Callosal and cortical contribution to procedural learning

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Summary
Acallosal and callosotomized subjects usually show impairments on tasks requiring bilateral interdependent motor control. However, few studies have assessed the ability of these subjects to learn a skill that requires the simultaneous contribution of each hemisphere in its acquisition. The present study examined whether acallosal and callosotomized subjects could learn a visuomotor skill that involved a motor control from either both or a single hemisphere. Eleven adult patients, six acallosal and five callosotomized, participated in this study. Seven of these patients had epileptic foci located in the frontal and/or temporal areas and one of the acallosal patients showed bilateral prefrontal atrophy following surgical removal of an orbitofrontal cyst. The performance of the experimental subjects was compared with that of 11 matched control subjects, on a modified version of a serial reaction time task developed by Nissen and Bullemer (Cogn Psychol 1987; 19: 1–32). This skill acquisition task involved bimanual or unimanual key-pressing responses to a sequence of 10 visual stimuli that was repeated 160 times. A declarative memory task was then performed to assess explicit knowledge of the sequence. None of the experimental subjects learned the task in the bimanual condition. Patients with frontal epileptic foci or orbitofrontal damage also failed to learn the task in the unimanual condition when they were using the hand contralateral to the damaged hemisphere. All other subjects, including the acallosal and callosotomized patients with temporal foci, learned the visuomotor skill as well as their controls in the unimanual condition. In spite of the absence of transfer and interhemispheric integration of procedural learning, some of the acallosal and callosotomized patients were able to learn the sequence explicitly. These findings indicate that the corpus callosum and the frontal cortical areas are important for procedural learning of a visuomotor skill. They also confirm the dissociation described by Squire (Science 1986; 232: 1612–9 and J Cogn Neurosci 1992; 4: 232–43) between the declarative and procedural memory systems and extend this dissociation to processes involving simultaneous bihemispheric co-operation.

Keywords: procedural memory; declarative memory; interhemispheric integration; callosal agenesis; callosotomy

Abbreviation: ANOVA = analysis of variance

Introduction
The corpus callosum links the two hemispheres and is responsible for interhemispheric integration and transfer of information. This structure can be divided in two principal parts: the anterior part (rostrum, genu and anterior body) which connects the frontal lobes, and the posterior part (posterior body, isthmus and splenium) which connects the temporal, parietal and occipital lobes (Pandya et al., 1971). The anterior part is involved in interhemispheric integration of motor information, whereas the posterior part is responsible for somaesthetic, auditory and visual integration (Pandya et al., 1971; Pandya and Seltzer, 1986).

Several studies have suggested that the anterior part of the corpus callosum is involved in bilateral motor co-ordination and in transfer of visuomotor tasks. Indeed, some deficits have been observed in acallosal subjects and anterior commissurotomy patients on tasks requiring interhemispheric integration of simultaneous, mutually adjusted movements of the upper limbs, in such manner that the movement of each limb requires continuous updating about the movement of the contralateral limb (Preilowski, 1972, 1975; Jeeves et al., 1988). Moreover, acallosal patients have been reported to show deficits on simple tasks of bimanual motor co-
ordination under speed stress (Jeeves, 1965, 1986; Chiarelli, 1980; Sauerwein et al., 1981) and they show impaired transfer of a unimanually learned tactuomotor skill such as stylus maze (Lehmann and Lampe, 1970; Ferriss and Dorsen, 1975; Gott and Saul, 1978; Jeeves, 1979) and formboard learning (Russell and Reitan, 1955; Ferriss and Dorsen, 1975; Reynolds and Jeeves, 1977; Jeeves, 1979). Deficits in transfer of unilateral visuomotor learning have also been observed (Lassonde et al., 1995).

So far, however, no studies have investigated the effect of callosal disconnection on the procedural learning of a visuomotor skill which requires the participation of both hemispheres in its acquisition. In fact, most studies that have focused on visuomotor learning involved bimanual motor control, and the few experiments that have assessed interhemispheric transfer of unimanual visuomotor learning, have employed tasks that were not automatized. The latter point is important in light of evidence from studies in split-brain cats indicating that overtraining may facilitate interhemispheric transfer in the absence of the corpus callosum (Lepore et al., 1982). The animals that were overtrained with one hemisphere on a visual pattern discrimination task showed a significant reduction in the time of acquisition when tested with the other (untrained) hemisphere. This pattern of performance was not observed in the normally trained split-brain animals.

Visuomotor learning is a subdivision of procedural memory which refers to the ability to acquire a motor skill or cognitive routine through practice (Cohen and Squire, 1980). This acquisition is expressed by a significant reduction of the reaction time or errors over trials. This type of memory can be dissociated from declarative or explicit memory which is the ability to store and consciously recall or recognize data in the form of words, visual pictures or events (Tulving, 1983; Squire, 1986). A dissociation between declarative memory and skill learning of a visuomotor task can be demonstrated in clinical populations. For instance, Alzheimer and amnesic patients are generally able to learn a pursuit-rotary task in procedural memory despite the fact that they are impaired in declarative memory for verbal recognition and delayed recall (Heindel et al., 1989). Similarly, patients with Korsakoff’s syndrome can learn new skills such as mirror reading, mirror drawing and pursuit rotor tracking although they are unable to recall the procedure (Corkin, 1965; Milner, 1965; Weiskrantz and Warrington, 1979). By contrast, Parkinson patients with bilateral striatal dysfunction fail to benefit from training even though they are able to verbalize the sequence used in the serial reaction time learning task (Doyon et al., 1997).

