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A split-brain model of Alzheimer's disease? Behavioral evidence for comparable intra and interhemispheric decline

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Abstract

It has been proposed that features of Alzheimer-type dementia (AD) reflect a breakdown in cortical connectivity that can be likened to a disconnection syndrome. One hypothesized consequence of this pathology is that AD patients should be disproportionally impaired on measures of interhemispheric transfer. However, there is a paucity of studies bearing on this prediction. We report the results from two measures of interhemispheric interaction obtained from healthy younger and older adults, and older adults with probable AD. One measure examined speeded simple manual responses to a lateralized light flash (i.e., the Poffenberger task) and the other examined the interhemispheric coordination of computational resources using within and across hemifield variants of visual letter-matching tasks. AD patients show an overall impairment of performance on both intra and interhemispheric conditions in all tasks. However, there is no indication of disproportionate alteration of interhemispheric processes mediating either visuomotor transfer or visual letter-matching and the allocation of computational resources. The results, therefore, call into question the appropriateness of a "split-brain" model for AD, at least in the domain of visual processing. Although the results are not specifically diagnostic of a disconnection syndrome, they are consistent with the possibility of a breakdown of cortico-cortical connectivity both within and between the hemispheres in AD.

Keywords: Alzheimer's disease; Interhemispheric interaction; Corpus callosum; Split-brain; Hemifield

Alzheimer-type dementia (AD) is a progressive neurodegenerative disorder, that according to the DSM-IV (American Psychiatric Association, 1994) is a probable diagnosis based on the combination of memory impairments and additional cognitive disturbances that have a gradual onset and a continual decline without any identifiable cause. The increasingly severe memory impairments in AD presumably arise from neuropathology affecting pyramidal neurons of the hippocampus and entorhinal cortex in the form of neurofibrillary tangles, senile plaques, and neuronal loss (Khachaturian, 1985). The widespread neocortical changes that increase over the course of the disease contribute to progressive memory loss and general cognitive declines in AD (Van Hoesen, 1990). Atrophic changes in frontoparietal and temporal areas include white matter loss and substantial damage to intra and interhemispheric associations pathways (Bartzokis, 2004; Kemper, 1994; Pantel et al., 1999). Senile plaques are most prominent in cortical layers II and III, which give rise to intrahemispheric association fibers and the interhemispheric fibers constituting the corpus callosum and the interhemispheric commissures (Morris, 1996a, 1996b).

Based on such neuropathological evidence, Morris (1996b) has proposed that some of the neuropsychological sequelea of AD may arise from disconnection-type deficits associated with the disruption of intra and interhemispheric corticocortical pathways (see also Morrison, Scherr, Lewis, Campbell, & Bloom, 1986). The broad impact of the disconnection account of AD is made evident in a recent review by Delbeuck, Van der Linden, and Collette (2003) that

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summarizes a variety of neuropathological, electrophysiological and neuroimaging evidence indicating that AD involves a fundamental breakdown in corticocortical connectivity, both within and between the hemispheres. For example, diffusion tensor imaging (DTI) of white matter pathways reveals declines in the splenium of the corpus callosum, and the longitudinal fasciculus, an intrahemispheric pathway connecting temporal and frontal cortices in AD (Rose et al., 2000). Likewise positron emission tomography (PET) during a memory task shows decreased interregional correlations between prefrontal cortex and the hippocampus consistent with a breakdown in functional connectivity in AD (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001).

The disconnection account of AD has stimulated interest in the corpus callosum as a potential marker for white matter neuropathology in AD. As the major white matter interhemispheric pathway, the corpus callosum is prominent on magnetic resonance images (MRI) and amenable to quantitative analyses. Indeed, numerous studies conducted over the past 15 years have reported reductions in callosal volume in AD patients compared to healthy age-matched controls. While there are inconsistencies about which callosal subregions are most affected (cf. Biegon et al., 1994; Janowsky, Kaye, & Carper, 1996; Weis, Jellinger, & Wenger, 1991; Yamauchi et al., 2000) reductions in total callosal area in AD range between 18 and 38% (for reviews see Delbeuck et al., 2003; Hampel et al., 1998). These structural declines suggest AD could be associated with neuropsychological signs of interhemispheric disconnection similar to those arising from pathology of the corpus callosum or surgical callosotomy—the so-called "split-brain" (Gazzaniga, Bogen, & Sperry, 1992).

Can neuropsychological measures of interhemispheric interactions serve as markers for a disconnection syndrome in AD? Behavioral tests of a split-brain model of AD necessitate a comparison of intra and interhemispheric conditions, and support for the model requires that interhemispheric processing is impaired relative to intrahemispheric processing. This outcome would suggest that callosal fibers are disproportionately affected in AD. Alternatively, equivalent performance declines on intra and interhemispheric conditions would be consistent with a pervasive disconnection pathology, or other global impairments (e.g., attentional dysfunction), but would challenge the split-brain model of AD. Thus, neuropsychological measures that assess the integrity of intra versus interhemispheric processing can shed light on the disconnection processes at work in AD and establish the validity of the split-brain model as a functional account of this disease. Only one published report to date has explicitly tested this account (Lakmache, Lassonde, Gauthier, Frigon, & Lepore, 1998).

