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Research Report

Brain mapping of emotional prosody in patients with drug-resistant temporal epilepsy: An indicator of plasticity

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ABSTRACT

Introduction: Emotional prosody, a suprasegmental component of language, is predominantly processed by right temporo-frontal areas of the cerebral cortex. In temporal lobe epilepsy (TLE), brain disturbances affecting prosody processing frequently occur. This research assesses compensatory brain mechanisms of prosody processing in refractory TLE using fMRI.

Methods: Patients with focal unilateral epilepsy, right (RTLE) (N = 19), left (LTLE) (N = 19), and healthy controls (CTRL) (N = 20) were evaluated during a prosody decoding fMRI task. The stimuli consisted in spoken numbers with different tones of voice (joy, fear, anger, neutral and silent trials). Participants were instructed to label the emotion with a keypad. "Joy" was removed from the analysis due to a high degree of variability. A lateralization index (LI) was used to see individual differences in the interhemispheric activations of each participant.

Results: Behaviorally, The LTLE and RTLE groups did not differ significantly from each other neither from CTRL. In Negative Emotions versus Baseline contrast, the whole sample analysis showed extensive activations in bilateral superior temporal gyrus, bilateral pre-central and post–central gyrus, right putamen, and left cerebellar vermis. Compared to the LTLE and CTRL, RTLE activated similar areas, but to a lesser extent. The LI analysis revealed

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significant differences in hemispheric laterality of the temporal lobe and the parietal lobe between RTLE compared to LTLE and CTRL, being the RTLE group lateralized towards the left, unlike the other two groups.

Discussion: The LI indicated that, since the CTRL and the LTLE groups recruited putative prosodic regions, the RTLE lateralized prosody processing towards the left, recruiting contralateral nodes, homotopic to the putative areas of the prosody. Considering that the groups did not differ in prosody task performance, the findings suggest that, in the RTLE group, alternative brain nodes were recruited for the task, demonstrating plasticity.

1. Introduction

Humans communicate emotion and affection in vocal signals, favouring personal interaction. This ability is called prosody, a suprasegmental cognitive function of language that transmits information beyond the lexicon or the syntactic order (Ross, 2000). Prosody allows to encode and decode emotions in speech (Ross, 1981), and it is a necessary skill for effective social communication, as it implies empathy, interpretation of social norms, and it is highly connected with theory of the mind (Chakrabarti & Baron-Cohen, 2006). Previous studies found that emotional prosody is processed by temporo-frontal areas predominantly of the right cerebral cortex (Alba-Ferrara et al., 2011; Ethofer et al., 2006; Frühholz et al., 2015).

In some neuropsychiatric diseases, prosody alterations have been reported. In autism spectrum disorders, reports found aprosody when patients red emotions in speech (Wang et al., 2007), as well as in more complex prosody tasks, including irony and context understanding (Wang et al., 2006). Prosody processing is also affected in other conditions. For example, patients with schizophrenia present deficits in prosody compared to patient with bipolar disorders and CTRL (Rossell et al., 2014). Such deficit is more severe in the subgroup of schizophrenia that suffers from auditory hallucinations (Alba-Ferrara & de Erausquin, 2013); or patients with comorbid depression (Koch et al., 2018).

Epilepsy is one of the most common neurological disease, affecting more of 50 million of people in the world (World Health Organization, 2021). Epilepsy may cause alterations in cognitive functions. One of the more common syndromes is TLE, including the mesial temporal lobe epilepsy and lateral temporal lobe epilepsy. TLE is especially studied in relation to language and sound perception (Caplan, 2019). In TLE, a functional compromise of temporal lobe mesial structures can be found during epileptic seizures, including, the amygdala, the hippocampus, and the entorhinal cortex, in addition to the lateral temporal cortex (Lee, 2010), which may cause disturbances in cognitive functions supported by those nodes. Drug resistance epilepsy can be treated by resective surgery. Presurgically, brain mapping of eloquent functions is carried out to minimize the possible sequelae and the potential risk of surgery. Language eloquent areas in candidates for temporal lobectomy can be localized with fMRI and compared to semantic components of language, prosody processing has been overshadowed in epilepsy research. fMRI also revealed dissociations between language subdomains in focal epilepsy (Alba-Ferrara et al., 2018). In some cases, even when the epileptogenic zone (EZ) overlaps putative areas for prosody processing, patients may not have difficulties in prosody tasks. In such cases, assessing the neural underpinning of prosody with fMRI might give hints regarding brain reorganization and plasticity.

Fowler and collaborators (2006) reported a behavioural study on emotion processing in patients with unilateral mesial TLE and amygdala damage. The auditory prosody test consisted in digits spoken with five differing emotional intonation, in which participants had to recognize the emotional valence. None of the twenty-eight patients differed significantly from the forty-six CTRL. Regardless of the compromised side, the results show no significant difference between groups with amygdala asymmetrical deficiency – had reduced volume – in accuracy scores (Fowler et al., 2006). Beyond the fact that the results did not evidence of specific deficiencies between the groups in the prosodic task (Fowler et al., 2006), the study could not disentangle the lateralization of function, neither dissociations between emotional valences.

Another behavioural investigation applied a task to distinguish emotional intonation in spoken sentences to refractory TLE patients before and after surgery, and it did not report significant differences in prosody recognition (Kho et al., 2008). They recruited sixteen left TLE patients and sixteen right TLE, as well as forty-seven CTRL, and applied four different prosody tasks, including an emotional prosody task consisting of neutral sentences (twenty-eight in total) pronounced in emotional tones. In the pre-operative performance of this particular task, the researchers found a significant difference between both groups of patients and the healthy control group. However, the difference was not seen after the surgery and there were no differences between RTLE and LTLE in the task (Kho et al., 2008). Also, the task has a higher semantic load and complexity compared to other emotional prosody tasks, so it is possible that emotional prosody was measured entangled with linguistic components. A previous study by Frühholz et al. (2012) showed that there are several nodes sensitive to subcomponents of prosody processing with high specificity and a delimited role. However, Kho et al. (2008) interpreted that the resected right hemisphere nodes were not essential to perform the tasks.

