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Short Communication

Corpus callosum function in verbal dichotic listening: Inferences from a longitudinal follow-up of Relapsing-Remitting Multiple Sclerosis patients

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ABSTRACT

This study conducted a follow-up of 13 early-onset slightly disabled Relapsing-Remitting Multiple Sclerosis (RRMS) patients within an year, evaluating both CC area measurements in a midsagittal Magnetic Resonance (MR) image, and Dichotic Listening (DL) testing with stop consonant vowel (C-V) syllables. Patients showed a significant progressive loss of posterior CC areas (isthmus and splenium) related to increasing EDSS scores and an enhancing right ear advantage (REA) over time. A significant correlation between posterior CC areas and DL scores emerged in both evaluations, being negative for the right and positive for the left ear. The pattern of correlations suggests that the CC can serve an inhibitory and also excitatory influence on the contralateral hemisphere when studying the phonological processing of language.

Statement of significance to the neuroscience of language: The scope of the manuscript is language lateralization. The task used in the experiment is a verbal dichotic listening task, tapping the most basic phonological aspects of language. Finally, the available research is scarce when focusing on the interhemispheric excitation or inhibition of the corpus callosum in linguistic functioning.

1. Introduction

The corpus callosum (CC) is the major fiber bundle in the human brain, with more than 200 million axons providing a large connection mainly between homologous cortical areas in mirror-image sites (Huang et al., 2005). The CC permits interhemispheric transfer of information but it is largely unknown how this manifests at a functional level, whether in an excitatory or inhibitory manner (Bloom & Hynd, 2005). The CC would have an excitatory role if the engagement of a specific region in one hemisphere tended to activate – via CC paths – the homotopic regions of the other hemisphere. The CC would have an inhibitory role if the processing of those homotopic regions were suppressed (Hellige, 1993). An example of the excitatory function is the callosal propagation of an epileptic focus, which acts as a facilitatory mechanism for the spreading of the seizure to the ipsilateral territory in both hemispheres (Brown, Day, Rothwell, Thompson, & Marsden, 1991). An example of inhibitory function is the deactivation of the ipsilateral primary motor (M1) areas during motor tasks, due to transcallosal inhibitory inputs from the contralateral M1 (Lenzi et al., 2007).

In this study our interest was to elucidate the functioning of the corpus callosum regarding excitation and/or inhibition but concerning specifically the phonological processing of language, involving concretely the speech/listening performance.

Multiple Sclerosis (MS) patients offer a reliable way to study the function of the CC since the pathological landmark of their disease, the demyeliniating plaques, tend to be located at periventricular brain areas, therefore affecting the corpus callosum. In addition, there is increasing evidence to consider MS as a neurodegenerative as well as inflammatory disease (Casanova et al., 2003), which should imply the loss of axons traveling through the CC, possibly due to Wallerian degeneration (Evangelou et al., 2000), and the subsequent callosal loss evolving over time (Juha et al., 2007).

In MS patients it seems worthwhile to apply a behavioral paradigm presenting lateralized stimuli, as the dichotic listening (DL) task, to study functional aspects of the CC. In DL, two different and competitive auditory stimuli are presented to both ears and, if they are verbal, a right ear advantage (REA, superior reporting of right ear stimuli) usually emerges (Hugdahl, 2003). The REA is classically interpreted as the result of stronger contralateral than ipsilateral auditory projections (so the right ear would be better connected with the left hemisphere and vice-versa) and a critical role for the CC in transmitting verbal information from the left ear via the acoustic cortex of the right hemisphere to

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language-processing areas of the left hemisphere. Reinforcing this, a number of studies (Gadea et al., 2002; Pelletier et al., 2001; Rao et al., 1989; Reinvang, Bakke, Hugdahl, Karlsen, & Sundet, 1994) have found significant correlations between DL scores and midsaggital CC area of MS patients, measured through Magnetic Resonance (MR) images. All these studies found a reduced left ear performance in DL for the patients compared with controls and also an inverse correlation between the REA and total callosal area. Thus, the thinning of the CC (especially at the posterior regions) was correlated with the highest REA. At first glance this would imply that the CC plays an excitatory role in interhemispheric communication: as it becomes smaller the observed behavioral laterality increases while that function is subsumed mainly by a unique hemisphere. However, the REA index is a combined measure that is calculated from the difference in raw scores inter-ears. Following the above model for the REA, one might expect only a positive correlation between the CC and the left ear, with no right-ear correlation, whose score does not depend on callosal transfer. Instead of this, when correlations by ear were performed in a sample of MS patients, the right ear score was inversely correlated (and the left positively) with the middle and posterior callosal sectors (Reinvang et al., 1994). This same finding was observed in a study performed in a sample of 25 Relapsing-Remitting MS (RRMS) patients with minimal physical disability and a disease of short temporal evolution (Gadea et al., 2002). Other authors have found the same pattern of correlations in normal subjects (Clarke, Lufkin, & Zaidel, 1993; Westerhausen, Woerner, et al., 2006).

