Differential contributions of inferior frontal gyrus subregions to sentence processing guided by intonation

Constantijn L van der Burght^{a,b,c}, Ole Numssen^b, Benito Schlaak^b, Tomás Goucha^{a*}, Gesa Hartwigsen^{b*}

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^a *Department of Neuropsychology,
Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*

^b *Lise Meitner Research Group Cognition and Plasticity,
Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*

^c *Psychology of Language department,
Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands*

** Authors contributed equally*

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Corresponding author:

Constantijn van der Burght
*Psychology of Language department
Max Planck Institute for Psycholinguistics
Wundtlaan 1, 6525 XD Nijmegen, The Netherlands
+31 24 3521367
stan.vanderburght@mpi.nl*

Abstract

Auditory sentence comprehension involves processing content (semantics), grammar (syntax), and intonation (prosody). The left inferior frontal gyrus (IFG) is involved in sentence comprehension guided by these different cues, with neuroimaging studies preferentially locating syntactic and semantic processing in separate IFG subregions. However, this regional specialisation has not been confirmed with a neurostimulation method. Consequently, the causal role of such a specialisation remains unclear. This study probed the role of the posterior IFG (pIFG) for syntactic processing and the anterior IFG (aIFG) for semantic processing with repetitive transcranial magnetic stimulation (rTMS) in a task that required the interpretation of the sentence's prosodic realisation. Healthy participants performed a sentence completion task with syntactic and semantic decisions, while receiving 10 Hz rTMS over either left aIFG, pIFG, or vertex (control). Initial behavioural analyses showed an inhibitory effect on accuracy without task-specificity. However, electric field simulations revealed differential effects for both subregions. In the aIFG, stronger stimulation led to slower semantic processing, with no effect of pIFG stimulation. In contrast, we found a facilitatory effect on syntactic processing in both aIFG and pIFG, where higher stimulation strength was related to faster responses. Our results provide first evidence for the functional relevance of left aIFG in semantic processing guided by intonation. The stimulation effect on syntactic responses emphasises the importance of the IFG for syntax processing, without supporting the hypothesis of a pIFG-specific involvement. Together, the results support the notion of functionally specialised IFG subregions for diverse but fundamental cues for language processing.

1. Introduction

Understanding spoken language is a rapid and efficient process. To accomplish such a complex task, listeners make use of various sources of information available in a sentence, such as grammatical or semantic cues. Additionally, listeners rely on the way in which a sentence is spoken. In particular, variations in speech melody, rhythm, and intensity, together called *prosody*, often play a decisive role in the interpretation of a sentence (Cutler, Dahan, & van Donselaar, 1997; M. Wagner & Watson, 2010). There are various ways in which prosody can steer sentence comprehension. In written form, the difference between “*the reviewer said: the author is mistaken*” and “*the reviewer, said the author, is mistaken*” is marked by punctuation, but in spoken language it is established exclusively by prosody. This clearly shows how the different use of pauses and pitch variations in a sentence dramatically changes its syntactic (grammatical) structure. By defining how words are grouped together, prosody directly affects the syntactic analysis of the sentence, and, consequently, how we interpret it. Additionally, prosody can influence semantic processing. In a sentence such as “Anna bought APPLES at the market”, prosody highlights prominent or important information in the sentence. Here, the capitalised word indicates a rise in pitch and intensity, which conveys that it was apples that Anna bought, as opposed to any other possible type of market produce. Taken together, prosodic information influences how syntax and semantic are processed (Dahan, Tanenhaus, & Chambers, 2002; Kjelgaard & Speer, 1999; Marslen-Wilson, Tyler, Warren, Grenier, & Lee, 1992; Speer, Kjelgaard, & Dobroth, 1996; Steinhauer, Alter, & Friederici, 1999).

In a recent study, we demonstrated that a single prosodic cue can establish expectations about both the syntactic and semantic properties of upcoming parts of the sentence (van der Burght, Friederici, Goucha & Hartwigsen, 2021). An example of syntactic information is the word order of a sentence: if we consider the sentence “The police officer arrested the thief”, we understand *who did what to whom* because “the police officer” occurs before the verb and “the thief” after. Another example of syntactic information can be found in languages with a case-marking system. In German, the particular word form of the determiner *the* can convey the subject or object role of the following (masculine) noun: *der* marks a subject, and *den* an object. In this way, the specific word form of the determiner

tells us which elements are the sentence subject and object—even if their order in the sentence was reversed. Finally, the sentence structure in the example above can be inferred from the semantic cues as well. We would still be able to extract the message from the semantics of the words, even without word order or case-marking cues: when presented with a word list containing “arrest”, “thief”, and “police officer”, we can infer the most probable role played by each of the actors. Specifically, the typical nouns associated with each of the thematic roles in relation to this specific verb provide a plausible explanation of *who did what to whom* (Ferreira, 2003; Trueswell, Tanenhaus, & Garnsey, 1994).

With respect to the neural correlates of these linguistic domains, previous work has demonstrated that prosody processing is supported by a bilateral network, including several cortical areas in the frontal and temporal lobes (Belyk & Brown, 2014; Friederici, 2011). The left hemisphere, in particular the inferior frontal gyrus (IFG), seems to be especially involved when prosody conveys linguistic information (Chien, Friederici, Hartwigsen, & Sammler, 2020; Friederici & Alter, 2004; van der Burght, Goucha, Friederici, Kreitewolf, & Hartwigsen, 2019; van Lancker, 1980). Specifically, the left IFG has been associated with processing pitch accents—the prosodic phenomenon that stresses certain words in a sentence (as in the example “Anna bought APPLES”). Pitch accents can place part of a sentence in so-called focus, highlighting novel or particularly relevant information in a sentence (Rooth, 1992). Most areas within the left IFG are involved when the pitch accent in a sentence (and therefore focus position) is incongruent with previous semantic and pragmatic expectations (Kristensen, Wang, Petersson, & Hagoort, 2013; van Leeuwen et al., 2014). Furthermore, the posterior IFG is increasingly recruited when processing pitch-accented sentences in comparison to neutral ones (Perrone-Bertolotti, Dohen, Lœvenbruck, Sato, Pichat, & Baciú, 2013). Finally, pitch accent processing preferentially recruits the left IFG as compared to emotional prosody processing (Wildgruber et al., 2004). Together, this supports early theoretical models stating that prosody processing is lateralised to the left hemisphere in sentences where the linguistic function of prosodic cues is emphasised (Friederici & Alter, 2004; van Lancker, 1980).

