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Interhemispheric disconnection syndrome in Alzheimer's disease

(corpus callosum/Alzheimer dementia/interhemispheric processing/sensory systems/motor system)

YAMINA LAKMACHE*, MARYSE LASSONDE*†, SERGE GAUTHIER‡, JEAN-YVES FRIGON*, AND FRANCO LEPORE*†

*Groupe de Recherche en Neuropsychologie Expérimentale, Département de Psychologie, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, PQ, Canada H3C 3J7; †Institut Universitaire de Gériatrie de Montreal, 4565 chemin Queen-Mary, Montréal, PQ, Canada H3W 1W5; and ‡McGill Center for Studies on Aging, 6825, Boulevard LaSalle, Verdun, PQ, Canada H4H 1R3

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ABSTRACT **It is commonly acknowledged that patients with Alzheimer's disease show memory and cognitive deficits that result from their cerebral histopathological abnormalities. We report new evidence showing that they also manifest deficits in interhemispheric integration of information, probably reflecting a corpus callosum dysfunction. Patients were given a battery of motor, somatosensory, and visual tests that had to be carried out by using either one or both hemispheres. Tasks were chosen such that subjects with Alzheimer's disease performed normally when using intrahemispheric processing. They, however, performed poorly when interhemispheric communication was required. This observation attests to the presence of a disconnection syndrome and suggests that these interhemispheric tasks can serve as diagnostic tools for the early assessment of their dementia.**

Alzheimer's dementia (ALZ) is especially well known for its deleterious effects on intellectual and memory functions (1, 2). Neuropathological studies have confirmed that these abnormal behavioral manifestations are related to the sites of the cerebral abnormalities associated with the dementia. In fact, anatomical anomalies (senile plaques, neurofibrillary tangles, granulovacuolar degeneration, and biochemical changes) are generally found in the hippocampus (3)—a structure involved in memory processes—and associative cortical areas (4–6)—regions considered essential for higher-level cognitive functioning. We report a new set of cognitive deficits compatible with a dysfunction of another major structure (7, 8), the corpus callosum (CC), whose principal function is to allow the exchange of information between the hemispheres. Results reported herein indicate that ALZ patients show an interhemispheric disconnection syndrome similar in nature to that demonstrated by split-brain subjects, i.e., patients whose CC was sectioned to alleviate intractable epilepsy (7, 8).

Disconnection symptoms may stem from the fact that anatomical abnormalities found in the cortex of ALZ patients affect mainly pyramidal neurons (6), from which originate callosal fibers. These neurons are also the principal recipients of input from the contralateral hemisphere (9, 10). The distribution of abnormalities is thus coincidental with neurons that form the CC. This is confirmed by findings that indicate that there is degeneration of this interhemispheric pathway in ALZ (11–13). Although this could be the manifestation of a secondary process caused by the degeneration of their cells of origin, it could also constitute part of the physiopathological process. Indeed, recent studies have suggested that cognitive decline in aging monkeys, rather than being related to a loss of cortical neurons or synapses, might be a consequence of the reduction in white matter, including the CC (14).

Callosal disconnection manifests itself through specific symptoms whose gravity depends not only on the function tested but also on the portion of transected CC. Thus, lesioning the genu (anterior portion) leads to bimanual coordination deficits (15), sectioning the body (middle part) results in somatosensory problems (16, 17), and ablating the splenium (caudal portion), disrupts visual integration (8, 18, 19). Moreover, given that linguistic functions are mainly situated in the left hemisphere, visual or tactile stimuli presented to the left side of the body and hence, the right hemisphere, will not be verbally encoded if the relevant portion of CC is missing (18, 19).

We carried out an extensive investigation to determine whether ALZ patients manifest any of the disconnection symptoms generally attributed to callosal pathology. The selected tests were highly sensitive to the effects of interhemispheric disconnection but could be carried out normally by ALZ patients using intrahemispheric processing. They were organized so as to sample performance along the entire antero-posterior axis of the callosum. Furthermore, most of them required comparable intra- and interhemispheric cognitive demands.