The goal of this study was to accomplish a follow-up of RRMS patients with a year interval, evaluating both CC area measurements and DL testing. We expected a decrease in midsaggital CC area together with an increase in behavioral laterality (thus, greater REA in DL). In addition, we explored the correlations of each ear separately with the CC area measurements, to help elucidate the excitatory versus inhibitory role of the CC in dichotic listening performance and interhemispheric communication.

2. Method

2.1. Subjects

A total of 13 right-handed subjects with clinically definite or probable Relapsing-Remitting Multiple Sclerosis disease (eight men and five women) underwent two evaluations with a year interval. Their mean age was 26.3 years (SD 4.3, range 19–32) with mean years of education of 13.1 (SD 3.4, range 8–17). At baseline, eight of them met the criteria of Poser et al. (1983) for clinically definite RRMS. Five were probable MS at baseline, according to MRI Barkhof's criteria (1997), and two of them developed definite MS within the year of follow-up. Their mean months of disease duration at the first evaluation was 22.15 (SD 12.11, range 10–48), and the mean score for the Kurtzke (1983) disability scale (EDSS) was 1.3 (SD 0.63, range 0–2.5). All patients were in clinical remission at the time of testing, met the audiometric criterion for inclusion (less than 10 dB ear difference at 500, 1000, 2000, 3000 and 6000 Hz), and had the same MR examination protocol at both time-points of the study. Although six patients were receiving at the second evaluation a specific treatment for MS (interferon B) as part of a clinical trial, there were not significant differences between treated and non-treated patients in any moment with regard to EDSS scores or disease evolution time.

2.2. Materials

2.2.1. Magnetic Resonance measurements

MR was performed on a 1.5-Tesla Gyroscan (Philips Medical Systems, The Netherlands). A sagittal acquisition was obtained with a T1-weighted echo-gradient sequence with prepulse inversion (repetition time = 20 ms, echo time = 5 ms). The images had 6 mm slice thickness, with 256 × 256 pixels acquisition matrix and 250 mm field of view.

The quantification of the CC area was performed in the midsagittal image and the measurements were done by a radiologist (E. A.) who was unaware of the hypothesis tested. On the digital image, the maximum distance between the anterior and posterior CC limits was bisected and the resulting halves bisected again. Perpendicular lines erected on the points of division intersected with the CC and defined four areas in mm^2 (A1, A2, A3 and A4). The sector A1 included the rostrum and the genu of the CC; A2 referred to the main body; A3 the posterior body and anterior isthmus; and A4 approximately the posterior isthmus and the splenium (Fig. 1).

2.2.2. Dichotic Listening test

The dichotic stimuli consisted of the six stop consonants paired with the vowel /a/ to form six consonant vowel (C-V) syllables (ba, da, ga, ka, pa and ta). The syllables were paired with each other in all possible combinations to form 36 different syllable pairs. From these, the homonymic pairs (e.g., ba–ba) were included in the test as a perceptual control, but they were not considered in the statistical analyses. The other 30 syllables were duplicated and randomly recorded, giving 60 test trials, with a maximum correct score of 60. This DL test has achieved a test–retest reliability of .86 (Gadea, Gomez, & Espert, 2000). The subjects were informed that different syllables would be presented to each ear simultaneously, and were asked to report only one syllable (the one perceived most clearly).

2.2.3. Design and statistical analyses

Normality of all tested variables was confirmed by the Kolmogorov–Smirnov test ($p > .05$). To assess reliability of the morphometric procedure over time, an intraclass correlation (two-way mixed effects model, absolute agreement) for total CC and each subregional area was calculated.