The left IFG is also known to be a key region for processing syntax and semantics (Goucha & Friederici, 2015; Graessner, Zaccarella, & Hartwigsen, 2021; Klimovich-Gray et al., 2018;

Matchin, Brodbeck, Hammerly, & Lau, 2018; Schell, Zaccarella, & Friederici, 2017). Specifically, the previously discussed linguistic subdivision between syntactic and semantic processing is thought to be reflected in a structural subdivision at the neural level. Indeed, models based on many years of neuroimaging research posit that a functional dissociation can be made in relation to anterior and posterior parts of the left IFG. These models, based on literature reviews (Friederici, Chomsky, Berwick, Moro, & Bolhuis, 2017) and meta-analyses (Hagoort & Indefrey, 2014), attribute syntactic processing predominantly to the posterior part of the IFG (pars opercularis), whereas semantics is predominantly processed in more anterior parts of the IFG (pars triangularis). These anatomically defined subregions, in turn, roughly correspond to a subdivision of the IFG into cytoarchitectonic areas, namely Brodmann area (BA) 44 (pIFG) and BA45 (aIFG) (Amunts et al., 1999). This double dissociation is established by a rich body of correlative neuroimaging studies, however, the functional relevance of different IFG subregions for syntax and semantics remains to be demonstrated.

The present study was designed to investigate the causal role of the left anterior and posterior IFG in sentence processing guided by prosodic cues. More specifically, we used transcranial magnetic stimulation (TMS) to probe the functional specialisation of IFG subregions for semantic and syntactic processing during sentence comprehension that relies on prosody. Combined with behavioural tasks, TMS can be used to study the functional relevance of a particular cortical area for a given cognitive process (Hallett, 2007; Hartwigsen, 2015). TMS has previously been employed to provide evidence for the functional specialization of two IFG subregions, demonstrating a key role of left pIFG for phonological processing and left aIFG for semantic processing (Devlin, Matthews, & Rushworth, 2003; Gough, Nobre, & Devlin, 2005; Hartwigsen et al., 2010; Klaus & Hartwigsen, 2019; Romero, Walsh, & Papagno, 2006). Yet, to the best of our knowledge, TMS has not yet been used to investigate whether a similar dissociation holds for semantics and syntax in the left IFG. Finally, linguistic prosody has so far been studied with TMS in an experiment involving single-word stimuli with a focus on the role of the right hemisphere (Sammler, Grosbras, Anwender, Bestelmeyer, & Belin, 2015), but the integration of prosodic information into sentence structure has yet to be studied.

We used a single experimental paradigm to ensure that our conditions were closely matched in their prosodic properties as well as in the task requirements. To this end, we employed a sentence completion task (see Figure 1) that required the integration of syntactic and semantic as well as prosodic information (van der Burght et al., 2021). In this task, participants listened to spoken sentences in which either the subject or object received focus by means of a prosodic cue (a pitch accent, see Figure 2). Participants then selected the continuation of the sentence that they considered most plausible—a preference established by the pitch accent in the sentence. This sentence completion task required isolated syntactic and semantic decisions per trial. During the task, short bursts of repetitive TMS (rTMS) were applied after the auditory sentence presentation, i.e., during the response phase, starting simultaneously with the onset of the visual presentation of the response options. Note that it was not possible to stimulate during an earlier time window, e.g., during the pitch-accented words, because listeners would easily detect the co-occurrence between sentence focus and stimulation, providing them with an undesired, non-prosodic cue. We used a within-subject design in which participants received rTMS over either aIFG, pIFG, or a control site (vertex), divided over three pseudo-randomised sessions. We hypothesised that rTMS of pIFG would selectively affect syntactic decisions, reflected in a delay in response times, a decrease in accuracy, or both. In contrast, rTMS of pIFG should not affect semantic decisions. Conversely, we expected that rTMS of aIFG would selectively impair behaviour during semantic, but not syntactic decisions.

2. Methods

The hypotheses and analysis plan of this experiment were preregistered at the Open Science Framework (<https://osf.io/7bx2k>). Raw data and analysis scripts can be found at <https://osf.io/5k8ze/>.

2.1. Participants

30 healthy native German speakers were included in the final analysis (18 females, age: $M=27.1$ years, $SD=3.9$, range=19-37). All were right-handed (handedness score: $M=91.0$, $SD=9.6$ (Oldfield, 1971)), none had a history of neurological or psychiatric disorders or other contraindications to TMS, and all gave written informed consent prior to participation. Sampling continued until 30 complete datasets (i.e., including three experimental TMS

sessions per participant) had been acquired. The sample size was defined to allow for a full balancing of the order of TMS sites (aIFG, pIFG, vertex) over the three experimental sessions. Participants were recruited from the database of the Max Planck Institute for Human Cognitive and Brain Sciences. Two volunteers dropped out because of excessive discomfort during stimulation of the IFG and were replaced with two new participants to complete the sample. The study was approved by the local ethics committee at the Medical Faculty of the University of Leipzig.