Lakmache et al. (1998) investigated 10 AD patients and 10 age-matched controls using tests designed to evaluate callosal subregions that mediate bimanual motor control, and the interhemispheric transfer of somesthestic and visual information. The motor task, which was limited by the absence of a unimanual comparison condition (see Brown, 2003), examined the accuracy of lines traced via the coordinated control of left and right-hand knobs that moved the *X–Y* position of a pen. AD patients displayed poorer bimanual coordination than controls but only in the time-limited condition. On measures of tactile localization, tactile shape and texture matching, and tactile object identification the AD group showed significantly lower accuracy on the interhemispheric compared to the intrahemispheric conditions. Controls showed this pattern, but to a lesser extent than AD patients, only for the texture matching task. The data for the visual modality are less clear. On one speeded measure of visuomotor transfer (Poffenberger, 1912), AD patients were slower in both intra and interhemispheric conditions, but the difference between these conditions was equivalent to controls. On letter and color matching AD patients were less accurate on the inter than intrahemispheric trials. However, because the control group performed almost flawlessly in both conditions (i.e., their performance was at ceiling) between group comparisons of the inter–intra difference are misleading. Despite this limitation and the small sample sizes, the findings suggest that AD includes a disproportional decline in interhemispheric processing at least for tactile information conveyed by the midbody of the corpus callosum.

If AD selectively disrupts interhemispheric processes as the above data suggest the consequences could be quite far reaching. Our own work indicates that normal aging promotes increased reliance on interhemispheric interactions (Reuter-Lorenz & Stanczak, 2000; Reuter-Lorenz, Stanczak, & Miller, 1999). Using PET, we originally reported that older adults show more bilateral activation than younger adults during verbal and spatial working memory tasks (Reuter-Lorenz et al., 2000). Moreover, our behavioral measures (see below), comparing within and across hemifield letter-matching, indicate that older adults benefit from using both hemispheres to process information on relatively easy tasks, whereas young adults show such performance benefits only on tasks that are more difficult (Reuter-Lorenz et al., 1999). Likewise, bilateral activation as measured by PET and fMRI has been found to correlate with higher memory performance in older adults (Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz et al., 2001; Rosen et al., 2002). These results suggest that bihemispheric recruitment and an associated increase in interhemispheric interactions may serve a compensatory role in normal aging (cf. Logan, Sanders, Snyder, Morris, & Buckner, 2002). Split-brain like effects in AD would preclude the use of such compensatory processes and thereby contribute to more pervasive cognitive decline.

Therefore, the aim of the present study was to obtain new evidence pertaining to the functional integrity of the corpus callosum in AD. We used variants of two time-honored experimental measures of interhemispheric transfer: the Poffenberger task, a measure of speeded sensori-motor transfer, and visual matching of stimuli presented in the same or in opposite visual hemifields (e.g., Reuter-Lorenz & Miller, 1998; Seymour, Reuter-Lorenz, & Gazzaniga, 1994). The Poffen-

berger task requires the participant to make a speeded unimanual response to the onset of a stimulus appearing in the left or right visual field. Uncrossed responses (left hand key presses to left visual field stimuli and right hand responses to right visual field stimuli) are typically several or more milliseconds faster than crossed responses (e.g., left hand responses to right visual field stimuli). The time difference between the crossed and uncrossed conditions is thought to relate to the requirement for interhemispheric transfer in the crossed but not in the uncrossed condition. Although the precise processes that give rise to the CUD are still unknown (see, e.g., Saron, Foxe, Schroeder, & Vaughan, 2003), the CUD has been widely used as an index of callosal function and dysfunction (see Zaidel & Iacoboni, 2003 for a review). The decision to include the Poffenberger task in the present investigation was motivated specifically by recent work from our laboratory and others showing an increased CUD in normal aging (e.g., Jeeves & Moes, 1996; Reuter-Lorenz & Stanczak, 2000) suggesting that this measure is sensitive to age-related changes in callosal function. The inconsistent outcomes reported by Lakmache et al. (1998) on their sensori-motor and visual matching tasks provides additional justification for examining the relationship between similar measures in a new and larger group of subjects with and without AD.

The visual matching tasks that we used were specifically selected to measure the relative efficiency of interhemispheric interactions under varying levels of cognitive demand (Banich & Belger, 1990; Banich & Karol, 1992; Belger & Banich, 1992). The low and high demand versions of the task are illustrated in Fig. 1. The letter below the fixation point (the target) can appear in either the left or right visual field. The participant decides whether the target matches a probe letter in the upper row. On within-hemisphere trials, the target item and the matching probe appear in the same visual field (projecting to the same hemisphere) whereas on across-hemisphere trials, they appear in opposite visual fields (projecting to opposite hemispheres).

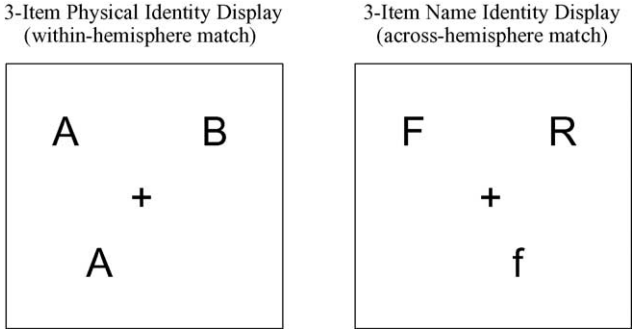

Fig. 1. Sample displays illustrating within-hemisphere and across-hemisphere matches across two levels of task difficulty. The target letter always appeared at the bottom of the display and the probe letters were always in the upper row of the display. In the physical-identity match trials, the target letter physically matched one of the probes (in this example, A–A). In the name-identity match trials, the target had the same name as one of the probes (in this example, f–F).

