Interhemispheric Transfer Deficit in Alexithymia: A Transcranial Magnetic Stimulation Study

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Transcranial magnetic stimulation • Paired pulse • Transcallosal inhibition • Interhemispheric transfer • Corpus callosum • Alexithymia

Abstract

Background: A deficit in interhemispheric transfer was hypothesized in alexithymia more than 30 years ago, following the observation that split-brain patients manifest certain alexithymic characteristics. However, direct evidence of interhemispheric transfer deficit has never been provided. This study investigated the hypothesis of a transcallosal interhemispheric transfer deficit in alexithymia by means of paired-pulse transcranial magnetic stimulation. Methods: A random sample of 300 students was screened for alexithymia using the Italian version of the 20-item Toronto Alexithymia Scale. Eight right-handed males and eight females with high alexithymic scores and an age- and gender-matched group with low alexithymic scores were selected. A first (conditioning) magnetic stimulus was delivered to one motor cortex followed by a second (test) stimulus to the opposite hemisphere at different interstimulus intervals for both motor cortices. Motor evoked responses were recorded from the abductor digit minimi muscles. Results: High alexithymic subjects showed reduced transcallosal inhibition as compared to low alexithymic subjects at interstimulus intervals of 10, 12 and 14 ms in the left-to-right and right-to-left interhemispheric transfer directions. Conclusions: Results point to functional differences in transcallosal interactions in high alexithymic as compared to low alexithymic subjects, supporting the hypothesis of an interhemispheric transfer deficit in alexithymia.

Introduction

The term ‘alexithymia’ (from the Greek \textit{a-lexis}: no words; \textit{thymos}: emotion) was coined by Nemiah and Sifneos [1, 2] on observing that a large proportion of patients with psychosomatic disorders showed difficulties in emotional self-regulation. Alexithymia refers to difficulties in identifying and describing feelings, distinguishing feelings from bodily sensations, and external orientation thinking, and is thought to be a risk factor for a variety of medical and psychiatric disorders [3–11]. Even though empirical evidence that this personality trait is linked to specific neurobiological markers is still scant, some models have been proposed [12–14]. The interhemispheric deficit model was proposed by Hoppe and Bogen [15], based on findings of alexithymic features in split-brain
patients. According to these authors, alexithymia is characterized by a relative lack of communication between right and left cerebral hemispheres [16,17] which leads to a deficit in the ability to verbally articulate (left hemisphere function) emotions (primarily processed by the right hemisphere). Some support to this hypothesis has been provided [18–21], while using transcranial magnetic stimulation (TMS), shorter transcallosal inhibition (TI) latencies have been found in both nonclinical [22] and clinical [23] populations of alexithymic subjects.

In the present study, we sought to more specifically test transcallosal communication using a paired-pulse TMS protocol. Since its introduction in 1985 [24,25], TMS has become increasingly popular and is now a well-established and noninvasive technique in cognitive neuroscience [26] as well as in the study of neurophysiological substrates of neurological and neuropsychiatric disorders [27–30].

Using the interhemispheric paired-pulse paradigm, it is possible to investigate the inhibitory effect of a conditioning magnetic stimulus (CS) over the motor cortex of one hemisphere on the size of motor evoked potentials (MEPs) induced by a magnetic test stimulus (TS) given over the opposite hemisphere. It has been hypothesized that this kind of paired-pulse inhibition is produced at a cortical level via callosal connections [31]. Recent studies have replicated this inhibitory effect in normal subjects and revealed its absence in patients with agenesis of the corpus callosum and a total or partial callosotomy [32–34]. Finally, direct support that this paired-pulse TMS paradigm specifically examines the function of inhibitory interhemispheric interactions has been provided [35].

Subjects and Method

The work was conducted in the sleep laboratory of the Department of Psychology, University of Rome ‘La Sapienza’. A random sample of 300 university students responding to an advertisement was screened for alexithymia using the Italian version of the 20-item Toronto Alexithymia Scale (TAS-20) – a validated 20-item self-report questionnaire that is the most commonly used scale to assess alexithymia [36–38]. Two groups of gender- and age-matched subjects were selected based on the TAS-20 scores (high alexithymic subjects with scores of ≥58 and low alexithymic subjects with scores of ≤45). Sixteen volunteers [mean age = 22.62 years (SD = 2.47)] with high scores (mean = 64.56, SD = 4.32) on the TAS-20 [8 males (mean = 64, SD = 3.33) and 8 females (mean = 65.12, SD = 5.30)], and 16 volunteers [mean age = 24.12 years (SD = 2.87)] with low scores (mean = 36.56, SD = 4.59) on the TAS-20 [8 males (mean = 35, SD = 3.42) and 8 females (mean = 38.12, SD = 5.28)], were selected for the study. The subjects were all right-handed, as assessed by a lateral preference questionnaire [39] with a handedness score of >0.70 (ranging from 1 to –1, where 1 defines maximal dexterity).

