Patterns of frontoparietal activation as a marker for unsuccessful visuospatial processing in healthy aging

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ABSTRACT

Visuospatial abilities are sensitive to age-related decline, although the neural basis for this decline (and its everyday behavioral correlates) is as yet poorly understood. fMRI was employed to examine age-related differences in patterns of functional activation that underlie changes in visuospatial processing. All participants completed a brief neuropsychological battery and also a figure ground task (FGT) assessing visuospatial processing while fMRI was recorded. Participants included sixteen healthy older adults (OA; aged 69-82 years) and 16 healthy younger adults (YA; aged 20-35 years). We examined age-related differences in behavioral performance on the FGT in relation to patterns of fMRI activation. OA demonstrated reduced performance on the FGT task and showed increased activation of supramarginal parietal cortex as well as increased activation of frontal and temporal regions compared to their younger counterparts. Performance on the FGT related to increased supramarginal gyrus activity and increased medial prefrontal activity in OAs, but not YAs. Our results are consistent with an anterior-posterior compensation model. Successful FGT performance requires the perception and integration of multiple stimuli and thus it is plausible that healthy aging may be accompanied by changes in visuospatial processing that mimic a subtle form of dorsal simultanagnosia. Overall, decreased visuospatial processing in OA relates to an altered frontoparietal neurobiological signature that may contribute to the general phenomenon of increasingly fragmented execution of behavior associated with normal aging.

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parietal lobe, temporal lobe

It is well-established that processing of visuospatial information preferentially declines in normal aging (Drag & Bieliauskas, 2010), and age-related visuospatial changes have long been readily apparent on figure-ground tasks (e.g., Axelrod & Cohen, 1961). It may be that the difficulty in visuospatial processing associated with aging stems from a breakdown in the ability to attend to multiple objects at once, a condition identified as "simultanagnosia." Figure ground tests such as the Hooper Visual Organization Test (Hooper, 1958) or the Southern California Figure Ground Visual Perception Test (Ayres, 1966) tap the ability to perceive multiple objects at once and are often used to test for this condition, and if the core deficits in simultanagnosia (i.e. inability to perceive individual objects simultaneously) can be considered to reflect a spectrum, spanning from normal to pathological functioning, it may be that the visuospatial deficits associated with normal aging reflect a more subtle form of this clinical disorder. "Dorsal simultanagnosia" results in an inability to detect more than one object simultaneously even with prolonged exposure (Dalrymple, Barton & Kingstone, 2013) and can occur with medial occipito-parietal junction lesions (Barton, 2011). The "dorsal" visual pathway is thought to be affected, and occipitoparietal networks may be preferentially compromised. In general, the dorsal visual pathway is thought to be involved in simultanagnosia and is likely activated, for example, while locating a checkbook from amongst the many items lying at the bottom of a purse (or identifying one's favorite candy bar amongst a shelf of various treats) while in line at a cash register. This circuit is concerned with locating items in space and guiding actions in the world, such as reaching and grabbing things; all necessary skills for efficiently moving through a grocery store line or completing other multi-step procedures such as driving, completing chores at home (e.g. doing the dishes), and dressing oneself. It thus follows that if the brain is delivering an increasingly fragmented "view" of the world, this would correspond to an inability to smoothly

integrate and carry out everyday activities such as those mentioned above. Two theories prevail regarding the underlying mechanism of simultanagnosia. On the one hand, a perceived array might be constructed from a sequence of short impressions of individual objects (O'Regan, 1992), requiring visual working memory to maintain the individual kernels of visual information over time. The dorsolateral prefrontal cortex has been suggested to be involved in such working memory processes (Friedman & Goldman-Rakic, 1994; Jiang et al., 2000). On the other hand, other empirical observations indicate a critical role of sustained visual attention as a requirement for the efficient integration of visual information (Rizzo & Robin, 1990). Recent neuroimaging work has shed light on these two contrasting theories of visuospatial processing.

Namely, although the parietal lobes, as well as association areas of temporal cortex, have traditionally been associated with various aspects of visuospatial functioning, recent neuroimaging investigations have identified a more complex relationship amongst the areas and systems of brain functioning that underlie age-associated changes in visuospatial ability. Specifically, imaging studies indicate that visuospatial processing is related to more widespread activation across a network of regions, including the prefrontal cortex, in older adults (Grady, Maisog, Horwitz, Ungerleider, Mentis, Salerno, Pietrini, Wagner, Haxby, 1994). This is consistent with the finding that older adults demonstrate regional inefficiencies in posterior areas (i.e., parietal and occipital regions) and compensatory increases in frontal and temporal areas during cognitive tasks (Madden, Turkington, Provenzale, Denny, Langley, Hawk, Coleman, 2002; Gong, Rosa-Neto, Carbonell, Chen, He, Evans, 2009; Cabeza, Daselaar, Dolcos, Prince, Budde, Nyberg, 2004). This pattern has been termed the "posterior-anterior shift in aging" (PASA; Davis, Dennis, Daselaar, Fleck, Cabeza, 2008). Similarly, the Scaffolding Theory of Aging and Cognition (STAC) identifies dedifferentiation of visual and motor areas, accompanied