Matching on the across-hemisphere trials requires integrating information about the target presented in one visual field and the matching probe presented in the other. For the low demand condition, the physical identity (PI) task illustrated on the left, performance is typically superior on within-hemisphere than across-hemisphere trials (Banich & Belger, 1990; Banich & Karol, 1992; Belger & Banich, 1992; Mikels & Reuter-Lorenz, 2004). Because interhemispheric processing includes interhemispheric transfer time, and potential degradation of transferred representations (see Braun, Achim, & Larocque, 2003 for a review), it is less efficient than intrahemispheric processing. If interhemispheric transfer is especially compromised due to pathology in AD, then the advantage of within-field matching relative to across-field matching on this task should be accentuated compared to healthy controls.

Of importance is the well-established finding that the relative advantage of these two presentation conditions reverses at higher levels of task demand (see Banich, 1998). When the number of probe letters is increased (not shown), and/or matches must be based on the name of the letter (i.e., cross-case or name identity (NI) matching illustrated on the right of Fig. 1) the across-hemisphere condition becomes increasingly advantageous to the point where performance surpasses the within-hemisphere condition (Banich & Belger, 1990; Banich & Karol, 1992; Belger & Banich, 1992; Mikels & Reuter-Lorenz, 2004)! On across-hemisphere trials the target and matching probe can be processed in parallel by opposite hemispheres. When task demands are high, the increased processing efficiency made possible by dividing the labor between the hemispheres outweighs the cost of interhemispheric transmission, resulting in a reversal of the typical within-hemisphere advantage (see Banich, 1998; Liederman, 1998 for further discussion; Reuter-Lorenz et al., 1999). One way to conceptualize the across-hemisphere advantage is in terms of greater availability of neural resources in this condition relative to the within-hemisphere condition (Banich, 1998; Mikels & Reuter-Lorenz, 2004). As the task demands increase, the recruitment of more neural circuits to meet higher demands is more efficient in the across-hemisphere than the within-hemisphere condition leading to the observed performance advantage (for further discussion see Banich, 1998; Liederman, 1998; Reuter-Lorenz et al., 1999). In support of this recruitment interpretation, a recent neuroimaging study revealed that high letter-matching demands produced bilateral activation in visual cortex in the across-field condition relative to the within-field condition despite the physical equivalence of the stimulus displays (Pollmann, Zaidel, & von Cramon, 2003).

The present study tests whether AD patients can perform across-hemisphere versus within-hemisphere matches on the one hand, and on the other hand, whether they can show a performance advantage for the across-hemisphere condition as processing demands increase. The split-brain model predicts that AD patients would be generally impaired in the across-hemisphere condition relative to the within-hemisphere con-

dition, and relative to age-matched controls. Moreover, disproportional callosal decline in AD should preclude the performance advantage of bihemispheric processing thought to be indexed by the shift to an across-hemisphere advantage in the more demanding matching task. Therefore, the split-brain model of AD would predict a within-hemisphere processing advantage regardless of task demand. Alternatively, AD patients could show equivalent performance decrements relative to controls, in both within-hemisphere and across-hemisphere conditions. This outcome would constitute evidence against a split-brain model of AD, although it would not be exclusively diagnostic of disconnection pathology per se. At minimum, a uniform performance decrement could be consistent with a pervasive disconnection phenomenon based on the assumption that the within-hemisphere task conditions also utilize intrahemispheric white matter pathways.

1. Method

1.1. Participants

Twenty-four patients diagnosed with probable Alzheimer's disease were recruited from the University of Michigan Medical Center through the Michigan Alzheimer's Disease Research Center. Patients were diagnosed with probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's disease and Related Disorders Association diagnostic criteria. All participants were at least high school educated, free of neurological disorders prior to the diagnosis, and had normal or corrected-to-normal vision. One patient was excluded due to an inability to complete the tasks. Of the remaining 23 patients, two were left handed.[1]

Twenty-three healthy age-matched control participants were recruited for participation through advertisements placed in the local newspaper. These older adults were also screened to assure that they were high school educated, free of neurological disorders, and had normal or corrected-to-normal vision. Additionally, 23 younger adults were recruited through the Introductory Psychology Subject Pool at the University of Michigan. All younger participants were free of neurological disorders, and had normal or corrected-to-normal vision. Informed consent was obtained from all participants in accordance with the requirements of the Internal Review Board of the University of Michigan.

The AD patients and the older adult participants were paid for their time and the younger adult participants received course credit. All participants completed a battery of neuropsychological tests that included the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), and several sub-tests of the WAIS-III: Vocabulary, Digit Span, Block Design, Matrix Reasoning, and Letter–Number Sequencing (Wechsler, 1997). The AD patients and the older adults were matched for gender, age, and level of education (all $p > 0.7$). The demographic information for these groups is presented in Table 1. Compared to the older and younger adults, AD patients were impaired on all of the neuropsychological tests, demonstrating broad cognitive impairments (all $p < 0.05$). The neuropsychological assessment of these groups is presented in Table 2.

Table 1
Participant demographic information by group

Group	*N* (female)	Age		Years of education
		M	S.D.	
AD	23 (11)	71.13	15.98	14.33
OA	23 (11)	70.87	14.70	14.20
YA	23 (11)	19.65	1.43	13.52

Note: AD, Alzheimer's disease patients; OA, older adults; YA, younger adults.

