining the reaction-time benefit apparent when a participant is presented with a warning signal alerting the participant to an incoming stimulus. It is conceptualized to rely on both brainstem projections and right fronto-parietal regions (Petersen & Posner, 2012). Findings from previous neuroimaging studies report associations with these regions, in addition to bilateral thalamus, temporoparietal junction, ACC, anterior insula, and IPS (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Xuan et al., 2016). The orienting network enables selective attention of external stimuli. Corbetta & Shulman (2002) discuss the dorsal and ventral attention networks (Corbetta & Shulman, 2002). The dorsal network, which relies on bilateral dorsal posterior parietal cortex and frontal cortex controls the top-down focus of attention towards sensory stimuli and responses. In contrast the ventral network, right lateralized and involving temporoparietal and ventral frontal cortex, detects external stimuli, particularly salient and previously unattended sensory events. It thus also oversees the ability to disengage attention from one stimulus and attend to another. Prior imaging studies have largely supported these neuroanatomical substrates (Fan et al., 2005; Xuan et al., 2016; Yin et al., 2012). Thus while

conceptually distinct, the underlying neural regions supporting the alerting and two orienting networks are somewhat overlapping, particularly with regards to the intraparietal sulcus, temporoparietal junction, and frontal cortex.

Within the framework of the Stroop task as administered here, it is difficult to tease apart the relative contributions of the alerting and orienting networks. As stated previously, both would need to be active for successful completion on all conditions of the task, allowing the patient the basic alertness necessary to engage in the task at hand (alerting), as well as selectively attend to the visual stimuli before them (orienting). In the analysis described here we observed associations with right parietal lobe, surrounding the IPS, during all three Stroop conditions. This is largely consistent with previous studies of the alerting and orienting (dorsal attention) networks. The findings described here suggest that in AD, the integrity of the IPS is essential for the ability for patients to maintain and direct attention to the task at hand. Indeed dysfunction of right parietal lobe is tied to deficits in orienting in AD (Vasquez, 2011).

4.2. Executive attention in AD

In its initial elaboration, the executive network was described as focal attention, or more specifically the process by which a target enters awareness or consciousness. Over time, theories of the executive network became more specifically focused on conflict. In the most recent elaboration, Petersen and Posner argue there are two independent networks within the executive network, influenced by the work of Dosenbach (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Both networks appear to carry information about task goals. The cingulo-opercular network is a maintenance system, and monitors the consequences of actions. The DLPFC (or frontoparietal) network controls task switching and adjustments in real time. Consistent with prior researchers, we posited that the Color-Word condition of the Stroop would tap into the executive network because it requires the inhibition of an overlearned response. When we examined the neural correlates of CW, we found associations with right anterior insula and DLPFC, amongst other more posterior regions. When we examined INT specifically, we saw associations with the medial PFC and insula. Thus, consistent with expectations, we observed that in AD conflict processing depends on the integrity of the cingulo-opercular executive network.

We observed right lateralized frontal/insular involvement in the present study. While there do not appear to be laterality predictions for the executive network, some previous work on intrinsic brain networks (IBN) from functional MRI (fMRI) is supportive of a laterality distinction. IBN models posit a reciprocal relation between two networks, the frontoparietal executive control network and the default mode network, regions involved in goal-directed processing versus internal thought, respectively. The salience network, and in particular the right insular-ACC region, appears in part responsible for switching between the two networks, but may help maintain set during goal-directed tasks (Sridharan, Levitin, & Menon, 2008). This network is analogous to the cingulo-operocular network as described above, positing a unique role for the right network in maintaining a task state. Work has also highlighted that aging is associated with reduced connectivity within the right insula (Muller, 2016), perhaps suggesting a vulnerability that may be worsened in

neurodegenerative disease. Prior work has suggested the Stroop interrogates a bilateral network, and that the right insula in particular may be important for task monitoring across a number of different types of inhibition tasks (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015). Prior work on Color-Word condition in dementia has found support for left laterialized frontal involvement in very mild AD (Bracco et al., 2007) or a mixed sample of dementia patients (Schroeter et al., 2012), right lateralized involvement in mild AD (Bracco et al., 2007), or bilateral frontal involvement in AD (Yun et al., 2011) and a mixed sample of dementia (Heflin, 2011). The heterogeneity is likely driven by differences in methodology, the patients being studied, and the severity of cognitive impairment in the cohort. The findings from our study extend prior work by highlighting that when other aspects of attention are removed, it is the integrity of the medial PFC and insula that predicts inhibition ability in AD.