by increased activation of frontal areas (Park and Reuter-Lorenz, 2009), as mechanistic in the cognitive and functional changes observed with aging. This model has been recently updated to incorporate lifespan influences on neuroplasticity and the relationship between those neuroplastic changes and functional decline often seen with aging (STAC-R; Reuter-Lorenz and Park, 2014). These models provide a framework for the present study. Specifically, the current study examined the functional correlates of age-related visuospatial changes and the possible neural compensation that may accompany it utilizing a standardized task that is often used to detect simultanagnosia. Specifically, older and younger adults completed a variation of the Southern California Figure Ground Test (FGT) while undergoing fMRI, and group differences in behavioral performance and functional brain activation were compared. We believe the Figure Ground Test (FGT) in general is a well validated neuropsychological test of simultanagnosia. Furthermore, we believe simultanagnosia is best construed as a descriptive term that has been used clinically; and there are no formal clinical criteria for calling a patient simultanagnosic. Indeed, many researchers have defined the presence of simultanagnosia based on performance on the same types of visuospatial tasks as used in the present study (Barton, 2011; Duncan et al., 2003; Riddoch et al., 2010; Vighetto, 2013) in patients with bilateral occipitoparietal lesions. Thus, we believe we are in good company in thinking about performance of the FGT as a means to capture a simultanagnosic *continuum*, which may include a subset of "healthy" aging individuals at one extreme, and full blown simultanagnosia, as described in case studies, on the other extreme. However, we do not imply that our participants (described below) are simultanagnosic in the classical sense. Rather, our central hypothesis was that healthy older adults would perform more poorly on a modified figure-ground test relative to younger adults (replicating findings from Roper et al., 2001), and this difference would be reflected in

differential patterns of frontal and parietal activation evoked during the completion of the figure-ground task. A priori regions of interest (ROI) included prefrontal cortex and the parietal lobes.

2. Materials and Methods

2.1 Participants

Data from 16 older adults (OA; aged 69-82 years) and 16 younger adults (YA; aged 20-35 years) were included in the study. All participants were right-handed males. The use of men only was decided based on prior literature showing a gender effect on visuospatial processing (Bieliauskas et al., 1988), with men generally having the advantage (although this effect varies across tasks and studies). Thus, we sought to eliminate this potential gender confound by utilizing a male only data set.

OA were recruited through an ongoing research participant database maintained by the Claude D. Pepper Older Americans Independence Center at the University of Michigan. YA were recruited through advertisements posted on an online clinical studies database through the University of Michigan. All participants provided informed consent to participate in the study. The study protocol was approved by the Institutional Review Board at the University of Michigan Medical School. Participants were excluded from the study for a history of psychiatric or neurological disorders; use of medications that may cause mental status changes such as benzodiazepines, psychotropics, or narcotics; dementia or demonstrated memory impairment as demonstrated by a score below 23 on the Mini Mental State Exam (MMSE; Folstein, Folstein, McHugh, 1975) or performance more than 2 standard deviations below age-corrected norms on memory measures; significant visuospatial impairments (a score below 23 on the Benton Visual Form Discrimination; BVFD; Benton, Sivan, Hamsher, Varney, Spreen, 1994); any visual or hearing impairment that would interfere with the cognitive tests; or any MRI contraindications.

One OA and one YA were excluded from the study due to memory impairment and two younger adults were excluded due to relocation. Data were collected in full for 16 individuals in each group. Demographic information for the 32 participants is displayed in Table 1. The OA and YA groups did not differ significantly in education or verbal ability as measured by the Shipley Institute of Living Scale - Vocabulary subtest (Zachary & Shipley, 1986).

2.2 Materials

2.2.1. Neuropsychological Tasks

Participants completed a neuropsychological battery covering multiple domains. The MMSE was used as a brief screen of mental status. Verbal knowledge was assessed with the Vocabulary Subtest from the Shipley Institute of Living Scale, a multiple-choice measure of vocabulary knowledge. Trails A and B of the Trail Making Test (Reitan, Wolson, 1985) were used to measure speeded visual attention. Verbal learning and memory abilities were assessed with a list learning task, the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, Ober, 2000). Immediate free recall and long-delay free recall from the CVLT-II were used as indices of immediate and delayed verbal memory. The BVFD is a multiple choice test assessing visual recognition of line drawings and was used to screen for basic visuospatial discrimination abilities.

2.2.2. Figure Ground Task

Stimuli from the Southern California Figure Ground Test were adapted with permission to create the version of the Figure Ground Task (FGT) used in the current study. This test measures visual perception and requires individuals to visually discriminate figures hidden in a complex background. All stimuli were presented as black and white line drawings and consisted of simple control figures (a line drawing used for target stimuli and control stimuli) and complex

experimental figures. The complex figures were either overlapping (e.g., an assortment of overlapping figures) or embedded (e.g., the target figure was embedded within the line drawing of the figure). For each experimental stimulus, a target figure was presented with a complex figure (either overlapping or embedded) simultaneously presented above it. Participants made yes/no decisions as to whether or not the target figure was present in the complex figure. A control condition was also created in which participants had to decide whether a simple target figure matched any of three simple figures above. Examples of a control stimulus, an experimental embedded stimulus, and an experimental overlapping stimulus are presented in Figure 1.

The FGT consisted of 60 experimental stimuli (30 embedded and 30 overlapping) and 60 control stimuli. Control stimuli were repeated in a counterbalanced fashion across task blocks; experimental stimuli were presented only once. Two alternate versions were created, each using stimuli from the same level of difficulty from amongst the original Southern California Figure Ground Test stimulus set. The FGT was created and presented on computers using E-Prime 1.3. One version was presented during the behavioral assessment session with the alternate version presented during the fMRI scan, with versions counterbalanced across participants. Following instructions orienting them to the task, participants viewed each stimulus on a computer screen for 4000 ms, followed by a 2000 ms response interval consisting of a blank screen with a crosshair. Participants were instructed to respond “Yes” or “No” during the response interval using either a keyboard (for the behavioral session) or a response pad (for the fMRI session). Blocks of three stimuli each were created for the control, embedded, and overlapping conditions, resulting in a blocked design with 40 epochs of 18 seconds each. The order of these blocks was fixed and based on a Latin square design. Difficulty of the embedded and overlapping blocks

increased as the task progressed. Wait time between epochs was jittered and ranged between 1500-3000 ms (*M* = 2250 ms) with a non-active rest period of 12 seconds after every two blocks. Because wait time was jittered, responses were still tallied even if they occurred after the 2000 *ms* mark but less than the 5250 *ms* mark (maximum). Thus, responses were counted as correct if they occurred within the first 2250 *ms*, and the number of responses made after that (i.e. "time out" errors), during wait time epochs were also tracked and analyzed.