Procedures and Results. Ten probable ALZ patients were selected on the basis of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association diagnostic criteria (20). They were classified as belonging to stages III (mild dementia) or IV (moderate dementia) according to the Reisberg Global Evaluation Scale (21). All patients had an ischemic score below 4 on the Hachinski Scale (22). They were recruited from patients at the McGill Center for Studies on Aging. The ALZ patients were compared with 10 control subjects chosen from a group of volunteers who responded to an advertisement placed on the bulletin board of residences for elderly people. To be selected, the control subjects had to have a normal score on the Mini Mental Status Examination (23). The ALZ patients and control subjects were matched on age (average, 70.35 yr), gender (six women, four men), education (average, 10.1 yr), manual dominance (right-handed), and general well-being, as measured by the Halls questionnaire (24). Subjects gave their informed, written consent to participate. The protocol was approved by the ethics committee of the Université de Montréal.

The 10-hour test battery was administered during three separate sessions. Preliminary tests assessing the integrity of vision, somesthesis, and motor functions were given during the first session. The experimental tests were completed during the following sessions to evaluate processing either by each hemisphere (intrahemispheric condition: INTRA) or the combined activation of both via the CC (interhemispheric condition: INTER). In most tasks, INTRA and INTER trials were interspersed. Numerous pauses were included to avoid fatigue.

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Abbreviations: CC, corpus callosum; ALZ, Alzheimer; INTER, interhemispheric condition; INTRA, intrahemispheric condition.

Statistical analyses were carried out by using ANOVAs and, when required, tests of simple effects and post hoc Newman–Keuls analyses were also performed.

Tests Specific to the Anterior CC or Genu (Joining the Frontal Lobes, Including the Motor Areas). A standardized preliminary test involving manual dexterity, the Purdue Pegboard Test (25), was administered to all subjects. To complete this test, subjects must fill-in as quickly as possible two parallel rows of holes with small pegs, first with one hand and then with both hands simultaneously. The results showed no differences between control subjects and ALZ patients, attesting to their ability to carry out fine motor activities, even under time constraints.

The experimental task, a computer adaptation of the Preilowski test (15), examined bimanual and hence, interhemispheric coordination. Subjects were required to draw on an X-Y plotter a line that matched as closely as possible a sample line (Fig. 1*C*). Subjects controlled the *x* axis by rotating one knob with the index and thumb of one hand and the *y* axis with those of the other hand. The relative speed at which each knob was turned determined the angle and position of the line with respect to the sample line. The latter subtended one of three angles from horizontal (±27° ±45° or ± 60°; see Fig. 1*B*) and originated either from the bottom left-hand corner or the bottom right-hand corner. Deviations were computed by adding the length (in mm) of virtual lines drawn orthogonal to the sample line and originating at each pixel making up this line. Deviations and execution time were computer-monitored. After initial practice, five trials were given for each of the six lines. Subjects were told to work as fast as possible but execution time was unlimited. During these trials, both groups performed equally well and required a similar amount of time (mean execution time: ALZ patients, 91, 27 s; control subjects, 92, 23 s). Subjects were subsequently asked to draw each of the six lines as quickly as possible, but they were told that they would be stopped after 30 s. In this case, ALZ patients made significantly more errors than control subjects (see asterisk Fig. 1*A*; $P < 0.05$). As illustrated in Fig. 1, ALZ patients often could either not finish the task (see traces 4 to 6), or showed erratic performance (traces 7 to 9) when compared with control subjects (traces 1 to 3).

Tests Specific to the Trunk of the CC (Connecting Parietal and Temporal Regions). The Finger Identification test (25) was carried out to screen out subjects having possible problems of distal somesthesis. In this test, one of the fingers was touched, out of sight, with the tip of a pencil and subjects reported which finger was involved. All subjects showed normal performance.

Four tasks were administered to assess intra- and interhemispheric processing. The first was a Tactile Localization Task (16, 17). Subjects were asked to keep their palms up and after one or two fingers were lightly touched, out of sight, they had to indicate with the thumb where the stimulus had been applied. Subjects responded by using either the stimulated (INTRA) or nonstimulated (INTER) hand. ALZ patients correctly localized the source of the stimulation when stimuli and responses were limited to the same side. However, they showed a deficit in cross-localization whether the task involved the stimulation of one [$F(1, 9)$ 8,22; $P = 0.02$] or two fingers [$F(1, 9)$ 5,92; $P = 0.04$].