These various double dissociations indicate that memory is supported by two anatomically independent systems: a declarative memory system, which appears to be mediated by a corticorhinalthalamocortical neural circuit and whose anatomical substrate is relatively well known (Mishkin and Appenzeller, 1987; Squire, 1992) and a procedural memory system, whose neural substrate has yet to be fully described. Some studies have demonstrated that a variety of skills may depend upon the integrity of the corticostriatal pathway (Saint-Cyr et al., 1988; Heindel et al., 1989; 1991; Harrington et al., 1990; Corkin et al., 1992; Doyon et al., 1996). Others indicate that the cerebellum may play a role in this form of memory (Fiez et al., 1992; Pascual-Leone et al., 1993; Doyon et al., 1996; 1997; Gomez-Beldarrain et al., 1998).

The frontal lobes also seem to be implicated in skill acquisition, particularly skills requiring the learning of ordered sequences (Moscovitch et al., 1993), the programming of spatial learning (Vilkki and Holst, 1989) and the bimanual co-ordination of parallel movements (Pascual-Leone et al., 1994). Recent findings also point to an important role of prefrontal cortical structures in skill acquisition. Neuroimaging studies revealed activation of prefrontal cortex during procedural and implicit learning (e.g. Jenkins et al., 1997). Moreover, there is evidence that patients with post-traumatic and cerebrovascular lesions in the prefrontal cortex perform more poorly on serial reaction time tasks when tested with the hand contralateral to the lesion (Pascual-Leone et al., 1995; Gomez-Beldarrain et al., 1997). Similarly, Pascual-Leone et al. (Pascual-Leone et al., 1996) have reported that transcranial magnetic stimulation applied to the contralateral dorsolateral prefrontal cortex markedly impaired procedural implicit learning of the performing hand in the serial reaction time task.

Given that the corpus callosum links cortical areas of both hemispheres, including the dorsolateral frontal areas, the study of interhemispheric integration and transfer of a visuomotor procedural skill in patients, whose interhemispheric communication is interrupted, provides an interesting model for the investigation of the cortical systems involved in this kind of procedural memory. Furthermore, considering the importance of the corpus callosum in bimanual co-ordination, the specific role of this structure in motor learning also needs to be defined.

The serial reaction time paradigm developed by Nissen and Bullemer (Nissen and Bullemer, 1987) has been employed in many studies investigating procedural memory. In its standard form, this test requires the participation of both hemispheres in its acquisition since both hands are used to learn a given visuomotor sequence. Thus, the first aim of the present study was to assess whether split-brain and acallosal subjects were able to learn this procedural task in its standard, ‘interhemispheric’ mode of presentation. After adapting this paradigm to unilateral learning, the second aim of this investigation was to assess if callosally deprived subjects could transfer the skill acquired within one hemisphere to the other untrained hemisphere. In light of previous findings, it was expected that split-brain and acallosal subjects would be able to learn a visuomotor skill with one hemisphere but would show deficits when interhemispheric integration was necessary to accomplish the task. A corollary objective of this study was to assess if procedural and declarative memory processes could be dissociated in the intrahemispheric and interhemispheric conditions of the visuomotor task.
Table 1  Profile of subjects with callosal pathology (callosal agenesis or callosotomy)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age (years)</th>
<th>IQ</th>
<th>Handedness</th>
<th>Focal activity/ cortical damage</th>
<th>Extent of section</th>
<th>Age at surgery (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acallosal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.G.</td>
<td>M</td>
<td>27</td>
<td>77</td>
<td>Left</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.G.</td>
<td>F</td>
<td>34</td>
<td>78</td>
<td>Right</td>
<td>Generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.G.</td>
<td>F</td>
<td>35</td>
<td>84</td>
<td>Right</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Pe.</td>
<td>M</td>
<td>31</td>
<td>107</td>
<td>Right</td>
<td>Bifrontal atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Po.</td>
<td>M</td>
<td>28</td>
<td>75</td>
<td>Left</td>
<td>Generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.V.</td>
<td>M</td>
<td>35</td>
<td>100</td>
<td>Right</td>
<td>Left and right temporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Callosotomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.S.</td>
<td>F</td>
<td>26</td>
<td>99</td>
<td>Right</td>
<td>Left frontal, right frontotemporal</td>
<td>Anterior 4/5</td>
<td>17</td>
</tr>
<tr>
<td>A.N.</td>
<td>F</td>
<td>31</td>
<td>93</td>
<td>Right</td>
<td>Left temporal, right frontotemporal</td>
<td>Anterior 3/4</td>
<td>19</td>
</tr>
<tr>
<td>A.P.</td>
<td>M</td>
<td>28</td>
<td>87</td>
<td>Right</td>
<td>Left temporal, right frontotemporal</td>
<td>Anterior 3/4</td>
<td>26</td>
</tr>
<tr>
<td>D.D.</td>
<td>M</td>
<td>19</td>
<td>100</td>
<td>Right</td>
<td>Left and right temporal</td>
<td>Total</td>
<td>18, 19</td>
</tr>
<tr>
<td>S.D.</td>
<td>M</td>
<td>20</td>
<td>75</td>
<td>Right</td>
<td>Left frontal</td>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>

Method

Subjects

Two groups of patients participated in this experiment. The first group was composed of six acallosal subjects and the second group included five callosotomized patients, two with complete section and three with partial (anterior) section of the corpus callosum. One of the two totally callosotomized patients (S.D.) was operated on at an early age and has consistently shown an absence of disconnection symptoms similar to that observed in callosal agenesis (e.g., Lassonde et al., 1986, 1991). The neuropsychological profile of the acallosal and callosotomized subjects is provided in Table 1. The performance of the patients was compared to that of 11 neurologically intact control subjects, matched with the experimental subjects on the basis of IQ, age and handedness. The control subjects had an IQ ranging from the dull to the normal range. The relatively low IQ of some of these subjects was attributable to a family history of lower intellectual functioning in the absence of any neurological dysfunction. Informed written consent was obtained from all subjects. The study was approved by the ethics comittee of the Faculte des Arts et des Sciences, Universite de Montreal.