2.3. Procedures

Participants completed a behavioral session and a fMRI session. The behavioral session consisted of informed consent and neuropsychological testing (including the FGT). The behavioral session was always conducted first to screen for cognitive impairment and familiarize participants with the FGT. The fMRI session was scheduled at least one day and no more than one month after the behavioral session. During the fMRI session, the task was briefly reviewed and then participants completed the FGT in the MRI scanner.

Statistical power was determined according to the method of Cohen. There were 16 OAs (and 16 YAs), and the power to detect a large fMRI effect (i.e. *d* = 2.79; calculated based on prior work by Walter and Dassonville, 2011) between experimental and control conditions in OA versus YA with a corrected significance criterion of 0.05 was 81%. The power to detect a large effect (i.e. *d* = 1.68; calculated based on the difference between the mean level of activation in the prefrontal ROI in OA versus YA observed in the present data set) between average brain activity (in pre-specified ROIs) and neuropsychological tests with a significance criterion of 0.05 was 46%.

2.3.1 fMRI data acquisition

fMRI images were acquired on a 3T GE Signa scanner equipped with a 30.5 cm i.d. 3-axis local gradient coil and a quadrature head-coil. Foam padding was used to limit head movements, and earplugs were used for hearing protection. Prism glasses (with correction, as necessary) were used to view the task, which was back-projected on a screen behind the participant's head. For fMRI data, a forward reverse spiral sequence was used with a 2000 ms repetition time (TR) and 30 ms echo time (TE). The field of view (FOV) was 22 cm, captured with 43 axial slices with 3 mm thickness. For co-registration purposes, a Fast Gradient Echo Sequence was acquired in the same FOV with 200 ms TR and 2.3 ms TE. A spoiled gradient recalled acquisition sequence was acquired for high resolution anatomical comparison and warping. This was a 9 ms TR, 1.8 ms TE with 500 ms T1 in a 25 cm FOV, with 124 slices of 1.2 mm thickness.

2.3.2. Behavioral data analyses

Data from the behavioral FGT session were available for only 22 of the 32 participants, secondary to a hard drive failure. Three older adult participants and seven younger adult participants had missing behavioral data. Given that the proportion of older adults versus younger adults with missing data was uneven, we did not conduct any additional analyses. Therefore, only FGT data from the fMRI session were analyzed. Performance was calculated as percent correct for each condition. For the purposes of fMRI, performance on overlapping and embedded stimuli was combined to examine overall performance on the FGT, which is the original manner in which the FGT was scored and normed (Ayers, 1966). In general, based on Roper et al. 2001, performance below 36% correct represents an impaired performance at 2 standard deviations below the mean, and a performance below 48% correct represents a low-

average performance at 1 SD below the mean (based on a sample of fifty-nine 66-79 year old men). Statistical analyses were conducted using SPSS 17 and 21.

2.3.3. fMRI data analyses

Image processing was completed using SPM5 within Matlab. This preprocessing stream is identical to other published work by our group (Langenecker, Kennedy, Guidotti, Briceno, Own, Hooven, Young, Akil, Noll, Zubieta, 2007; Langenecker, Weisenbach, Giordani, Briceño, Guidotti, Schallmo, Leon, Noll, Zubieta, Schteingart, Starkman, 2012) including slice timing, co-registration, realignment, warping, and smoothing with full width half maximum (FWHM) of 5 mm.

3. Results

3.1. Neuropsychological data

All participants performed within normal limits on screens for general mental status (MMSE>23) and basic visual discrimination (BVFD>23). There were no significant differences between the OA and YA on vocabulary knowledge ($F(1,30) = 3.52$, $p = ns$), or education ($F(1,30) = 0.23$, $p = ns$). OA showed reduced performance compared to the YA on CVLT-II immediate recall ($F(1,29) = 39.27$, $p < .001$), CVLT-II long-delay free recall ($F(1,29) = 19.31$, $p < .001$), time to completion on Trails A ($F(1,30) = 10.68$, $p < .05$), time to completion on Trails B ($F(1,30) = 14.94$, $p < .001$), and the MMSE ($F(1,30) = 5.88$, $p < .05$). These neuropsychological data are displayed in *Table 1*.

3.2. FGT data

FGT data from the fMRI session are displayed as percent correct in Table 1 for OAs and YAs. There were no significant group differences in accuracy for the control condition of the FGT, $F(1,30) = 2.05$, $p = ns$. YAs demonstrated significantly better performance than the OAs

for both the overlapping condition, $F(1,30) = 7.63$, $p < .05$, and the embedded condition, $F(1,30) = 20.14$, $p < .001$. Furthermore, the embedded condition was significantly more difficult for both the YAs ($F(1,30) = 9.54$, $p < .05$) and OAs ($F(1,30) = 24.55$, $p < .001$) relative to the overlapping condition (*Table 1*). The correlation between the embedded condition and the overlapping condition was .52 across the sample as a whole. The age (old versus young) × condition (control, embedded, overlapping) interaction was significant at the 0.01 level, $F(1, 30) = 12.07$, $p < .05$, with best performance, in order, across both groups on the control task, followed by the overlapping condition, and worst performance on the embedded condition. The interaction effect suggests that level of performance varies according to group membership, with worst performance in the OA group in the embedded condition.