The second task consisted of a comparison between pairs of common three-dimensional shapes (star, square, etc. measuring 5 × 5 × 2 cm) or textured surfaces (sandpaper squares (5 × 5 cm) varying in grain from 24 to 280) (26). Sixty paired comparisons were carried out in each case. In the INTRA and INTER conditions, the pairs of stimuli were touched with one or two hands, respectively (Fig. 2*C*). Whereas the INTER condition required a simultaneous comparison of the discriminanda, the INTRA condition involved their successive manipulation, thus adding a memory component. The stimuli were presented out of view with a Lafayette Inter-Sensory Transfer Stimulator equipped with a timer for recording response times. The stimuli were fastened on the rotating drums. A photocell mounted to the left and right of the opening on the inside of the front panel activated a clock when the subject's hand(s) touched the stimuli. The clock stopped when subjects responded into a microphone connected to an electronic voice relay. Subjects were asked to judge as quickly as possible whether the stimuli were the same or different.

Results showed that ALZ patients and control subjects performed equally well when the paired shapes were examined with either the left or the right hand (Fig. 2*A*). The ALZ patients' performance, however, dropped significantly when the comparisons were carried out intermanually, in spite of the fact that this condition, unlike the intramanual one, comprised no memory component [$F(1, 9)$ 11,43; $P < 0.01$] (see asterisk, Fig. 2*A*). This pattern was found for both accuracy and response time. As for texture discrimination, both groups performed better in the intra- than in the interhemispheric condition [$F(1, 9)$ 26,652; $P < 0.001$] (see asterisks, Fig. 2). However, a significant group ×condition interaction was found, indicating that the drop of performance was more

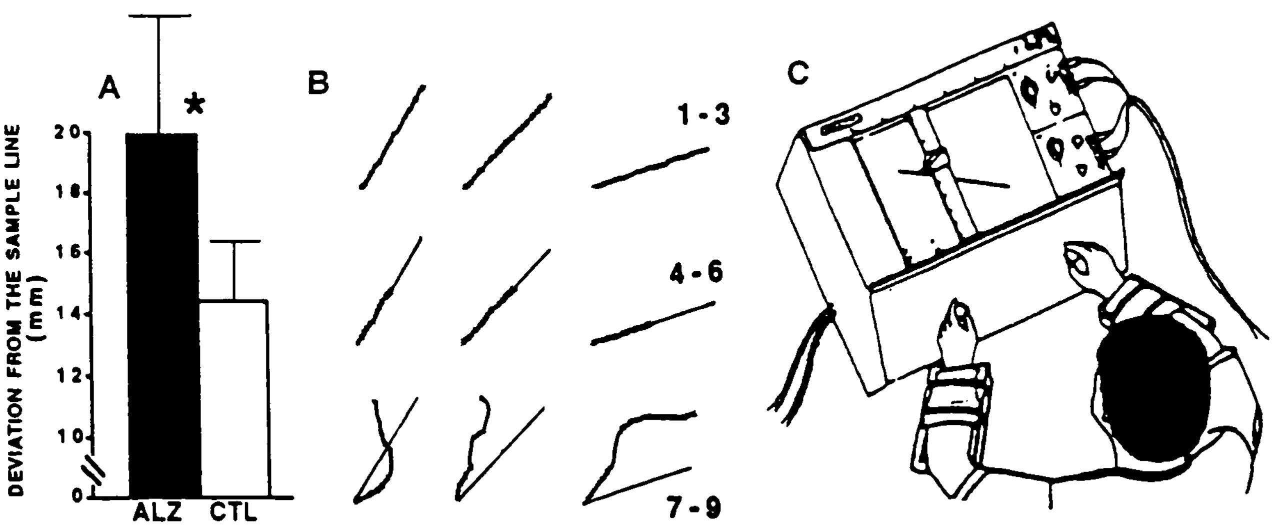

FIG. 1. (*A*) Average deviations from the sample line obtained by ALZ patients (ALZ) and the control subjects (CTL). (*B*) Examples of the performance of control subjects (1 to 3) and ALZ patients (4 to 9) when the task had to be carried out within 30 s. (*C*) Experimental set-up (a computer controlled *x-y* plotter) used to evaluate bimanual coordination.