Figure 1 Overview of the experimental design with within-subject factors *decision type*, *focus position*, and *TMS site*. Trials of each decision type and focus position were presented pseudo-randomly within each session. During each session, participants received short TMS bursts (5 pulses at 10 Hz, starting 100 ms after the visual onset of the determiner or noun response options) over one of the three TMS sites. The order of TMS site across experimental sessions was counter-balanced across participants. Circles illustrate the three stimulation sites. aIFG: anterior inferior frontal gyrus. pIFG: posterior inferior frontal gyrus. NOM: nominative. ACC: accusative. FEM: feminine. MASC: masculine.

2.2. Task

Participants performed a sentence completion task (Figure 1) in which they were presented with spoken sentences of the type (A) or (B), containing a pitch accent on the subject or

object of the sentence, respectively (Figure 2; see Supplementary table 5 for acoustic analyses). In these sentences, the subject/object roles of the noun phrases are expressed through the case marking of the respective determiners, indicated with NOM (nominative) or ACC (accusative). Furthermore, the subject/object roles are indicated by semantic cues: police officers are more likely to arrest someone than to be arrested by someone, whereas thieves are generally more likely to be arrested. Focus, as assigned by a pitch accent, is indicated with F.

(A) Yesterday, [the^{NOM} POLICE OFFICER]_F arrested the^{ACC} thief, not ...

Gestern hat [der POLIZIST]_F den Dieb verhaftet, nicht ...

(B) Yesterday, the^{NOM} police officer arrested [the^{ACC} THIEF]_F, not ...

Gestern hat der Polizist [den DIEB]_F verhaftet, nicht ...

Figure 2: Pitch contours and sound pressure waves illustrating the difference between subject focus (A) and object focus (B) in the example sentence *Yesterday, the policeman arrested the thief* ("Gestern hat der Polizist den Dieb verhaftet"). The noun phrase that is placed in contrastive focus bears a pitch accent (indicated by capital letters), whereas it is deaccented in the other condition. Note the difference in pitch increase and intensity in the accented noun phrase as compared to the same noun phrase in the deaccented condition.

Participants were asked to complete these spoken sentences with two consecutive words presented visually in a two-alternative forced choice task by button-press. Participants made two consecutive decisions: they first selected a determiner and then a noun. In the syntactic condition, the task-relevant choice involved participants choosing between two case-marked masculine determiners signalling either subject (*der/the^{NOM}*) or object (*den/the^{ACC}*). By presenting the determiners first rather than simultaneously with the noun,

the decision on the determiner was purely syntactic, preventing a possible semantic influence from the noun. In the semantic condition, the nouns were presented in their feminine versions to prevent an explicit syntactic judgement prior to the task-relevant choice between the two nouns. As the feminine determiner in German does not differ between nominative and accusative case (both are indicated with *die*), the first decision on the determiner was meaningless. The subsequent decision on the noun ("*police officer^{FEM}*" or "*thief^{FEM}*") was therefore mainly a semantic one, since no meaningful syntactic judgment had been made previously. Participants were instructed to select the determiner and noun that would complete the sentence in the way they deemed most sensible and to give their response as quickly and accurately as possible. Together, each experimental item consisted of one verb (e.g., *to arrest*) coupled with two typical agents (*police officer, inspector*) and two typical patients (*thief, murderer*). These experimental items were created and selected after a norming study based on Ferreira (2003); see Van der Burght *et al.* (2021) for full details.

2.3. Experimental design and procedure

We used a 2x2x3 factorial, within-subject design with the factors *decision type* (syntactic; semantic), *focus position* (subject; object), and *stimulation site* (pIFG; aIFG; vertex), as illustrated in Figure 1. Experimental trials were divided over four blocks separated by a self-timed break (minimum pause duration: 20 s). During each block, 48 trials were presented pseudo-randomly, with a maximum of two consecutive repetitions of the same decision type and focus position. Each unique verb-noun combination occurred once per block. The order of TMS sites across experimental sessions was assigned pseudo-randomly and counter-balanced across participants. Stimulus presentation, collection of the responses, and timing of the TMS trains was controlled using the software Presentation (Neurobehavioral Systems, Inc., Berkeley, CA; www.neurobs.com).

2.4. Repetitive transcranial magnetic stimulation

To determine the stimulation sites in anterior and posterior IFG, mean coordinates were taken from a meta-analysis of neuroimaging studies on syntactic and semantic processing (Hagoort & Indefrey, 2014). This study reported local maxima plus standard deviations for syntactic processing (pIFG, corresponding to BA44) and semantic processing (aIFG,

corresponding to BA45). To prevent overlap of the stimulation area at the two sites, we chose coordinates that were at least 20mm apart, but still fell within the standard deviation of each region. These coordinates were transformed from Talairach to Montreal Neurological Institute (MNI) space (BA44: x, y, z = -51, 11, 14; BA45: x, y, z = -51, 33, 2). Finally, these coordinates were transformed into individual subject space by using the inverse of the normalisation matrix obtained in SPM 12 (www.fil.ion.ucl.ac.uk/spm, Wellcome Trust Centre for Neuroimaging, London, UK). T1-weighted images had been previously acquired on a 3T MRI scanner (Siemens Healthcare, Erlangen, Germany) using a magnetization-prepared rapid gradient echo (MPRAGE) sequence in sagittal orientation (inversion time = 650 ms, repetition time = 300 ms, flip angle = 10°, field of view = 256 mm × 240 mm, voxel-size = 1mm × 1mm × 1.5mm). Individual coordinates were visually inspected based on macroanatomical landmarks: pIFG was defined as the portion of the gyrus located anterior to the precentral sulcus and posterior to the ascending branch of the lateral fissure, whereas the aIFG as the portion of the gyrus between the ascending and horizontal branches of the lateral fissure. In case the target coordinates in subject space were not located within these regions (but rather, e.g., in the sulcus) they were manually adjusted. The vertex (control) site was determined manually in each individual as the midpoint between two lines on the surface of the scalp, one connecting the tragi of the left and right ear and the other connecting the nasion and inion.