We also calculated the number of participants that made a response after the two second window but before the 2.25 second mark, and found that only 5 older adults made at least one response after the two second mark but before the 2.25 second mark, and in the older adult group the means and standard deviations were as follows for responses made after two seconds but before 2.25 seconds ($N = 15$): control (M=0.15, SD=.376), embedded (M=.15, SD=.376), overlapping (M=.08, SD=.277). In the younger group, only one participant responded after the 2 second mark but less than the 2.25 second mark, and the following descriptive statistics were obtained across the entire young adult group ($N = 16$): control (M=0.13, SD=.50), embedded (M=.00, SD=.00), overlapping (M=.00, SD=.00). When compared statistically, the young and older group did not differ for any condition in terms of number of responses made after the two second mark but before the 2.25 second mark (all p's > .11). Furthermore, regarding responses made after the 2250 *ms* mark, during the wait time epoch, a one way ANOVA revealed that the

groups did not differ significantly across conditions in terms of number of "time out" errors made between 2250 *ms* and a maximum of 5250 *ms* post-stimulus offset.

Signal detection measures of *d*' and β were calculated to further examine group differences in the overlapping and embedded conditions. To correct for hit rates of 1, the formula *1-1/2N* was used with N = total number of possible hits. To correct for false alarm rates of 0, the formula *1/2N* was used with N = the total number of possible false alarms. Mixed ANOVAs were conducted with group (YA and OA) as the between-subjects factor and condition (embedded and overlapping) as the within-subjects factor. For *d*', there was a main effect of group, $F(1,30) = 20.23$, $p < .001$ and condition, $F(1,30) = 47.27$, $p < .001$ with d' values higher in YA compared to OA, M(*SD*) = 2.19 *(.64)* and 1.39 *(.95)*, respectively, and greater discriminability for the overlapping compared to the embedded condition, M*(SD)* = 2.28*(0.59)* and 1.30 *(0.92)*, respectively. There was also a significant interaction effect between group and condition, $F(1,30) = 4.35$, $p < .05$ with greater age-related discrepancies in the embedded compared to overlapping conditions. There were no significant differences between OA and YA in β in the embedded condition, $F(1,30) = 1.34$, $p = ns$, or the overlapping condition, $F(1,30) = 0.71$, $p = ns$.

To examine cognitive correlates of the FGT, correlations between the FGT embedded and overlapping conditions and raw scores on select neuropsychological tasks were analyzed for all participants (The BVFD was not included in these analyses due to performance ceiling effects). All significant correlations were in the expected direction, with better performance on the FGT associated with better performance on other cognitive tasks (*Table 2*).

Given the significant and positive association between FGT performance and various types of other neuropsychological measures, we included cognitive factors as covariates in our

subsequent analyses to control for the effects of more generalized cognitive ability. To reduce Type I error (e.g., Blakesley et al., 2009), we chose to include only three scores which we felt were representative of the cognitive domains that correlated with FGT performance: general fluid ability, learning, and memory. Specifically, the Shipley Abstraction score was used in covariate analyses given that this score correlated positively with the FGT *and* also correlated highly (and negatively) with Trails A and Trails B. In contrast, both the CVLT-II Immediate Recall and Delayed Recall scores were entered as covariates in regression models because immediate and delayed memory correlated with FGT performance but did not correlate with the Shipley Abstraction score (both *p*'s > .14). Therefore, they were both entered into regression models as covariates. By doing this, we were able to reduce the number of predictors included in our models, reducing the chance of a false positive error.

3.3. fMRI Data

To examine fMRI signal change during the processing of experimental versus control stimuli, activations from the control blocks were subtracted from activations from the experimental blocks. Comparisons between OA and YA in experimental-minus-control activations revealed that OAs significantly activated several regions more so than YAs (*Table 3;* all *p*-values have been corrected for multiple comparisons using the Bonferroni method, with significant effects identifiable by a *p*-value < 0.002). We selected cortical regions that showed the most extreme correlation differentials between younger and older adults (e.g. medial frontal gyrus and supramarginal gyrus) for further analysis. *Figure 2* depicts clusters of interest analyses based on data presented in *Table 3*. Activations in the medial frontal gyrus and supramarginal gyrus were significantly associated with significantly *improved* FGT performance in OA and thus these regions were the focus of subsequent analyses.

Analyses were conducted within the OA and YA group to examine the relationship between fMRI activations in medial frontal and supramarginal gyri and behavioral performance on the FGT overlapping and embedded figures subtests. As noted above, fluid reasoning and memory scores were entered as covariates to control for more generalized cognitive abilities. Given performance differences between the FGT conditions, regression analyses were run separately with either FGT embedded or overlapping performance as the dependent variable. In the OA group, FGT performance on the overlapping figures (but not the embedded figures subtest) was positively (and linearly) related to activation in the medial prefrontal cortex (R^2 = 40%, p = .047, Cohen's effect size f^2=1.44; *Figure 3A*) even with Shipley Abstraction, CVLT Immediate Recall and Delayed Free Recall, and FGT embedded condition scores included in the model as covariates. This effect was absent in the YA group and to statistically compare this relationship in the YA and OA group, an interaction term was created with group and medial prefrontal activation and entered into a regression analysis with all participants. The interaction term was significantly related to performance in the FGT overlapping condition, $p < .05$, suggesting that the relationship between medial prefrontal cortex activation and FGT overlapping performance differs between the YA and OA groups. Similarly, in the OA group only, greater supramarginal activity (represented by a positive and significant quadratic term) predicted FGT performance on the embedded figures subtest even with Shipley Abstraction, CVLT Immediate Recall and Delayed Free Recall, and FGT overlapping scores entered into the model as covariates (R^2 = 60%, p = .007, Cohen's effect size f^2=1.281; *Figure 3B*). The interaction term of group and supramarginal activation trended towards significance, p = .09. Parietal and frontal activation were significantly correlated in YA (r = .59, p = .02), but not in OA (r = -.02, p = .94). Note that the values in each graph have been standardized given that

multiple variables with differing scales were used in the regression. In Figure 3A, the negative x-values signify that those OA who responded with activation in the medial prefrontal cortex below the mean during the experimental condition relative to the control condition performed more poorly on the FGT-overlapping subtest. Figure 3B is depicting the *standardized* quadratic term, and that is why there are negative numbers. Negative numbers indicate scores below the mean.