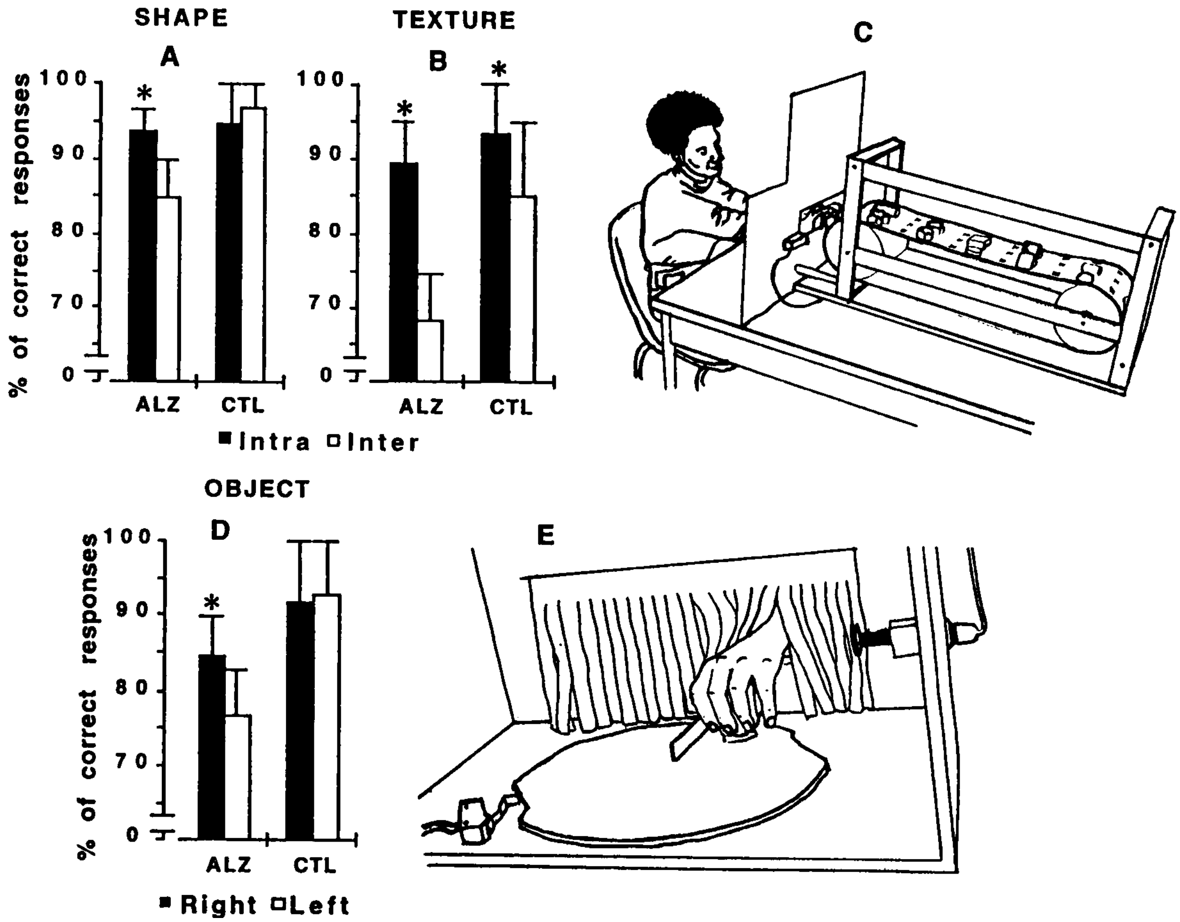

FIG. 2. (*A*) Intra- and interhemispheric performances of ALZ patients (ALZ) and the control subjects (CTL) for tactile shape discrimination. (*B*) Intra- and interhemispheric performances in the tactile discrimination of textured surfaces. (*C*) Experimental set-up used to test tactile discrimination of shapes and textured surfaces. (*D*) Performance of ALZ patients and control subjects in the identification task when objects were palpated either by the right hand or the left hand. (*E*) Experimental set-up to test object identification.

pronounced for ALZ patients in the interhemispheric condition [F (1, 9) 20,09; $P < 0.001$]. In fact, ALZ patients performed close to chance level in this condition.