A neuronavigation system (TMS Navigator, Localite, Sankt Augustin, Germany) was used to navigate the TMS coil and maintain its location and orientation throughout the experimental sessions. The coil was placed over the IFG with an angle of 45° to the sagittal plane whereas vertex stimulation was achieved holding the coil parallel to the midline with the handle oriented posteriorly.

Simulation intensity was set at 90% of the individual resting motor threshold, following similar studies from our research group that targeted the IFG (Hartwigsen et al., 2010; Kuhnke, Meyer, Friederici, & Hartwigsen, 2017), which resulted in a mean stimulation intensity of $45\% \pm 3\%$ (1SD) of maximum stimulator output. Each participant's resting motor threshold was determined at the beginning of the first experimental session, using an electromyogram measured at the first dorsal interosseous muscle on the right hand. The motor hotspot was located by systematically searching the scalp contralaterally to the right hand at a low stimulation intensity. As a starting point, a mean coordinate of M1 was used

(x, y, z = -37, -21, 58 mm, taken from Mayka *et al.* (2006)), transformed to individual subject space (see above). The motor hotspot was then defined as the location which yielded the largest and most consistent motor evoked potential. Subsequently, resting motor threshold was determined as the lowest stimulator output intensity to evoke a motor evoked potential in the relaxed muscle with a peak-to-peak amplitude larger than 50 μ V in 5 out of 10 consecutive stimuli (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

During each experimental trial, a 5-pulse train of 10Hz TMS was applied over left aIFG, pIFG, or vertex (see Figure 1). The pulse train started 100ms after onset of the visual imperative stimulus, lasting until 600ms into the decision-making process on syntactic or semantic continuation on the sentence. This stimulation window was chosen to avoid interference with either early visual processing (see Devlin *et al.*, (2003) for a similar rationale) or with the motor execution of the response. This allowed stimulation to cover similar processing stages in both syntactic and semantic conditions. A further motivation for this stimulation window rather than during the presentation of the auditory stimulus was the possible confounding effect of rTMS pulses on the perception of focus position. Since listeners were required to interpret which noun received pitch accent, the simultaneous presence of rTMS on the pitch-accented word would have provided an additional, unwanted non-prosodic cue. Although this confound could have been circumvented by a counter-balanced design (stimulation during the pitch accented and non-pitch accented nouns across trials), this would have led to an undesired inflation of an already complex study design. rTMS was applied using a figure-of-eight coil (type C-B60; outer diameter = 7.5 cm) connected to a MagPro X100 stimulator (MagVenture, Farum, Denmark). The overall application of TMS pulses was well within safety limits (Rossi *et al.*, 2009; Rossini *et al.*, 2015).

2.5. Data analysis

Response times for correct trials were log-transformed and analysed with a Linear Mixed Model. Accuracy rates were analysed using a Generalised Linear Mixed Model (GLMMs) with a binomial distribution (Baayen, Davidson, & Bates, 2008). An advantage of LMMs over a classical ANOVA analysis is that they capture the variance offered by the single trial data, avoiding the necessity of computing grand mean reaction times (Singmann & Kellen, 2019). Furthermore, unlike ANOVAs, the GLMMs can accommodate for the binomial distribution of

the error rates (Jaeger, 2008). In both models, the full model included the fixed effects *TMS site*, *decision type*, and *focus position* as well as two two-way interaction terms. The interaction between *TMS site* x *decision type* was specified, since we expected the TMS effect to be both task-specific (i.e., disrupting either syntactic or semantic decisions) and location-specific (i.e., selectively interfering with aIFG or pIFG, relative to the vertex). The interaction between *decision type* and *focus position* was modelled as well, because we found a significant interaction between both factors in our previous behavioural study (van der Burght et al., 2021). A possible interaction between *TMS site* and *focus position* was not part of our research questions and therefore not included in the model. Consequently, no three-way interaction was included. For inclusion in the fixed effects analysis, factors were dummy coded: the factors with two levels were sum-coded and the fixed effect with three levels (*TMS site*) was treatment-coded with the vertex condition as reference level. We aimed to include a maximal random effects structure (Barr, Levy, Scheepers, & Tily, 2013). In case of convergence issues, we simplified the random effects structure by first removing the correlations between intercepts and slopes, then the random slopes for the interaction terms (*decision type* x *focus position*, *TMS site* x *decision type*, in that order), and the simple effects of each factor within participant and within item. For the reaction time analysis, this resulted in the following model: $\log RT \sim \text{decision} * \text{TMS} + \text{decision} * \text{focus} + (1 + \text{decision} * \text{TMS} + \text{focus} \mid \text{participant}) + (1 \mid \text{item})$. For the accuracy analysis, we used the following model: $\text{accuracy} \sim \text{decision} * \text{TMS} + \text{decision} * \text{focus} + (1 + \text{decision} + \text{TMS} \mid \text{participant}) + (1 \mid \text{item})$. In the model formulas, the tilde (~) stands for “in function of”. The pipe (|) indicates that the random intercept or slope is modelled by item or by participant. Statistical inference was performed using likelihood-ratio test comparing the full model to a reduced model lacking the term of interest (Singmann & Kellen, 2019). We used the package emmeans for pair-wise follow-up comparisons to further explore significant interactions (Lenth, Singmann, Love, Buerkner, & Herve, 2021). *P*-values below an alpha-level of .05 were considered significant.