To analyze callosal MR imaging measures (total area and four regions), a paired t test was applied between the two measures taken at the first and second moment. Regarding DL testing, an Analysis of Variance (ANOVA) was performed on the raw scores (correctly reported items) according to design 2 (ear input – RE versus LE) × 2 (moment – first versus second) with repeated measurements on both factors. Preliminary analyses showed that sex had no effect on the results so this variable was removed. Post-hoc paired t tests were also applied. Finally, Spearman rank

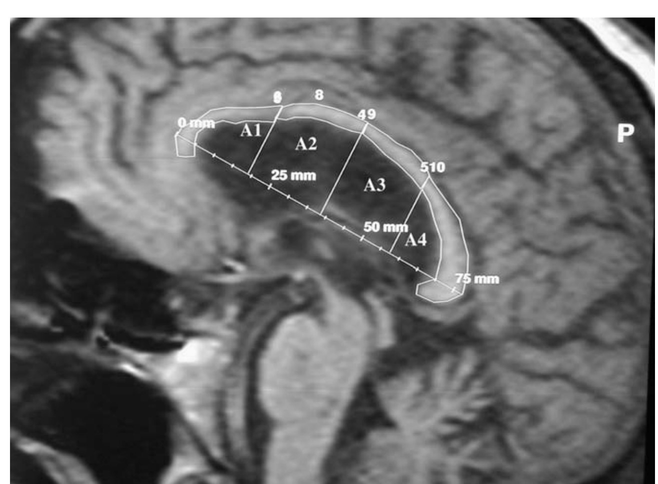

Fig. 1. Measurement of the corpus callosum.

correlation coefficients were calculated between DL variables, CC neuroimage measures and clinical variables (EDSS and months of disease duration at first evaluation) stratified by the time.

Results are presented in means and standard deviations. Confidence intervals for the mean and the d index for size effect are reported when appropriate. All analyses were performed with the SPSS .14 software (Chicago, IL, USA).

3. Results

Callosal measures showed a marginally significant decrease for the total CC area (t (df 12) = 2.1, $p = .06$) at the follow-up examination, with an intraclass correlation of .85. When analyzing the main different areas, a significant decrease was found for the sector A3 (t (df 12) = 2.73, $p < .01$; $d = .75$; confidence intervals for the first versus the follow-up were 96.3/120.1 and 86/111, respectively) and also for the sector A4 (t (df 12) = 2.23, $p < .04$; $d = .62$; confidence intervals for the first versus the follow-up were 184.2/219.5 and 173.1/212.1, respectively), with intraclass correlations of .83 for A3 measure and .92 for A4 measure. The high intraclass correlations assured comparability of measurements between MR scans at both baseline and follow-up. Table 1 shows means and standard deviations for the CC measurements in both moments.

When looking for correlations between clinical (EDSS and months of evolution) and CC measures, a significant negative relation between EDSS and A3 at the follow-up examination emerged (Rho = −.55, $p < .04$).

Regarding the dichotic listening measures, the main effect for the factor "ear" was significant ($F(1, 12) = 35.9$, $p < .0001$) indicating a REA in both examinations. The factor "moment of examination" did not reach significance, but the interaction "ear × moment" was significant ($F(1, 12) = 11.58$, $p < .005$). Post-hoc t test revealed that this was due to a significant right ear increase in the follow-up: means from 36.2 (SD 8.6) to 39.3 (SD 6.7), (t (df 12) = 3.68, $p < .003$; $d = 1.02$; confidence intervals for the first versus the follow-up were 30.9/41.4 and 35.2/43.4, respectively) and a left ear decrease of the mean, from 16.4 (SD 6.2) to 14.7 (SD 6), that approached to statistical significance (t (df 12) = −2.04, p < .06).

Table 1
Mean and Standard Deviations for total area (ATOT) and four callosum sectors in Multiple Sclerosis patients, separated by moment (1: first evaluation, 2: evaluation after a year).

Callosum sectors	A11	A21	A31[a]	A41[a]	ATOT1
Area (mm^2)					
Mean	192.2	117.5	108.2	201.8	619.9
SD	23.1	19.4	19.6	29.1	64.4
Correlations					
RE	.21	−.13	−.41	−.70**	−.32
LE	−.09	.07	.33	.64*	.28
Callosum sectors	**A12**	**A22**	**A32[a]**	**A42[a]**	**ATOT2**
Area (mm^2)					
Mean	193.8	109.1	98.4	192.6	594
SD	29.8	22.8	20.6	32.3	69.9
Correlations					
RE2	.18	−.30	−.34	−.67*	−.35
LE2	−.17	.26	.45	.58†	.39

[a] The difference for A3 and A4 means between moment 1 and 2 is significant (see text). Spearman correlations between dichotic listening variables and callosal measures appear bellow. RE: right ear, LE: left ear.
** $p < .008$.
* $p < .01$.
† $p < .03$.