1.2. Apparatus

A Macintosh PowerPC with PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993) was used for stimulus presentation and data acquisition. Participants sat with their chin in a headrest to ensure a constant viewing distance of 57 cm. An experimenter was seated in the testing room facing the subject at all times. To insure compliance with the instruction to fixate, the experimenter observed the participant's gaze and intermittently reminded the participant of this requirement as needed.

1.3. Simple reaction time (Poffenberger) task design

A red upper case "X" (0.21 lx) was centered on a black background (0.16 lx) of the computer screen and remained visible throughout each experimental block. A white circle (approximately, $0.5^\circ \times 0.5^\circ$, 0.26 lx) served as the command stimulus to which the participants responded. It appeared for 50 ms 5.25° to the left or right of the fixation point with equal probability. Fourteen percent of the trials were catch trials in which no target occurred and participants were to refrain from responding. There was a 1-s interval between trials.

1.4. Simple reaction time task procedure

Participants were instructed to maintain their gaze on the central fixation stimulus throughout each trial and prompted to so by the experimenter as needed. A trial began with the simultaneous onset of a 200-ms warning tone and a 100 ms offset of the fixation stimulus followed by an interval that varied randomly between 500 and 1000 ms (at 100 ms intervals). Participants were instructed to respond to the onset of the circle as quickly as they could without sacrificing accuracy by pressing the space bar with the designated index finger. The testing session began with a practice block of 42

[1] All of the analyses described below were also run excluding these two left-handed patients. Excluding these two patients made no appreciable difference to the results. Thus, they are included in the following analyses.

Table 2
Neuropsychological test score means and S.D. by group

Neuropsyhological test	OA		AD		YA	
	M	S.D.	*M*	S.D.	*M*	S.D.
MMSE (maximum = 30)	28.70	1.46	22.22	3.04	29.87	0.46
Vocabulary[a] (maximum = 66)	52.78	10.05	35.83	12.86	55.91	4.38
Digit-Symbol Coding[a] (no maximum, 120 s.)	61.79	17.38	32.78	17.84	94.78	14.64
Matrix Reasoning[a] (maximum = 26)	14.70	6.07	7.78	5.43	20.61	3.75
Block Design[a] (maximum = 68)	32.57	10.55	19.57	16.56	55.65	8.28
Digit Span[a] (maximum = 30)	16.61	4.28	13.57	3.20	20.96	4.45
Letter–Number Sequencing[a] (maximum = 21)	11.04	2.77	4.96	2.80	13.13	2.49
Verbal Fluency (no maximum, 60 s)	12.22	4.21	9.78	4.25	13.39	3.61

[a] From the WAIS-III.

trials for each hand. This was followed by eight 70-trial experimental runs, four for each hand. These blocks were run in a counter-balanced order between participants.

1.5. Letter-matching task design

The two letter-matching tasks varied in cognitive complexity: the 3-PI and 3-NI tasks. In the 3-PI task, all letters were upper case and the target letter presented below the fixation cross physically could match one of the two probes above the fixation cross (see Fig. 1). In the 3-NI task, the two probes above the fixation cross were upper case, whereas the target below the fixation cross was lower case. Thus, matches were based on nominal identity (see Fig. 1).

In both tasks, the stimulus displays had the same spatial arrangement. The target letter appeared 1.4° below and 1.4° to the left or right of the central fixation cross, and the two probe letters appeared 1.4° above the fixation cross and 2.8° to the left or right of the fixation cross (one letter in each visual field). Each letter subtended a maximum of 0.85° horizontally and 1.2° vertically. Targets and probes were chosen randomly from the following set of letters: A, B, D, F, G, H, M, N, R, S, and T.

The targets were presented randomly and with equal probability in the left or right visual field. On half of the trials, the target matched one of the probes, whereas on the other half, no match was present. When the target matched a probe, the matching probe was equally likely to appear in the same visual field as the target (a within-hemisphere match) or in the visual field opposite to the target (an across-hemisphere match).

1.6. Letter-matching task procedure

Participants were instructed to focus on a central fixation cross during each trial and prompted to do so by the experimenter as needed.[2] At the beginning of each trial, the fixation cross flashed and a beep sounded. After a 500 ms pause, the letter array appeared for 200 ms. Participants were instructed to press the space bar with their right index finger as quickly as possible without compromising accuracy only if the target matched one of the probes. They had 2 s to respond. Participants were instructed to refrain from responding if the target did not match one of the probes (a go/no-go procedure). Each task contained one practice block and three experimental blocks and all blocks consisted of 64 trials.

1.7. Overall procedure

Participants first signed and dated the informed consent document, completed a demographics questionnaire, the Edinburgh handedness inventory, and the MMSE. They then completed a "supra-block" of two to three consecutive blocks of letter-matching or simple RT interleaved with a block of two or three neuropsychological tests. The "supra-blocks" of letter-matching or simple RT tasks were administered in a counterbalanced order.

2. Results

2.1. Simple reaction time task

Two AD patients were excluded from these analyses due to their failure to respond on at least 50–60% of the target trials. Thus, the following analyses are based on data from 21 AD patients, 21 age-matched older adults, and 21 younger adults.