2.6. Electric field simulations

To better understand the relationship between stimulation and behaviour we used a recently established approach to relate the induced electric fields to our behavioural effects (Numssen et al., 2021; Weise, Numssen, Thielscher, Hartwigsen, & Knösche, 2020). We

performed individual electric field simulations to investigate whether behaviour could be explained by the intensity of the electric field strength elicited by TMS in the IFG during the two critical sessions (those where aIFG and pIFG were targeted). To accurately compute the TMS-induced electric fields on the subject level, high-resolution head models were created for each individual participant from anatomical MRI images. The resulting head models were then combined with the recorded coil positions obtained from the neuronavigation software for each session and participant to calculate the spatial distribution and strength of the TMS-induced electric field. In the motor domain, such simulations have been used to accurately map the cortical localisation of motor evoked responses (Numssen et al., 2021). Recently, electric field simulations have also been related to behavioural stimulation effects in the language domain: Kuhnke et al. (2020) demonstrated a significant correlation between the individual electric field strength in the target area and the behavioural perturbation effect during a conceptual task. Due to large interindividual variance in head and brain anatomy, e.g., in gyrification patterns and cortex-skin distances, these individual electric field calculations allow for the precise quantification of inter- and intraindividual differences in stimulation exposure. All high-resolution head models and subsequent individual field simulations were computed with SimNIBS v3.1 (Saturnino, Madsen, & Thielscher, 2019; Thielscher, Antunes, & Saturnino, 2015).

First, we generated individual head models from structural MR images using the headreco pipeline (Puonti, Iglesias, & Van Leemput, 2016), employing SPM12 and CAT12 (Dahnke, Yotter, & Gaser, 2013). The final head models were composed of $\sim 1.7 \times 10^6$ nodes and $\sim 9.5 \times 10^6$ tetrahedra. T1 images and, where available, T2 images were used for segmenting the following tissues: scalp, skull, grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), and eyes. To define the position and orientation of the coil for each subject and condition for the field simulations we recorded the instrument markers with the neuronavigation software during the experimental sessions (Numssen et al., 2021; Weise et al., 2020). We then calculated the electric field for 1 A/ μ s scaled to the realised stimulator intensity using the following isotropic conductivity values: $\sigma_{\text{Scalp}} = 0.465$ S/m, $\sigma_{\text{Skull}} = 0.01$ S/m, $\sigma_{\text{GM}} = 0.275$ S/m, $\sigma_{\text{WM}} = 0.126$ S/m, $\sigma_{\text{CSF}} = 1.654$ S/m (Thielscher, Opitz, & Windhoff, 2011; T. A. Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004). We visually assessed the quality of the head reconstructions and electric field simulations, which are presented in

Supplementary Figure 4. Finally, the electric field of each participant per session was mapped to fsaverage space for group analyses (Fischl et al., 2008). Peak electric field magnitudes were extracted from the grey matter surface regions of interest (ROIs) in the anterior and posterior IFG for each subject and stimulation site. These ROIs were defined as BA45 (anterior IFG) and BA44 (posterior IFG) using the spatial probability maps available in FreeSurfer (Fischl et al., 2008).

To assess whether the electric field strength in each IFG subregion modulated behaviour, we ran additional (Generalised) Linear Mixed Models that included the electric field strength per participant, stimulation condition and ROI. Since both IFG subregions received stimulation in each of the two active stimulation sessions, this model included a value from the aIFG and pIFG ROIs per participant per session across trials (data from the vertex session was excluded because the IFG effectively received no stimulation here, see Supplementary Figure 3). To increase the interpretability of the slope estimates for the electric field factors, the electric field values were z-transformed. To investigate whether there was a differential effect of stimulation strength in the two IFG subregions on performance in each of the task conditions, we tested the interaction effects of *electric field strength* ($|E|$) with *decision type* (syntactic or semantic). The full model then included the following fixed effects: the interaction terms $|E|_{aIFG} * \text{decision type}$ and $|E|_{pIFG} * \text{decision type}$, as well as the interaction term $\text{decision type} * \text{focus position}$, and finally *session number* (1, 2, or 3) as main effect. This specification of session number allowed us to account for order effects and ensured that the model contained a representation for the data originating from three separate sessions (note that in the behavioural model, the *session number* term was not required because the *TMS site* term represented the different sessions). The random effect structure included by-participant random intercepts and slopes for decision type and focus position, as well as by-item random intercepts (after more complex random structures (Barr et al., 2013) had failed to converge, this was the most complex random structure that could be obtained). This resulted in the following full model for the reaction time analysis: $\log RT \sim |E|_{aIFG} * \text{decision} + |E|_{pIFG} * \text{decision} + \text{session} + \text{decision} * \text{focus} + (1 + \text{decision} + \text{focus} | \text{participant}) + (1 | \text{item})$. The same full model was used for the accuracy analysis using correct/incorrect as dependent variable. As in the main analysis, statistical inference on the interaction terms was performed by model comparisons between the full model and a

reduced model leaving out the interaction term of interest. Significant interactions were resolved using the *emmeans* function from *emmeans* (Lenth et al., 2021).

3. Results

3.1. Response times

We did not find a significant interaction between *TMS site* and *decision type* in the response times ($\chi^2(2)=3.84$, $p=.147$; Figure 3A). That is, TMS over aIFG, pIFG, or vertex did not differentially affect response speed in the syntactic and semantic decisions. Regarding focus position, we replicate the results from our behavioural study (van der Burght et al., 2021), with a significant interaction between decision type and focus position ($\chi^2(1)=31.19$, $p<.001$; Supplementary Figure 2). Post-hoc comparisons revealed that responses were slower in semantic as compared to syntactic decisions after both subject focus ($z=-6.47$, $p<.001$) and object focus sentences ($z=-7.90$, $p<.001$). Additionally, responses were faster after object focus as compared to subject focus sentences in the syntactic decisions ($z=2.90$, $p=.011$), whereas the semantic decisions showed the opposite pattern ($z=-2.50$, $p=.012$). The model output from all (G)LMMs can be found in Supplementary Tables 1-4.