There were no significant relations between clinical variables and DL measurements. In search for correlations between DL and CC measurements (Table 1), a significant association for A4 in the first and also in the follow-up emerged, being negative for the right and positive for the left ear.

Moreover, the absolute difference between the initial and follow-up examinations for RE and LE scores (e.g. RE1 minus RE2, as a measure of functional relative loss) were also correlated with callosal measures. Interestingly, only a significant positive relationship for the RE impairment-score and callosal measures (A3 and A4 for both temporal moments) emerged (correlations ranging from .59 to .69, $p < .01$) with no relationship for the LE impairment-score.

4. Discussion

The general aim of this study was to examine a specific aspect of the CC function in the human brain, by the accomplishment of a one-year follow-up study investigating callosal loss in early RRMS and its correlation with interhemispheric communication measured with dichotic listening. A significant loss of the callosum area for the posterior CC regions, mainly the isthmus and splenium, was observed. In this sense, Juha et al. (2007) reported a persisting loss of CC area in a 9-year longitudinal study representing four decades of disease duration of MS for all MS courses. When studying RRMS patients, Pelletier et al. (2001) reported callosal loss in a 5-year longitudinal study and Simon et al. (1999) found similar results in a 2-year longitudinal work on brain atrophy. Finally, in a 15-month follow-up study including different clinical MS phenotypes, Pagani et al. (2005) showed again CC loss being distinctive for the RRMS course. In fact, callosal loss seems to evolve since the very early stage of MS (clinical isolated syndrome, CIS) (Audoin et al. (2007). Anyway, note that the callosal decreasing could be part of a more general process of tissue damage and brain volume loss.

So, given that the mean CC area for our sample at baseline (6.19 cm^2) was quite close to healthy population (6.27 cm^2, Mitchel et al., 2003) and thus supposing that the CC loss we observed represents the initial stage of the process, then it could be that the posterior CC was a premature target of MS when compared with the anterior CC. This possibility states as an heuristic for future research guidelines. In addition, the above commented longitudinal studies and also transversal ones (Schreiber et al., 2001) found small (−.15) to moderate (−.58), but usually significant, correlations between CC area and EDSS scores, thus supporting our present clinical association (−.55) between the posterior body and anterior isthmus callosum loss and disability status.

With regard to dichotic listening parameters, a test of verbal material (stop CV syllables) with no specific instructions about allocation of attention was applied. This procedure is believed to evaluate a bottom–up or stimulus driven component of functional laterality, more closely related to the interhemispheric connectivity "per se" (Hugdhal, 1995). Interestingly, the evolution of our patients showed mainly a significant increase for the right ear score together with a slight non-significant decrease for the left ear score. Both features led to an enhanced REA over time in MS patients.

Research on split-brain (commissurotomized) patients has largely pointed out an exaggerated REA as a marker of their disconnection syndrome, despite the absence of a standardized REA cut point to diagnose the presence of disconnection. This inflated REA has usually been attributed to left ear items extinction, with reports under chance level. It is important to note, however, that almost all tested patients have also displayed an increased reporting of right ear items, sometimes even to 100% accuracy (Sidtis, 1988). As stated in the introduction, MS is also considered a disconnection syndrome relative to callosal injury, although in less intensity than commissurotomy. Most transversal studies addressing DL in MS have focused only on the REA index or the left ear score, but when the right ear score was registered, its enhancement could be observed in some studies (Lindeboom & Horst, 1988; Wishart, Strauss, Hunter, & Moll, 1995).

In the unique existing study that applied DL and CC measures to MS patients in a longitudinal fashion (Pelletier et al., 2001), the authors also demonstrated an enlarged REA overtime together with a progressive loss of the CC, but unfortunately they did not explore the evolution of performance for each ear separately nor their correlations with the CC area. Since we have already shown a reduced left ear score when compared to a control group for the present sample (Gadea et al., 2002), it might be that two consecutive stages emerge in the development of an exaggerated REA, first appearing left ear loss followed in time by a pathological right ear enhancement. In absence of more evidence this suggestion remains speculative until further longitudinal studies will be developed.