Acallosal subjects

M.G. is a 27-year-old, left-handed man. He is the youngest of a family of four children, three of whom have callosal agenesis. His complete history has been described elsewhere (see Sauerwein et al., 1981; Lassonde et al., 1988). He was first seen by a neurologist at the age of 4 years and 11 months because of prolonged enuresis, poor motor coordination and retarded language acquisition. A pneumoencephalogram revealed complete agenesis of the corpus callosum. The diagnosis was later confirmed by CT scan. M.G. has a global IQ of 77. At the time of the testing, M.G. was taking Prozac for depression.

L.G., a 34-year-old, right-handed woman, is the third child of the same family. Her detailed case history has been reported before (see Sauerwein et al., 1981; Lassonde et al., 1988). She was born prematurely in the seventh month of gestation. At the age of 3.5 years, she was hospitalized because of a light cranial trauma due to a fall. The EEG showed a slow dysrythmia without epileptic foci. At the age of 6 years, she was rehospitalized for elective mutism and ataxia. Callosal agenesis was then diagnosed by pneumoencephalography and has since been confirmed by CT scan and MRI. She has recently started to have epileptic seizures. The EEG shows a generalized pattern of electrical abnormalities. At the time of testing, she was taking anticonvulsant medication (carbamazepine). She continues to have one epileptic seizure a month but was reportedly seizure-free during the 3 weeks prior to the experimentation. L.G. has a full scale IQ of 78.

S.G., a 35-year-old, right-handed woman, is the oldest sister of M.G. and L.G. A CT scan performed at our request because of the high incidence of callosal agenesis in the family, revealed complete callosal agenesis. S.G. was asymptomatic except for slow acquisition of motor milestones and motor inco-ordination which is frequently observed in callosal agenesis during development. S.G. has a global IQ of 84.

S.Pe. is a 31-year-old, right-handed man. A basal transpalatal encephalocele was diagnosed at birth and was surgically removed through a bifrontal craniotomy at the age of 18 months. At that time, he was diagnosed as having complete agenesis of the corpus callosum. His MRI also shows agenesis of the anterior commissure and bilateral prefrontal atrophy related to surgical removal of the orbitofrontal cyst. S.Pe. obtains a global IQ of 107.

S.Po. is a 28-year-old, left-handed man. The patient reported that he had cerebral concussions during childhood but none of these events were registered in his medical file. He started to have absence seizures at age 23 years, following ventroperitoneal derivation for hydrocephaly. He has been seizure-free for 2 years and no longer requires medication. The MRI shows complete absence of the corpus callosum. S.Po. has a full scale IQ of 75.
C.V. is a 35-year old, right-handed man. He has had one or two epileptic seizures per month since the age of 14 years. EEG recordings show bitemporal foci. The MRI reveals complete callosal agenesis with right parietal (pararolandic) cortical dysplasia, particularly on the mesial side, and right parietal occipital cortical heterotopia. C.V. had an epileptic seizure 1 week prior to testing and was taking anticonvulsant medication (phenobarbital and carbamazepine) at the time of testing. He has a global IQ of 100.

Callosotomized patients
J.S. is a 26-year old, right-handed woman. At age 17 years, she underwent section of the anterior four-fifths of the corpus callosum confirmed by MRI. Before surgery, she had simple partial seizures (150 per month), absences (20 per month) and complex partial seizures (20 per month). The EEG revealed epileptic foci in the left frontal and right frontotemporal regions. J.S. had an epileptic seizure 1 day prior to testing. At the time of testing, she was taking phenobarbital and carbamazepine and her seizures were well under control. J.S. has a full scale IQ of 99.

A.N. is a 31-year old, right-handed woman. She began to experience epileptic seizures at the age of 12 years. Twelve years before testing she underwent a callosotomy that involved the anterior three-quarters of the corpus callosum. The extent of the section was confirmed by MRI. Prior to callosotomy, she had on average 30 epileptic crises, eight complex partial crises and four tonic-clonic seizures per month. Her epileptic foci are located in the right frontotemporal and left temporal regions. At the time of testing, she was taking both phenobarbital and carbamazepine. A.N. has a global IQ of 93.

A.P. is a 28-year old, right-handed man. His seizures started at the age of 14 years. Partial callosotomy of the anterior three-quarters of the corpus callosum was performed at the age of 26 years. The extent of the section was confirmed by MRI. Prior to surgery, A.P. had many absences and complex partial seizures (up to 15 per month of both types). EEG recordings revealed epileptic foci in the right frontotemporal and left temporal regions. A.P. experienced an epileptic seizure 2 days before testing. At the time of testing, he was on phenobarbital and valproic acid. A.P. obtains a global IQ of 87.

D.D. is a 19-year old, right-handed man. He began to have seizures when he was 2 years old. A total callosotomy was performed in two stages with a 6-month interval when he was 18 years old. Before the operation, he had frequent absences (40 per month) and complex partial seizures (30 per month). The EEG revealed epileptic foci in the right and left temporal regions. He reported having had an absence seizure the day before the experimentation. He was on phenobarbital and carbamazepine. He has a global IQ of 100.

