TITLE

What happens to the inhibitory control functions of the right inferior frontal cortex when this area is dominant for language?

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ABSTRACT

A low number of individuals show an atypical brain control of language functions that differs from the typical lateralization in the left cerebral hemisphere. In these cases, the neural distribution of other cognitive functions is not fully understood. Although there is a bias towards a mirrored brain organization consistent with the Causal hypothesis, some individuals are found to be exceptions to this rule. However, no study has focused on what happens to the homologous language areas in the right frontal inferior cortex. Using an fMRI-adapted stop-signal task in a healthy non right-handed sample (50 typically lateralized and 36 atypically lateralized for language production), our results show that atypical lateralization is associated with a mirrored brain organization of the inhibitory control network in the left hemisphere: inferior frontal cortex, presupplementary motor area, and subthalamic nucleus. However, the individual analyses revealed a large number of cases with a noteworthy overlap in the inferior frontal gyrus, which shared both inhibitory and language functions. Further analyses showed that atypical lateralization was associated with stronger functional and structural interhemispheric connectivity. Importantly, we did not find task performance differences as a function of lateralization, but there was an association between atypical dominance in the

inferior frontal cortex and higher scores on schizotypy and autistic spectrum traits, as well as worse performance on a reading accuracy test. Together, these results partially support the Causal hypothesis of hemispheric specialization and provide further evidence of the link between atypical hemispheric lateralization and increased interhemispheric transfer through the corpus callosum.

KEYWORDS: Lateralization, hemispheric specialization, language, inhibitory control, inferior frontal cortex, left-handers, corpus callosum, schizotypy, autistic spectrum disorder, dyslexia.

INTRODUCTION

One of the oldest findings in human neuroscience is that the brain control of language is lateralized to the left hemisphere[1–3]. However, not all individuals present a typical organization of this function. Some left-handers (22-24%) show an atypical lateralization of language – right or ambilateral[4–6]. Also, this atypical organization is observed in some neurodevelopmental disorders such as schizophrenia, dyslexia, or autistic spectrum[7–9].

How these atypical individuals organize the rest of their lateralized functions has been an extensively researched question. Historically, two different hypotheses

have been proposed to explain the hemispheric specialization of the brain. The Causal hypothesis[10,11] argues that rapid activities requiring the implementation of sequences of cognitive processes are better performed from a single, unilateral control. As a result, these activities are innately programmed to be lateralized, and, according to this model, some functions will be performed better if they are controlled by different hemispheres. The Statistical hypothesis[12], on the other hand**,** postulates that each cognitive function lateralizes independently from the others, making the probability of finding an atypical hemispheric dominance merely a statistical phenomenon. The evidence supporting each theory is mixed. Some studies have obtained data favoring the Statistical hypothesis when analyzing language, visuospatial attention, and face processing[13–15]. Most investigations, however, have demonstrated a mirrored organization of praxis[16,17], visuospatial attention[14,17,18], face recognition[14,17,19], and emotional prosody[17] in most individuals with atypical lateralization of language. Nonetheless, it should be noted that this reversed pattern is not observed in all atypical participants, and all the studies found specific cases in favor of both theories[17].

All these studies have employed a production task to investigate language lateralization in the inferior frontal cortex (IFC), classifying left-handed

68 participants into typical and atypical groups. The rest of the lateralized cognitive
69 functions have been examined using several tasks, but they all mainly depended
70 on posterior parts of the brain. This may have limited the results, given that they
71 were not dealing with directly homotopic functions, which would have been the
72 most sensitive scenario to the proposed advantages of hemispheric
73 specialization[20,21]. To directly address the language production function, which is
74 typically dependent on the left IFC, we would have to use a cognitive task that is
75 typically dependent on the homotopic right IFC. According to previous
76 literature, this function would be inhibitory control. Extensive results support
77 the notion that stopping an ongoing response involves a rightward network that
78 includes the IFC, presupplementary motor area (preSMA), and subthalamic
79 nucleus (STN)[22–25]. Thus, inhibitory control and language production together are
80 the ideal candidates to investigate the Causal vs. Statistical disjunctive. But
81 surprisingly, no investigation to date has analyzed this.

82 In this study, we explored the relationship between the lateralization of
83 language production and inhibitory control. To do so, we divided non-right-
84 handed participants into typically lateralized and atypically lateralized for
85 language using the verb generation task. These two groups then completed the
86 stop-signal task. We hypothesized that the atypical group would show a

mirrored brain organization during the stop-signal task. Additionally, we investigated if a relation existed between the lateralization of both functions and inter-hemispheric structural-functional connectivity[26], as well as with behavioral markers of certain clinical conditions that have been related with atypical lateralization[7–9].

METHOD

1. Participants

Eighty-six participants were included in the present study. They were selected following a functional magnetic resonance imaging (fMRI) language lateralization assessment via a verb generation task. Hence, 50 were typically lateralized for language – left-dominant – (mean ± SD age = 22.4 ± 3.6 years; 24 male, 26 female) and 36 were atypically lateralized (mean ± SD age = 23.4 ± 4 years; 16 male, 20 female).