Another important variable is the age of onset of epilepsy. Laurent et al. (2014) evaluated a total of thirty-nine children

from five to nineteen years with TLE and seventy-two healthy participants. This behavioral study applied socio-visual and socio-auditory tasks –including one of emotional prosody. The prosody recognition task consisted of spoken sentences with an emotional tone, where the meaning was incongruous with the emotional tone (Laurent et al., 2014). The results of this research did not show differences in performance between groups (Laurent et al., 2014). It can be inferred the children with TLE could carry out the task successfully due to a possible brain reorganization of the function. This last possibility is unknown since the research was at the behavioral level, but it can be hypothesized that the appearance of epilepsy during childhood could have led to an optimal reorganization of brain functions, which explains the negative finding.

In summary, the search for dissociation could lead to better understanding of the neural underpinnings of function, its relationship with other language subdomains and would also shed light into the modularity of the mind. A key point of the debate is the laterality of the function (Kotz et al., 2003, 2006; Schirmer & Kotz, 2006). Following this methodological and theoretical line, Alba-Ferrara (2011, 2012, 2018) suggests that the recruitment of left frontal temporal areas may not be indispensable, although they might be associated with the task. Following this last hypothesis, left temporal areas underpin semantics interpretation, and frontal areas are activated for the processing of complex emotions – which require a greater socio-cognitive demand, such as the attribution of the state of mind – but right temporal lobe areas are crucial for prosody.

Alba-Ferrara et al. (2011, 2012) delimited the functional location of the prosody. They determine the participation of the superior left temporal gyrus (LSTG) and right superior temporal gyrus (RSTG) for semantic and prosodic processes delimitating the critical role of RSTG for prosody (Alba-Ferrara et al., 2012). In another fMRI study, they analyzed the independence of prosodic network in relation to the frontal areas and the networks related to executive functions, allowing an understanding of the network of temporal areas, for processing basic and complex emotions (Alba-Ferrara et al., 2011). In the latest study on prosody, Alba-Ferrara et al. (2018) discussed the role of epileptogenic seizures in prosody processing. The central hypothesis is that epilepsy promotes neural reorganization of prosody processing, which explains why patients with RTLE not always present emotional prosody deficits. Such patients might compensate by a recruitment of alternative brain networks via the corpus callosum (Alba-Ferrara et al., 2018). Fibers connecting homotopic areas of the left and right cortices present a crosstalk phenomenon, where atypical areas are actively processing function (e.g., prosody) whose putative node is disturbed. This assumption can also be supported by the reports of cases with alterations of the corpus callosum and aprosodia; e.g., a study by Paul (2003) explains how people with agenesis of the corpus callosum seem to lack an interhemispheric interaction of critical aspects of language processed by the right hemisphere.

It is not uncommon for patients with refractory TLE to present multiple foci, called secondary foci. This is known as secondary epileptogenesis (Scharfman, 2002), a type of maladaptive plasticity. An adaptive functional reorganization may also occur. The formation of new foci has been seen in animal experiments with the technique of kindling, in which the brain is stimulated electrically with a stimulus that initially leads only to an after-discharge but eventually causes the formation of an epileptogenic focus (Goddard, 1967), and this could be an explanation of what happens in relation with the plasticity in epilepsy.

The current study aims to find neural compensatory mechanisms of emotional prosody recognition in patients with drug resistant TLE (right or left). We expected to find similar performances between the right and left TLE groups in the behavioral task, particularly in accuracy, and differences in functional activation elicited by the task between TLE groups and CTRL. We also hypothesized that we would find good behavioral performance and activation of the RSTG (emotional prosody area) in LTLE and CTRL. On the contrary, we predicted atypical activations in patients with RTLE compared to the other two groups.

2. Methods

2.1. Subjects

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1.1. Temporal lobe epilepsy patients

19 LTLE and 19 RTLE candidates for unilateral temporal lobectomy for relief of drug resistant epilepsy were recruited from Hospital "El Cruce Nestor Kirchner" in Florencio Varela, Province of Buenos Aires, Argentina. The group was formed by patients with unilaterally temporal lobe epilepsy (for more information, see the supplementary material). All patients underwent video EEG to determine the EZ and to differentiate epileptic seizures from non-epileptic seizures of psychogenic origin. Inclusion criteria consisted in at least one characteristic clinical event documented by simultaneous ictal abnormalities, evidenced in the EEG, confirmed by VEEG, and diagnosed according to the ILAE nomenclature (Berg et al., 2010; Scheffer et al., 2016). We excluded patients who did not complete all diagnostic steps, or who did not sign informed consent and/or have mental retardation (attendance at a special school and/or have intellectual disability (attendance at a special school and/or IQ equal to or less than 70 on the Wechsler IQ Test). The patients did not report any hearing problems.

2.1.2. Control group

20 healthy participants (14 female) were recruited for the control group (CTRL). Some were students (6 graduate and 9 undergraduate) of the Faculty of Medicine of the University of Buenos Aires, others had university technical training (2 graduates and 1 undergraduate) and 2 were high school graduates. The participants did not report any hearing problems (Table 1). Significant differences between the control group, the RTLE and LTLE groups was found in the years of education (Table 1).

Table 1 – Demographic data.

	CTRL n: 20	LTLE n: 19	RTLE n: 19	*One-Way* ANOVA
	M (SD)	*M (SD)*	*M (SD)*	
Sex (F/M)	14/6	11/8	12/7	
Age	30.75 (11.48)	34.26 (10.61)	30.0 (10.04)	$p = NS$
Years of Education[a]	15.47 (2.75)	10.78 (2.91)	13.10 (2.72)	$p < .05$
Onset Epilepsy	–	13.33 (9.25)	11.25 (8.06)	$p = NS$

CTRL, healthy controls; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; S.D., standard deviation.
[a] Difference between the RTLE and LTLE with the CTRL, group was significant at $p < .05$ (One-Way ANOVA test, DSM post hoc test).

2.1.3. *Contentment*

All participants (CTRL and TLE) signed an informed consent to participate voluntarily and could leave the experiment at any time. Also, the study has the approval of the Bioethics Commission of Hospital "El Cruce" and Instituto de Oncología Ángel H. Roffo, based on the Declaration of Helsinki. All participants complied with the current guidelines for fMRI research. No part of the study procedures, analyses was preregistered prior to the research being conducted.

2.2. *Materials and procedure*

2.2.1. *Psycholinguistic assessment*

Manual dominance was evaluated through the Edinburgh Handedness Inventory, which provides a handedness index (Oldfield, 1971). All subjects were assessed with the Word Accentuation Test (WAT) (Burin et al., 2000) to estimate premorbid verbal IQ. Subjects were also evaluated with the Digit Span to measure their attentional capacity (Wechsler, 2002), where significant differences between the CTRL, the RTLE and LTLE groups were found (Table 1).