3.3.2.

Discussion

As expected, OA demonstrated poor performance compared to YA on the FGT, a relatively pure measure of visuospatial processing. Signal detection analyses suggested age-related differences in signal-noise discrimination but not response bias. FGT performance was not correlated with measures of intelligence (i.e., Shipley vocabulary) or broad mental status (i.e., MMSE), suggesting that these differences do not merely reflect a global decline in cognitive ability.

fMRI data were examined to identify differences in functional patterns that may underlie these changes in visuospatial abilities. Overall, consistent with the PASA framework, increased activity in frontal and parietal cortex was observed in OA relative to YA during visuospatial processing/reasoning. Activity in prefrontal and parietal regions uniquely predicted enhanced FGT performance within the OA group (though OA group performance remained below YA group performance). Two routes for reduced OA performance on the FGT were identified: (1) reduced parietal activity was associated with poor performance on the embedded figures subtest, and (2) reduced frontal activity related to reduced performance on the overlapping figures subtest. Note that these frontal and parietal activations were not correlated in OAs despite our

finding of a significant correlation in YA. Thus, OAs demonstrated a dissociation in frontoparietal network activation, with the parietal aspect of the network uniquely mapping on to the parsing of items on the embedded figures task, whereas enhanced activation of the frontal aspect of the network exclusively related to performance on the overlapping figures subtest. This dissociation likely contributes to OAs overall reduced ability to solve both types of visuospatial problems, as a compensatory and coordinated increase in both regions is likely necessary for optimal performance on these types of tasks, particularly the embedded portion of the task, in OA. These findings are consistent with a previous study conducted by Walter and Dassonville (2011) in which younger adults' performance on an embedded figures test was related to *dual* increases in frontal and parietal activity.

Importantly, related to Salthouse's (1996) distinction between general and specific mediation of adult age differences in cognitive functioning, the relation between brain activation and performance on the FGT in OA remained significant despite the inclusion of multiple covariates that also related to FGT performance, namely fluid reasoning, learning, and memory. This adds to our confidence that our results cannot be attributed to more generalized cognitive abilities but rather are likely to be specific to visuospatial processing. Furthermore, although successful completion of the FGT requires sustained attention, visual scanning, working memory (as the stimuli are removed prior to the participant's response), and sufficient response speed, we used regression analysis to eliminate working memory and general cognitive decline as potential explanations of the age difference in FGT performance. Additionally, we believe our analysis of "time out" errors/non-response errors mitigates processing speed as an explanatory factor. We also believe that visual scanning is not a plausible explanatory factor as all conditions required some element of visual scanning. Instead, what does separate the control task and the

experimental tasks is the element of superimposed images. In other words, the "simultanagnosia feature/aspect" of the experimental images is what set them apart from the control images, and thus, we believe that our results reflect a core simultanagnosia-based deficit, rather than a discrepancy in visual scanning ability per se. To support this claim that visual scanning is not a plausible explanatory variable for the presented results, we call on the work of Dalrymple et al. (2009), which suggests that visual scanning problems are not sufficient to characterize simultanagnosic performance on a visuospatial task. These researchers found that a patient with simultanagnosia, relative to a brain damaged control participant and a completely healthy set of age matched participants, did complete visual scanning in a similar manner as controls, and was not "missing" key elements during scanning that would preclude the patient from correctly identifying the global object of interest. Thus, they concluded that "connecting the dots" visually--of the distinctive parts of a global shape--is neither necessary nor sufficient for the patient with simultanagnosia to correctly discern the object's identity. Instead, the authors' ad-hoc hypothesis was that a person with simultanagnosia does not correctly *integrate* the information that he or she obtains from successive eye fixations, and this may result from an inability to maintain continuous visuospatial attention across an array.

We believe our finding of altered frontoparietal activation in older adults versus younger adults during the FGT generally supports the sustained visual attention hypothesis, as frontal and parietal regions acting *together* likely facilitate the smooth integration of complex visual scenes, and the reduced performance of older adults across the overlapping and embedded subtests is directly due to dysregulated frontoparietal activity (with kernels of activation in frontal or parietal regions relating to increased performance in older adults, yet still below younger adult performance); which we believe is the overall primary explanatory variable in our results.

Overall, our data point to the breakdown of anterior-posterior visuospatial processing networks with aging, with OAs exhibiting increased yet uncorrelated activity in prefrontal and parietal regions relative to YA. OA showed age-related decrements in figure-ground discrimination and we tentatively speculate that the breakdown in visuospatial processing associated with aging may resemble a subtleform of dorsal simultanagnosia. The STAC-R model (Reuter Lorenz and Park, 2014) would suggest that such visuospatial processing degradation, while engendering more anteriorly-related compensation, nevertheless suffers from decreased efficiency. Research done at the Mayo Clinic already suggests that simultanagnosia may be an early symptom of abnormal aging, i.e., dementia (Graff-Radford, Bolling, Earnest, Shuster, Caselli, Brazis, 1993). In addition, functional abnormalities in the dorsal visual pathway have been observed in individuals with mild Alzheimer's disease relative to a healthy control group during visuospatial processing (Bokde, Lopez-Bayo, Born, Ewers, Meindl, Teipel, Faltraco, Reiser, Moller & Hampel, 2010). Future work is needed to determine the extent to which increased yet uncoordinated frontoparietal activity may be a risk factor for neurodegenerative disease in OA.