S.D. is a 20-year old, right-handed man. His seizures started at the age of 3 years and soon became intractable. His preoperative EEG showed a right centroparietal focus with frequent secondary generalizations. He underwent total callosotomy at the age of 6 years and 10 months. Completeness of the callosal section was confirmed by MRI. Since the surgery, he has had only two or three minor seizures, but a recent EEG shows an epileptic focus in the left frontal region. He experienced an epileptic seizure 1 month prior to testing and is currently taking anticonvulsant medication (Tegretol). S.D. has a global IQ of 75.

In sum, apart from the callosal lesion, six of the experimental subjects had epileptic foci located in the frontal and/or temporal regions (see Table 1). Furthermore, one of the callosal patients had a bilateral prefrontal atrophy consecutive to surgical removal of an orbitofrontal cyst.

Preliminary tests
All subjects performed two preliminary tests: a short-term memory test (digit span subtest of the Wechsler adult intelligence scale—revised) to assess whether they had similar short-term memory abilities and a motor test (Purdue Pegboard Test, Lezak, 1995) to evaluate manual dexterity.

Stimuli and apparatus
The stimuli were asterisks 0.35 cm in diameter. They were presented at one of four horizontal locations, on an IBM (AST.810NB) computer screen at 14.5 cm below the top and 7 cm above the bottom of the screen. The horizontal separation of the stimuli was 2 cm. The monitor screen was positioned in such manner that the stimuli appeared at the subjects’ eye level.

Subjects responded by pressing one of four keys on the top row of the computer keyboard, which was positioned below and in front of the monitor such that the four keys were aligned with the four stimulus locations. The four keys were the numbers 5, 6, 7 and 8 of the keyboard. They were taped over with white paper to cover the numbers. The rest of the keyboard was covered by a white carton to prevent accidental touching of the other keys. The keys corresponded to the asterisk from left to right in such manner that key 5 corresponded to the leftmost asterisk, key 6 to the next asterisk on its right and so on. Correct responses, errors and reaction times for correct responses were computer-recorded. Once the correct key was pressed, the asterisk disappeared and the next one appeared following a delay of 500 ms. If the subject pressed a wrong key, the trial was counted as an error but the asterisk remained on the screen until the correct key was pressed.

Procedure
Learning
Subjects were seated in a quiet room facing the computer. They were tested in two conditions: a unimanual and a bimanual condition. Both conditions comprised four sessions
for a total of eight sessions of a duration of one half hour each. In the bimanual condition, subjects had to rest the forefinger and the middle finger of the left hand on the keys 5 and 6 and the forefinger and the middle finger of the right hand on the keys 7 and 8 during all four sessions. They were instructed to press the key corresponding to the asterisk as fast as possible without making errors. In the unimanual condition, subjects had to rest the forefinger, middle finger, ring finger and little finger of one hand on the four keys for the first two sessions (1 and 2) and the corresponding fingers of the other hand for the other two sessions (3 and 4).

Each session was composed of four repeated blocks and one random block. For the repeated blocks, the location of the stimulus followed a specific sequence of 10 positions. The sequence was different for each condition. Hence, if one was to designate the four possible locations as A, B, C and D from left to right, the sequence was D-B-C-A-C-B-D-C-B-A for the bimanual condition, and B-A-B-D-C-A-C-B-D-A-C for the intramanual condition. Although the two sequences have certain similarities, they vary with regard to their initial items and the inversion of two elements in the sequence. This manipulation should be sufficient to transform the learning task considering that an increase in reaction times can be observed following the change of a single element from the previously learned sequence (Stadler, 1992).

Each sequence comprised 10 trials and each block of trials was composed of 10 continuous repetitions of this 10-trial sequence so that each block appeared as a continuous series of 100 trials. The end of one 10-trial sequence and the beginning of the next one was not marked in any way and the subjects were not informed that the sequence was repeated. For the random blocks, the location of the stimulus followed a random sequence. This block was also composed of 100 trials. The random blocks were introduced to ascertain the presence of learning by comparing reaction times between random and repeated sequences as suggested by Cohen and Curran (Cohen and Curran, 1992).

Twenty blocks (four sessions) were administered in each condition (uni- and bimanual). Blocks 5, 10, 15 and 20 were designated as random blocks while the remaining blocks (1–4, 6–9, 11–14 and 16–19) constituted the learning blocks. The experimental protocol was counterbalanced between subjects and conditions following an ABBA protocol. A 2-min break was allowed after each block. Furthermore, each session was followed by a 10-min pause which could be extended if the subject was tired. Finally, a 1-h break was included between the first four sessions and the last ones.

Explicit memory
Following the last session, the subjects had to complete another block of 100 trials in a self-generated sequence task corresponding either to the unimanual or the bimanual sequence, depending on the last condition that was administered to the subject. In this task, the subjects were asked to press the key where they thought the next stimulus should appear in the sequence. If they made an error, the asterisk that represented the last correct response remained on the screen until the correct key was pressed. Subjects were informed that this time, response accuracy was more important than response speed.

Statistical analyses
Statistical analyses were performed comparing the performance of the acallosal and callosotomized subjects to that of the control subjects. The dependent measures were the median reaction times of the correct responses, the mean number of correct responses on the procedural task and the mean number of correct responses on the declarative memory task derived from the self-generated sequences.

Results
Preliminary tests
An analysis of variance (ANOVA) revealed no significant differences in performance on the digit span subtest between experimental subjects (4–6 digits) and control subjects (4–7 digits). Analysis of the performance on the Purdue Pegboard yielded a group effect for the dominant hand \(F(2,17) = 8.79, P < 0.003\), the non-dominant hand \(F(2,17) = 4.4, P < 0.03\) and bimanual co-ordination \(F(2,17) = 4.7, P < 0.04\). Post hoc analyses using the Tukey method (Winer, 1962) revealed that in these three conditions, the callosotomized subjects were slower than the controls, but that the acallosal and callosotomized subjects did not differ from each other. No significant differences were observed between patients with frontal and temporal foci.