All the participants were non-right-handed, according to the Edinburgh Handedness Inventory[27,28]. There were no significant between-group differences in age (t_{84} = 1.28; P = 0.2), sex (χ^2 =0.11; P = 0.74), or general intelligence by WAIS-IV matrix reasoning subtest[29] (t_{84} = 1.8; P = 0.08). The participants had no

history of any neurological or psychiatric disorders or head injury with loss of consciousness. Written informed consent was obtained from all participants following a protocol approved by Universitat Jaume I. All methods were carried out in accordance with approved guidelines and regulations.

2. Experimental Design

Participants were recruited via multiple advertisements across Castellón and Valencia universities (bulletin boards, mass emailing, etc.) asking for the collaboration of left-handers in an fMRI brain study. Persons older than 36 years or younger than 16 years were discarded. Valid participants were cited for a first fMRI session, in which they completed the verb generation task and the resting-state acquisition. During this session, we used the BrainWave software (GE HealthCare Technologies Inc.) to visualize real-time data and roughly categorize participants as potentially typical or potentially atypical. 43 participants were found potentially atypical for language lateralization, and were invited to a second fMRI session, along with 43 potentially typical participants. During this second session, participants completed the stop-signal task (scanner) and a reading skill test (out of scanner). Also, data regarding schizotypy personality and autistic spectrum was gathered via self-questionnaires. Note that classification of participants as potentially typical or potentially atypical was

used for screening purposes, and it did not completely match the final assessment.

2.1 Verb generation Task

Expressive language function was measured via fMRI during a computerized verb generation task[30,31] that consists of a 2-block design paradigm with intercalating activation and control blocks. In the activation blocks, participants are asked to overtly say the first verb that comes to mind when visually presented with a concrete noun. In the control blocks, they have to read visually-presented letter pairs aloud. This task lasted for 6 minutes, with a block duration of 30 seconds (6 activation blocks and 6 control blocks), a stimulus duration of 1500 ms, and a blank inter-stimulus interval of 1500 ms. Before entering the scanner, participants practiced with a different version of the task for 1 minute. Stimuli were presented using MRI-compatible goggles (VisuaStim Digital, Resonance Technology Inc.), and responses were recorded with a noise-cancelling microphone (FOMRI III+, Optoacoustics Ltd.) to verify that each participant was engaged correctly in the task.

2.2 Stop-signal Task

Response inhibition was measured via fMRI during a computerized stop-signal task adapted from another study[23]. The task consists of an event-related design paradigm with 'Go' and 'Stop' trials. In the 'Go' trials, participants are asked to manually answer by pressing a button if the visually presented string is a word (has a meaning) or a pseudoword (mimics typical word structure but has no meaning). Words require an index button press, whereas pseudowords require a thumb button press. However, on the 'Stop' trials, the string is followed by a 'beep' noise that signals to the participants to inhibit their response and refrain from pressing any button. The instructions emphasized the importance of going correctly and stopping correctly. However, participants were asked to respond as quickly and accurately as possible and avoid withholding their responses in anticipation of a possible 'beep'.

This task took 13 minutes and 28 seconds, and it was divided into two runs that lasted 6 minutes and 14 seconds each, separated by a 1-minute rest. Each run consisted of 135 trials, of which 32 (23.7%) were 'Stop' trials. All the trials randomly presented words or pseudowords. The trial structure consisted of a fixation crosshair (500 ms), a word or pseudoword (1000 ms, during which the 'beep' may or may not be presented at some point), and a blank inter-stimulus interval (ranging from 500 to 4000 ms, sampled from an exponential distribution

159 truncated at 4000 ms, with mean of 1000 ms). The Stop Signal Delay or SSD (the
160 amount of time after the onset of the word or pseudoword when the 'beep' is
161 presented during 'Stop' trials) changed dynamically during the task after each
162 'Stop' trial, depending on whether inhibition was successful (+25 ms) or
163 unsuccessful (−25 ms), with a minimum of 100 ms and a maximum of 800 ms.
164 The lower the SSD, the easier it is to inhibit the response, and vice versa. Hence,
165 a dynamic SSD normalizes the task's difficulty across all participants based on
166 their performance, aiming at a 50% successful inhibition rate. The SSD used for
167 the first 'Stop' trial was estimated for each participant based on their practice
168 session before entering the scanner. This practice session lasted 6 minutes and
169 used a different set of words and pseudowords. Stimuli were presented using
170 MRI-compatible goggles and headset (VisuaStim Digital, Resonance Technology
171 Inc.), and responses were recorded via an MRI-compatible response-grip
172 (ResponseGrips, NordicNeuroLab). The 'beep' volume was kept at a comfortable
173 level and was constant across participants.

174 **2.3 Resting-state**

175 Functional connectivity was measured via fMRI during a resting-state session[32].
176 In this paradigm, participants were presented with a fixation crosshair and

instructed to just lie in the scanner with their eyes open and try not to sleep or think about anything in particular. This session lasted for 7 minutes. Seven participants did not complete this session due to time constraints, and they were subsequently removed from the functional connectivity analyses.

2.4 Behavioral measures

Individual inhibition speed was estimated by calculating the Stop-Signal Reaction Time (SSRT)[33]. SSRT was computed as the difference between the median reaction time (RT) on correct 'go' trials and the mean SSD on the stop-signal task. It should be noted that technical problems involving the MRI-compatible response-grip invalidated the SSD data of four participants, and so their SSRT was estimated using the SSD data from the practice session instead.