The correlations performed on the raw scores of DL linked positively the left ear to the posterior callosum, reaching significance to the splenium, at baseline and also after a year. Turning to split-brain patients, lesions of the posterior part of the callosum trunk (isthmus) and/or the splenium have the most pronounced effect on their left ear suppression (Pollman, Maertens, von Cramon, Lepsien, & Hugdahl, 2002). This agrees with these regions being the auditory transfer of left ear items. Modern maps of probabilistic MR diffusion tensor imaging (DTI) tractography support the above anatomical assumption (Huang et al., 2005) since they show interhemispheric crossing of the parietal and temporal fibers (including auditory) through the anterior splenium (A4 in the present study). In addition to these data, a recent study with functional MR imaging (Rimol, Specht, Weis, Savoy, & Hugdahl, 2005) has found a phonetic/phonological processor implicated on the decoding of stop consonants to be located almost exclusively at temporal regions of the left hemisphere. So, several pieces of evidence support the assumption of a left ear transfer of stimuli from the right auditory temporal cortex by the anterior splenium to the left hemisphere to be processed, just as the classical callosal relay model suggests. According to Hellige (1993) the corpus callosum would be then mainly excitatory in nature.

At this point, we found a highly significant negative correlation of the right ear with the anterior splenium and, moreover, after applying an index of functional relative impairment for each ear we observed that only the right ear impairment was related to the posterior callosum sectors volume loss. It seems to be that a small CC results in right ear magnification, pointing to functional inhibition of the CC in the sense of Hellige (1993) as advanced by other authors (Clarke et al., 1993; Reinvang et al., 1994; Westerhausen, Woerner, et al., 2006). Our interest here is to give a tentative explanation for that right ear enhancement, being this an alternative to the classical interpretation of "release from interference from left-ear inputs", given the above reports connecting the callosum only with the right ear and other observing that increased right ear in the absence of a decreased left ear in MS (Lindeboom & Horst, 1988; Wishart et al., 1995).

The first question that arises here is the direction of the inhibition: which hemisphere is inhibiting the contralateral?. The available theories of callosal inhibition (Chiarello, 1995) postulate that it is the dominant hemisphere for a given function which inhibits the non-dominant (e.g. the left hemisphere, specialized for word generation, inhibiting the right, Westerhausen, Kreuder, et al., 2006), leading the two hemispheres to become dominant for complementary functions. However, the present data are best explained in terms of the non-dominant-for-language right hemisphere sending inhibitory projections to the dominant left hemisphere (as Hellige's proposal states). An interesting question then is the origin of that inhibitory signal. Pollmann, Maertens, and von Cramon (2004) observed that splenial lesions lead to supramodal (auditory and visual) target detection deficits. They suggested a role for the right hemisphere temporo-parietal junction (TPJ) in sending fibers via the splenium for signaling the presence of a currently unattended stimulus. The right TPJ in dominant for redirecting attention to non-attended stimuli (Corbetta & Shulman, 2002) so it could be the right TPJ sends splenial fibers to suppress (inhibit) the left hemisphere processing of right ear stimuli, in an intention of guaranteeing some processing of the simultaneously transferred left ear items.

Moreover, following the model recently proposed by Hugdahl (2003) for a two channel threshold of callosal transfer, the small-diameter nonmyelinated fibers that are responsible for transfer of cognitive information (Aboitiz & Montiel, 2003) would be recruited only in situations of increasing cognitive interhemispheric load. A good example of that situation is an MS patient performing a DL test, so the pattern of correlations observed here, and specially the inhibitory function pointed above, might reflect the functioning of those specific fibers.

In few words, we suggest that there are sufficient data in the literature to acknowledge a dual function for the CC in DL. One, excitatory and in accordance with the callosal relay model, and second, inhibitory and attentional in nature, with the right TPJ sending signals to the LH to compete with the processing of the right ear items. This view would account for the DL data obtained from split-brain patients and disconnection syndromes in general, since in the absence of both types of interhemispheric communication (excitation and inhibition) the outcome observed in verbal DL would be the working of the left hemisphere phonetic/phonological processor in isolation, therefore, greater REA due to both left ear extinction and right ear enhancement, as we have found in our series.

In summary, this study shows an early volume loss in posterior callosal areas of RRMS patients, related to the evolution of their functional disability, with an increasing functional disconnection in a short one year period. The observed pattern of correlations supports the notion that the CC can serve both an inhibitory and excitatory influence on the contralateral hemisphere when studying the most basic aspects of a higher order cognitive function as language.

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