Experimental tests: unimanual learning condition
Reaction times
A one-way ANOVA comparing the performance on the first block of training by the experimental and control groups was performed to examine whether each group started at the same level; separate analyses were conducted on blocks 1 and 11, each of these blocks representing the initial performance for each hand.

A two-way ANOVA (Group × Session) with repeated measurements on the first two sessions of the training blocks carried out by one hand, was performed to assess learning with that hand. Another ANOVA was performed on the following two sessions, carried out by the other hand, to assess learning with that hand. Moreover, a two-way ANOVA (Group × Block) comparing the last block of training (carried out by each hand) and the last random block was performed to obtain an additional measure of training (between blocks 9 and 10 for one hand and between blocks 19 and 20 for the other hand).

Finally, a two-way ANOVA (Group × Block) comparing
Learning with the first hand. Analysis of the reaction times obtained on sessions 1 and 2 yielded a main effect for Session \[ F(1,17) = 26.0, P < 0.001 \], revealing that the reaction times of all groups decreased between sessions 1 and 2. The results suggest that all subjects were able to learn the task with one hand. The absence of a group effect further suggests that the pattern of results was similar for the three groups.

The difference between the last block of training (block 9) and the last random block (block 10) was significant for all groups \[ F(1,17) = 8.7, P < 0.009 \]. Subjects took more time to perform block 10 than block 9, confirming that learning occurred in all groups. No group effect was observed suggesting once more that the three groups did not differ in the reaction time measure in these two blocks.

Learning with the second hand. The analysis comparing sessions 3 and 4 showed a significant effect of Group \[ F(2,17) = 5.07, P < 0.01 \]. Post hoc analyses indicated that the experimental groups were slower than the control group when using their second hand but the acallosal and callosotomized groups did not differ from each other. In addition, there was a significant effect of Session \[ F(1,17) = 20.7, P < 0.003 \] indicating that the experimental groups and their controls were able to learn the visuomotor skill with the second hand.

The ANOVA comparing the last block of training (block 19) and the last block of the random condition (block 20) yielded a significant effect of Group \[ F(2,17) = 4.5, P < 0.02 \]. Multiple comparisons revealed that the acallosals were slower than the callosotomized patients and the control group on these blocks. The latter two groups showed similar patterns of results. Furthermore, a significant effect of Block was observed \[ F(1,17) = 4.4, P < 0.05 \], indicating that all subjects were faster on the last block of training than on the last block of the random condition. These results suggest that all three groups were capable of unimanual (unihemispheric) visuomotor learning with either hand.

Transfer. Transfer of training between the two hands was assessed by computing the difference in response times between blocks 9 and 11. The analysis revealed a significant Group × Block interaction \[ F(2,15) = 4.8, P < 0.02 \]. Post hoc analysis indicated that both acallosal and callosotomized subjects showed a significant increase in reaction time between blocks 9 and 11 while the controls did not show any difference between these two blocks. The latter finding suggests that transfer of training between the hands occurred in the control group but not in the acallosal or callosotomized groups.

In sum, the acallosal and callosotomized groups were slower than their controls in the first block of training performed with the second, untrained, hand but not on the initial block of training performed with the first hand. Despite the fact that they were slower with the second hand, they were able to learn the visuomotor skill with this hand as well as with the first hand. However, in contrast to the control group, both acallosal and callosotomized subjects failed to transfer the learning between the hands.

**Fig. 1** Visuomotor skill learning in the unimanual condition of (A) acallosal and (B) callosotomized subjects (filled circles) expressed as mean reaction times for training blocks 1–4, 6–9 (first hand), 11–14, 16–19 (second hand) and random blocks 5 and 10 (first hand), 15 and 20 (second hand). Open squares = controls.
Table 2 Mean number of errors in the unimanual and bimanual learning conditions in acallosal, callosotomized and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Unimanual sessions</th>
<th>Bimanual sessions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1 2 3 4 1 2 3 4</td>
<td>1 2 3 4 1 2 3 4</td>
</tr>
<tr>
<td>Blocks</td>
<td>1–4 6–9 11–14 16–19</td>
<td>1–4 6–9 11–14 16–19</td>
</tr>
<tr>
<td>Acallosal</td>
<td>16.9 18.2 17.4 12.0</td>
<td>17.3 14.2 18.4 22.6</td>
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<tr>
<td>Callosotomized</td>
<td>12.5 10.2 15.5 12.5</td>
<td>14.8 7.7 10.9 14.1</td>
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<tr>
<td>Controls</td>
<td>9.7 7.5 6.3 4.1</td>
<td>15.0 14.5 15.1 10.6</td>
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</table>

**Accuracy**

Comparisons between sessions 1 and 2 performed with the first hand of training yielded only a group effect \( F(2,17) = 4.4, P < 0.04 \), indicating that the acallosal subjects were less accurate than the controls (see Table 2). However, they did not differ significantly from the callosotomized subjects. Similarly, responses on sessions 3 and 4, corresponding to the second hand of training, were less accurate for the experimental groups than for the control group \( F(2,17) = 3.22, P < 0.04 \). Again no group differences between acallosal and callosotomized subjects were revealed. No significant reduction in number of errors was observed within each hand in all groups.