Reading skill was evaluated using the word reading subtest of the PROLEC-SE-R[34], a battery that assesses reading processes in Spanish. Participants had to read four lists of words consisting, respectively, of short familiar words, long familiar words, short unfamiliar words, and long unfamiliar words. Responses were recorded with a microphone, and their accuracy and speed were subsequently measured by computing length (performance during short words

– performance during long words) and familiarity (performance during familiar words – performance during unfamiliar words) indicators.

Schizotypal traits were explored with the SPQ[35], a preclinical self-report questionnaire modeled after DSM-III criteria[36]. This questionnaire evaluates schizotypy based on the three-dimensional model: disorganized traits, cognitive-perceptual traits, and interpersonal traits. For two participants, these data were not collected due to time constraints.

Autistic spectrum traits were explored with the AQ[37], a preclinical self-report questionnaire modeled after DSM-IV criteria[38]. This questionnaire evaluates autistic spectrum based on the "triad" of impaired communication, impaired social skills, and a restricted and repetitive way of acting[39], plus two sub-scales for imagination and attention to detail. For two participants, these data were not collected due to time constraints.

3. Image acquisition and processing

Images were acquired on a 3T General Electric Signa Architect magnetic resonance imaging (MRI) scanner. A 3D structural MRI was acquired for each subject using a T1-weighted magnetization-prepared rapid gradient-echo

sequence (TR/TE = 8.5/3.3 ms; matrix = 512 × 512 × 384; voxel size = 0.47 × 0.47 × 0.5). For the fMRI, a gradient-echo T2*-weighted echo-planar imaging sequence was used in the acquisition of 150 functional volumes on the verb generation task (TR/TE = 2500/30 ms; matrix = 64 × 64 × 30; voxel size = 3.75 × 3.75 × 4), and a different sequence was used in the acquisition of 374 functional volumes during the stop-signal task and 210 functional volumes in the resting-state (TR/TE = 2000/30 ms; matrix = 64 × 64 × 27; voxel size = 3.75 × 3.75 × 4.5).

Task functional images were processed using the Statistical Parametric Mapping software package (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing followed the default pipeline and included: (a) alignment of each participant's fMRI data to the AC-PC plane by using the anatomical image; (b) head motion correction, where the functional images were realigned and resliced to fit the mean functional image; (c) co-registration of the anatomical image to the mean functional image; (d) re-segmentation of the transformed anatomical image using a symmetric tissue probability map; (e) spatial normalization of the functional images to the MNI (Montreal Neurological Institute, Montreal, Canada) space with 3 mm^3 resolution; and (f) spatial smoothing (FWHM = 4 mm). The general linear model for the verb generation task was defined for each participant by contrasting *activation > control blocks*.

The general linear model for the stop-signal task was defined for each participant by contrasting *correct 'stop' > correct 'go' trials.* For both tasks, the BOLD (Blood-Oxygen-Level-Dependent) signal was estimated by convolving the task's block/trial onsets with the canonical hemodynamic response function. Six motion realignment parameters extracted from head motion preprocessing were included as covariates of no interest, and a high-pass filter (128 s) was applied to the contrast images to eliminate low-frequency components. After that, mean BOLD values were extracted from the stop-signal contrast images for the main components of the inhibitory control network: pars opercularis, pars triangularis, preSMA, and STN. Pars opercularis and pars triangularis of the IFC were defined following the criteria of the Harvard-Oxford atlas[40–43]. For the PreSMA region, we used the SMA region, as defined by the same atlas, but including only voxels anterior to MNI Y = 0[44]. STN was defined by a 10mm box centered at MNI coordinates 10, −15, −5[22,45]. Lastly, we computed whole-brain voxel-wise functional asymmetry maps from the stop-signal contrast images. To do so, stop-signal contrast images were flipped at midline, inverting the right and left hemispheres, and subsequently subtracted from the original unflipped contrast images[46].

Resting-state functional images were processed using the Data Processing Assistant for the Resting-State toolbox (DPARSFA)[47], which is based on SPM and the Data Processing & Analysis of Brain Imaging toolbox (DPABI)[48]. Preprocessing steps included: (a) slice-timing correction for interleaved acquisitions; (b) head motion correction (no participant had a head motion of more than 2 mm maximum displacement in any direction or 2° of any angular motion throughout the scan); (c) co-registration of the anatomical image with the mean functional image; (d) new segmentation to DARTEL; (e) removal of nuisance variance through linear regression: six parameters from the head motion correction, white matter signal, cerebrospinal fluid signal, and global mean signal; (f) spatial normalization to the MNI (3 mm^3); (g) spatial smoothing (FWHM = 4 mm); (h) removal of the linear trend in the time series; (i) band-pass temporal filtering (0.01–0.1); (j) normalization to a symmetric template; (k) Voxel-Mirrored Homotopic Computation (VMHC)[49], calculated as the Pearson correlation coefficient of every voxel with its hemispheric counterpart; and (l) normalization of all voxel-wise time courses to Fisher *z* values. Finally, mean VMHC values were extracted for the pars opercularis and pars triangularis regions, as defined by the Harvard-Oxford atlas[40–43].