2.2.2. *Psychiatric evaluation*

A Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV or SCID-I Spanish version (First et al., 1999) was conducted for all participants to rule out comorbidities with Axis I mental disorders. Prior to the interview, the subjects were asked about possible anxious symptomatology, with the State-Trait Anxiety Inventory (Spielberger et al., 1971) and depressive symptoms, with the Beck Depression Inventory (BDI-II, Argentine adaptation) (Beck et al., 2006; Brenlla & Rodriguez, 2006) (Table 1). Legal copyright restrictions prevent public archiving of the various assessments and diagnostic instruments used in this study, which can be obtained from the copyright holders in the cited references in sections 2.21 and 2.22.

2.2.3. *Emotional prosody tasks (Stimuli)*

The task consisted in sixty-four (64) recorded stimuli from actors pronouncing three-digit numbers in Spanish, imposing different tones of voice (happy, fearful, angry, and neutral). Sixteen (16) stimuli were included for every emotional valence, and sixteen (16) silent events were also presented. This task was based on a study on vocal emotional expression (Banse & Scherer, 1996). The vocalizations were made by two professional actors (men) recorded on two (2) channels, with a sampling rate of 22.05 kHz, and microphones, mounted on a stand. The sound files were encoded in 16-bit PCM interleaved format, high byte format first. The utterances lasted a mean of 1916 msec (SD = 24).

Participants were instructed to label the emotion of the voice by a key press. All participants performed practice trials offline before undergoing the MRI session. Once in the scanner, participants were comfortably positioned in dorsal decubitus, with MRI compatible pneumatic headphones. In the acquisition of volumetric T1 images, the technician assured the stimuli could be heard properly. Participants were given a response box to answer. Before the start of each run, participants were reminded of the instructions through the intercom. The experiment consisted in two runs of five (5) minutes and twenty (20) seconds (excluding the 10 sec. we collect 5 dummies during instruction time) in which the stimuli were presented in an event related manner and silent trials were used for jittering. Stimuli were pseudo-randomly presented with E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania), each trial lasted 4000 msec, with an intertrial interval of ±500 msec (mean).

2.3. *fMRI*

2.3.1. *Image acquisition*

fMRI's images were acquired with a Siemens 3T Trio scanner with a standard 8-channel SENSE birdcage head coil. Functional images were acquired through a sequence sensitive to BOLD contrast. Volumes were acquired following the orientation AC-PC (anterior–posterior commissure). Each cut had a resolution of 64 × 64 pixels, a voxel size of 3.75 × 3.75 × 4 mm3, with no space between cuts and were acquired in an interleaved sequence. The volumes were recorded at a repetition time (TR) of 2 sec, echo time (TE) of 35 msec. and a radiofrequency pulse angle of 900. A total of 165 volumes were collected on each run, of which the first five were discarded to ensure the stabilization of the signal. The whole run lasted 5.5 min and and the whole session had a duration of around twenty-five minutes. For patients and CTRLs the MRI was performed according to the temporal lobe epilepsy protocol, which consists of sagittal plane in volumetric T1 (mprages), field mapping to correct signal loss in areas adjacent to the cavities (orbitofrontal, lateral temporal), and T1* sequence (functional). The T1 3D data were acquired in the sagittal plane with TR = 2 msec., TE = 3.7 msec.; inverted angle = 80, feld of view (FOV) in plane = 214 × 214 mm and matrix of size 240 × 240, coding phase in antero-posterior direction and from left to right, block thickness = 128 mm, Nav = 1 (average number of signals), voxel size = .89 × .89 × 1.0

mm3, acquisition of bandwidth = 191.5 Hz/pixel, and parallel image (SENSE factor = 8).The images were reconstructed with an intra-plane interpolation of factor = 2 in each dimension.

All row data and digital study materials are available on the following link: https://osf.io/tz3y2.

2.3.2. *Image processing*

The functional images were pre-processed and analysed with the SPM12 software (https://www.fil.ion.ucl.ac.uk/). The images were realigned by applying a rigid body spatial transformation of each of the BOLD volumes in the fifth volume of the first run to eliminate motion artefacts. Functional images were recorded together with the anatomical image and were normalized stereotactically in the space of the INM (https://www.mcgill.ca/neuro/) based on the 3D structural volume weigh.

2.3.3. *Analysis*

A statistical analysis was performed based on the general linear model using SPM12. In a design related to events, for each of the different emotional tones of the voices, as well as for the neutral stimuli, the expected hemodynamic response was modeled by the canonical hemodynamic response function HRF (Friston et al., 1998) and its temporary derivative, as implemented in SPM12, with silent tests that serve as a baseline and for jittering. Subsequently, estimates of HRF regressor parameters for each of the different conditions were calculated from the adjusted least squares of the model to the time series. The resulting contrast images were subjected to a sample test that was subsequently explored at a threshold of $p < .001$. The correction for multiple comparisons with $p < .05$ was achieved using a group extension threshold procedure first described by Slotnick (2003; 2004). The procedure of threshold of the extension of the grouping is based on the fact that, given the spurious activity or the noise (error of type I with respect to the voxels), the probability of observing groups of bigger activity (spatially contiguous) decreases. Therefore, the threshold of the cluster extension can be applied to ensure an acceptable level of type I error corrected for the cluster. For a single voxel type I error of $p < .001$, this procedure identified a group extension of 18 contiguous resampled voxels as needed to correct for multiple whole-brain voxel comparisons in $p < .05$. We used a model that uses a regressor that reflects the standardized estimates (Z-scores) of each test by emotional valence. In this way, the effect of the tone on the HRF amplitude between conditions is controlled. The images of the individual contrasts of the first level were subjected to a second level factorial model, resulting in a group analysis to observe the main effects and interactions between the group and each condition. We observed that the exclusion of Joy trials increased signal to noise ratio without compromising the main fMRI results. For that reason, we eliminated these trials from the analysis.