**Qualitative analysis**

Most callosotomized patients and some of the acallosal subjects suffered from epilepsy. A posteriori, a qualitative analysis of the reaction times was performed in order to evaluate whether their response pattern could distinguish them with regard to the site of their epileptic foci. The analysis showed that the subjects could, in fact, be divided in two groups: one group with temporal epileptic foci and another with frontal damage. Patients with temporal foci were able to learn the task when using the hand contralateral to their epileptic focus. This was not the case for patients with frontal damage. Figure 2A and B illustrates this dissociation in a patient with bitemporal epileptic foci and a patient with bifrontal atrophy.

It can be noted from this figure that the callosotomized patient D.D. with a left and a right temporal epileptic focus (Fig. 2A) showed a decrease in reaction time similar to that of his control between blocks 1 and 9 and blocks 11 and 19. These results suggest that this patient was able to learn the task within each hemisphere as well as his control. A different pattern of results was obtained from patient S.Pe. with bifrontal atrophy (Fig. 2B). The performance of this patient was much more variable. Unlike his control subject, S.Pe. showed very little savings between blocks 1 to 9. The same applied to his performance on blocks 11–19. These results illustrate the inability of this patient to learn the task with either hand. The same general pattern of performance could be observed within the same individual. A.P., who has both a left temporal and a right frontotemporal epileptic focus, showed no savings between blocks 11 and 19 performed with the hand contralateral to his frontal focus but did learn the task when using the hand contralateral to his temporal focus (Fig. 2C).

**Experimental test: bimanual learning condition**

**Reaction times**

A one-way ANOVA comparing the performance by the experimental and control groups on the first block of training was carried out to determine whether each group started at the same level. Moreover, a two-way ANOVA (Group × Session) with repeated measures on the last factor was performed on the training blocks of the four sessions. This analysis evaluated the presence of learning as assessed by a reduction in response time with increasing practice. Furthermore, a two-way ANOVA (Group × Block) comparing the performance on the last block of training (block 19) with that in the last random block (block 20) was used to further evaluate the presence of learning. Considering that the acallosal subject S.Pe. was unable to learn the unimanual task with either hand, the results of this patient in the bimanual condition were excluded from the statistical analyses on the acallosal group. In contrast, the patients with unilateral frontal foci were able to learn the task when using the hand contralateral to the intact hemisphere. Their results were therefore included in the group analyses in the bimanual condition. For graphic representation, however, the scores of the patient D.D., who has bitemporal foci and who could learn the task with either hand (see Fig. 2), are depicted separately from the callosotomized patients who showed unilateral frontal deficits.

**Initial performance.** Figure 3 shows the mean reaction time data of the acallosal, callosotomized and the control subjects on the 16 repeated blocks and on the four random blocks in the bimanual condition. No significant difference was observed between experimental and control subjects in the first block of training suggesting that they started at the same level.
Learning. With regard to visuomotor learning (sessions 1–4), the ANOVA yielded a significant interaction between the experimental groups and the control group [Group × Session effect: $F(6,42) = 3.1, P < 0.02$]. Post hoc analyses indicated that control subjects showed a reduction in reaction time with training, whereas the acallosal and callosotomized subjects, including subject D.D., did not show such savings (see Fig. 3B). The last two groups did not differ in their pattern of performance. These results suggest that both experimental groups failed to learn the visuomotor skill.

As mentioned above, an analysis comparing the last block of training (block 19) and the last block of the random condition (block 20) was also performed to assess the presence of learning. The difference between these two blocks was significant only for the control group who required considerably more time to realize the random block than the
training block. This effect was less pronounced in the acallosal and callosotomized subjects [Group × Block effect: $F(2,12) = 5.2, P < 0.02$]. Again, no differences were noted between acallosal and callosotomized patients.

In sum, acallosal and callosotomized subjects started at the same level in the first block of training but neither of the two experimental groups learned the procedural visuomotor skill in the bimanual condition.

**Accuracy**

Table 2 presents the mean number of errors obtained in the bimanual learning condition by the acallosal, callosotomized and control subjects. An inspection of Table 2 reveals that the experimental groups were as accurate as the controls in the first block of learning. It also shows that the acallosal subjects were less accurate than the callosotomized and control subjects in the training sessions [Group effect: $F(2,42) = 2.9, P < 0.02$]. Unlike controls, acallosal and callosotomized subjects did not improve their performance with practice, suggesting that they did not learn the task as well as the controls [Group × Session effect: $F(6,42) = 3.9, P < 0.007$].

**Experimental tests: additional statistical analyses**

To exclude the possibility that extensive training and/or the similarity between the unimanual and bimanual sequences might have influenced the procedural learning in the second condition administered to the subjects, further statistical analyses were carried out comparing the performance on the first block of training realized by half of the subjects at the beginning of the experiment (naive subjects) under one condition with the performance on the first block of training realized by the other half of the subjects (trained subjects) in the second part of the experiment under the same condition. If the learning of one sequence had some influence on the subsequent sequence, the performance of the subjects who had been exposed to prior learning (trained subjects) should be better than that of naive subjects when tested under the same condition. The ANOVA performed on the results of the unimanual condition did not reveal any differences between these two blocks for either the acallosal, callosotomized or control subjects ($P > 0.5$). The same pattern of results was observed in the bimanual condition for the three groups ($P > 0.5$). These results indicate that previous learning of one sequence had no effect on subsequent learning of a second sequence.

**Experimental test: self-generated task**

A one-way ANOVA was performed on the mean number of correct responses obtained on the declarative memory task to study whether experimental and control groups differed in their explicit knowledge of the task.

