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Neurocognitive Relations between Language and Thought

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ABSTRACT OF THE DISSERTATION

Neurocognitive Relations between Language and Thought

by

Micah Alan Johnson
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2020
Professor Martin M. Monti, Chair

The relation between language and thought – whether or not they function independently of each other – remains a mystery in philosophy and science. One approach for investigating this problem focuses on hierarchical processing as a fundamental feature of language and many other cognitive domains. Hierarchical processing involves the construction of temporally ordered sequences from integration of finite elements in embedded structures, such as the creation of sentences from letters, chord progressions from keys, formulas from symbols and operators, and complex actions from simple movements. Prominent theories propose that the hierarchical similarities between language and other cognition may derive from shared neural resources. These theories were tested in this dissertation with three different methodological approaches. In the first study, a behavioral dual task experiment revealed that simultaneous processing of language and music produced bidirectional interference of performance driven mostly by syntactic structural complexity rather than syntactic working memory demands. Cross-domain interference also occurred when syntactically critical words and keys temporally coincided. These novel findings support theoretical predictions of shared syntactic integration resources between language and music. In the second study, a Bayesian meta-analysis of neurostimulation experiments spanning six cognitive domains – action, artificial grammar, language, logic, math, and music – provided novel evidence of the potentially causal role of Broca's area, based mostly on the pars opercularis subregion of the left inferior frontal gyrus (LIFG), as a shared neural resource for hierarchical processing. In the third study, a within-subjects neurostimulation experiment provided tentative evidence for potentially shared neural resources between language and math such that transcranial magnetic stimulation (TMS) of either the pars opercularis or the right intraparietal sulcus modulated performance of both linguistic and algebraic hierarchical processing. Taken together, these complementary studies support theories of shared resources across cognition and demonstrate the benefits of a multi-pronged research approach for exploring neurocognitive relations between language and thought.

The dissertation of Micah Alan Johnson is approved.

Marco Iacoboni

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Martin M. Monti, Committee Chair

University of California, Los Angeles

2020

DEDICATION

To my brothers and sisters

who have been a constant source of inspiration to me

and whom I admire immeasurably.

To all those who struggle to free their mind.

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Featured Publications

Dell'Italia, **Johnson,** Vespa, & Monti (2020). Accounting for changing structure in functional network analysis of TBI patients [Preprint]. *Frontiers in Systems Neuroscience, doi: 10.3389/fnsys.2020.00042*

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Featured Invited Talks

Brain structural dynamics of disorders of consciousness (2018, UCLA, Cognitive Forum)

Where cerebral water flows may expose how time shows memory highs and lows (2017, The Quale)

Bayesian statistics for the cognitive scientist (2017, Pomona College, Cog Sci Dept)

What diffusion MRI tells us about word finding failures and aging (2017, Pomona College, Cog Sci Dept)

Exploring brain function and dysfunction with structural MRI (2017, Casa Colina Hospital)

Chapter 1

General Introduction and Background

In this dissertation, three studies were conducted – a behavioral experiment, a meta-analysis, and a neurostimulation experiment – in order to test theories of shared resources between language and other forms of cognition. All studies focused on hierarchical processing and compared language to one or more cognitive domains. Chapter 2 describes a behavioral dual task experiment that investigated the degree to which language and music share syntactic resources. The work described in Chapters 3 and 4 leveraged neuromodulatory approaches for testing the specificity of Broca's area (mostly based on the pars opercularis subregion of the left inferior frontal gyrus, LIFG) for hierarchical processing of language. Chapter 3 describes a Bayesian meta-analysis on published neurostimulation literature with the aim of comparing language to five domains – action, artificial grammar, deductive reasoning, math, and music. Chapter 4 reports a neurostimulation experiment that compared language and algebra performance before and after transcranial magnetic stimulation (TMS), using continuous theta burst stimulation (cTBS), of the pars opercularis subregion of the LIFG, a region often but not always associated with language, as well as the horizontal segment of the right intraparietal sulcus (RIPS), a region typically associated with mathematical cognition. Chapter 5 concludes with a summary and discussion of these various experimental findings.