3.2. Accuracy

Participants performed above chance in all conditions, which shows that overall, responses were made according to the pitch accent and focus position perceived (all z -values >12.56 ; all p -values $<.001$). In the accuracy rates (Figure 3B), there was no significant interaction between *TMS site* and *decision type* ($\chi^2(2)=0.15$, $p=.929$), meaning that we did not find evidence for location-specific effects of stimulation on syntactic and semantic decisions. However, a significant main effect of TMS site ($z=-2.53$, $p=.011$) indicated an overall increase in error rates for pIFG TMS as compared to vertex TMS in both syntactic and semantic decisions. There were no significant differences when comparing pIFG TMS to aIFG TMS ($z=1.61$, $p=.107$) or aIFG TMS to vertex TMS ($z=-1.07$, $p=.285$). In agreement with our previous behavioural study, the interaction of decision type x focus position was also significant ($\chi^2(2)=10.31$, $p=.001$). Post-hoc pairwise comparisons revealed lower accuracy for semantic decisions after object focus sentences when compared to subject focus sentences ($z=5.73$, $p<.001$), as well as when compared to syntactic decisions after object focus ($z=3.89$, $p<.001$).

To exclude that the increase in error rates under pIFG stimulation reflected a general speed-accuracy trade-off, we ran correlation analyses between the individual response times and error rates for each task condition and stimulation session (that is, correlations between the average response time and accuracy per participant for the syntactic responses in aIFG, pIFG, and vertex sessions, and for the semantic responses in aIFG, pIFG, and vertex sessions). None of these correlations were significant (all r -values $>-.21$ -and $<.01$; all p -values $>.300$), which does not support such a trade-off effect.

3.3. *Impact of electric field strength on task performance*

To assess whether variability in response times could be explained by the strength of the electric field induced by rTMS, we conducted additional analyses including the evoked electric field in aIFG and pIFG for each participant (the vertex (control) session was excluded from this analysis). Here, we found a significant interaction between condition and the electric field strength in aIFG ($\chi^2(1)=27.92$, $p<.001$) and in pIFG ($\chi^2(1)=3.99$, $p=.046$; Figure 4B). Resolving the interaction effect in the aIFG subregion revealed differential effects of electric field on response times in the syntactic and semantic decisions: syntactic decisions became faster with higher rTMS-induced electric field strength in the stimulated area ($z=-3.56$, $p<.001$), whereas semantic decisions were slowed down ($z=3.77$, $p<.001$). In the pIFG subregion, stronger electric fields were related to faster responses in the syntactic domain as well ($z=-3.78$, $p<.001$). This effect was condition-specific as there was no significant effect of electric field on response times in the semantic condition ($z=-0.95$, $p=.340$); Figure 4B). Finally, there was a main effect of session ($\chi^2(2)=738.86$, $p<.001$), indicating that participants gave faster responses across sessions (Supplementary Figure 1).

In the accuracy rates, there were no effects of electric field strength in the aIFG ($\chi^2(1)=0.07$, $p=.792$) or pIFG ($\chi^2(1)=.46$, $p=.497$) subregions.

Figure 3 Response times (A) and error rates (B) for each decision type and TMS site. In (A), the asterisk indicates a main effect of decision type. The upper and lower bounds of the boxes correspond to the 3rd and 1st quartiles, respectively. The whiskers represent 1.5 times the interquartile range. In (B), the asterisk indicates the main effect of TMS site (pIFG contrasted to vertex). Error bars reflect ± 1 SEM. Lines connect subject-wise data.

Figure 4 Electric field simulations revealed differential effects of alFG and pIFG stimulation on response times. (A) Electric fields induced by TMS for the alFG and pIFG stimulation conditions in a representative sample subject. The white line indicates the border between the parts of the gyrus belonging to cytoarchitectonic regions BA45 (alFG) and BA44 (pIFG). (B) Response times per task condition plotted in function of the electric field strength in the alFG and pIFG ROIs. In both ROIs, a significant interaction between field strength and decision type was found. Higher electric field strength in the alFG led to delayed response times in semantic, but faster response times in syntactic decisions. In the pIFG, higher electric field strength was related to a task-specific facilitation of responses in syntactic trials, with no significant effect on semantic trials. The lines represent the model estimate (confidence intervals indicated by the shaded area). Dots represent single subject peak electric field strength and mean response time. Note that for each participant, two electric field values are plotted per ROI, obtained from each stimulation session (alFG and pIFG).

4. Discussion

This study probed the functional relevance of the left IFG in sentence processing guided by prosodic cues. In our paradigm, successive syntactic and semantics processing steps were performed in isolation from one another. This allowed us to use focal perturbation induced

by rTMS to test the hypothesis that anterior and posterior parts of the IFG are specialised for semantic and syntactic processing, respectively. Our results do not fully support this hypothesis. In our initial behavioural analysis, we observed no significant rTMS modulation of response times, but an unexpected cross-domain effect on accuracy: both semantic and syntactic decisions were impaired when rTMS targeted pIFG as compared to the control site. A subsequent analysis of the impact of the induced electric fields by rTMS on response speed revealed more fine-grained and specific results, indicative of functional and regional specialisation within the IFG. Specifically, we found a site-specific rTMS effect on semantic processing: higher stimulation strength in aIFG yielded slower response times, whereas pIFG stimulation did not significantly delay semantic decisions. Furthermore, we found polarity-specific effects on syntactic processing in both IFG subregions. Stronger stimulation of either aIFG or pIFG was associated with *faster* responses in syntactic but not semantic trials. Overall, these results are in line with our hypothesis that pIFG is involved in syntactic decisions guided by a prosodic cue. However, this effect was not site specific as aIFG stimulation yielded similar results: contrary to our hypothesis of a task-specific effect of aIFG stimulation on semantic decisions, rTMS over this region modulated both semantic and syntactic processing, albeit with opposite polarity. Together, the results are in line with previous work suggesting a syntax-specific role of posterior IFG and a more cross-domain function for anterior IFG subregions (Hagoort & Indefrey, 2014).