The present study is limited by sample size, and replication is needed with a larger sample. Also of note, the Southern California Figure Ground test was originally normed on males, though at least one follow-up study was conducted with women. A gender effect has been reported on this task (with men scoring higher than women; Bieliauskas et al., 1988) and thus we limited our sample to males to limit the heterogeneity of our sample. However, this limits our ability to generalize our findings across genders and thus replication with a mixed sample is needed with an examination of gender-specific differences in functional activation. In addition, there is a need to investigate the overlapping and embedded portion of the FGT

separately in the context of mild cognitive impairment and dementia. Also, given that young and older participants differed in their reaction time, it is possible that the BOLD response (neural activation) recorded from younger adults significantly differs from the time course recorded from older adults simply because the subject who spends the entire two second response duration on the task will inevitably produce a different BOLD response than someone who takes less than a second, for example, to respond. Our results therefore have to be tempered given this possibility.

In conclusion, this study demonstrates that visual processing is associated with an altered pattern of frontoparietal brain function in older adults relative to younger adults. Difficulties in this domain may reflect difficulty with the perception and integration of multiple, simultaneously presented stimuli related to changes in frontoparietal mediated sustained visual attention.

Disclosures

Drs. Drag, Light, Langenecker, Hazlett, Wilde, Welsh, Steinberg, and Dr. Bieliauskas declare that they have no conflict of interest.

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Table Captions

Table 1. Demographic information and mean (*SD*) performance on neuropsychological tasks.

Table 2. Experimental minus Control Activations: Group Comparisons

Table 1.

	Younger Adults (YA)	Older Adults (OA)
N	16	16
Age*	24.13 (*4.13*) Range: 20-35	75.06 (*4.28*) Range: 69-82
MMSE*	29.33 (*0.90*) Range: 27-30	28.38 (*1.26*) Range: 26-30
Shipley Vocabulary	33.34 (*3.23*)	35.66 (*3.41*)
Shipley Abstraction**	36.25 (2.30)	25.56 (9.97)
Trails A (seconds)*	23.06 (*8.49*)	37.56 (*15.59*)
Trails B (seconds)**	51.06 (*12.52*)	95.94 (*44.72*)
CVLT Immediate Recall Raw Score**	60.06 (*5.83*)	43.13 (*8.98*)
CVLT Long-Delay Free Recall Raw score**	13.44 (*1.79*)	9.40 (*3.18*)
BVFD	30.06 (*2.32*)	28.25 (*3.23*)
FGT control	.97 (*.08*)	.94 (*.06*)
FGT overlapping*	**.87 (*.08*)** } $p<.05$	**.78 (*.11*)** } $p<.001$
FGT embedded**	**.77 (*.11*)**	**.59 (*.11*)**

Note: All scores are raw scores. CVLT = California Verbal Learning Test; BVFD = Benton Visual Form Discrimination; MMSE = Mini Mental State Examination; ***p* < .05, ****p* < .001

Table 2.

Correlations between performances on neuropsychological tasks

	Figure Ground Experimental (Overlapping + Embedded)	Figure Ground Experimental (Overlapping Only)	Figure Ground Experimental (Embedded Only)
N	32	32	32
Shipley Abstraction	.59**	.48**	.54**
CVLT Immediate	.76**	.63**	.69**
CVLT Delayed	.79**	.64**	.73**
Trails A (seconds)	-.54**	-.57**	-.40*
Trails B (seconds)	-.66**	-.58**	-.58**

Note: All scores are raw scores unless otherwise noted. CVLT = California Verbal Learning Test.

Table 3.

Experimental-Control Activations: Group Comparisons

Lobe	Location	BA	Z	p-value	mm^3	Talairach Coordinates X	Y	Z	Result	FGT Correlations OA(YA)
Frontal	Medial Frontal*	10	3.53	0.000416	752	-1	55	-1	OA>YA	.41(.02)
	Cingulate	24	3.93	0.000085	352	-4	-15	39	OA>YA	-.40(-.33)
		31	3.70	0.000216	152	-6	-25	39	OA>YA	-.28(-.08)
	Precentral	4	3.51	0.000448	168	36	-13	52	OA>YA	-.24(-.39)
Temporal	Middle Temporal	21	3.59	0.000331	128	-57	-19	-15	OA>YA	.21(.31)
Parietal	Supramarginal*	40	4.01	0.000061	360	52	-52	27	OA>YA	-.47(.37)
	Angular	39	4.68	<0.00001	1440	-36	-71	33	OA>YA	.02(.30)
Subcortical	Cerebellum, pyramis	--	4.73	<0.00001	544	-24	-83	-31	OA>YA	-.29(-.17)
		--	3.65	<0.00001	456	10	-69	-2	OA>YA	-.29(-.17)
	Cerebellum, tuber	--	3.99	0.000066	312	22	-85	-29	OA>YA	-37(-.29)
Frontal	Superior Frontal	6	3.52	0.000432	120	-13	16	46	YA>OA	-.32(-.16)
Parietal	Superior Parietal	7	4.12	0.000038	1176	-29	-56	46	YA>OA	-.07(-.01)
	Inferior Parietal	40	4.89	<0.00001	1880	40	-42	50	YA>OA	-.44(.03)
		40	3.65	0.000262	256	-43	-44	49	YA>OA	.07(.10)
		40	3.36	0.000779	120	-38	-44	40	YA>OA	.11(.25)
	Precuneus	7	3.91	0.000092	608	22	-67	47	YA>OA	-.26(.17)
Temporal	Fusiform	19	3.76	0.00017	208	34	-67	-6	YA>OA	.09(.14)
	Hippocampus	--	3.75	0.000177	680	-29	-25	-7	YA>OA	-.20(.10)
Occipital	Lingual	18	3.84	0.000123	2136	4	-73	5	YA>OA	-.32(.01)
		18	3.57	0.000357	144	-34	-67	-6	YA>OA	.14(.10)
		--	3.81	0.000139	280	20	-65	2	YA>OA	-.62(.13)
Subcortical	Caudate	--	4.41	0.00001	1512	10	1	14	YA>OA	.19(.28)
	Thalamus	--	3.89	0.0001	520	-8	-9	15	YA>OA	.15(.13)
	Claustrum	--	3.82	0.000133	280	29	6	-5	YA>OA	-.06(.09)