4.3. Other neural correlates of the Stroop in AD

Investigating the neuroanatomical regions associated with each condition revealed several unique relationships. Cerebral metabolism in the fusiform gyrus was uniquely related to WORD. This is consistent with studies that cite a relation between the fusiform gyrus and word reading (Cohen et al., 2000), but particularly in the left fusiform. Unexpectedly, our study found a significant association between the right fusiform in particular. One possibility is that the reading of color names generates the semantic representations of the colors themselves, thus recruiting the right fusiform (Dehaene, 2002). A second possibility may be related to the AD process such that the left fusiform no longer is able to carry out the function of word reading due to significant atrophy.

4.4. Attention dysfunction in AD

Not surprisingly, the regions implicated in the five attentional networks include regions that are also involved in the neuropathology of AD, particularly with respect to the parietal cortex. Additionally, from a neurochemical perspective, depletion in acetylcholine, necessary for the orienting network, is associated with AD. Furthermore, cholinesterase inhibitor medications are approved for treatment of AD and are thought to ameliorate cognitive deficits by increasing cholinergic tone in the brain (Potter, 2015). Consistent with this, research investigating attention in AD has found support for a selective deficit in the orienting aspects of attention (Tales, 2006), including reduced connectivity within the dorsal and attention networks (Zhang, 2015).

4.5. Methodological comment

The interference score used in this study was specifically selected because it is believed to control for the effects of general cognitive slowing. Past studies (Bracco et al., 2007; Yun, 2011) have utilized several measures of interference, some of which do not account for such slowing. Lansbergen, Kenemans, & van Engeland (2007) describe the problematic nature of two common methods of measuring interference: 1) difference scores between individual Color and Word scores and Color-Word, and 2) differences between a predicted Color-Word score and actual Color-Word score (Golden, 1978; Lansbergen, Kenemans, & van Engeland, 2007). In a cognitively normal sample, smaller differences indicate less interference. However, in impaired populations (such as in AD), these measures will provide a biased

estimate of interference as they do not account for general speed of processing (Lansbergen et al., 2007). Consequently, they will overestimate the degree of interference. Utilizing a measure of interference that accounts for speed of processing and specifically isolates the functioning of the executive system is imperative when investigating neurobiological mechanisms underlying Stroop performance within the AD population, as was done in the current study.

4.6. Limitations

There are several study limitations to be considered when interpreting the findings. The study examined cerebral metabolism underlying Stroop performance via FDG-PET. This method allows for identification of specific regions of cerebral hypometabolism that correlate to neuropsychological functioning; however, given the correlational nature of the study, it remains possible that there are areas important to Stroop performance that do not reach significance in our sample. We used an uncorrected threshold in interpreting findings ($p<.001$ with a cluster size of 50 voxels), which may be vulnerable to **type I error**. Additionally, AD represents diffuse degeneration of neural structures and networks; thus, regions that correlate with Stroop performance in our sample may not necessarily reflect those important to performance in healthy samples. Relatedly, regions that are identified here may not be functionally important to the Stroop but rather reflect connected areas of the brain that are pathologically compromised due to AD. The ability to make inferences regarding the specific neural correlates of the five attentional networks, and their interactions, during performance on the Stroop, is limited due to the lack of temporal resolution inherent in FDG-PET. Additional limitations include those pertaining to the sample itself (e.g., predominantly male, a sizeable group taking cholinesterase inhibitors and/or anti-depressants) and the use of multiple PET tomographs. These findings specifically apply to sources of visual attention. While the executive network may be supramodal, there is evidence to suggest that the alerting and orienting network may be sensory specific (Spagna, 2015).

4.7. Conclusions

In sum, this study highlights the neural regions underlying poor attention in AD. Findings in the study are largely consistent with predictions from cognitive neuroscience models of attention. Hypometabolism in the parietal lobe, particularly inferior parietal lobule/IPS is associated with worse performance on all attention measures, highlighting that compromise to this region underlies poor alerting and top-down attention processes in AD. Poor response inhibition is subserved by cingulate and insular operations. Overall these findings suggest that in AD, attention difficulties reflect compromise to multiple brain networks thought to underlie attention processing.