266 Structural images were processed via voxel-based morphometry (VBM) using
267 the CAT12 toolbox[50], which is based on SPM. Preprocessing steps followed the
268 recommended pipeline and included: (a) segmentation into grey matter, white
269 matter, and cerebrospinal fluid; (b) registration to the ICBM standard template;
270 (c) modulated normalization of grey matter and white matter segments to the
271 MNI template; (d) spatial smoothing (FWHM = 6 mm); and (e) extraction of
272 Regions of Interest (ROIs) values from native space. Three ROIs were delimited
273 by the voxels mapped as genu, body and splenium of the corpus callosum
274 according to the Mori atlas[51]. Total intracranial volume was also extracted for
275 use as covariate of no interest.

276 **4. Individual assessment of functional lateralization**

277 Individual functional lateralization was assessed by calculating the Laterality
278 Index (LI) on the unflipped contrast images[30,31]. We used the bootstrap method
279 implemented in the LI-toolbox[52], based on SPM. LI is a proportion of the brain
280 activation between the two hemispheres, thus giving us information about the
281 direction and degree of hemispheric specialization during a particular function
282 in a single individual. LI ranges from +1 (totally leftward function) to −1 (totally
283 rightward function). For both the verb generation task and the stop-signal task,

284 we explored the LI of the inferior frontal region roughly corresponding to the
285 classic Broca's area: pars opercularis and pars triangularis of the inferior frontal
286 gyrus, according to the Harvard-Oxford atlas[40–43]. This region is critical for both
287 language production[3] and response inhibition[24], depending on the hemisphere.
288 During the verb generation task, language production was classified as typically
289 lateralized (LI higher than +0.4) or atypically lateralized (LI lower than +0.4). We
290 used +0.4 as a cut-off point (contrary to the more traditional +0.2), based on
291 previous findings that emphasized the importance of lateralization strength
292 when grouping individuals[6,53].

293 **5. Statistical analyses**

294 We performed different analyses to investigate the hypothesis that the atypical
295 group would show a mirrored brain organization during the stop-signal task.
296 First, a series of ROI analyses were employed to compare the functional
297 asymmetry of the main components of the inhibitory control network (during
298 the stop-signal task) between typically and atypically lateralized groups. Hence,
299 four repeated-measures MANOVAs (one for the mean BOLD value inside each
300 ROI: pars opercularis, pars triangularis, preSMA, and STN) were calculated,
301 including Hemisphere (left/right) as within-subject factor and Group

302 (typical/atypical) as between-subject factor. All *p*-values were FDR-corrected for
303 four comparisons. This analysis was complemented with whole-brain functional
304 asymmetry contrast maps from the stop-signal task that were compared in
305 typically and atypically lateralized groups based on language production. To do
306 so, we performed a whole-brain two-sample *t*-test (voxel-wise $P < 0.001$; FWE
307 cluster-corrected at $P < 0.05$) via SPM12. Next, a Pearson's correlation was
308 carried out between the LI from the verb generation task and the LI from the
309 stop-signal task used in the individual lateralization classification ($P < 0.05$, 1-
310 tailed). Finally, we explored the functional overlap between both tasks in the
311 subgroup of participants that presented an ambilateral organization of at least
312 one function (n = 48). To do so, we overlayed two one-sample *t*-tests restricted
313 to the IFC: one for the stop-signal task (voxel-wise $P < 0.001$; FWE cluster-
314 corrected at $P < 0.05$), and one for the verb generation task (voxel-wise $P < 0.05$;
315 uncorrected). Functional overlap was then expressed as the proportion of
316 overlapped voxels for every function and hemisphere.

317 Using the LIs from the verb generation and stop-signal tasks, we tested if a
318 linear relationship existed between the functional lateralization of an individual,
319 and several behavioral tests and neuroanatomical measures. Partial Spearman's
320 correlations were computed between the LI of both tasks and: stop-signal task

performance (RT, accuracy, and SSRT), SPQ derived-scores, AQ derived-scores, reading test performance (length and familiarity effects on speed and accuracy), functional connectivity measures (VMHC), and white matter volume of the callosal genu. Age and general intelligence were included as covariates in all analyses. Total intracranial volume was also included as covariate in the volumetric analysis.

RESULTS

1. Inhibitory control shifts its lateralization according to language production

Inhibitory control components during the stop-signal task were defined by four Regions Of Interest (ROIs) and subsequently analyzed by computing MANOVAs, including Hemisphere as within-subject factor and Group (typical/atypical) as between-subject factor. Results showed that all the tested structures presented a statistically significant Hemisphere × Group interaction in their BOLD signal during the 'correct stop > correct go' condition (pars opercularis $F_{1,84} = 25.59$, $P < 0.001$; pars triangularis $F_{1,84} = 19.95$, $P < 0.001$; preSMA $F_{1,84} = 7.63$, $P = 0.007$; STN $F_{1,84} = 14.24$, $P < 0.001$; FDR-corrected for 4 comparisons; see **Fig 1a**). In the atypical group, all the regions seemed to have a shift towards leftward lateralization of brain function.

339 A voxel-wise whole-brain analysis of the functional asymmetry maps during the
340 stop-signal task was performed to complement the ROI results. Two-sample *t*-
341 test comparisons of the typical and atypical groups during the 'correct stop >
342 correct go' condition showed a differential asymmetry pattern in all the ROI-
343 corresponding areas, while also revealing differences in other cortical and
344 subcortical regions, including the angular gyrus, middle temporal gyrus, and
345 caudate (**Fig 1b**). Specifically, the typical group presented a rightward activity in
346 these regions, whereas the atypical group exhibited a leftward shift (**Fig 1c**).