In a clinical interview, the subjects reported no epilepsy or any other neurological condition in themselves and in their family history, no other medical or psychiatric disorder and no contraindication to TMS [40]. All women were tested in the luteal phase of the menstrual cycle in order to avoid the confounding effect of the cyclical ovarian hormonal impact on the transcallosal transfer of young women [41] and none of them used contraceptives. The local ethics committee approved the study and subjects gave their written informed consent.

Materials

Two monopolar magnetic stimulators (Magstim 200) with two figure-of-eight coils with external wing diameters of 9 cm (Magstim Co., Ltd., UK) were linked using a Bistim module (Magstim). The peak magnetic field produced by these coils is about 2.0 T. MEPs were recorded from the abductor digiti minimi (ADM) muscles in both hands. Two Ag-AgCl surface cup self-adhesive electrodes with 9 mm diameter were used. The active electrode was placed over the muscle belly, while the reference electrode was placed over the tendon of the little finger. MEPs were recorded according to standard procedures [42,43] and were stored and analyzed off-line with an EMG-dedicated software (Myto, EBNeuro, Italy).

Procedure

The subjects sat on a comfortable reclining chair and were instructed to keep their hands still and as relaxed as possible, with their eyes open and looking at a point on the wall. First, the junction region of the figure-of-eight coil was positioned approximately over the central sulcus and then moved in 1 cm steps. This procedure was adopted to find the optimal sites of stimulation able to induce MEPs of maximal peak-to-peak amplitude in the contralateral ADM muscle. The coil was held tangential to the scalp and oriented in a posteroanterior direction 45° from the midsagittal axis of the subject’s head. This orientation was chosen because it leads to stronger transcallosal inhibitory effects [44,45]. The individual motor threshold (MT) was assessed following a standardized procedure [43] and defined as the lowest intensity level of stimulation able to produce MEPs of 100 μV amplitude (peak-to-peak) in at least 3 out of 6 consecutive stimulations. This procedure was repeated for both hemispheres. The positions of the coils, marked on the scalp, were kept constant throughout the stimulation.

In the interhemispheric paired-pulse technique, the CS applied to one hemisphere modifies the response to the TS applied to the other hemisphere. The effects depend on the intensity of the CS, the interval between the stimuli (ISI), and the intensity of the TS [46–49]. The following ISIs were used: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 ms. The intensity of CS and TS was set at 120% of the individual MT [31]. Twelve responses per condition were collected and the peak-to-peak amplitude of the induced MEPs in the ADM contralateral to the TS was measured off-line and, subsequently, averaged. The experimental session included 22 blocks of trials [10 conditioned blocks + 1 baseline] × 2 hemispheres. The order of the blocks was randomized and counterbalanced across subjects.
Data Analysis

MTs as well as MEP amplitudes were analyzed by means of a repeated measure analysis of variance (ANOVA) with the between-subject factor group (high vs. low alexithymic subjects) and the within-subject factor hemisphere to assess cortical excitability in high and low alexithymic subjects. Changes in the amplitude of the MEPs induced by TS as a consequence of the preceding CS were expressed as the ratio between conditioned responses (for each ISI) divided by unconditioned responses (to TS alone). A logarithmic transformation was carried out in order to reduce variability of data.

The existence of a TI was first assessed in the two groups (high and low alexithymic subjects) using a four-way repeated measure analysis of variance (ANOVA) with gender (male, female), stimulus (conditioning, conditioned), hemisphere (right, left), and ISI (2, 4, 6, 8, 10, 12, 14, 16, 18, 20 ms) as within- (stimulus, hemisphere, ISI) or across-subject (gender) factors. Callosal inhibition effects that are expressed as significant reductions in MEP amplitude to conditioned (as compared to unconditioned) stimuli are centered around 12 ms ISI [46–49]. After defining the time window critical for callosal transfer (10–14 ms ISIs) via within-group comparisons, differences between low and high alexithymic subjects were compared applying a three-way mixed-design ANOVA with group (low and high alexithymic subjects) as between-subject factor, and hemisphere (right, left) and ISI (10, 12 and 14 ms ISIs) as within-subject factors.