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Highlights

- The Stroop test measures word reading, color naming, and interference.
- Hypometabolism of inferior parietal lobe predicts poor performance on all conditions.
- Interference is associated with metabolic rate in medial PFC and insula.
- AD is characterized by hypometabolism in alerting, orienting, and executive networks.

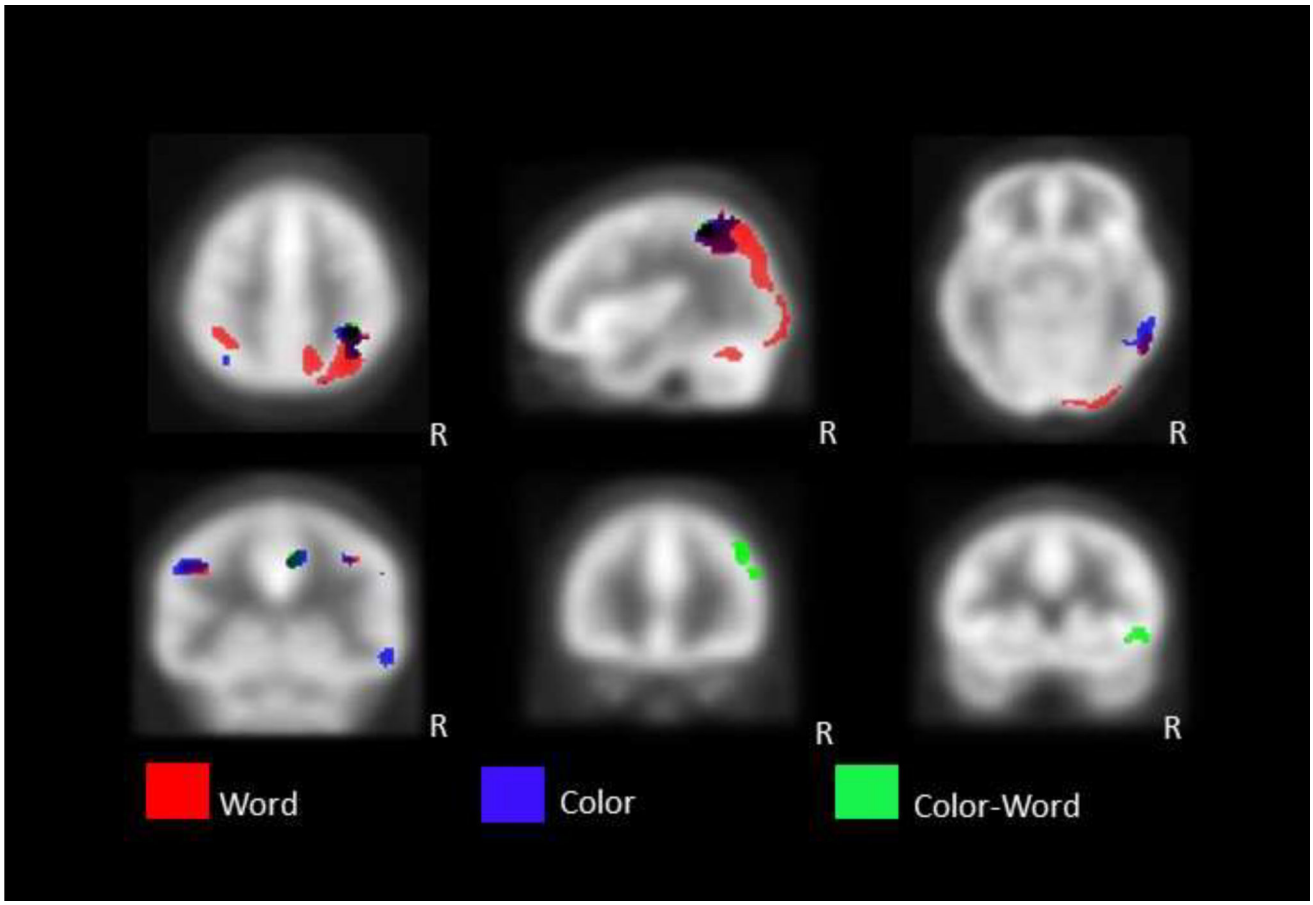

Figure 1.
Metabolic correlates of WORD, COLOR, and CW. Image shown at p<0.001 uncorrected, extent threshold=50 voxels.