2.3.4. *Laterality Index*

A toolbox of SPM was used to estimate the lateralization of activations at the individual level (Wilke & Lidzba, 2007). The 5000 most activated voxels in both cerebral hemispheres were considered, excluding the 5 mm tissue to the left and right of the interhemispheric fissure, the cerebellum, and clusters of less than 50 voxels (Wilke & Lidzba, 2007; Wilke & Schmithorst, 2006). The LIs were calculated using the LI-toolbox masks for different regions of interest (ROI): the frontal, temporal and parietal lobes separately. LI was calculated based on the following formula:

$$LI = \frac{(\sum activation_{left})/mwf - \sum activation_{right}}{(\sum activation_{left})/mwf + \sum activation_{right}}$$

The LI ranges from −1 to 1, and a negative LI implies relatively more activation of the right hemisphere during the task, whereas a positive LI implies more activation of the left hemisphere (Wilke & Lidzba, 2007; Wilke & Schmithorst, 2006). If the activations of left hemisphere and right hemisphere are identical, LI will be equal to zero.

3. Results

3.1. *Neuropsychological and psychiatric results*

The results of the neuropsychological evaluation are shown in Table 2.

3.2. *Behavioral results*

The three groups were able to carry out the prosodic task successfully. Different One-Way ANOVAs showed that there were no significant differences among the groups in accuracy or in reaction times (Table 3).

3.3. *Neuroimaging results*

Firstly, a whole sample analysis with the three groups collapsed was performed for the contrast negative emotions (fear and anger) minus baseline (neutral and silence). In a preliminary analysis, it was observed that joy contrast generated more variance in the study.

3.3.1. *Activation in whole groups*

The emotional trials activated extensive clusters within the temporal lobes in the STG. Significant additional activations were also observed in the right precentral gyrus, the right putamen, and the cerebellum (Table 4, Fig. 1).

3.3.2. *Activations in individual groups*

3.3.2.1. Activations of negative emotions versus baseline in CTRL group. An analysis of the CTRL group was carried out comparing negative emotions (trials of fear and anger) versus baseline (neutral trials and silences). Emotional trials had a higher BOLD response within the RSTG and the LSTG. Additional activations were also observed in the right putamen, the left cerebellum, the left precentral gyrus, and the supplementary motor area (Table 5, Fig. 2).

3.3.2.2. Activations of negative emotions versus baseline in LTLE group. An analysis of the LTLE group was carried out comparing negative emotions (trials of fear and anger) versus the baseline (neutral trials and silences). This contrast elicited BOLD response within the temporal lobes in the left middle

Table 2 – Neuropsychological and psychiatric results.

	CTRL n: 20	LTLE n: 19	RTLE n: 19	*One-Way* ANOVA
	M (SD)	*M (SD)*	*M (SD)*	
Edinburgh	73.15% (44.97)	80.73% (23.73)	92.66% (10.33)	$p = NS$
Digit Span[a]	10.70 (2.43)	7.68 (2.76)	7.73 (2.44)	$p < .05$
WAT	5.38 (2.59)	9.67 (3.51)	9.29 (5.81)	$p = NS$
BDI[b]	4.44 (4.42)	13.29 (10.94)	7.19 (6.03)	$p < .05$
STAI-S	21.68 (10.68)	16.05 (10.85)	16.14 (10.92)	$p = NS$
STAI-T	27.0 (12.22)	22.35 (12.63)	22.21 (10.04)	$p = NS$

CTRL, healthy controls; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; S.D., standard deviation; WAT, Word Accentuation Test (number of errors); Edinburgh, Manual dominance BDI, Beck Depression Inventory; STAI-S, State-Trait Anxiety Inventory-State; STAI-T, State-Trait Anxiety Inventory-Trait.

[a] Difference between the CTRL and LTLE, group was significant at $p < .05$ (One-Way ANOVA test, DSM post hoc test).

[b] Difference between the RTLE and LTLE with the CTRL, group was significant at $p < .05$ (One-Way ANOVA test, DSM post hoc test).

temporal gyrus followed by an activation of the RSTG. Significant additional activations were also observed in the left supplementary motor area, the left inferior frontal gyrus, the left parietal inferior lobe, the left inferior post–central gyrus, the left putamen, and the right cerebellum (Table 6, Fig. 3).

3.3.2.3. Activations of negative emotions versus baseline in RTLE group. An analysis of the RTLE group was carried out comparing negative emotions (trials of fear and anger) versus baseline (neutral trials and silences). Emotional trials elicited BOLD response within the temporal lobes in the RSTG followed by an activation of the LSTG. Significant additional activations were also observed in the left inferior precentral gyrus, posterior ramus, the right cerebellum, the left putamen, the left supplementary motor area, and the left inferior post–central gyrus (Table 7, Fig. 4).

3.4. *Laterality Index results*

Three One-Way ANOVAs show differences between the groups in the temporal, parietal, and frontal lobe activations during prosody processing. By applying an inclusive mask, significant difference in LI was found among the groups RTLE (M = .26, SD = .36), LTLE (M = −.06, SD = .30) and CTRL (M = .01, SD = .34) [F (2,55) = 4.89, $p < .01$] in the temporal lobe during the task. A DSM post hoc test showed that the RTLE lateralized prosody more to the left temporal lobe than CTRL ($p = .025$) and the LTLE ($p = .004$). There was no statistically significant difference between the CTRL and the LTLE ($p = .473$). By using another inclusive mask of the parietal lobe, a One-Way ANOVA test showed that there were significant differences among the groups RTLE (M = .47, SD = .28), LTLE (M = .21, SD = .37) and CTRL (M = .15, SD = .32) [F (2,55) = 5.21, $p < .01$] during the task. A DSM post hoc test showed that the RTLE lateralized more to the left than the CTRL ($p = .003$) and the LTLE ($p = .019$). There was no statistically significant difference between the CTRL and the LTLE ($p = .531$). The last One-Way ANOVA with an inclusive mask of the frontal lobes show significant differences among the groups RTLE (M = .42,

Table 4 – Overview of results obtained during Negative Prosody > Baseline contrast (FWE$p < .0001$).

Site	Region	Side	T	k	MNI Coordinates
Temporal Lobe	STG	L	19.79	15,726	−54, −16, 4
	STG	R	19.05	3897	58, −22, 6
Cerebellum	Declive	L/R	14.10	2333	−26, −60, −26
Lenticular Nucleus	Putamen	R	12.16	1193	24, 12, 2
Frontal Lobe	PCG	R	10.72	651	54, 2, 42

R, right; L, left; T, peak level; k, cluster size in the number of voxels; MNI, Montreal Neurological Institute; STG, superior temporal gyrus; PCG, precentral gyrus.