The percentages of correct responses in this task are presented in Table 3. Separate analyses were performed for the acallosal and callosotomized groups and their respective controls. The results revealed no significant differences between the performance of acallosal and control subjects, suggesting that they did not differ in their declarative knowledge of the sequence at the end of training. However, a significant difference was observed between the callosotomized group and their controls [$F(1,10) = 17.8, P < 0.005$] indicating that the controls had a better declarative knowledge of the sequence than the callosotomized patients. Qualitative analysis of the data obtained from the callosotomized group revealed that the performance of the patients with temporal epileptic foci was poorer than that of the patients with frontal epileptic foci (29% versus 54%, respectively). It is also noteworthy that, among the acallosal subjects, patient C.V, who has bitemporal epileptic foci, showed the poorest performance in this declarative task.

A correlational analysis was performed to assess if the amount of learning observed on the last condition realized by the subjects had any influence on the explicit knowledge of the sequence. The percentage of learning was defined by the following formula: score on the first block of training minus the score on the last block of training divided by the score on the first block of training. No correlations were found between the amount of learning observed in the unimanual or bimanual conditions and the score obtained in the self-generated task for any of the three groups. This is best exemplified by the performance of the acallosal subject S.G. and the early-callosotomized subject S.D.; neither showed any implicit learning in the bimanual condition, but they nevertheless obtained a high rate of accuracy (82% and 83%, respectively) in the self-generated task performed after completion of this condition.

Finally, a correlational analysis was performed between the IQ of the experimental group and their performance in the self-generated task. No correlation was observed between these factors which excludes the possibility of a systematic relationship between the performance in the declarative memory task and IQ in these subjects.

**Discussion**

The principal aim of this study was to examine whether subjects without a corpus callosum were able to learn a procedural visuomotor skill that involved simultaneous motor control from both hemispheres and whether they could transfer a procedural visuomotor skill acquired with one hemisphere to the other, untrained, hemisphere. Another aim was to examine whether procedural and declarative memory processes could be dissociated in this learning.

As predicted, split-brain patients and acallosal subjects showed no visuomotor learning when bihemispheric integration was required, whereas they could learn the skill...
when only one hemisphere was involved in the task. Yet, in spite of the absence of interhemispheric transfer of procedural learning, some of the acallosal and callosotomized patients were able to learn the sequence explicitly. An incidental finding was that patients with frontal lobe damage failed to learn the task when they used the hand contralateral to the damaged hemisphere. This was not seen in patients with temporal epileptic foci who had no problems acquiring the visuomotor skill with either hand.

For the callosotomized patients, the absence of interhemispheric integration of the visuomotor skill was expected since these patients have often been reported to manifest deficits in bimanual co-ordination. Division of the corpus callosum is known to produce disconnection deficits in this kind of task (Preilowski, 1972, 1975). The facts that most of the patients had an intact splenium and that unrestricted exploration of the visual stimuli was possible rule out a visual component in the production of this deficit. The observed deficit must rather be related to the motor component of the task. Typically, the callosotomized patients were slower than the control subjects in the preliminary motor test (Purdue Pegboard), a finding which might be explained, at least in part, by the long-term epileptic condition of these patients. Nevertheless, they were able to learn the task unilaterally without trade-off between speed and accuracy, and their pattern of performance was similar to that of the acallosal subjects who did not display motor deficits in the preliminary test. Their motor slowness can therefore not explain the deficits in interhemispheric integration and transfer of the procedural visuomotor skill.

By the same token, the deficit cannot be ascribed to fatigue. First, several pauses were included during testing. Secondly, most subjects were able to learn the task in the unimanual condition in spite of the fact that half of them performed this condition after the bimanual one. Conversely, in half of the subjects, deficits in the bimanual condition were observed in the initial blocks of training, at which point in time no fatigue effects should be evident. Finally, the deficit in bimanual learning cannot be entirely related to the deficit in unimanual learning which was present in many of the patients, since the callosotomized patient D.D., who showed a normal performance with either hand in the unilateral condition, was also deficient in the bimanual condition. This finding, coupled with the fact that the acallosal subjects had the same bimanual deficit, in spite of having normal unilateral performances, rather suggests that the corpus callosum is crucial for the interhemispheric integration of a procedural visuomotor learning.

The callosotomized patients showed a deficit in intermanual transfer of learning regardless of the hand used for the initial learning. It could be argued that this deficit is attributable to a problem of intermanual transfer of the sequence per se. Indeed, Wachs and colleagues (Wachs et al., 1994) have reported that, in normal subjects, interhemispheric transfer of sequential finger movements can occur only when the sequence realized with the second hand is the mirror image of the sequence used with the first hand. The results with our control subjects suggest, however, that intermanual transfer of learning can take place even when the same, non-mirror, sequence is used. Thus, the absence of the corpus callosum appears to be responsible for the lack of transfer.

The same line of reasoning could be applied to the acallosal subjects. The deficit in interhemispheric integration of a visuomotor skill could be explained by an impairment in bimanual co-ordination such as observed in previous studies (Jeeves, 1965, 1986; Chiarello, 1980; Sauerwein et al., 1981,
Jeeves et al., 1988). Similarly, the absence of interhemispheric transfer seen in the acallosal group is in line with the findings of impaired transfer of a unimanually learned tactuomotor skill such as stylus maze (Lehmann and Lampe, 1970; Ferriss and Dorsen, 1975; Gott and Saul, 1978; Jeeves, 1979) and formboard learning (Russell and Reitan, 1955; Ferriss and Dorsen, 1975; Reynolds and Jeeves, 1977; Jeeves, 1979). Moreover, unlike in the split-brain cat (Lepore et al., 1982) overtraining of the procedure failed to improve transfer and integration of learning. These results stress once more the important role of the corpus callosum in interhemispheric integration of procedural visuomotor learning.