347 Finally, the Pearson's correlation between the frontal LIs (pars opercularis + pars
348 triangularis) from the verb generation task and the stop-signal task revealed a
349 strong inverse correlation ($r_{84} = -.58$; one-tailed $P < 0.001$; $R^2 = .34$) (**Fig 2**). Out
350 of 50 typically lateralized for language, 33 (66%) presented a typical right
351 lateralization for inhibitory control, and 17 (34%) showed an atypical (left –
352 ambilateral) lateralization. Among the 36 individuals from the atypical group,
353 only 8 (22.2%) presented a typical lateralization during the stop-signal task,
354 whereas 28 (77.8%) showed an atypical lateralization. Importantly, no
355 participant presented a leftward + leftward or rightward + rightward
356 segregation pattern for language production and response inhibition. Strong
357 segregation of both functions into different hemispheres was observed in 38

358 participants (44.2%). The remaining 48 individuals (55.8%) presented an
359 ambilateral representation of one or both functions, with an important level of
360 spatial overlap in their activations (see **Fig 1d**). In this ambilateral group,
361 language production presented an overlap in 32.3% of its voxels in the left
362 hemisphere, and in 58.6% of its voxels in the right hemisphere. Inhibitory
363 control showed an overlap in 57.2% of its voxels in the left hemisphere, and in
364 22.8% of its voxels of the right hemisphere.

365 **2. Laterality Indexes correlate to interhemispheric connectivity and preclinical**
366 **markers**

367 Correlational analyses revealed certain links between the functional
368 lateralization of both tasks and behavioral, neuroanatomical and connectivity
369 measures (**Table 1**).

370 First, we studied how the structural and functional connectivity between both
371 IFC behaved in relation to LI. Volume in the genu, body and splenium of the
372 corpus callosum was inversely related with language LI (respectively: $\rho_{83} = -.25$,
373 $P = 0.02$; $\rho_{83} = -.26$, $P = 0.02$; and $\rho_{83} = -.25$, $P = 0.02$). However, only the callosal
374 genu was found related with inhibition LI ($\rho_{83} = .25$, $P = 0.02$). That is, the
375 volume of the callosal genu increased as functional organization of the IFC

became more atypical, extending this effect to the whole corpus callosum when considering exclusively language lateralization. On the same line, ROI interhemispheric functional connectivity analyses at rest revealed that VMHC of the pars triangularis also increased as a function of inhibition LI (ρ_{77} = .26, P = 0.02), but a similar relation failed to be found for language LI (ρ_{77} = −.12, P = 0.3). No statistically significant linear relationships were found when exploring the VHMC of the pars opercularis.

Behaviorally, performance (RT, SSRT and accuracy) during the scanner stop-signal task did not correlate with language and inhibition LIs. Regarding the reading test, accuracy for word length and word familiarity were found correlated with both LIs (length and language: ρ_{84} = −.24, P = 0.03; length and inhibition: ρ_{84} = .21, P = 0.04; familiarity and language: ρ_{84} = −.23, P = 0.03; familiarity and inhibition: ρ_{84} = .3, P = 0.01). That is, an atypical organization was related with a higher rate of errors when reading long words and unfamiliar words. No significant correlations were found when exploring reading speed. SPQ score was found significantly related with inhibition LI (ρ_{82} = .25, P = 0.02), but it did not reach statistical significance when paired with language LI (ρ_{84} = −.19, P = 0.08). AQ, on the other hand, presented an association with language LI (ρ_{84} = −.25, P = 0.02) but not with inhibition LI (ρ_{84} = .08, P = 0.5).

DISCUSSION

The present study employed the stop-signal task to investigate brain areas involved in the inhibitory control function in two different groups of individuals: typically and atypically lateralized for language production. As expected, the atypical participants showed, as a group, a mirrored brain organization of the inhibitory control function compared to the typical group. This leftward organization affected the entire inhibitory control network, including the IFC, preSMA, and STN. However, some participants manifested a clear overlap in the control of language and inhibitory functions. Our results also demonstrate that atypical organization of language production is associated with an increased white matter volume of the corpus callosum, and that atypical lateralization of inhibitory control is related with a higher interhemispheric functional coupling of the IFC. Behaviorally, atypical lateralization was not associated with performance on the task, but an association existed with worse reading accuracy, and more schizotypy and autistic traits.

Our first relevant result is that the group of individuals with atypical lateralization of language presented a mirrored brain organization during the stop-signal task compared to the typically lateralized group. Remarkably, the hemispheric asymmetry differences obtained affected the entire inhibitory

414 control brain network[25]. The inferior frontal cortex, or IFC, associated with the
415 initiation of the stop command and the main cortical area of this system,
416 showed a clear lateralization effect, with the typical group almost exclusively
417 using the right part and the atypical group mostly activating the left part. The
418 presupplementary motor area, or pre-SMA, related to the implementation of
419 the stop command, was more bilaterally involved in both groups, although
420 atypicals activated the left part more and typicals activated the right part more.
421 Importantly, the hemispheric reversal of organization also affected the
422 subcortical structures participating in this network, namely the STN and
423 thalamus. These structures displayed a lateralization pattern similar to the
424 preSMA, with a more pronounced bilateral engagement but higher involvement
425 of the right part in typicals and of the left part in atypicals. Thus, this is the first
426 demonstration that an entire cerebral network controlling a cognitive function
427 shows a completely flipped organization in an atypical population for language,
428 which supports the Causal hypothesis of lateralization[10,11]. Moreover, this result
429 reveals that hemispheric lateralization goes beyond cerebral cortices, and even
430 interhemispheric connectivity, through the corpus callosum, given that it also
431 involves frontal-subcortical circuits. Additionally, the specificity of this result to
432 the areas of the proposed network is another element that supports the
433 relevance of this system in inhibitory control.