Table 3 – Overview of the behavioral results of the prosody task.

Emotional Valence		CTRL *M (SD)*	RTLE *M (SD)*	LTLE *M (SD)*	*One-Way* ANOVA
Joy	Accuracy	75% (31)	70% (28)	71% (24)	$p = NS$
	RT (msec)	1994 (654)	1682 (343)	1838 (293)	$p = NS$
Anger	Accuracy	61% (36)	61% (31)	64% (31)	$p = NS$
	RT (msec)	1732 (1093)	1635 (414)	1870 (322)	$p = NS$
Fear	Accuracy	79% (25)	70% (29)	67% (31)	$p = NS$
	RT (msec)	1980 (694)	1705 (269)	1735 (358)	$p = NS$
Neutral	Accuracy	79% (27)	74% (28)	69% (32)	$p = NS$
	RT (msec)	1969 (624)	1742 (375)	1774 (360)	$p = NS$
Total prosody	Accuracy	74% (25)	69% (26)	69% (26)	$p = NS$
	RT (msec)	1919 (708)	1691 (282)	1808 (291)	$p = NS$

RT, Reaction Times; M, mean; SD, Standard Deviation; msec, milliseconds.

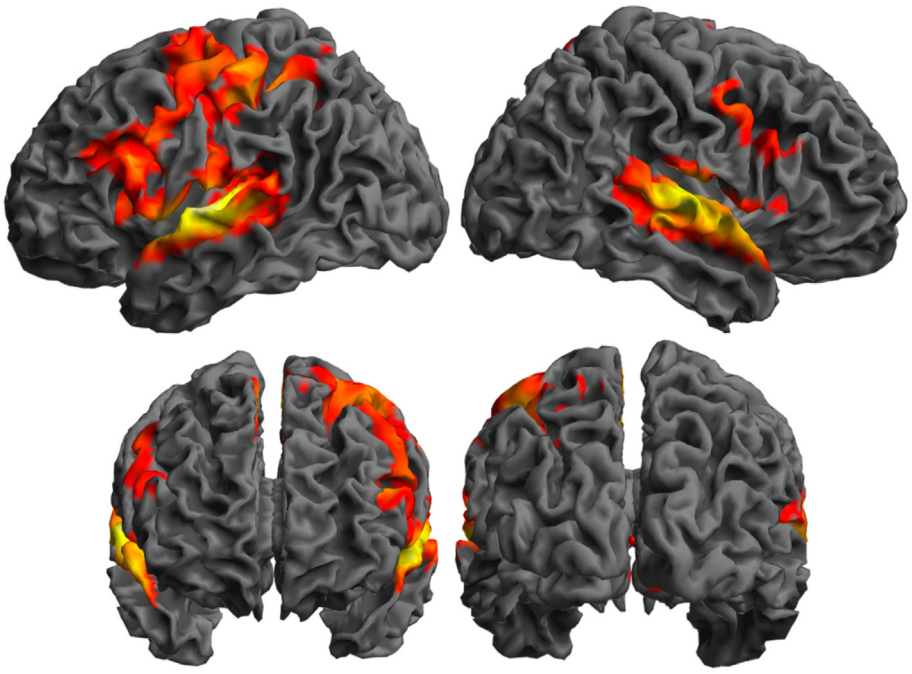


Fig. 1 – Overview of results obtained during Negative Prosody > Baseline contrast (FWE*p* < .0001).

Table 5 – Overview of results obtained from the CTRL during Negative Prosody > Baseline contrast (FWEp<.05).

Site	Region	Side	T	k	MNI Coordinates
Temporal Lobe	STG	R	12.69	1624	62, 0, −6
	STG	L	11.93	1582	−56, −6, −4
Lenticular Nucleus	Putamen	R	11.71	127	24, 12, 4
Cerebellum	Declive	L	9.78	46	−24, −64, −22
Parietal Lobe	PCG	L	9.78	623	−46, −32, 44
Extra-Nuclear	Putamen	L	9.70	338	−30, 0, −2
Frontal Lobe	SMA	R/L	9.56	250	−2, −4, 58

R, right; L, left; T, peak level; k, cluster size in the number of voxels; MNI, Montreal Neurological Institute; STG, superior temporal gyrus; PCG precentral gyrus; SMA, supplementary motor area.

SD = .30), LTLE (M = .50, SD = .30) and CTRL (M = .17, SD = .40) [F (2,55) = 5.04, $p < .010$] during the task. A DSM post hoc test showed that the RTLE ($p = .026$) and LTLE ($p = .004$) lateralized more to the left than the CTRL ($p = .025$). There was no statistically significant difference between the RTLE and the LTLE ($p = .453$) (Graphic 1).

4. Discussion

The present investigation sought to understand the compensatory cerebral mechanisms of prosody processing in refractory TLE through an fMRI task. Behaviorally, all groups were able to perform the task above chance level and did not

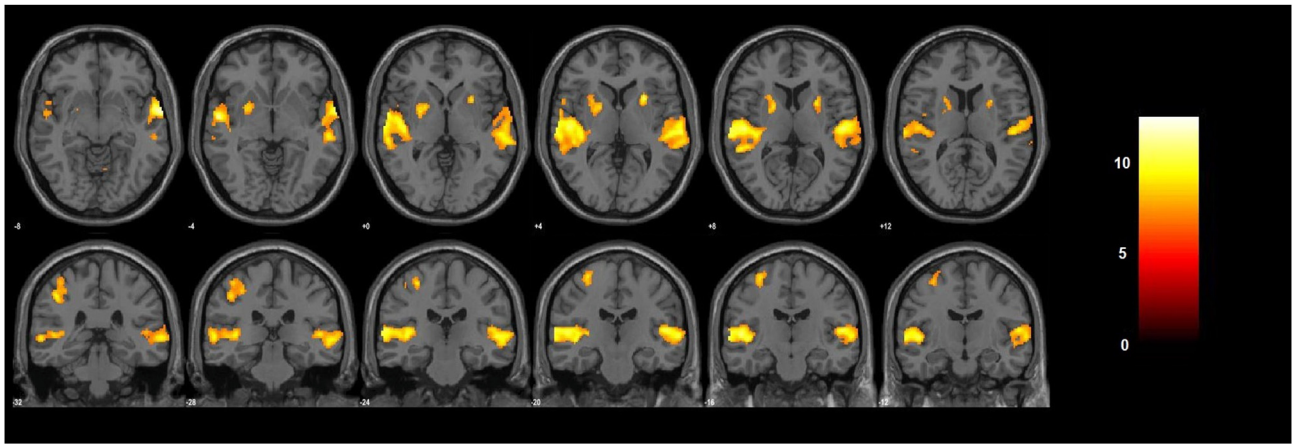


Fig. 2 – Overview of results obtained from the CTRL during Negative Prosody > Baseline contrast (FWEp<.05).