Hierarchy in cognition

Following Fitch and Martins (2014), the term *hierarchy* refers to a fully connected tree-like structure (i.e., an acyclic connected graph) where subordinate elements combine into progressively larger structures to create one superordinate element (i.e., the root). In an *ordered* or *structured* hierarchy, the integration of relations between elements in a temporal sequence depends on sequential order, local and nonlocal dependencies, and movement of constituent elements. See Figure 1.1 for an example in language. The root denotes the abstract representation of the entire sequence (i.e., the meaning of the phrase) which is constructed from an ordered hierarchical structure of local and nonlocal relationships between elements (i.e., the words). Notice that the root element changes with movement of the subordinate elements: the phrase "hierarchy parallels between cognitive domains" means something different than the phrase "hierarchy domains between cognitive parallels". These ordered hierarchical structures of language, also known as *syntactic structures*, represent part of the construction of the grammar of natural language (Chomsky, 1957). *Syntactic processing* usually refers to the process or rule-based procedure of constructing syntactic structures (i.e., ordered hierarchical structures), based on parsing, dependency, and locality (Gibson, 2000), in order to enable abstract representations and language comprehension (Hartmann & Stork, 1972; Pickering & Gompel, 2006). Throughout this dissertation, for ease of description, the terms hierarchical structures (or structured hierarchy) and syntactic structures are often used interchangeably, and the term hierarchical processing refers to the mental computation of forming such hierarchical or syntactic structures into abstract representations.

In a landmark paper entitled “The problem of serial order in behavior” which helped to catalyze the cognitive science revolution, Lashley (1951) overturned the associative chaining models of sequential processing, which postulated serial excitation of elements. In the domain of action, for example, he argued instead for parallel activations of action sets or chunks – a “schema for action” or a “syntax of action” – whereby a set of unordered elements (simple actions) could be integrated temporally into an ordered, hierarchically structured sequence (complex actions) according to specific rules and operations (i.e., syntax) and an action plan (a goal for the complex action). Lashley (1951) emphasized that this syntax of action conceptually extends to the syntax of language and music. This idea helped to spawn a rich literature of ongoing research on the computational similarities between language syntax (Chomsky, 1957; Hauser et al., 2002) and the hierarchical or syntax-like processing of other cognitive domains including action planning and understanding (Botvinick, 2008; Pulvermüller, 2014; Rosenbaum et al., 2007), musical cognition (Koelsch et al., 2013; Lerdahl & Jackendoff, 1985), artificial grammar (Bahlmann et al., 2008; Friederici, 2004), deductive reasoning (Monti & Osherson, 2012), mathematical reasoning such as algebra (Chomsky, 1997; Ernest, 1987), problem solving (Dehaene & Changeux, 1997), mentalizing within Theory of Mind (Gallese, 2007; Oesch & Dunbar, 2017), and even computer programming (Fitch et al., 2005).

In action planning, for example, a complex action such as making coffee can be seen as constructed from a structured hierarchy of individual actions (e.g., opening the coffee lid, dipping a spoon in the coffee jar, etc; see Figure 1.2, from Botvinick, 2008). Much like natural language, different hierarchical arrangements of the same individual actions, if meaningful, would result in different root elements. The parallels between the syntax-like structures of music (see Figure 1.3) and those of natural language have also long been discussed (Fay, 1971; Lerdahl & Jackendoff, 1985; Patel, 2003; Riemann, 1877; Rohrmeier, 2011), with some even proposing that the two domains represent a unitary phenomenon encompassing the very same processes and representations operating over different “building blocks” (i.e., lexical items in natural language, and pitch-class and chord quality in music; Katz & Pesetsky, 2011). Both algebra and deductive reasoning (see Figure 1.4) also present several analogies with the syntactic structures of natural language (Ernest, 1987; Monti et al., 2012). As explained in Varley et al. (2005), for example, there are several intuitive parallels between algebra and natural language, including the sensitivity to structure (e.g., compare the relationship between the two sentences “man kicks statue” and “statue kicks man” with that between the two algebraic statements “2 – 6” and “6 – 2”) and the ability to recursively embed structures within other structures (e.g., adding “Jack said that […]” to any well-formed sentence or adding “3 + […]” to any well-formed algebraic statement). Finally, Theory of Mind – the ability to attribute mental states, beliefs, and desires to others – can be described as often hinging on a process of hierarchical embedding (such as the mentalizing example in Figure 1.5) analogous to sentential complements in natural language (de Villiers & de Villiers, 2014).