The third task (Fig. 2*E*) required subjects to name 60 familiar objects (comb, spoon, etc) fastened to an electronically-controlled motorized rotating wheel. Response times were measured in the same manner as in the tactile discrimination task. Subjects were asked to palpate the objects out of sight and to name them as quickly as possible (27). Results indicated that the two groups were equally able to name the objects manipulated by the right hand (projecting to the left, language-hemisphere). By contrast, as illustrated in Fig. 2*D*, ALZ patients showed a significantly poorer performance than control subjects when they had to name objects handled by the left hand (projecting to the right hemisphere) [$F(1, 9)$ 5,44; $P <$ 0.05].

Somesthetic interhemispheric transmission times were assessed in the fourth task (28, 29). This task is based on Poffenberger's paradigm for the visual system (30, 31). Subjects were required to press a key with the index finger as soon as they felt a puff of air presented in the central palmar area. A computer-controlled electronic air valve directed the puff to one of the hands. Reaction times were computed for the hand ipsilateral (INTRA) or contralateral (INTER) to the puff. Interhemispheric transmission times were derived by subtracting the INTRA and INTER response times. As expected, reaction times were longer in the INTER than in the INTRA condition for both groups (mean ipsilateral reaction times, ALZ patients: 755, 6 ms, control subjects: 616, 68 ms; mean contralateral reaction times, ALZ patients: 810, 3 ms, control subjects: 639, 7 ms) [$F(1, 9)$ 7,02; $P < 0.03$]. The ANOVA also revealed that ALZ patients had longer reaction times than control subjects in all conditions. However, the significant interaction between groups and conditions indicated that this effect was more pronounced when the task required the coactivation of the two hemispheres, where the stimulus projected to one hemisphere and the response originated in the other (Interhemispheric transmission times for ALZ patients: 54, 5 ms; interhemispheric transmission times for control subjects: 23,03 ms; {F (1, 9) 8,88; $P < 0.02$}).

Tests Specific to Posterior CC or Splenium (Connecting the Visual Areas). The preliminary tasks included identification of single and double visual stimuli (Visual Field Confrontation; ref. 25) and the assessment of visual acuity (Rosenbaum Pocket Vision Screener). Results indicated that all subjects had intact visual fields and normal or corrected vision.

Two tasks were used to investigate visual function. As shown in Fig. 3*C*, pairs of visual stimuli (letters or color plates) were placed either on the same side (INTRA presentation) or on opposites sides (INTER presentation) of midline. The stimuli were manually placed and the fixation point was a red spot light-emitting diode (LED). The room was kept totally dark except during the stimulus placement at which time a curtain blocked the subject's view of the stimuli. Ocular movements were recorded using three electrodes (Beckman) connected to an oculograph (Grass model 79D). Trials were automatically rejected whenever an eye movement greater than 2° was detected during the presentation of a stimulus, in which case it was repeated at the end of each block. When the subjects' eyes fixated the central LED, the stimuli were briefly illumi-