Table 6 – Overview of results obtained from the LTLE during Negative Prosody > Baseline contrast (FWE*p* < .05).

Site	Region	Side	T	k	MNI Coordinates
Temporal Lobe	STG	L	14.40	1529	−54, −18, −4
	STG	R	12.79	1575	56, −24, 6
Frontal Lobe	SMA	L	10.97	696	−6, 12, 46
	IFG	L	10.92	227	−48, 16, 22
Parietal Lobe	SMG	L	10.35	526	−44, −42, 50
	PTCG	L	10.35	49	−54, −20, 26
Lenticular Nucleus	Putamen	L	10.34	189	−20, −2, 8
Cerebellum	Culmen	R	10.23	324	12, −48, −18

R, right; L, left; T, peak level; k, cluster size in the number of voxels; Z, Z-Score; STG, superior temporal gyrus; SMA, supplementary motor area; IFG, inferior frontal gyrus; SMG, supramarginal gyrus; PTCG, postcentral gyrus.

Table 7 – Overview of results obtained from the RTLE during Negative Prosody > Baseline contrast (FWE*p* < .05).

Site	Region	Side	T	k	MNI Coordinates
Temporal Lobe	STG	R	14.64	1296	58, −18, 0
	STG	L	13.78	1723	−64, −10, −2
Frontal Lobe	PCG	L	12.18	524	−54, 6, 30
Cerebellum	Culmen	R	11.47	234	10, −58, −12
Lenticular Nucleus	Putamen	L	9.63	348	−24, −4, 4
Frontal Lobe	SMA	L	9.47	317	−6, 8, 44
Parietal Lobe	PTCG	L	8.66	352	−46, −26, 58

R, right; L, left; T, peak level; k, cluster size in the number of voxels; MNI, Montreal Neurological Institute; STG, superior temporal gyrus; PCG, precentral gyrus; SMA, supplementary motor area; PTCG, postcentral gyrus.

differ in accuracy or reaction time. The ability to decode prosody was intact also in the RTLE group. The neuroimaging results showed an essential role of the RSTG for emotional prosody perception, in line with previous findings from the literature (Alba-Ferrara et al., 2011, 2012; Ethofer et al., 2006, 2012; Mitchell & Ross, 2008; Ross et al., 1988; Wildgruber et al., 2006). Our results offer additional support to Ross and Mesulam's hypothesis (1979), as we found a predominant role of the right hemisphere in emotional prosody, which connects and interacts with the functional anatomical organization of propositional language in the left hemisphere. In other words, just as the left posterior superior temporal lobe is essential for verbal-semantic comprehension, the homologous contralateral region, the right posterior-superior temporal lobe (BA 22) is essential for the understanding of emotional prosody (Ross & Monnot, 2008). Since prosody is a suprasegmental component of the language, the activation of the STG bilaterally is expected in any prosody task. Still, right hemisphere putative nodes are meant to have a crucial role. Importantly, activations in left putative language areas may underlie explicit labeling of the emotion during the task. In summary, whole group findings demonstrated that emotional prosody trials elicited extended clusters within an interhemispheric network (Frühholz et al., 2012) composed of the temporal lobes in the STGs, reinforcing models on of the importance of the right hemisphere for prosody (Ross & Monnot, 2008).

4.1. *Prosodic recognition in the control group and the left temporal lobe epilepsy*

In the CTRL and the LTLE groups, the activation of the RSTG was greater than its contralateral side, showing recruitment of an extensive region which included Brodmann's area 22 and other nodes mirroring language related areas (e.g., BA 41,42). Another elicited activation was the LSTG, overlapping Wernicke's area. This activation may be due to the verbal labeling of the emotional valences, and not related to prosody *per se* (Mitchell & Ross, 2008). Wernicke's area is essentially associated with verbal-semantic comprehension, being a vital part of language processing, since its alteration can lead to both semantic and phonological problems (Mesulam et al., 2015).

Our results also showed other areas of interest associated with prosody processing, which are also in line with previous research (Mitchell & Ross, 2008; Wildgruber et al., 2006). The recruitment of the Lenticular Nucleus and the Putamen was expected, as these nodes are functionally connected during the decoding of vocal emotion (Leitman et al., 2010; Paulmann et al., 2008; Péron et al., 2015; Ross & Monnot, 2008). The cerebellum is related to the cognitive-affective response necessary for language and prosody (Argyropoulos et al., 2020),

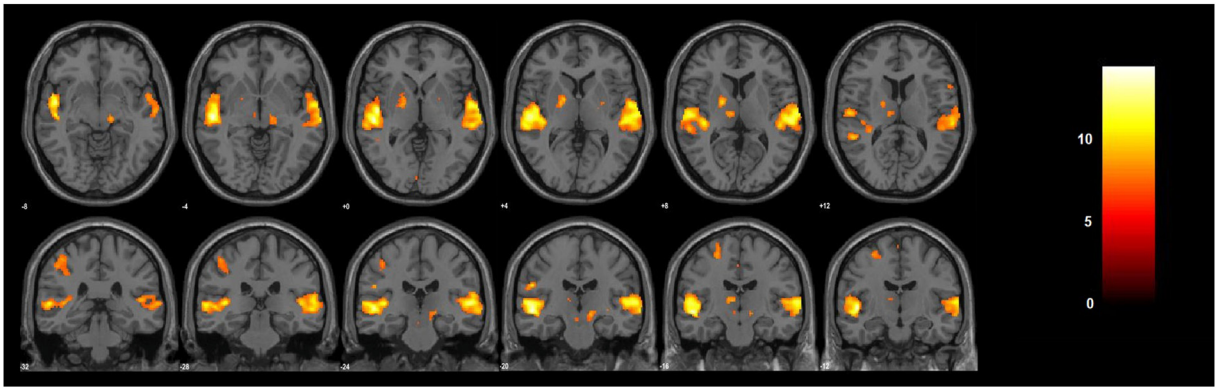


Fig. 3 – Overview of results obtained from the LTLE during Negative Prosody > Baseline contrast (FWE*p* < .05).