Language, thought, and Broca’s area

For centuries, many thinkers have debated the potential interdependence between language and thought (Monti, 2017), a longstanding mystery encapsulated by the challenging question: to what degree does thinking depend on language or vice versa? The realization of analogous hierarchical structures and hierarchical processing in many cognitive domains has inspired the notion that the relation between language and forms of thought may depend on the degree to which they share the same computations of hierarchical processing and/or depend on the degree of shared neural resources or mechanisms. Whether or not the computational parallels between language and nonlanguage domains are substantial, based on shared resources, or superficial, based on analogy only, has been a vibrant area of research and debate.

Much of the literature has focused on the search for the neural basis of language syntax in the brain and the degree to which it seems specific to language syntax or shared by the hierarchical processing of other domains. Although still under ongoing experimental scrutiny, the syntactic processing of language appears to recruit a widely distributed frontotemporal network of cortical regions, predominantly in the left hemisphere (based mostly on right-handed individuals). Two key nodes of this network include the posterior superior temporal sulcus (pSTS; e.g., Blank et al., 2016; Bornkessel et al., 2005; Grewe et al., 2007; Xiao et al., 2015; Zaccarella et al., 2017), the middle frontal gyrus (e.g., Blank et al., 2016), and either the *pars opercularis* (e.g., Fiebach et al., 2005; Friederici, 2018; Vigneau et al., 2006) and/or the *pars triangularis* (e.g., Blank et al., 2016; Teichmann et al., 2015) of the left inferior frontal gyrus (LIFG; together known as Broca's area). However, the selectivity of this network for language syntax still remains an open question.

Broca's area, in particular, features in numerous theoretical models (e.g., Fadiga, Craighero, & D'Ausilio, 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Jeon, 2014; Patel, 2012; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012) as one of the most likely candidates for a shared neural resource (i.e., a multi-modal or cross-domain hub) between language and other hierarchically structured cognition. Much neuropsychological and functional magnetic resonance imaging (fMRI) research has implicated Broca's area (either the pars opercularis or pars triangularis, depending on the study) in action cognition (Clerget et al., 2013; Fadiga et al., 2009; Fiebach & Schubotz, 2006; Koechlin & Jubault, 2006), music cognition (Chiang et al., 2018; Koelsch et al., 2002), deductive reasoning (Goel et al., 1997, 1998; Knauff et al., 2003; Reverberi et al., 2007; Tsujii et al., 2010), arithmetic and algebraic cognition (Chochon et al., 1999; Dehaene et al., 1999; Friederici et al., 2011; Maruyama et al., 2012; Stanescu-Cosson et al., 2000), and artificial grammar processing (Friederici et al., 2011; Uddén et al., 2008; Uddén & Bahlmann, 2012). Yet to the contrary, other research has not found involvement of Broca's area in domains such as math (Amalric & Dehaene, 2017; Fedorenko et al., 2011; Monti et al., 2012; Zago et al., 2001), deductive reasoning (Coetzee & Monti, 2018; Goel & Dolan, 2001; Monti et al., 2007, 2009; Parsons & Osherson, 2001), and music (Fedorenko et al., 2011; Rogalsky et al., 2011).