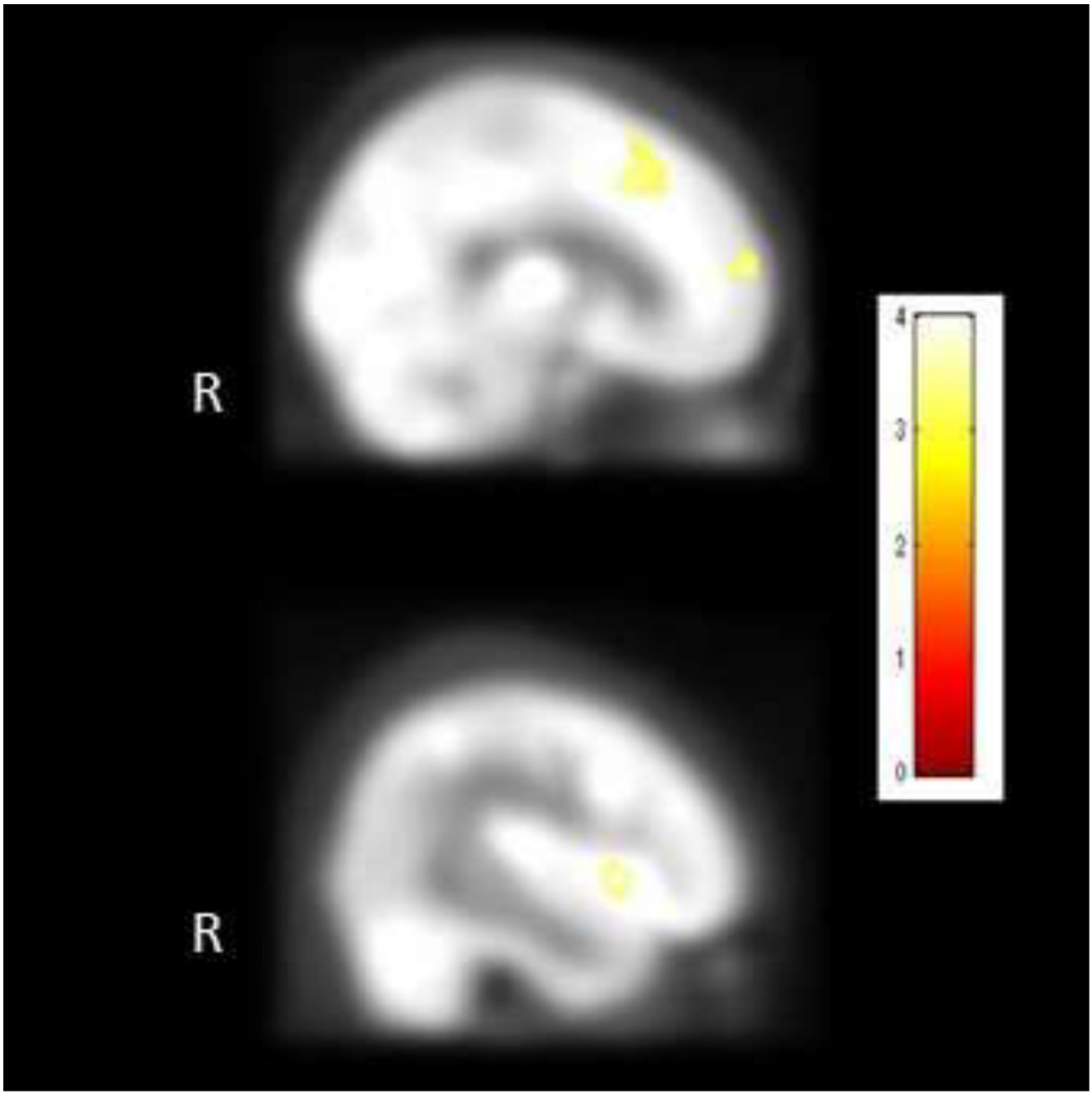

Figure 2.
Association between INT and metabolism. Image displayed at p<0.001 uncorrected, extent threshold=50 voxels.

Table 1

Patient demographic characteristics and neuropsychological performances.