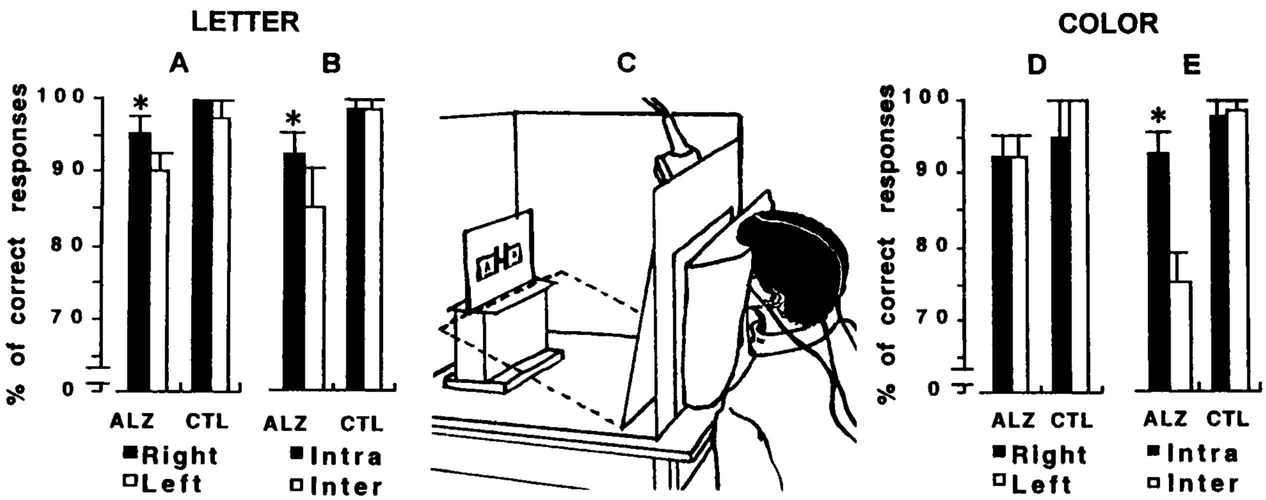

FIG. 3. Performance of the ALZ patients (ALZ) and the controls subjects (CTL) in the letter and color discrimination tasks. Results obtained when the letters were presented in each hemifield (*A*) or when they were reorganized so as to show intra- vs. interhemispheric performance (*B*). Experimental apparatus (*C*) used to assess intra- and interhemispheric comparisons of letters and colors. Results obtained when color plates were presented within each hemifield (*D*) or when rearranged to show intra- vs. interhemispheric performance (*E*).

nated (150 ms) by a stroboscopic light mounted on top of the apparatus. Both letters or color plates (1.5° × 1.5°) were presented at 3° eccentricity (32). Subjects had to state as quickly as possible if the stimuli were the same or different.

In the first condition, which is considered a visual verbal task, subjects had to compare two letters presented one on top of the other in the right or left visual hemifield (INTRA) or on either side of the fixation point (INTER). In the INTER condition, 24 pairs of letters were presented in each hemifield. The INTRA condition included 48 trials, namely, 24 for each hemifield. To ascertain that subjects based their discrimination upon verbal rather than on shape identity, upper- and lower-case letters had to be compared.

The same paradigm was used in a second visual discrimination task, where subjects had to compare different color plates. The two color plates were presented either in one hemifield (n = 20 for each hemifield, INTRA) or separate hemifields (n = 20, INTER).

Results confirmed in both cases the working hypothesis. Thus, in the first task, control subjects showed no differences in performance when the letters were presented in the right or left hemifield. ALZ patients also performed well when the pairs of letters were presented in the right hemifield (left hemisphere) but they showed a significant decline in performance (P = 0.05) when the letters were presented in the left hemifield (right hemisphere). Moreover, whereas the control subjects' performance was identical in the intra- and interhemispheric conditions, ALZ patients showed a further reduction in performance in the latter condition (P = 0.05; see Figs. 3 *A* and *B*). When pairs of color plates were presented within one hemifield, no differences in performance were found between the right and left hemifield for both groups. Similarly, control subjects did not show any differences in performance when the stimuli appeared in each hemifield. By contrast, ALZ patients showed a reduced performance when the comparisons were carried out interhemispherically (P = 0.01). This is demonstrated in Figs. 3 *D* and *E*.

Visual interhemispheric transmission times (30, 31, 33), similar to the somesthetic interhemispheric transmission times described above, were also examined. In this task, the stimulus consisted of a flashing spot of light emitted from a red LED, presented at 10° eccentricity on either side of a central fixation point. Eye movements were controlled electrophysiologically as described above. One hundred presentations in each condition (the stimulus and response involved either the same or opposite hemispheres) were used.