Results

Cortical Excitability

The group (high vs. low alexithymic subjects) × hemisphere ANOVA on MT values showed a significant main effect for group (F1,30 = 5.93; p = 0.02). For high alexithymic subjects, the mean MT at rest was 36.49% (SD = 4.41) of the maximum output of the magnetic stimulator, while for low alexithymic subjects the MT at rest was 32.84% (SD = 4.08) of the maximum output of the magnetic stimulator. The main effects for hemisphere (F1,30 = 0.32; p = 0.58) and group × hemisphere interaction (F1,30 = 0.23; p = 0.64) were not significant. The same ANOVA design on MEP amplitudes induced by the TS alone showed a close-to-significance effect for group (F1,30 = 3.2; p = 0.08). The main effect for hemisphere (F1,30 = 1.38; p = 0.25) and the group × hemisphere interaction (F1,30 = 0.61; p = 0.44) were not significant. For high alexithymic subjects, the mean MEP amplitude was 1,022.1 μV (SD = 345.78), while for low alexithymic subjects, the MEP amplitude was 1,300.62 μV (SD = 512.54).

Interhemispheric Inhibition

For subjects with low alexithymic scores, the ANOVA (gender × stimulus type × hemisphere × ISI) showed main effects for stimulus type (F1,14 = 28.65; p ≤ 0.0001) and ISI (F9,126 = 5.34; p ≤ 0.00001), and a significant stimulus × ISI interaction (F9,126 = 4.57; p ≤ 0.0001). Bonferroni corrected (α = 0.005) post-hoc comparisons of this interaction pointed to significant differences in the 8–18 ISI range, showing a robust effect of reduced MEP amplitudes centered around 12 ms, thus reproducing the findings on interhemispheric interaction found in previous studies [46–49]. This analysis served to confirm the reliability of our methodology and the suitability of our low alexithymic (control) subjects. The same ANOVA in high alexithymic subjects showed a main effect for stimulus type (F1,14 = 6.83; p ≤ 0.05) and a main effect for ISI (F8,126 = 2.48; p ≤ 0.05). No significant effect for gender (F1,14 = 0.094; p = 0.76), stimulus type × gender (F1,14 = 0.02; p = 0.89), hemisphere (F1,14 = 0.13; p = 0.72), stimulus type × hemisphere (F1,14 = 0.01; p = 0.93), or other significant main effects or interactions were found, but there was a trend in the stimulus type × ISI interaction (F9,126 = 1.71; p = 0.09). Exploratory, Bonferroni-corrected (α = 0.005) post-hoc comparisons of this interaction pointed to significant differences at 10

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**Fig. 1.** Mean changes in MEP amplitudes (and SD) in low (■) and high (○) alexithymic subjects at different ISIs. The asterisks indicate the significance of differences in MEP amplitude reduction: *p ≤ 0.05; **p ≤ 0.01.
and 12 ms ISIs, showing only a slight effect of reduced MEP amplitudes.

As presented in figure 1, low and high alexithymic subjects show a similar modulation of the interhemispheric inhibition curve. However, the ‘degree’ of this inhibition appears to be different between low and high alexithymic subjects at different time windows. Therefore, responses in low and high alexithymic subjects were compared for 10, 12 and 14 ms ISIs – the critical time window for callosal transfer. Again, a main effect for ISI (F2,56 = 4.04; p = 0.02) was found with smaller MEP ratios at 12 rather than 10 ms ISIs (p ≤ 0.05 in planned comparisons) and at 14 ms ISIs (p ≤ 0.01 in planned comparisons). More importantly, a main effect for group (F1,28 = 6.08; p = 0.02) was found. The amount of MEP amplitude reduction produced by the TS was significantly greater in the low than in the high alexithymic group (fig. 1). No significant group × gender (F1,28 = 0.34; p = 0.57) and group × hemisphere (F1,28 = 0.91; p = 0.35) interactions were found, and the other main effects or interactions were not significant.