[2] In similar letter-matching tasks, an additional high-acuity, central discrimination task has been used to insure and monitor fixation (e.g., Belger & Banich, 1992). We opted against this strategy for several reasons. First, the same results (i.e., shift in bihemispheric advantage with increasing task demands) are typically observed in lateralized matching experiments even without this fixation procedure (Reuter-Lorenz et al., 1999; Weissman & Banich, 1999, 2000). Second, this procedure would introduce a dual-task demand that would differentially disadvantage the three participant groups, and complicate the interpretation of our results. Third, the use of bilateral displays on all trials together with a fixation point makes it highly unlikely that saccade initiation times will be faster than the 200 ms exposure duration (Trappenberg, Dorris, Munoz, & Klein, 2001) especially for the older participants whose saccadic reaction times are likely to exceed this value even under viewing conditions intended to optimize speeded oculomotor responses (i.e., sudden high luminance onsets in dark adapted observers in a darkened environment without a visual fixation point (Abel, Unverzagt, & Yee, 2002; Munoz, Broughton, Goldring, & Armstrong, 1998)).

Table 3
Average response times and S.D. (in ms) for older adults, Alzheimer's disease patients, and younger adults in the simple reaction time task under both crossed and uncrossed conditions for each hand, and the crossed–uncrossed difference scores for each group by hand

Group	Left hand						Right hand					
	LVF		RVF		CUD		LVF		RVF		CUD	
	M	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.
AD	396.35	55.55	396.94	63.72	.93	–	401.93	62.41	390.31	68.29	11.62	–
OA	352.01	75.47	353.36	74.19	1.35	–	350.01	76.74	342.94	68.90	7.07	–
YA	322.86	77.61	324.21	79.34	1.35	–	324.21	74.56	317.78	82.52	6.43	–

Note: AD, Alzheimer's disease patients; OA, older adults; YA, younger adults.

Response times faster than 200 ms were designated as outliers and excluded from the analyses. This amounted to less than 1% of the data for each group. RTs falling outside of 2.5 S.D. of the participant's mean score for each condition (left hand-LVF, left hand-RVF, right hand-LVF, and right hand-RVF) were then trimmed. This trimming procedure eliminated approximately 2% of the data for each group. Four means were then calculated based on the remaining data set: left hand-LVF, left hand-RVF, right hand-LVF, and right hand-RVF.

2.1.1. Reaction time

The RT data (see Table 3) were analyzed using a three-way analysis of variance with group (AD, OA, YA) as a between-subjects factor, and condition (crossed, uncrossed) and hand (left, right) as within-subject factors. AD patients were significantly slower than the older adults and younger adults, $F(2, 60) = 5.86$, $p < .005$. There was also a main effect for condition, such that the uncrossed condition was performed overall with greater speed than the crossed condition, $F(2, 60) = 14.78$, $p < .0005$. The marginally significant interaction of hand and condition ($F(2, 60) = 4.00$, $p < .06$) indicates that the main effect for condition was driven primarily by the right hand. There were no other main effects or interactions. To further explore this hand effect, left and right hand CUD scores were calculated for each subject in each group and the resulting average CUDs were compared to zero via a one-tailed *t*-test. Only the right hand CUDs differed from significantly from zero ($p < .002$). Finally, the above ANOVA was repeated using the medians of each condition for each subject and the same results emerged. Here, we report only the means in order to be consistent with our previous published work using this task, and because of bias that potentially affects medians when an unequal number of trials contribute to these estimates due to differential errors rates as is clearly the case in the present data set (see Miller, 1988).

2.1.2. Accuracy

The accuracy data (percent hits, see Table 4) were also analyzed using a three-way ANOVA with group (AD, OA, YA) as a between-subjects factor, and condition (crossed, uncrossed) and hand (left, right) as within-subject factors. AD patients had a significantly lower percentage of hits than the older adults and younger adults who did not differ, $F(2, 60) = 12.16$, $p < .0005$. The only other effect was a group by condition interaction, $F(2, 60) = 4.19$, $p < .05$, such that AD patients and OA demonstrated a minimal and nonsignificant uncrossed advantage but did not differ from each other, whereas the younger adults showed a nonsignificant difference in the opposite direction. Indeed, in a separate ANOVA comparing only the AD and OA groups there was no hint of an interaction with group indicating the equivalent crossed–uncrossed difference in these two groups, $F(1, 40) = 2.12$, $p > .15$. Finally, whereas responses on catch trials were rare for all three groups, AD patients made significantly more false alarms than the other two groups, $F(2, 60) = 4.58$, $p < .02$ (AD: $M = 1.17\%$; OA: $M = 0.42\%$; YA: $M = 0.31\%$).

2.2. Letter-matching task

For all participants *d*-prime scores were calculated and used as an exclusion criterion. *d*-Prime has the advantage of measuring a participant's ability to discriminate matches from non-matches independent of a participant's bias to report whether or not a match was present. Participants were excluded from subsequent analyses if they had a *d*-prime

Table 4
Average accuracy and S.D. for older adults, Alzheimer's disease patients, and younger adults in the simple reaction time task under both crossed and uncrossed conditions for each hand, and the crossed–uncrossed difference scores for each group by hand

Group	Left hand						Right hand					
	LVF		RVF		CUD		LVF		RVF		CUD	
	M	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.
AD	90.62	13.18	91.59	9.83	.97	–	90.50	13.03	93.91	5.82	−3.41	–
OA	98.76	1.70	98.81	1.89	.05	–	98.56	1.96	99.04	1.53	−.48	–
YA	98.65	1.73	99.26	1.17	.61	–	99.00	1.28	98.45	3.06	.55	–

Note: AD, Alzheimer's disease patients; OA, older adults; YA, younger adults.