Characteristic	Mean	SD	Range
Age (years)	78.7	6.2	64–93
Education (years; *N* = 61)	14.2	3.7	6–24
Gender (percent female; *N* = 66)	22.7%	-	-
Years since diagnosis (*N* = 61)	3.0	2.4	0–10
MMSE	20.5	5.1	6–30
Mattis DRS (*N* = 65)	107.4	15.3	54–136
Stroop Raw Scores			
Word	57.0	20.6	14–100
Color	32.8	14.6	5–70
Color-Word	12.0	9.9	0–44
Color-Word Interference	0.35	0.21	0–1
Stroop Normative Scores			
Word	5.8ss	3.1	2–14
Color	5.2ss	2.9	2–14
Color-Word	5.0ss	3.1	2–16

Note: MMSE = Mini-Mental State Examination; DRS = Dementia Rating Scale; ss = scaled score. Stroop Normative Scores are derived from the Mayo's Older Adult Normative Studies (MOANS).

Table 2

SPM results of the association between WORD and cerebral glucose metabolism.

Region	BA	Side	x	y	z	t-value	p-value	k	r
Superior parietal lobe, angular gyrus, supramarginal gyrus, occipital cortex, inferior/middle temporal gyrus	7/39/40/37/17/18	R	40	−54	44	5.15	<0.001	4624	.499
Supramarginal gyrus/Intraparietal sulcus	40	L	−40	−46	38	4.39	<0.001	410	.483
Superior Parietal Lobe	7	L	−12	−80	46	3.62	<0.001	52	.402

Note: Statistics shown for the peak voxel within each cluster. BA = approximate Brodmann's area; R = right, L = left; *x,y, z* = MNI (Montreal Neurological Institute) coordinates; *p-value* is uncorrected; *k* = number of voxels within each cluster; *r*=correlation between the parameter estimates and WORD; degrees of freedom= (1, 64).

Table 3

SPM results of the association between COLOR and cerebral glucose metabolism.

Region	BA	Side	x	y	z	t-value	p-value	k	r
Occipital cortex	19	R	24	−70	24	3.86	<0.001	54	.417
Angular gyrus/Intraparietal sulcus	39/40	R	36	−48	50	4.35	<0.001	1345	.468
Angular gyrus/Intraparietal sulcus	39/40	L	−42	−48	38	4.49	<0.001	464	.488
Inferior/middle temporal gyrus	20/21/37	R	60	−48	−12	3.81	<0.001	448	.423
Posterior Cingulate	31	R	12	−40	46	4.29	<0.001	161	.468

Note: Statistics shown for the peak voxel within each cluster. BA = approximate Brodmann's area; R = right, L = left; *x,y, z* = MNI (Montreal Neurological Institute) coordinates; *p-value* is uncorrected; *k* = number of voxels within each cluster; *r*=correlation between the parameter estimates and COLOR; degrees of freedom= (1, 64).

Table 4

SPM results of the association between CW and cerebral glucose metabolism.

Region	BA	Side	x	y	z	t-value	p-value	k	r
Superior parietal lobe, Intraparietal sulcus	7/40	R	36	−46	52	4.00	<0.001	80	.422
Posterior cingulate cortex	23	R	10	−36	44	4.09	<0.001	120	.452
Insula		R	58	8	−6	3.88	<0.001	100	.441
Middle/Inferior frontal gyri	45/46	R	44	34	34	4.12	<0.001	108	.440
Inferior frontal gyrus	46	R	56	30	24	3.97	<0.001	70	.430

Note: Statistics shown for the peak voxel within each cluster. BA = approximate Brodmann's area; R = right, L = left; *x,y, z* = MNI (Montreal Neurological Institute) coordinates; *p-value* is uncorrected; *k* = number of voxels within each cluster; *r*=correlation between the parameter estimates and CW; degrees of freedom= (1, 64).

Table 5

SPM results of the association between INT and cerebral glucose metabolism.

Region	BA	Side	x	y	z	t-value	p-value	k	r
Insula		R	50	10	−2	4.01	<0.001	179	.452
Middle cingulate, supplementary motor area	6/24/32	R	6	26	52	3.57	<0.001	204	.432
Superior frontal gyrus (medial aspect)	10	R	10	62	10	3.86	<0.001	105	.447

Note: Statistics shown for the peak voxel within each cluster. BA = approximate Brodmann's area; R = right, L = left; *x,y, z* = MNI (Montreal Neurological Institute) coordinates; *p-value* is uncorrected; *k* = number of voxels within each cluster; *r*=correlation between the parameter estimates and INT; degrees of freedom= (1, 64).