Discussion

Using the interhemispheric paired-pulse paradigm in an alexithymic sample, we directly demonstrated, for the first time, the presence of a specific interhemispheric transfer deficit in alexithymia. The amount of MEP amplitude reduction induced through the TS by a previous CS, within the time window of callosal transfer, was significantly greater in low than in high alexithymic subjects. This reduced interhemispheric inhibition in the high alexithymic group similarly affected the left-to-right and right-to-left transfer, suggesting the existence of a bidirectional deficit without any involvement of a specific hemispheric dysfunction. The results of the present study thus confirm most of the early findings of empirical and indirect studies [15–20] in which the efficiency of interhemispheric transfer in alexithymia was assessed, and provide direct support for the hypothesis that alexithymia is associated with a reduced coordination and integration of the specialized activities of the two cerebral hemispheres [15, 50]. Two recent TMS studies [22, 23] show shorter TI latencies in high as compared to low alexithymic subjects, which are interpreted as a facilitated TI, contrasting with the hypothesis of a transcallosal transfer deficit in alexithymia. However, these results [22, 23] rather suggest that in alexithymic subjects the TI is anticipated (i.e. shorter TI latencies) in time and normal in duration, but they do not provide any quantitative estimate of the amount of this transfer. By using the paired-pulse TMS paradigm, the present study provides a direct measure of the ‘degree’ of the TI, which we have shown to be reduced in magnitude in our high alexithymic sample.

The following points have to be taken into consideration when interpreting our results. First, since the present study does not involve an emotional processing task we may have missed a specific hemispheric dysfunction. Moreover, testing the interhemispheric transfer deficit hypothesis within pathways of the motor system might limit the generalization of our results to emotional processing. However, inhibitory and excitatory networks are present in all areas of the brain as served by different and interconnected neuromodulatory systems. A direct link between emotion and motor control in the human brain could be explained by anatomical, neuroimaging and neurophysiological evidence supporting the existence of anatomical-functional links from the limbic association cortex to premotor-motor areas. Specifically, the caudal portion of the supplementary motor area, with direct connections to the primary motor area, is richly linked with motor cingulate areas which are in turn connected with anterior cingulate areas [51]. This link is likely to represent the anatomical substrate for providing limbic influences at several levels of motor control. An anatomical or functional alteration in one of these regions and its underlying pharmacology could therefore affect other linked functions [52–54]. Several neuroimaging studies point to significant functional [50, 55–57] and anatomical [58] alterations in the right anterior cingulate cortex, posterior cingulate cortex [59] and in other prefrontal areas [50, 56, 57] as well as in the corpus callosum [55] of alexithymic subjects during emotional processing. In normal subjects, Critchley et al. [60] showed that the anterior cingulate cortex is involved in the regulation of autonomic activity. Accordingly, several studies also point to modifications of autonomic responses to emotional stimuli in high alexithymic subjects [61–64]. Taken together, these data suggest a profound modification of the complex interaction pathways that control emotional regulation in alexithymia. Here, we propose a dysfunction of the GABAergic system as a candidate underlying mechanism accounting for the reduced TI found in the present study. It has been recently proposed that TI may be mediated by the GABA A interneurons [65, 66]. Furthermore, in the callosal synapse of the cat motor cortex, TI has been shown to be regulated by presynaptic GABA A receptors [67]. GABAergic interneurons, with their sub-
classes of receptors widely distributed in the corticolimbic system, are indeed critical to the formation of complex behaviors. A defect in their functioning can give rise to a broad range of disturbances in cognitive functioning, such as those observed in schizophrenia [68] and in affective disorders [69].

With respect to the between-group difference in MT and MEP amplitudes, the present results were unexpected. In fact, Richter et al. [23] did not report any difference in MT even though their study had been conducted on a clinical population, while Grabe et al. [22] did not report MT estimations. Therefore, based on our preliminary findings, cortical excitability in alexithymia should be further investigated. It should also be mentioned that these differences could represent a possible confounding factor in interpreting the present results. However, this possibility seems unlikely since an ANCOVA, with group (low and high alexithymic subjects), hemisphere (right and left) and ISI (10, 12 and 14 ms) as factors and MT values as a covariate, still showed the significant differences between high and low alexithymic subjects (F1, 28 = 5.76; p = 0.02).

In conclusion, the interhemispheric transfer deficit is likely to represent a reduced coordination and integration of the high-level cognitive specialized activities of the two cerebral hemispheres, as part of more complex interaction pathways that control emotional regulation, probably through the alteration of the GABAergic system in high alexithymic subjects.

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References