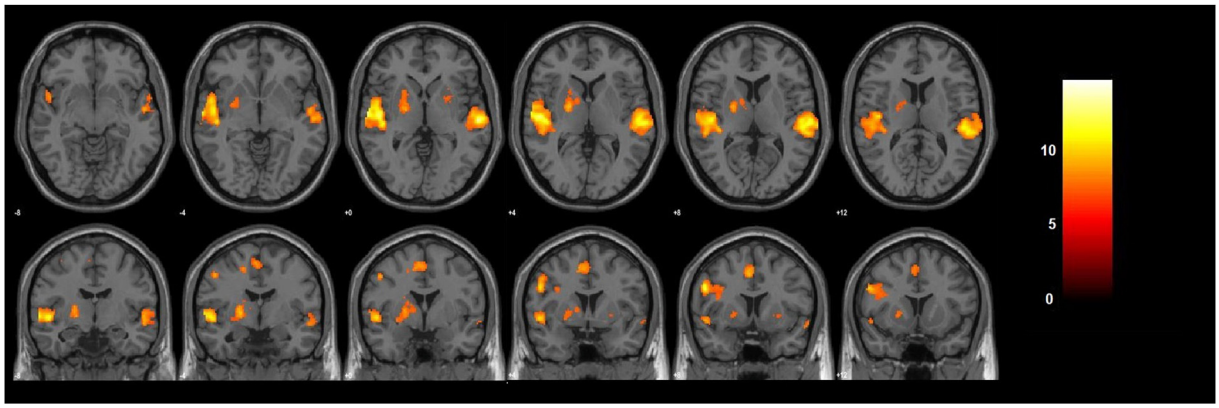
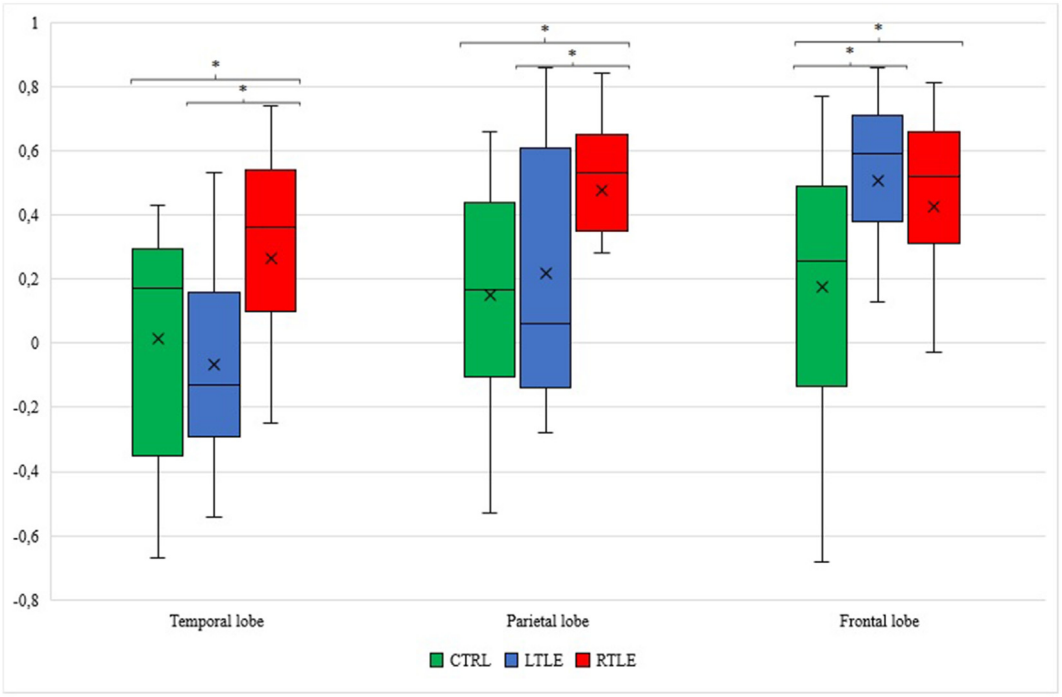


Fig. 4 – Overview of results obtained from the RTLE during Negative Prosody > Baseline contrast (FWE*p* < .05).



Graph 1 – Laterality Index results of the temporal, parietal, and frontal lobe from the individual cases. R, right hemisphere; L, left hemisphere; CTRL, healthy controls; LTLE, left temporal lobe epilepsy; RTLE right temporal lobe epilepsy. Several One-Way ANOVAs presents differences between the groups in the temporal, parietal and frontal lobe and deferments DSM post hoc test showed that significant differences between the RTLE and the LTLE and the CTRL group.

together with the basal ganglia (Paulmann et al., 2008), but it has also been postulated as a central node for the recognition of musical rhythms (Nozaradan et al., 2017). Other activations may be due to the motor response for the task. For example, the inferior postcentral gyrus, may relate to the sensitive response of the task activity (press the button) and the medial frontal gyrus, may relate to the motor planning of the response, or with the motor activation provoked for a preparation of motor responses to the perceived emotion (a mimic of a communicative gesture to respond to emotion) (Warren et al., 2006). In the view of this result, the LTLE group presented similar activations to the CTRLs, without significant differences in the temporal and parietal areas. However, the frontal areas were differentially activated in LTLE compared to CTRL and both groups also differed in frontal lobe laterality strength – with the direction towards the left in LTLE (see graphic 1). This result may be due to a particular cognitive strategy of LTLE when carrying out cognitive tasks with semantic content.

4.2. *Prosody and right temporal lobe epilepsy*

Patients with RTLE presented more extensive activations of the LSTG than CTRL and LTLE. Although the EZ coincided with

the putative prosody nodes (RSTG), the group successfully performed the prosody recognition task – possibly, recruiting nodes contralateral to the putative pathway (see Table 2). The significant differences in the LI (see graphic 1) between the RTLE and the other two groups reinforces the hypothesis of a reorganization of function in left temporal zones. The lateralization towards left nodes represents an abnormality of the typical activations of emotional prosody recognition, a domain that was previously categorized as principally lateralized towards right temporal zones. It could be speculated that the activation of the LSTG could be linked to semantic comprehension processing, however, it is unlikely as the applied paradigm had minimal semantic content and a lack of syntax (spoken digits). It is noteworthy that RTLE patients' performance did not differ from that of the other two groups, although their EZ was right sided, affecting putative prosody nodes. This result hints at the cerebral reorganization of prosody in the contralateral hemisphere.