Table 5
Average response times and S.D. (in milliseconds) for older adults, Alzheimer's disease patients, and younger adults in each letter-matching task under within-hemisphere and across-hemisphere conditions, and the average of these conditions

	Three-item physical identity		Three-item name identity	
	Mean	S.D.	Mean	S.D.
Older adults				
Within-hemisphere	596.78	74.20	845.86	172.18
Across-hemisphere	662.11	113.28	767.81	138.66
Average	629.45	93.74	806.84	155.42
Alzheimer's patients				
Within-hemisphere	665.28	154.89	913.55	184.42
Across-hemisphere	702.15	128.14	866.87	191.83
Average	683.72	141.52	890.21	188.13
Younger adults				
Within-hemisphere	507.74	48.66	693.88	94.11
Across-hemisphere	524.95	41.83	645.88	76.60
Average	516.35	45.25	669.88	85.36

score lower than 0.5 on either task.[3] Five AD patients were excluded for this reason. Thus, the following analyses were conducted on 18 AD patients, 18 age-matched older adults, and 18 younger adults. The AD patients and the older adults were once again matched for gender, age, and level of education.

In order to eliminate outliers and reduce the skew of the RT distributions the following trimming procedure was used. First, response times faster than 200 ms were designated as outliers and removed, amounting to be less than 1% of the data for each group. For each participant an overall average and standard deviation were then calculated for each task. Scores falling outside a 2.5 standard deviation window were then eliminated (we cut approximately 2% of all responses).

Separate repeated-measures analyses of variance were computed for the mean latency and accuracy data with the between-subjects factor of group (AD, OA, YA) and the two within-subject factors of task (3-PI, 3-NI) and trial condition (within-hemisphere, across-hemisphere). Again, an analysis of the reaction time medians for all conditions was also conducted and produced the identical pattern of results. For the reasons explained above, we report only the means. Note that the accuracy analyses are based on match trials only, because non-match trials cannot be classified as within-hemisphere or across-hemisphere.

2.2.1. Reaction time

The mean RTs and S.D. are reported in Table 5. The ANOVA conducted on these RT data revealed a main effect for group, $F(2, 51) = 16.29$, $p < .001$. Paired comparisons indicated that the younger adults ($M = 593.11$, S.D. = 104.28) were faster than the older adults ($M = 718.14$, S.D. = 160.24) and the Alzheimer's patients ($M = 786.96$, S.D. = 195.96), who were significantly slower than both groups. The ANOVA also revealed a main effect for task, $F(2, 51) = 183.77$, $p < .001$, indicating that the 3-PI task ($M = 609.83$, S.D. = 124.95) was performed more quickly than the 3-NI task ($M = 788.98$, S.D. = 176.22). In addition, this analysis revealed a task by condition interaction, $F(2, 51) = 73.78$, $p < .001$, making evident a within-hemisphere advantage on the 3-PI task in contrast to an across-hemisphere advantage on the 3-NI task across all groups. This interaction was further qualified by a task by condition by group interaction, $F(2, 51) = 4.33$, $p < .05$. Interpreting this interaction is aided by considering the difference between the across-hemisphere and the within-hemisphere RTs. We refer to this as the advantage score. When the average within-hemisphere RT is subtracted from the average across-hemisphere RT, a positive score indicates a within-hemisphere advantage and a negative score indicates an across-hemisphere advantage. These advantage scores were submitted to a repeated-measures ANOVA, which revealed a task main effect ($F(1, 51) = 73.78$, $p < .0005$) as well as a task by group interaction ($F(2, 51) = 4.33$, $p < .05$). As can be seen in Fig. 2, the older adults show the strongest within-hemisphere advantage on the PI task, and the strongest across-hemisphere advantage on the NI task compared to the other groups. This pattern of an enhanced bihemispheric advantage for normal aging ($p < .08$, one-tailed) replicates our previous results using a similar task. The younger adults show the weakest within-hemisphere advantage on the PI task, and the weakest across-hemisphere advantage on the NI task. The AD patients fall between these two groups. However, the critical shift from a relative within-hemisphere advantage on the 3-PI task to an across-hemisphere advantage on the 3-NI task was evident in all three groups.

Finally, we tested the possibility of greater right than left hemisphere aging (see Reuter-Lorenz, 2000 for a review) by examining only the within-hemisphere match trials. A repeated-measures ANOVA with group, task, and hemisphere (left or right) as factors revealed no significant main effect for

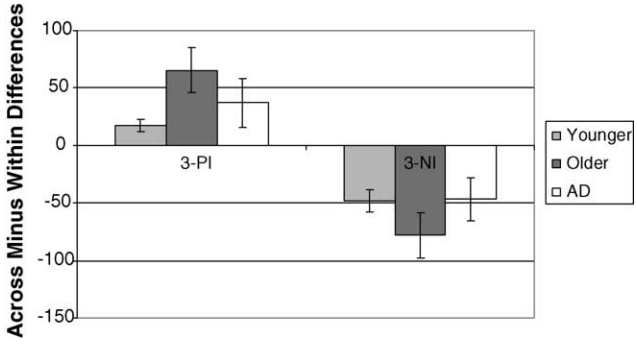

Fig. 2. Across-hemisphere minus within-hemisphere reaction time differences for each letter-matching task with standard error bars.