The observed cross-domain effect of pIFG stimulation on task accuracy in our initial behavioural analysis is likely explained by a spread of stimulation across the larger IFG region. Indeed, our electric field simulations suggested that stimulation of the two IFG target regions differed in the focality of the electric fields. In the aIFG session, stimulation was mostly restricted to the target region (aIFG), covering both pars triangularis and extending into pars orbitalis. In contrast, in the pIFG session, the induced stimulation covered both pIFG and the posterior part of the aIFG (as well as part of premotor cortex). We are therefore unable to attribute the increase in error rates to stimulation of either subregion or the larger IFG. In contrast, we found more specific effects when relating the induced electric field strength per region to semantic and syntactic response speed.

Analysis of the electric field strength induced by rTMS revealed a site-specific effect on semantic processing, showing that stimulation over aIFG had an inhibitory effect on the semantic decisions. This analysis uses high-resolution individual head models to calculate the TMS-induced electric fields for each participant. The strength of these electric fields in aIFG and pIFG ROIs was then used to explain variability in the response times in each task. The result showed an inhibition of semantic responses for stronger stimulation in aIFG, corroborating functional neuroimaging work that attributed semantic processing to the anterior part of the IFG (Goucha & Friederici, 2015; Graessner et al., 2021; Klimovich-Gray et al., 2018). The finding is also in line with previous TMS studies that required processing of single words (Gough et al., 2005; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011; 2012) or multiple words (Devlin et al., 2003; Klaus & Hartwigsen, 2019), and therefore extends previous findings from the word level to the sentence level. More specifically, beyond word-level processing such as lexical access and synonym judgement, our results underline the functional relevance of aIFG in semantic processing for which sentence-level prosodic information is required. The finding may be surprising considering the broad cortical distribution of the semantic network (Binder & Desai, 2011; Ralph, Jefferies, Patterson, & Rogers, 2017), which in principle allows for compensatory activity from other regions beyond the IFG. In fact, there is a high degree of flexibility with which cortical areas within the same network can redistribute after disruption of a specific node (Hartwigsen, 2018). Yet, in our study, aIFG stimulation alone interfered with semantic processing, showing the importance of this node in the semantic network, at least in the type of semantic processing investigated with our paradigm.

The electric field strength analysis further revealed a task-specific effect in pIFG: in this subregion, rTMS modulated syntactic but not semantic processing. The involvement of IFG has repeatedly been found for processing syntactic structure, for example in predicting word category information (noun or verb) (Bonhage, Mueller, Friederici, & Fiebach, 2015). Notably, syntactic pre-activation of left pIFG has been shown in response to a prosodic cue. In Swedish, the pitch height at the beginning of a sentence can be predictive of upcoming sentence structure: more constraining syntactic predictions activated pIFG as well as the adjacent anterior insula (Söderström, Horne, Mannfolk, van Westen, & Roll, 2018). Another recent study found involvement of the left pIFG in syntactic surprisal (Henderson, Choi,

Lowder, & Ferreira, 2016). Together, these studies point to a role for pIFG in processing syntax, particularly in a predictive fashion (Ferreira & Qiu, 2021). Although our paradigm did not evaluate linguistic predictions in the strictest use of the word (i.e., as an automatic and implicit process (Huettig, 2015; Pickering & Gambi, 2018)), it did require intact expectations concerning upcoming syntactic positions to perform an explicit judgment. In addition, the task required matching this syntactic expectation formed by prosody (subject or object) with the appropriate determiner presented on the screen (nominative or accusative). Whether the two processing stages—forming the expectation or the subsequent template matching—can be attributed to the two IFG subregions separately or whether the two processes are distributed across both subregions remains to be further investigated. Aside from predicting syntax, there is also EEG evidence for the involvement of left frontolateral regions in predicting prosodic structure (Heim & Alter, 2006). However, since the current study was designed to investigate syntactic and semantic expectations that were cued by prosody rather than expectations on prosodic structure as such, future work is required to investigate the possible role of IFG subregions in expectations in all three domains.

Although our results suggest pIFG to be selective to syntax, the aIFG subregion was shown to be involved in both syntactic and semantic decisions. Notably, the syntactic and semantic effects in aIFG exhibited opposite directionality, which we will turn to later in the discussion. The fact that we found effects on both processing domains in aIFG is contrary to our initial hypothesis, which posited a double dissociation between IFG subregions in syntactic and semantic processing. However, syntactic effects in aIFG as well as pIFG have been reported previously. For example, an fMRI study by Santi & Grodzinsky (2010) showed that some syntactic operations could be attributed to pIFG, but others to aIFG. Furthermore, the meta-analysis (Hagoort & Indefrey, 2014) that provided our rTMS target coordinates reported involvement of aIFG in both high syntactic and high semantic demands (albeit with less activation for high syntactic vs. semantic demands). As such, using neurostimulation, our findings corroborate functional neuroimaging work suggesting that aIFG responds to both syntactic and semantic manipulations. Contrastingly, we found pIFG to be involved in complex syntactic processing only, in line with our hypothesis. The present results therefore support the notion that pIFG is specialised for syntactic computations (Goucha & Friederici, 2015; Schell et al., 2017; Zaccarella, Meyer, Makuuchi, & Friederici, 2015), but that syntactic

processing may engage aIFG as well (Santi & Grodzinsky, 2010; Hagoort & Indefrey, 2014; Matchin, Hammerly, & Lau, 2017; Nelson et al., 2017).

While a large body of work has attributed syntactic and semantic processes to different IFG subregions, the role of the IFG in processing prosody has been less clear. Effects of prosody in IFG have been found in several fMRI studies, showing activity constrained to specific IFG subregions (Meyer, Steinhauer, Alter, Friederici and Von Cramon, 2004; Perrone-Bertolotti et al., 2013) or spanning several IFG subregions (Kristensen et al., 2013; Van Leeuwen et al., 2014; Van der Burght et al., 2019). However, there is considerable variation in the type of prosodic processing investigated in these studies, ranging from effects of acoustic modulations (Meyer et al., 2004), to processing linguistic focus (Perrone-Bertolotti et al., 2013; Kristensen et al., 2013; Van Leeuwen et al., 2014) and disambiguating sentence structure using prosody (Van der Burght et al., 2019). Whether these different prosodic processes can be attributed to subregions of the IFG, and if so, to which subregions exactly, requires future investigation. A similar open question concerns phonological and syntactic processing, which have both been associated with posterior IFG. Yet, whether overlapping or different regions of pIFG contribute to these two processing domains has remained unclear. We are not aware of any neuroimaging or neurostimulation studies that systematically compared the two processes within the same design. Such future work would certainly be worthwhile to investigate this question.