The debate surrounding the cross-domain role of Broca's area may in part derive from its remarkable profile of subregional heterogeneity of structure and function. Such heterogeneity includes cytoarchitectonic differences (Schenker et al., 2008), differences in cortical folding patterns (Fischl et al., 2008), different profiles of white matter connectivity and functional connectivity with other brain regions and networks (Anwander et al., 2007; Catani & Budisavljević, 2014; Du et al., 2020; Duffau, 2018; Friederici, 2009), and differences in language-specific versus domain-general subregions depending on individual differences, task contexts, and the methods of fMRI analysis (Blank et al., 2014, 2016; Blank & Fedorenko, 2017; Fedorenko & Thompson-Schill, 2014). The debate of Broca's area may also partly derive from the predominance of neuroimaging methods (e.g., fMRI, or electroencephalography, EEG), which provide only correlational evidence of neurocognitive relations, and the relative dearth of neurostimulation studies, which can potentially provide causal evidence. This issue is discussed in more depth in the section below.

Methodological approaches

The work in this dissertation employed two different methodologies to explore potentially shared cognitive resources (using the dual task paradigm) and shared neural resources (using neurostimulation) between language and other cognitive domains. These methodological approaches are briefly introduced below.

Shared cognitive resources. In this dissertation, a *shared cognitive resource* is defined as some computational process which appears necessary for two or more cognitive systems or domains such that both domains depend on this same process. The dual task paradigm provides an intervention technique to assess potentially shared cognitive resources. The logic of this paradigm is that simultaneous processing of two cognitive domains should lead to interference effects in one or both domains if they both depend on the same cognitive process manipulated by the task. Many studies have used dual task paradigms to test for shared resources between cognitive domains, although uncertainty still remains regarding interpretations of cognitive structure, flexibility, and plasticity (Koch et al., 2018). Some dual tasks have compared between language and music (Hoch et al., 2011; Kunert et al., 2016) in order to test a prominent model, the shared syntactic integration resource hypothesis (SSIRH; Patel 2003, 2012), which posits that language and music share a domain-general system of syntactic structural integration between domain-specific syntactic processes which may depend on Broca's area as a shared neural resource. The SSIRH specifically predicts that if language and music share syntactic integration costs, then simultaneous processing of both domains should show cross-domain interference. Based on this logic, an experiment was designed for the present dissertation (see Chapter 2) which used the dual task paradigm in a novel way to demonstrated bidirectional interference between language and music based mostly on syntactic complexity of structural integration rather than syntactic working memory. Cross-domain interactions also preferentially occurred when syntactically critical words and keys temporally coincided across language and music sequences. This experiment provided new evidence in support of the hypothesis (SSIRH) of shared syntactic integration resources between language and music.

Shared neural resources. In this dissertation, a *shared neural resource* is defined as some neural component of information processing (i.e., region, circuit, network, etc) whose function appears necessary for two or more cognitive systems, such that both systems depend on this same neural component (for a more nuanced discussion, see Wolff & Ölveczky, 2018). Neurostimulation techniques can contribute uniquely important information about shared neural resources because, unlike neuroimaging (e.g., fMRI, EEG), they have potential for direct causal manipulation of specific regional or network dynamics to test for causal brain-behavior relations. However, the mechanisms of neurostimulation and their causal efficacy seem to depend on various experimental and neurobiological factors. The following section focuses on transcranial magnetic stimulation (TMS), although many of the issues about causality also apply to other techniques like transcranial direct or alternating current stimulation (tDCS, tACS), direct brain stimulation (DBS), and transcranial ultrasound stimulation.

Transcranial magnetic stimulation (TMS) works by running electrical current through an induction coil in order to generate a high intensity, time-varying magnetic field (i.e., a pulse) perpendicular to the coil, which when placed over a person's scalp, passes through their skull and induces electrical current changes (via Faraday's law) in the underlying cortical tissue as well as potentially other distant cortical or muscular tissues depending on their structural or functional connections with the target region (Bestmann & Feredoes, 2013; Pascual-Leone et al., 2000; Sack, 2006; Siebner et al., 2009). The consequent changes in the cortex can include transient or long-term excitation (e.g., generation of action potentials causing a motor evoked potential in a distant muscle, or long-term potentiation of postsynaptic activity) or inhibition (e.g., long-term depression, activation of inhibitory interneurons) depending on numeric factors such as TMS parameters and neural variables.