434 It should be noted that this pattern of atypical brain specialization was observed
435 in the absence of a relation between functional lateralization and performance
436 differences during the 'go' or 'stop' conditions. Even though the 'go' condition
437 involves a lexical decision requiring language processing, and the 'stop'
438 condition consists of inhibiting a linguistic process, the functional organization
439 of the IFC during the tasks did not affect the response speed (RT and SSRT) or
440 the 'go' accuracy in either case. Thus, brain organization for language and
441 inhibition, as initially defined in our study, and cognitive efficiency are not
442 directly related, based on our data. This finding is consistent with previous
443 reports showing that cognitive deficits appear only in specific cognitive
444 domains[17,54].

445 Importantly, despite observing a complimentary relationship between language
446 production and inhibitory control at the group level, not all the individuals
447 presented a strong and segregated distribution of these two functions. The vast
448 majority of hemispherically segregated individuals showed the typical
449 segregation of language in the left hemisphere and inhibitory control in the right
450 hemisphere, whereas only a low percentage displayed the opposite segregated
451 organization. The rest, in agreement with similar reports on other functions[19],
452 lacked a clear hemispheric lateralization of language production, inhibitory

453 control, or both. In all cases, this implied some level of overlapping or sharing of
454 the same area of the inferior frontal cortex. Both the low ratio of atypical
455 segregation and the high ratio of bilateral inhibitory control could be explained
456 by the fact that typical right hemispheric functions (such as inhibition) seem to
457 be more bilaterally represented than typical left functions (such as language)[55].
458 Some conclusions can be extracted from this: (1) Although infrequent, a strong
459 atypical segregation of the two functions is possible; (2) Our data have not
460 revealed any case with a segregation of both frontal cognitive functions in the
461 same hemisphere; and (3) A large percentage of participants with a strong left
462 lateralization of language presented a bilateral control of inhibition, showing
463 that a typical dominance for language does not imply a strongly lateralized
464 organization of other cognitive functions. The existence of exceptions to the
465 group pattern of mirrored brain organization requires us to use caution when
466 interpreting these data as supporting the causal hypothesis. Although the
467 negative correlation between the lateralization indexes during the verb
468 generation task and the stop-signal task is strong at the group level, some
469 individual data support the statistical hypothesis[12] instead. Given that we found
470 no cases of both cognitive functions completely sharing a hemisphere (see **Fig**
471 **2**), we propose that causal-supporting vs. statistical-supporting results reflects
472 two different pathways to cognitive control. On the one hand, the segregated

473 pathway (in line with the Causal hypothesis) develops due to the cerebral bias
474 towards lateralizing certain cognitive functions in a single hemisphere. On the
475 other hand, the integrated pathway (in line with the Statistical hypothesis),
476 appears when ontogenetic development towards strong lateralized control fails
477 in some way.

478 The corpus callosum is the main cerebral structure in interhemispheric
479 connectivity, with the genu area being responsible for the connectivity between
480 the two inferior frontal gyri[56]. Phylogenetic data have demonstrated a negative
481 association between the corpus callosum volume and hemispheric
482 specialization, suggesting that the ontogenetic development of the brain is
483 supported by a decrease in interhemispheric connectivity to potentiate and
484 establish intrahemispheric connectivity and hemispheric specialization[57]. There
485 is evidence of this mechanism in language development[58] and in agenesis of the
486 corpus callosum, which has been associated with lower lateralization of
487 language and worse language performance[59,60]. In line with this proposal, we
488 have replicated the relation between callosal enlargement and atypical
489 functional organization found in a previous study[53]. Moreover, in our data, this
490 structural correlation was accompanied by an association between atypical

491 lateralization of inhibitory control and strength of interhemispheric functional
492 connectivity in the pars triangularis of the IFC.

493 As hypothesized, when considering the functional lateralization during both
494 tasks, atypical organizations were found linearly related with higher scores on a
495 schizotypy test (only for inhibitory control), higher scores on an autistic
496 spectrum test (only for language production), and a higher rate of reading errors
497 (both language production and inhibitory control). The first result is consistent
498 with previous structural, functional, and behavioral data that have shown
499 reduced language lateralization in schizophrenia patients[8,61]. In the case of
500 schizotypy, the evidence for reduced lateralization of cognitive functions is
501 mixed and may respond to differences in the methodology employed[62].
502 However, consistently with the present results, this condition has been
503 previously associated to impaired behavioral and neural processing during the
504 stop-signal task[63], and to an abnormal frontal functional asymmetry[64]. The
505 second result relates atypical language lateralization with the presence of
506 autistic traits, a result consistent with data obtained in autism[65]. The third result
507 shows that atypical organization was related with a higher rate of reading errors
508 when considering word length and word familiarity. The length effect has been
509 considered a pathognomonic symptom of reading disorders such as

developmental dyslexia[66] and pure alexia[67]. These disorders have also been characterized by a weak language lateralization[7]. Thus, presented results support the hypothesis that atypical hemispheric specialization is related with worse cognitive performance in the linguistic domain, and even preclinical traits of some neurodevelopmental disorders among healthy population.