* Clusters of interest in post-hoc analyses; BA = Brodmann Area

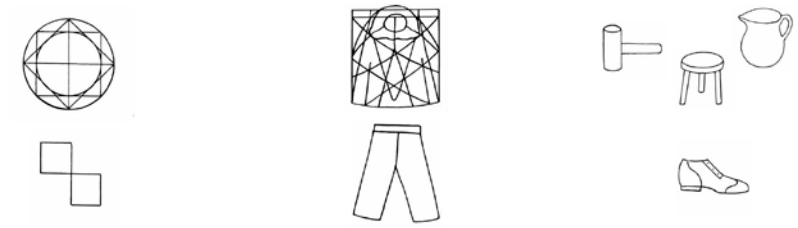
Figure Captions

Figure 1. Sample stimuli from the Figure Ground Task (FGT).

Figure 2. Activation Comparisons for the Older and Younger Groups in the Experimental-minus-Control Condition. Green depicts activation that is greater in YA relative to OA in the experimental minus control task contrast. Cyan depicts activation that is greater in OA relative to YA in the experimental minus control task contrast.

Figure 3. (A) Greater activation in medial prefrontal cortex predicted better performance on the Overlapping Figures subtest in OA (B) Greater activation in supramarginal gyrus predicted better performance on the Embedded Figures subtest in OA.

Figure 1.



Embedded Overlapping Control

Figure 2.

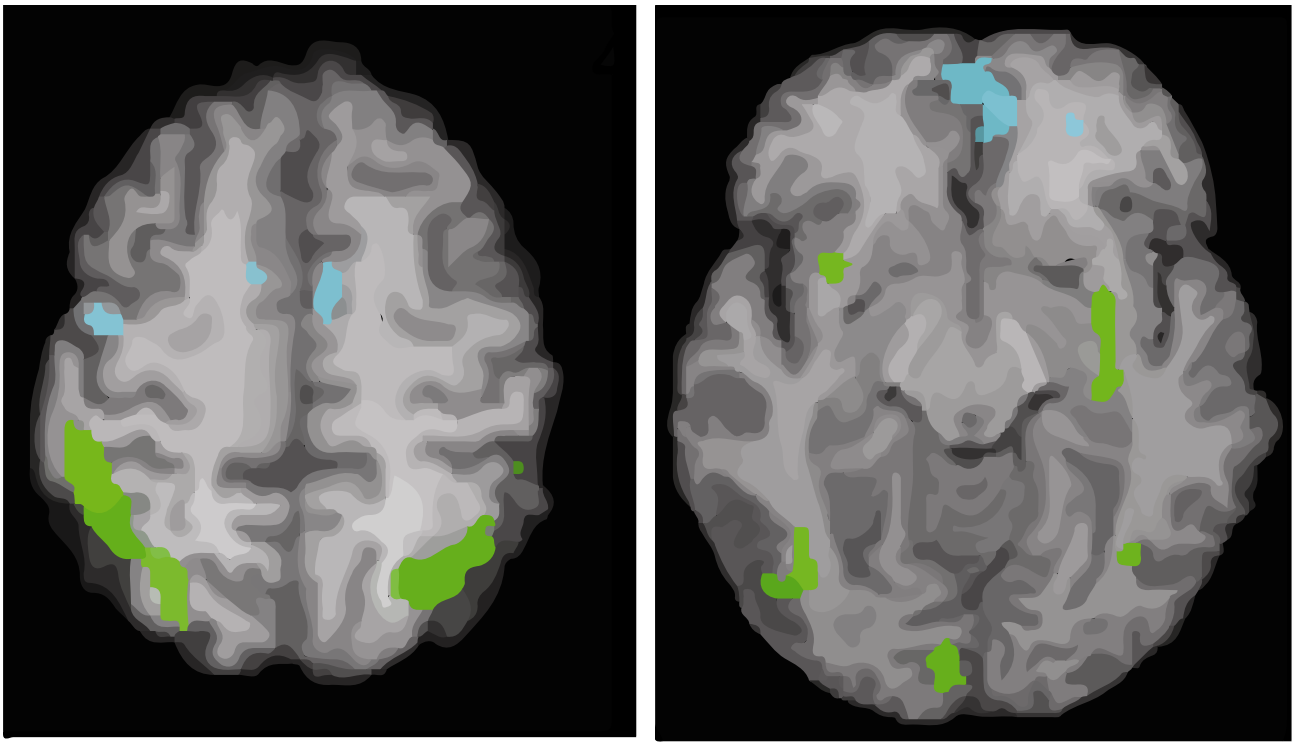
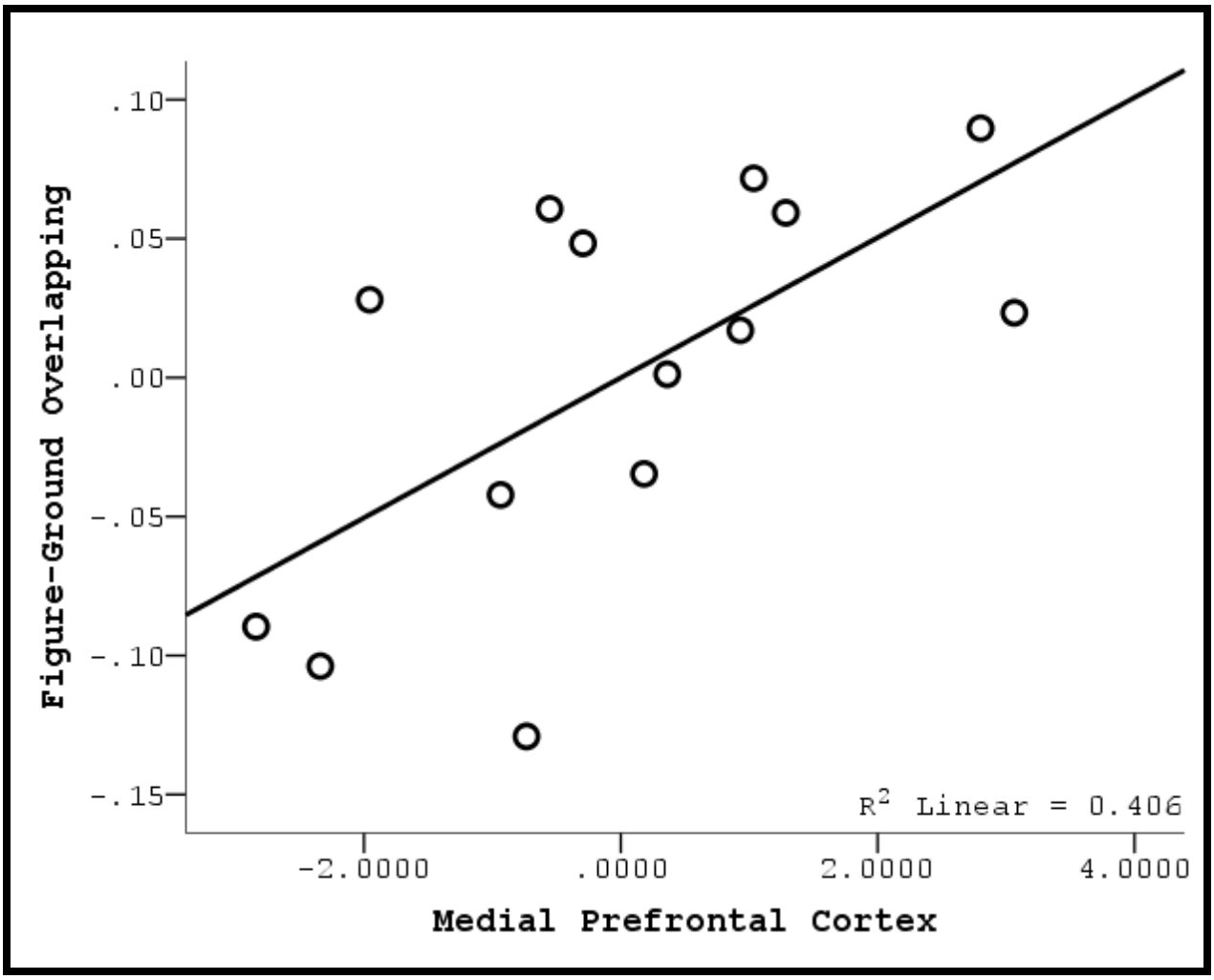