[3] Using a more lenient or a more stringent criterion does not change the pattern of results. We conducted the analyses on the entire sample of 23 participants per group, as well as on a more restricted sample of 16 participants per group (*d*-prime scores of 1.0 on each task), and the patterns do not change.

Table 6
Average percent correct and S.D. for older adults, Alzheimer's disease patients, and younger adults in each letter-matching task under within-hemisphere and across-hemisphere conditions, and the average of these conditions

	Three-item physical identity		Three-item name identity	
	Mean	S.D.	Mean	S.D.
Older adults				
Within-hemisphere	90.56	11.69	80.33	14.76
Across-hemisphere	87.11	12.32	87.38	11.07
Average	88.84	12.01	83.86	12.92
Alzheimer's patients				
Within-hemisphere	70.58	26.91	56.39	24.66
Across-hemisphere	67.19	25.97	63.33	23.41
Average	68.89	26.44	59.86	24.04
Younger adults				
Within-hemisphere	98.89	2.05	96.81	4.50
Across-hemisphere	99.08	2.05	98.97	2.46
Average	98.99	2.05	97.89	3.48

hemisphere or interactions of hemisphere with group and/or task (all $p > .1$).

2.2.2. Accuracy

The accuracy data are presented in Table 6. A significant main effect for group emerged in the analysis of variance for accuracy, $F(2, 51) = 30.57$, $p < .001$. AD patients were less accurate ($M = 64.38$, S.D. = 25.56) than the older adults ($M = 86.34$, S.D. = 12.96) and the younger adults ($M = 98.44$, S.D. = 3.06). Consistent with the RT data, a significant main effect for task, $F(2, 51) = 15.19$, $p < .001$, was also present in accuracy indicating better performance in the 3-PI task ($M = 85.57$, S.D. = 20.86) than in the 3-NI task ($M = 80.53$, S.D. = 22.45). As with the RT data, a task by condition interaction emerged, $F(2, 51) = 35.85$, $p < .001$, indicating a within-hemisphere advantage on the 3-PI task and an across-hemisphere advantage on the 3-NI task. A task by condition by group interaction also emerged, $F(2, 51) = 4.92$, $p < .05$. As with the RT data, we calculated advantage scores by subtracting within-hemisphere accuracy from across-hemisphere accuracy (positive values indicate across-hemisphere advantages and negative values indicate within-hemisphere advantages). For these scores, see Fig. 3. These advantage scores were submitted to a repeated measures ANOVA that resulted in a task main effect ($F(1, 51) = 35.85$, $p < .0005$) and a task by group interaction ($F(2, 51) = 4.92$, $p < .05$). The means represented in Fig. 3 indicate that all groups showed a stronger across-hemisphere advantage for the NI task than for the PI task. This was particularly true for the OA and AD groups, who show very similar patterns. The YA group shows a less robust advantage shift from one task to another, but this is likely a ceiling effect due to the high accuracy of this group on both tasks.

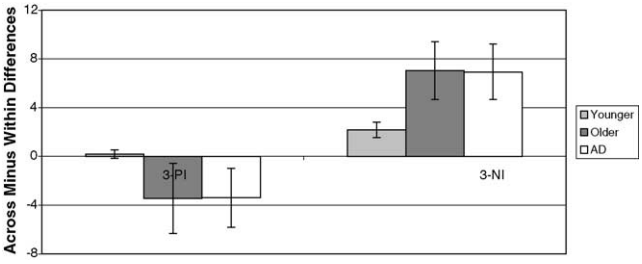

Fig. 3. Across-hemisphere minus within-hemisphere accuracy differences for each letter-matching task with standard error bars.

We again examined the effect of left versus right hemisphere presentation on performance in the within-hemisphere trials of both tasks. These analyses once again revealed no main effect for hemisphere or interactions of hemisphere with task and/or group (all $p > .15$).

3. General discussion

Across all measures, both neuropsychological and experimental, AD patients performed more poorly than age and education matched, healthy, older adults. Response times were universally slower, and response accuracy universally lower for AD patients than their healthy counterparts. Nonetheless, the impairments associated with across-hemisphere and within-hemisphere task conditions are approximately equivalent in the AD group. The results show no evidence to indicate a disproportional impairment on conditions requiring interhemispheric as opposed to intrahemispheric processing.

Several aspects of these results require comment, beginning with the simple RT task. Previous work from our laboratory using this same task revealed longer crossed than uncrossed RTs in older than younger adults (Reuter-Lorenz & Stanczak, 2000), an effect also reported by Jeeves and Moes (1996). In our prior report, this age difference was primarily due to performance of the right hand, where a 13-ms advantage emerged for the uncrossed condition in older adults. The left hand showed an effect due to crossing for the older group, and for younger adults, neither hand showed an effect, with an average crossed–uncrossed difference of 1.5 ms. In the present data set the right hand also appears more sensitive to crossing than the left hand; however, both the younger and older adults show a 7 ms advantage for the uncrossed condition. The AD patients have an insignificantly larger 11 ms advantage. So, in comparison to our previous work, the younger adults show a larger crossed–uncrossed difference, the older adults show a smaller difference, and the AD group shows an effect that is statistically identical to these other groups and commensurate with healthy older adults reported previously. Furthermore, the present results replicate in a larger sample the effects from a similar task reported by Lakmache et al. (1998) where the AD patients and healthy controls showed similar increases in RT due to crossed visual field stimulation. Taken together these results further reveal the variability inherent in the Poffenberger task and suggest that future work should utilize many more than the present 600 observations in order for the CUD (see, e.g., Iacoboni & Zaidel, 2000) to

serve as a reliable measure of normal or pathological age-related changes in callosal function.