Results indicated that for both groups, reaction times were longer when the stimulus and response required the coactivation of the two hemispheres (ALZ patients = 452,55 ms vs. control subjects = 392,1 ms) than when the task was carried out intrahemispherically (ALZ patients = 432,65 ms vs. control subjects = 373,4 ms). However, no significant interaction was observed between groups and conditions, indicating that visual-interhemispheric transmission times were similar for both groups [ALZ patients: 20 ms; control subjects: 18, 70 ms, $F(1, 9)$ 0,03; P = 0.85].

DISCUSSION

When compared with appropriately matched controls, the results indicate that ALZ patients show few deficits for basic motor and sensory functions in the early stages of their disease. Thus, both groups showed normal visual acuity and intact visual fields as well as comparable tactile sensitivity for each hand and fine uni- and bimanual motor control. These results correlate well with neuropathological studies showing that the primary motor and sensory areas are only affected late in the disease process (5, 6, 34, 35). A different pattern of results was observed when higher functions involved interhemispheric integration.

For motor functions, ALZ patients, like anterior callosotomized patients (15), showed deficits on tasks requiring bimanual/interhemispheric coordination. Their performance during the time-limited trials was abnormal, showing that interhemispheric communication was inadequate. Alternately, it could be argued that, because of limitations in cognitive resources (36), ALZ patients showed difficulties in performing this task because it required a certain amount of divided attention. Although this argument might apply in part for this task, it cannot account for the findings obtained from testing interhemispheric communication within the somatosensory and visual systems. When asked to compare pairs of tactile or visual stimuli within one hemisphere, ALZ patients were as proficient as controls. Their deficits only emerged when the same comparisons were performed interhemispherically, clearly indicating the presence of a disconnection syndrome.

Tactuo-motor bihemispheric coordination, as indicated by reaction times (somesthetic interhemispheric transmission times), also showed that the interhemispheric route was slower in ALZ patients than in control subjects. Visual interhemispheric transmission times, on the other hand, did not appear to follow this pattern: both groups produced high interhemispheric transmission time values, possibly reflecting aging factors (37), but no significant differences were found in transmission times between ALZ patients and control subjects. This indicates that the neuropathological process in ALZ has a different time course for the various sensory areas. Such heterogeneity across systems and within different levels of the same system is quite common for this disease. Thus, a dissociation is found between more primitive sensory and more cognitive processes within the visual modality. Furthermore, the finding that, unlike vision, somesthetic interhemispheric transmission times were deficient supports the suggestion that the occipital regions, especially the primary visual areas, are affected at a later stage (5, 38) than the parietal region underlying the somatosensory system (6, 35, 38). Nonetheless, this series of experiments does establish that specific interhemispheric motor and visual abilities are impaired even at the intermediate stages of ALZ, in spite of histopathological research showing that the motor and visual cortices are only affected late in the disease's progression (5, 38).

ALZ patients, like control subjects, do not show impairments in the intrahemispheric condition for most tasks. However, for the object naming and letter discrimination tasks, where they are asked to verbalize the material presented in the left hemibody or hemifield (projecting to the right hemisphere), ALZ patients do show a deficit. This difference cannot be ascribed to subtle right-hemispace neglect because ALZ patients showed no difficulties discriminating shapes and colors presented to the left hand and hemifield, respectively. Rather, this lateralized deficit appears to be limited to verbal analysis, arguing in favor of our hypothesis. The verbal identification of stimuli projecting to the right hemisphere must necessarily be transmitted via the CC to be processed in the left hemisphere (7, 8, 18, 19). The absence of naming deficits when the stimuli were presented to the right hand and hemifield (left hemisphere) and their presence when they project to the right hemisphere constitute convincing proof of impaired transfer.

The ensemble of results shows that ALZ patients exhibit callosal deficits that resemble those observed in split-brain subjects. The robustness and generality of the results therefore suggest that an hemispheric disconnection syndrome should be taken into consideration, along with memory and cognitive abilities, when assessing residual functions in ALZ patients. The systematic use of tasks designed to measure interhemispheric integration may constitute an additional powerful tool in the early diagnosis of ALZ dementia.

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