The unexpected facilitatory effect of TMS on syntactic response speed, revealed by the analysis of the electric field strength in both IFG subregions, requires further explanation. The 10 Hz rTMS protocol used in the current study is frequently thought to inhibit neural processing and therefore task performance (Hallett, 2007; Hartwigsen, 2015). However, (unexpected) facilitation effects by TMS over language areas are not uncommon (Andoh et al., 2006; Klaus & Hartwigsen, 2019; Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004; Sliwinska et al., 2017; Sparing et al., 2001), especially when TMS is given directly during the task. Effects of opposite polarity within the same study have previously been found, for example by Klaus & Hartwigsen (2019), where 10 Hz rTMS over pIFG *facilitated* responses in a phonological task while applying the same protocol over aIFG *inhibited* semantic performance. Note that in our task, the semantic condition yielded longer

response times as compared to the syntactic decisions, replicating results from our previous behavioural study (van der Burght et al., 2021). This difference can be accounted for by the increased reading time and harder lexical access involved for nouns (semantic decisions) as compared to determiners (syntactic decisions). Furthermore, as a necessary consequence of our design, the nouns differed across the experimental items, whereas the determiners did not. The syntactic task was therefore more automatized and constrained in its options than the semantic task. This difference may explain the different directions in rTMS effects for syntactic and semantic decisions. On average, the syntactic decisions were faster than the semantic ones by an order of magnitude of hundreds of milliseconds. It is therefore conceivable that the pulse trains in our protocol, lasting 500 milliseconds each, interfered with different stages of each decision type and, therefore, different cognitive states involved in each decision. Indeed, facilitatory effects of TMS on neural activity have been explained in terms of *state dependency*, positing that the ongoing neuronal state during which TMS is applied may determine the direction of the behavioural effect (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Silvanto & Cattaneo, 2017). It was argued that for some conditions, rather than inducing noise, TMS-induced activity might be synchronised with ongoing, task-relevant neural activity (Miniussi, Ruzzoli, & Walsh, 2010), resulting in a neural signal that is beneficial instead of detrimental to the task at hand (Miniussi, Harris, & Ruzzoli, 2013). Such state-dependent effects may be particularly relevant when TMS is applied during a given task, as was the case in the present study.

To summarize, our electric field simulations revealed task-specific as well as site-specific stimulation effects. However, we found no evidence for a strict functional-anatomical double dissociation between syntax and semantics. One could question if the paradigm was sufficiently sensitive to dissociate both processes. Yet, since we were able to replicate the results from our previous behavioural study, this paradigm seems validated in its ability to dissociate syntactic and semantic processing guided by a prosodic cue (van der Burght et al., 2021). A more likely explanation for the limited dissociation between anterior and posterior IFG is the limited focality of the electric fields induced by TMS which warrants further investigation, especially when studies aim to dissociate neighbouring cortical regions. A further explanation can be found in the between-subject neuroanatomical variability of the inferior frontal cortex. The IFG is known to show large interindividual variability, both in

terms of the organization of gyri and sulci and in the way cytoarchitectonic regions relate to them (Amunts et al., 1999). To circumvent this issue, a functional localiser may have been necessary to target the exact areas supporting syntactic and semantic processing in each individual. Indeed, it has been argued that functional localisers are beneficial for dissociating functional areas within the IFG, for example to distinguish language-specific from domain-general regions (Fedorenko & Blank, 2020). Since individual localizers are time consuming and may be tricky to design if repetition of the same task and stimuli needs to be avoided, we relied on transferring mean group coordinates from previous fMRI studies to the individual subject level in our study. This approach has been successfully employed to demonstrate functional specialization of different subregions for various language tasks in our previous studies (Hartwigsen et al., 2010; 2016; Klaus & Hartwigsen, 2019; Kroczeck, Gunter, Rysop, Friederici, & Hartwigsen, 2019; Kuhnke et al., 2017). Yet, future TMS studies investigating high-level cognitive processing in adjacent cortical areas may benefit from a functional localiser approach (Sack et al., 2009; Sparing, Buelte, Meister, Paus, & Fink, 2008).

In conclusion, our study provides evidence for the functional specialisation of subregions of the left IFG for syntactic and semantic processing. In particular, our data suggest that the aIFG is an important cortical area for semantic computations that are cued by prosody. In addition, this region was shown to support syntactic processing. In contrast, stronger electric field strength in pIFG was associated with modulatory effects on response speed selectively for syntactic processing. As such, the present data are inconclusive concerning a strict functional-anatomical double dissociation between the aIFG for semantic processing and the pIFG for syntactic processing when assigning grammatical roles during sentence comprehension. Rather, our study suggests that in forming expectations about upcoming sentence material, the aIFG is functionally relevant for processing both semantic and syntactic properties, while the pIFG may be relevant for processing syntactic properties only. Future studies may use smaller TMS coils with increased focality to further explore gradients in functional specialization within the larger left inferior frontal cortex and consider the strong interindividual variability of the region. Yet, despite this interindividual variability, we were able to demonstrate TMS effects on language processing that exhibited anatomical specificity and task specificity. In summary, our results provide first evidence for

a functional specialization within IFG for syntactic and semantic processing guided by prosody.

Data availability

Raw data and analysis scripts are available at <https://osf.io/5k8ze/>.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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