Our finding of a larger right hand than left hand CUD is opposite to the hand effect that is typically found with this task (e.g., Braun et al., 2003; Marzi, Bisiacchi, & Nicoletti, 1991). One difference in our methodology that could have contributed to this pattern is our use of 14% catch trials during which responses were withheld. Because right inferior frontal regions seem to play a dominant role in response inhibition of this sort (e.g., Konishi et al., 1999; Rubia, Smith, Brammer, & Taylor, 2003), this demand could conceivably have altered the hemispheric requirements of the task, in addition to leading to slower responses overall. The important point however, is that like Lakmache et al., who did not use catch trials, we found no differences in interhemispheric efficiency between AD patients and age-matched controls.

The letter-matching task produced several interesting results, but not any clear indication of isolable interhemispheric deficits in AD. In fact, one of the most striking aspects of the present results is that AD patients show a reliable shift from a within-hemisphere to an across-hemisphere advantage due to increased letter-matching demands. That is, like healthy younger and older adults, the AD patients showed a within-hemisphere advantage when matching letters based on their physical identity and an across-hemisphere advantage when matching letters based on their name (i.e., cross-case matches).

Overall, we find that AD patients show the same patterns of performance as older adults, while being markedly slower and less accurate. Indeed, on a basic test of letter-matching, the AD group made over 30% errors on average. Such global performance decline could have numerous causes, including lower levels of overall arousal and impaired attention. The important outcome, however, is that the interhemispheric condition was not disproportionately impaired in this group, and moreover, that AD patients can gain a performance advantage from bihemispheric processing that resembles the levels found in the control groups.

Our results challenge the split-brain model of AD because we find no indication of a disproportional impairment in AD patients on task conditions that require callosally-mediated interhemispheric interactions. Consistent with the report by Lakmache et al. (1998), AD patients do not differ from their healthy age-matched counterparts on speeded simple RT measures of visuomotor interhemispheric transfer. However, unlike this earlier previous report, we also fail to find any indication of interhemispheric disconnection-like effects on visual matching tasks but instead we observe task-appropriate shifts indicative of interhemispheric cooperation and bihemispheric recruitment.

Two points are important to consider in attempting to reconcile the present results with those reported by Lakmache and colleagues. First, their visual matching tasks were comparatively simpler than those used in the present experiment, and accuracy was the only dependent measure they reported in detail. The ceiling level of performance of their control subjects precludes a comparison of within- and across-hemisphere conditions in this group thereby calling into question any conclusions about relative group differences in interhemispheric transfer efficiency in these tasks. Thus, the discrepancy between our results and theirs may be more apparent than real. Note that in the present study, when performance was below ceiling, the within-across hemisphere accuracy differences were evident and equivalent for the healthy older adult and AD groups, whereas the ceiling effect in the younger groups resulted in equivalent within- and across-hemisphere accuracy. Second, their strongest evidence for disproportional interhemispheric disconnection effects came from the tactile modality, which relies on the midbody of the callosum, a region that is anterior to the splenium. The visual tasks used in the present study are more sensitive to interactions between occipital areas via the splenium (e.g., Pollmann et al., 2003), although the Poffenberger includes multiple interhemispheric relays via anterior callosal regions as well. Nevertheless, it is possible that AD could have different effects on different cortical regions and on their intra and interhemispheric projections, which could, in turn, produce more pronounced interhemispheric disconnection deficits for some functions (i.e., tactile tasks) than for others. This possibility awaits future research.

In summary, the present data indicate obvious impairment in AD patients on both within- and across-hemisphere conditions compared to age-matched controls. It is important to bear in mind that the original proposal of a "disconnection syndrome" associated with AD was not restricted to claims about interhemispheric pathways but included a putative breakdown of intrahemispheric corticocortical connections as well (Delbeuck et al., 2003; Morris, 1996a; Morrison et al., 1986). In contrast, the split-brain corollary of the disconnection hypothesis requires selective interhemispheric deficits and is thus supported only when interhemispheric measures are inferior to intrahemispheric measures. To the extent that AD is associated with a commensurate breakdown of both intra and interhemispheric connectivity, the split-brain model of this disease is inappropriate. We note that our finding of equivalent inter and intrahemispheric declines is consistent with global disconnection, but not specifically diagnostic of it because other global neuropsychological processes (e.g., attentional impairment) could produce the general reduction in performance that we observed. The present neuropsychological evidence suggests that while a disconnection syndrome may be one of several viable accounts of AD performance, the split-brain model may not be, at least within the domain of visual processing.

While the present results challenge the split-brain model of AD, they highlight the importance of continued investigation of a disconnection basis for AD symptomatology. In particular, it will be crucial to obtain structural and functional measures of the corpus callosum and other white matter pathways using DTI, along with volumetric, functional imaging and behavioral measures in the same individuals. Through the combined application of multiple research

methodologies it will be possible to clarify the relationships between specific structural declines and their functional consequences.

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