Other activations (e.g., in the frontal lobe, cerebellum, and the putamen), similar in the other groups, could be interpreted as part of the emotional prosody pathway. However, it is important to note, beyond the other areas involved, the LSTG seems to have played a central role in the RTLE group in prosody processing. Prosody did not move to the left side of the brain, since the activation of the right lateral temporal lobe remained in some cases with RTLE, but in these patients there was evidence of a left hemispheric dominance for prosody processing. A possible explanation for this functional reorientation could be that given by Tompkins and Flowers (1985), who argue that faced with a complex or difficult stimulus or task, the demand for information from the left auditory cortex will be greater. This hypothesis is in line with our results in the RTLE group, as the putative nodes for prosody might be perturbed by the abnormal epileptogenic tissue, increasing the difficulty to perform the task, and thus recruiting supplement nodes.

Left hemisphere can be coactivated in its attempt to extract phonetic-segmental information from acoustic stimuli, independently of whether these contain significant phonetic-segmental information. Activation of the left auditory cortex during the decoding of emotional prosody seems to depend on the verbal complexity or linguistic load of the processing task (Mitchell & Ross, 2008), or even on the damage of a prosody putative area (Alba-Ferrara et al., 2018). In summary, emotional prosody activations in RTLE are signs of plasticity (Alba-Ferrara et al., 2018) and the activation of the bilateral STG may be caused by the reorganization of the neural correlates of prosody processing in patients.

Unlike diseases such as Parkinson's (Pell & Leonard, 2003) – an example of neurological disease in which prosody alterations have been detected – a characteristic of focal epilepsy is that it favors the reorganization and plasticity of mental functions, similarly to cerebrovascular accidents (Starkstein et al., 1994). The results of the present investigation appear to illustrate the use of unconventional networks, depending on the EZ. The EZ, even if not fully overlapping a function's putative area, can perturb adjacent nodes, triggering brain reorganization by recruiting alternative compensatory pathways. The unique characteristics of drug resistant epilepsy and the continuous advances in fMRI have allowed the elucidation of brain reorganization in semantic language (Hamberger & Cole, 2011) and in memory (Bonelli et al., 2013), and our results extend it to prosody. The results of previous investigations are in agreement with our findings (Fowler et al., 2006; Kho et al., 2008; Laurent et al., 2014).

Brain reorganization of cognitive functions may also be influenced by medication (Selai et al., 2005). Our study was carried out with patients with drug resistant epilepsy. Given the results of the present study, it is not possible to rule out the atypical representation of prosody might have been influenced by the medication. Nevertheless, the fact that the RTLE group is different from the other two groups makes this possibility unlikely– since both groups of epilepsy (left and right) were medicated (see supplementary material).

Unlike aphasic syndromes, the organization of emotional prosody in the brain has created controversies, because emotional prosody deficits can occur after left or right brain damage (Ross & Monnot, 2008). Because its dependency and connection with structuring of general semantics (as a suprasegmental function), and with the most primitive emotions, it is expected that emotional prosody is reorganized in other brain structures. In conclusion, the lateralization of language functions is more relative, rather than absolute in epilepsy (Friederici & Alter, 2004; Mitchell & Ross, 2008).

We speculate that, in patients with refractory TLE, an adaptive functional reorganization is possible thanks to the corpus callosum. This network of fibers allows emotional prosody, which requires a great deal of paralinguistic interpretation, to be carried out by exciting and inhibiting of the interhemispheric zones connecting the temporal areas. It is possible to hypothesize that brain alterations caused by refractory RTLE do not impair prosodic processing because the corpus callosum, necessary for the normal processing of prosody, has allowed the reorganization of the prosodic network.

We foresee further lines of research comparing the pre and postoperative processing of prosody. In this next step, it would be expected that, after a temporal lobectomy, patients who have already been evaluated preoperatively can carry out the prosodic task with a similar performance as before surgery. More precisely, postsurgically, we would expect to find similar prosody brain organization than presurgically, as LTLE prosody nodes would have been untouched and RTLE would have already switched putative prosody representation before surgery due to the overlapping with the EZ. In line with our speculation, at the behavioral level it has been shown that prosody processing performance does not decrease after surgery, regardless whether temporal lobectomy was left or right sided (Milesi et al., 2014; Prete et al., 2014).

5. Conclusion

The present investigation carried out an evaluation of emotional prosody brain representation in a population with drug resistant TLE, candidates for lobectomy, obtaining information about the compensatory cerebral mechanisms of prosody processing in epilepsy. When collapsed across hemispheric focus, the patients showed bilateral activations in the temporal lobes, specifically the STG, during emotional prosody processing. When separating the groups, LTLE and

CTRL recruited the same putative prosody regions on the right. Our results showed the group with RTLE recruited the STG in the left hemisphere, homotopically to the putative areas of prosody processing, indicating a brain reorganization for prosody in patients with RTLE. In short, the precision in the task did not differ between groups, although they recruited different brain nodes that assumed the function successfully. This study concludes that when the prosody processing network is affected by TLE, cerebral plasticity may occur. A further line of research should investigate the reorganization of emotional prosody after temporal lobectomy, since there is scant evidence from longitudinal studies comparing the recognition of prosody pre- and post-surgically.

Credit author statement

All authors have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design analysis, writing, or revision of the manuscript.

B. Elizalde Acevedo drafted the first version of the manuscript and participated in data acquisition, analysis, and interpretation of the results.

M. A. Olano carried out data acquisition, analysis, and interpretation of the results.

M. Bendersky helped with data analysis.

S. Kochen assisted with participant recruitment and revised the manuscript critically.

V. Agüero Vera assisted with participant recruitment and data acquisition.

N. Chambeaud assisted with participant recruitment and data acquisition.

M. Gargiulo assisted with participant recruitment and data acquisition.

J. Sabatte assisted with participant recruitment and data acquisition.

Á. Gargiulo assisted with participant recruitment and data acquisition.

L. Alba-Ferrara designed the study and revised the manuscript critically for important intellectual content.

Open practices

The study in this article earned an Open Data – Protected Access badge for transparent practices. Materials and data for the study are available at https://osf.io/tz3y2.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2022.04.014.

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