DATA AVAILABILITY

All data presented in this study are included in the following public dataset: https://doi.org/10.6084/m9.figshare.22047299.

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AUTHOR CONTRIBUTIONS

Conceptualization, C.A. and M.-A.P.; Methodology, E.V.-R. and C.A.; Formal Analysis, E.V.-R.; Investigation, E.V.-R., C.C.-M., and L.M.-M.; Data Curation, E.V.-R. and C.C.-M., Writing, E.V.-R., C.A. and M.-A.P.; Supervision, C.A.; Project Administration, C.A.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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FIGURES

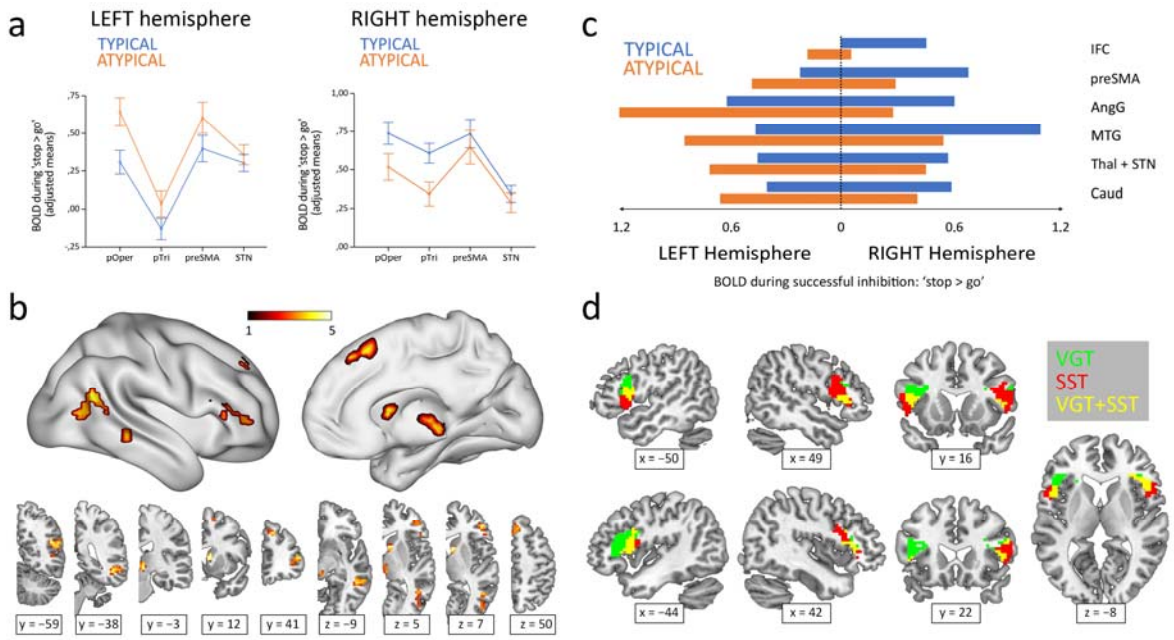
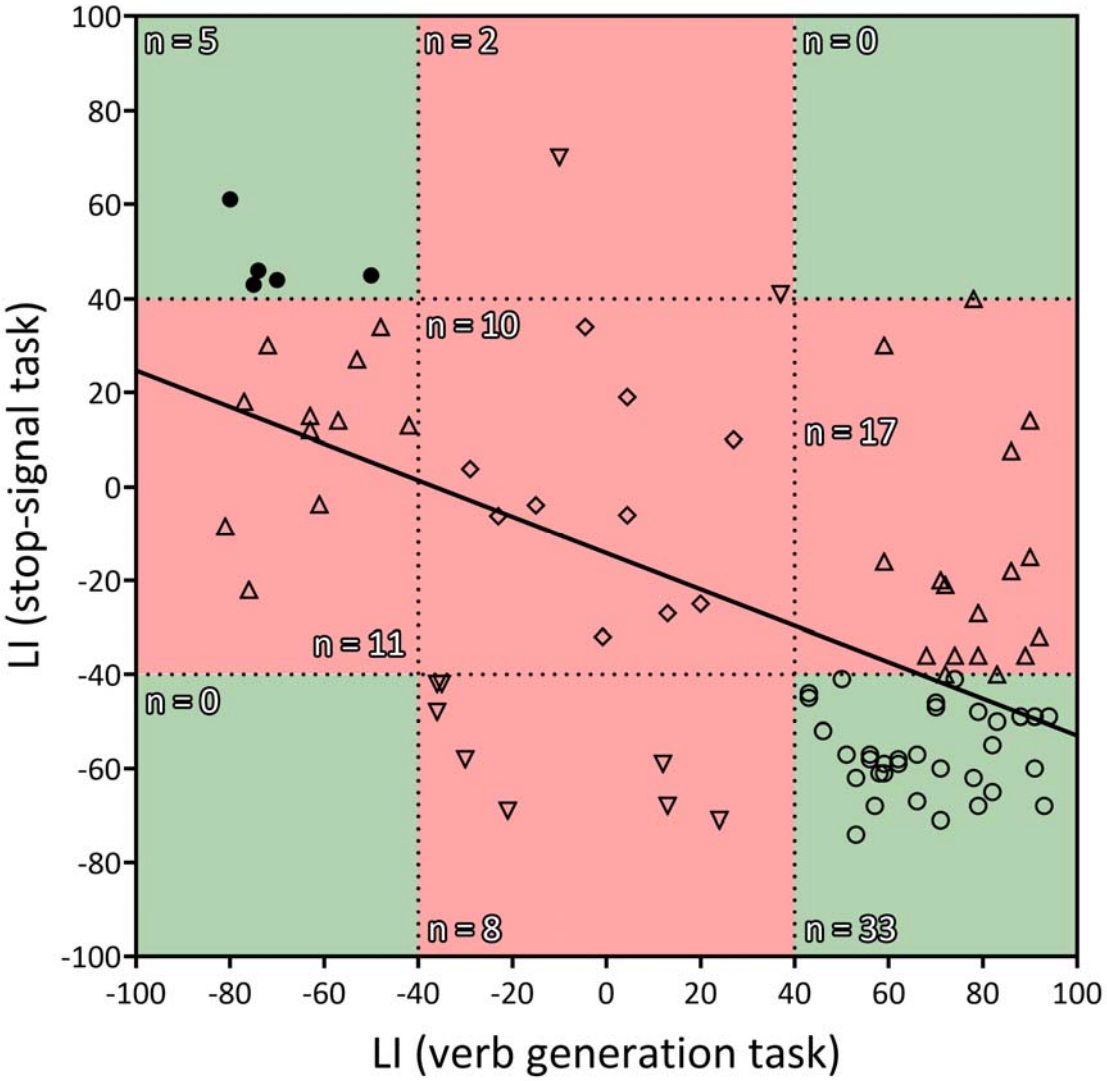