Previous studies have often reported the absence of disconnection deficits in acallosal individuals (Jeeves, 1965; Sauerwein et al., 1981; Lassonde et al., 1988). This phenomenon has been attributed to cerebral plasticity which would allow for the use of alternate neuronal structures in interhemispheric communication. Our results suggest that cerebral plasticity is limited when a motor component is involved, a point which we and others have made previously (Dennis, 1976; Jeeves, 1986; Lassonde, 1994; Lassonde et al., 1995). The limits of cerebral plasticity are also evident in our split-brain patient S.D. who underwent callosotomy in childhood. Although this patient has shown no impairment on a cross-localization task (Lassonde et al., 1991), which makes greater cognitive demands than the present visuomotor task, he nevertheless failed to transfer the visuomotor learning in this experiment. It thus seems that the compensatory mechanisms in the case of early section or congenital absence of the corpus callosum, proposed by a number of authors, are effective primarily for transfer in the sensory modalities but that they seem to be inefficient when a motor component has to be transferred. The absence of plasticity in motor cross-integration may be related to the fact that the cortical areas subserving these motor functions, namely the frontal lobes (Botez, 1996), do not reach their functional maturity before puberty (Huttenlocher, 1990). In contrast to the regions that mediate the sensory modalities (Chiron et al., 1997), the full maturation of the frontal lobes may take place after completion of the critical period of callosal plasticity, which would explain the limited adjustment to callosal absence in tasks requiring motor control.

Another interpretation can be given to the limited amount of compensation seen in the acallosal patients. The nature of the task used in the present study requires implicit processing. Both Milner (Milner, 1994) and Berlucchi and colleagues (Berlucchi et al., 1995) have argued that the compensation seen in callosal agenesis may be limited to interhemispheric processes that require an access to consciousness. Because of cerebral plasticity, acallosal individuals could well make use of compensatory pathways to perform explicit interhemispheric comparisons. However, the efficiency of these pathways would be limited when implicit or unconscious processes are involved, perhaps because of their lesser functional or ecological value. Our results could support such a notion but, clearly, further investigation is needed to confirm this hypothesis.

In this context, it could be argued that the extended training as well as the relative similarity between the sequences used in the bimanual and unimanual conditions should have increased the explicit knowledge of the sequences and hence facilitated the procedural learning (Willingham et al., 1989). This was not the case, however. None of the subjects, including the controls, showed any advantage of having performed one condition before the other. Moreover, no correlations were observed between the amount of procedural learning and the performance in the declarative memory task for any of the subjects. These results indicate that these two processes seem to be relatively independent.

A further distinction between implicit and explicit learning was also observed in the split-brain and acallosal subjects. In spite of the absence of transfer and interhemispheric integration of procedural learning, many of these patients were able to learn the sequence explicitly. Another dissociation was seen in the patients with frontal and temporal dysfunction. The patients with frontal damage showed a better explicit knowledge of the procedure but a poorer implicit learning of the task than the patients with temporal dysfunction. These double dissociations confirm the independence of procedural and declarative memory processes reported in the literature (Cohen et al., 1990; Perruchet and Amorin, 1992; Squire, 1992; Willingham et al., 1993). They also extend the distinction between implicit and explicit memory to processes involving simultaneous bihemispheric co-operation and further suggest that the frontal and temporal cortical areas may play a differential role in the implicit and explicit components of this simple serial reaction time task.

Overall, the findings of this study point to an important callosal involvement in procedural learning. In fact, the anterior commissure, which is known to relate to the basal ganglia (Pandya and Seltzer, 1986), was intact in most of our patients but deficits were observed in spite of its presence. Considering that all of our patients had absence of the anterior part of the corpus callosum, it may be inferred that the connections between the anterior cortices are essential for transfer and integration of visuomotor learning. Thus, it would appear that the contribution of these anterior cortical connections is as important as that of the striatum or the cerebellum for the acquisition of a bimanual visuomotor skill. The impairment in unimanual acquisition of the procedural skill observed in the patients with frontal lobe damage also points to the role of the frontal cortex in procedural learning and allows definition of the neural pathways involved in this type of learning and memory.

The frontal cortex is known to have strong projections to the striatum. The striatum, on its part, projects to the internal globus pallidus, which in turn projects to thalamic nuclei. The latter projects back to the frontal area of origin (Heilman and Watson, 1991). Previous reports indicate that unilateral visuomotor learning requires the integrity of these structures as well as that of the cerebellum.
(Pascual-Leone et al., 1993; Doyon et al., 1996, 1997; Gomez-Beldarrain et al., 1998). Our own results support those previous studies (Pascual-Leone et al., 1995, 1996; Gomez-Beldarrain et al., 1997) that emphasize the implication of the prefrontal cortex in this unilateral visuomotor loop. Transfer of unilateral procedural learning, on the other hand, seems to require the additional integrity of the corpus callosum which would connect the two separate neural loops. It would thus seem that the anterior part of the corpus callosum connects two independent procedural loops, and that interruption of these connections affects the integration of a procedural skill but not the functioning of each independent loop, provided that each hemisphere subset is intact.

In summary, the results of this study suggest that the frontal lobes are important for unilateral procedural learning and that the anterior part of the corpus callosum, which connects these lobes, is crucial for integration and transfer of a procedural visuomotor skill. The findings also confirm the previously reported independence of declarative and procedural memory systems proposed by Squire (Squire, 1992). This dissociation was demonstrated by the observation that the acallosal subjects had explicit knowledge of the procedure although they were incapable of learning the skill implicitly when it required interhemispheric integration. These data also add to the number of disconnection deficits in acallosals that are increasingly reported in the literature (e.g. Lassonde, 1994; Lassonde et al., 1995).

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