Figure 3.

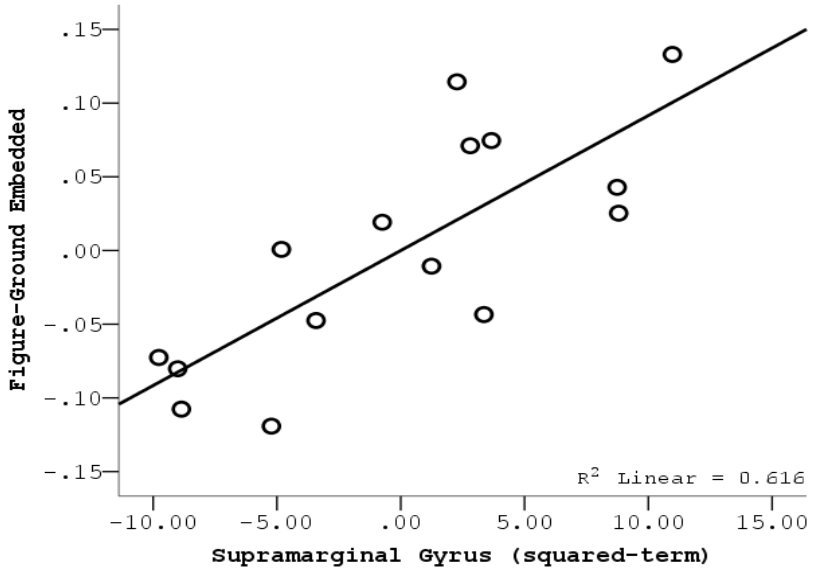
A. Partial Regression Plot.



Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	.764	.120		6.395	.000
1. Medial PFC (linear)	**.025**	**.011**	**.470**	**2.340**	**.047**
2. Shipley Abstraction	-.001	.002	-.134	-.639	.541
3. CVLTSDFR	.042	.017	1.254	2.472	**.039**
4. CVLTLDFR	-.017	.016	-.526	-1.055	.322
5. Embedded Figures	-.133	.220	-.147	-.604	.563

Dependent Variable: FGT-Overlapping Figures subtest; CVLTSDFR = CVLT-II Short Delay Free Recall; CVLTLDFR = Long Delay Free Recall

B. Partial Regression Plot



Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	.359	.146		2.452	.040
1. Shipley Abstraction	-.001	.002	-.057	-.334	.747
2. CVLTSDFR	.053	.021	1.422	2.527	.035
3. Overlapping Figures	.003	.235	.003	.014	.989
4. CVLTLDFR	-.031	.019	-.846	-1.626	.143
5. SPG (quadratic term)	**.009**	**.003**	**.895**	**3.581**	**.007**
6. SPG (linear term)	-.009	.009	-.233	-.994	.349

Dependent Variable: Embedded Figures subtest; CVLTSDFR = CVLT-II Short Delay Free Recall; CVLTLDFR = Long Delay Free Recall; SPG = Supramarginal Gyrus.