Fig 1. Hemispheric lateralization of inhibitory control according to language lateralization.

(A) ROI analysis of the main components of the inhibitory control network. Graphs depict adjusted mean BOLD signal during successful inhibitions on the stop-signal task ('stop > go' contrast) for both hemispheres and both groups. All four structures showed significant Hemisphere × Group interactions. Error bars represent one standard error. pOper = pars opercularis, pTri = pars triangularis, preSMA = presupplementary motor area, and STN = subthalamic nucleus. **(B)** Voxel-wise whole-brain analysis of functional asymmetry. Significance maps (voxel-wise $P < 0.001$; FWE cluster-corrected at $P < 0.05$; color bar represents *t*

742 value) are displayed in three-dimensional reconstructions plus coronal and
743 transversal slices using MNI space. (**C**) Mean BOLD values of the significant
744 regions found in the voxel-wise whole-brain analysis. Graphic depicts BOLD
745 values for every region, hemisphere, and group. IFC = inferior frontal cortex,
746 preSMA = presupplementary motor area, AngG = angular gyrus, MTG = middle
747 temporal gyrus, Thal = thalamus, STN = subthalamic nucleus, Caud = caudate.
748 **(D)** Functional overlap between language production and inhibitory control in
749 the IFC of ambilateral participants. Conjunction maps for inhibition (voxel-wise
750 $P < 0.001$; FWE cluster-corrected at $P < 0.05$) and language (voxel-wise $P < 0.05$;
751 uncorrected) are displayed in coronal, sagittal and transversal slices using MNI
752 space. VGT = verb generation task, SST = stop-signal task.



753

754 **Fig 2. Correlation between the LIs of the verb generation and stop-signal tasks.**

755 r = −.583, one-tailed P < 0.001, R^2 = .339. Negative values indicate rightward
756 lateralization, whereas positive values indicate leftward lateralization.
757 Segregated and ambilateral phenotypes are also depicted according to the
758 background color. The green area corresponds to segregated individuals (both

759 functions strongly lateralized), and the red area corresponds to integrated
760 individuals (at least one function ambilaterally controlled). Numbers inside each
761 quadrant denote the number of individuals (n) contained in it. Each individual
762 datapoint is symbolized according to its functional organization: ○ = typical
763 segregation; ● = reversed segregation; △ = ambilateral inhibition; ▽ =
764 ambilateral language; ◇ = ambilateral language and inhibition.

765 **TABLES**

	Verb generation task LI		Stop-signal task LI	
	Spearman's ρ	*P*	Spearman's ρ	*P*
Callosal genu volume	−.249	.021*	.251	.02*
Callosal body volume	−.258	.017*	.132	.224
Callosal splenium volume	−.249	.021*	.118	.279
Pars Opercularis VMHC	−.062	.584	.148	.192
Pars Triangularis VMHC	−.119	.295	.258	.022*
'Go' reaction time	.125	.251	−.041	.71
'Go' accuracy	−.076	.489	.039	.724
SSRT	.173	.111	−.038	.726
Reading length accuracy	−.237	.028*	.214	.047*
Reading familiarity accuracy	−.232	.032*	.301	.005**
Reading length time	.054	.622	−.184	.068
Reading familiarity time	.091	.403	−.198	.091
SPQ	−.194	.078	.247	.023*
AQ	−.247	.023*	.075	.498

766 **Table 1. Spearman's partial correlations between task LIs and**

767 **neuroanatomical plus behavioral variables.**

768 General intelligence and age were included as covariates of no interest. Callosal

769 volume correlations were additionally corrected for total intracranial volume.