Different TMS protocols such as repetitive TMS (rTMS), continuous theta burst stimulation (cTBS), and intermittent theta burst stimulation (iTBS) are created by changing various parameters of stimulation (e.g., number of pulses, pulse intervals, intensity of magnetic field, etc). Typically, low frequency rTMS ($\leq$ 1 Hz) produces inhibitory effects whereas high frequency rTMS (> 1 Hz) produces excitatory effects (Guse et al., 2010; Wassermann, 1997). Most of the time, cTBS produces inhibitory (e.g., long-term depression) effects and iTBS produces facilitation (e.g., long-term potentiation) effects after stimulation of motor regions (Huang et al., 2005, 2011; Suppa et al., 2016) or nonmotor/cognitive regions (Demeter, 2016; Sandrini et al., 2011). Interestingly, cTBS has been shown to sometimes produce unexpected facilitation in motor regions depending on the level of excitation in the cortex prior to, during, or after the stimulation (Doeltgen & Ridding, 2011; Gentner et al., 2008; Huang et al., 2008), as well as in nonmotor or cognitive regions depending on task contexts, neurobiology, and other factors (Acheson & Hagoort, 2013; Suppa et al., 2016; Viejo-Sobera et al., 2017; Xu et al., 2013). In one proposed explanation, inhibition of normally inhibitory interhemispheric connections could produce excitatory outcomes (Suppa et al., 2016), an idea which has guided some recent neurotherapy applications such as stroke rehabilitation (Boddington & Reynolds, 2017).

It also seems likely that neural characteristics of (meta)plasticity (Abraham & Bear, 1996; Galanis & Vlachos, 2020; Müller-Dahlhaus & Ziemann, 2014; Rioult-Pedotti et al., 2007), state dependency (Bestmann, 2008; Siebner et al., 2009; Silvanto & Cattaneo, 2014), network connectivity (Bestmann & Feredoes, 2013; Pascual-Leone et al., 2000; Sack, 2006; Siebner et al., 2009), neurotransmitter and neuroreceptor factors (Stagg et al., 2009; Suppa et al., 2016), and other neural dynamics (Chervyakov et al., 2015) of the stimulated cortical regions or networks could produce unpredictable effects, including the stimulated region or network adapting to, or compensating for, the stimulation effect in order to maintain function (Chung et al., 2017; Graaf & Sack, 2011; Pascual-Leone et al., 2000; Sack, 2006). This phenomenon could partly account for the well-known high interindividual variability in responses and cognitive outcomes from applications of TMS and TBS to both motor and nonmotor regions (Acheson & Hagoort, 2013; Guerra et al., 2020; Jannati et al., 2017, 2019; Ji et al., 2017; Rocchi et al., 2018; Suppa et al., 2016; Viejo-Sobera et al., 2017; Xu et al., 2013).

To conclude, even though exact mechanisms and causal efficacy of TMS and other neurostimulation techniques remain currently unresolved although actively researched, cognitive neurostimulation can uniquely contribute to experimental investigations of potentially causal relations between brain and behavior. Despite the relative scarcity of neurostimulation studies on hierarchical cognition when compared to neuroimaging research, the novel meta-analysis in Chapter 3 illustrates that enough neurostimulation literature already exists to enable preliminary investigation of their contribution for assessing shared neural resources (e.g., Broca's area, based mostly on the pars opercularis subregion) hierarchical processing between language and other cognition. The neurostimulation experiment in Chapter 4 also takes advantage of neuromodulation to directly test the notion of potentially shared neural resources (specifically, the pars opercularis of Broca's area, and the right intraparietal sulcus) between the hierarchical processing of language and algebra.

Summary

The work in this dissertation explored the elusive relationship between language and thought with a trifecta of behavioral, meta-analytic, and neuromodulatory approaches which yielded novel findings about shared neurocognitive resources between linguistic and nonlinguistic hierarchical processing. The work in Chapter 2 directly tested theoretical predictions of shared syntactic resources between language and music. The work in Chapters 3 and 4 directly tested the hypothesis of Broca's area as a cross-domain network hub for hierarchical processing.

Figures

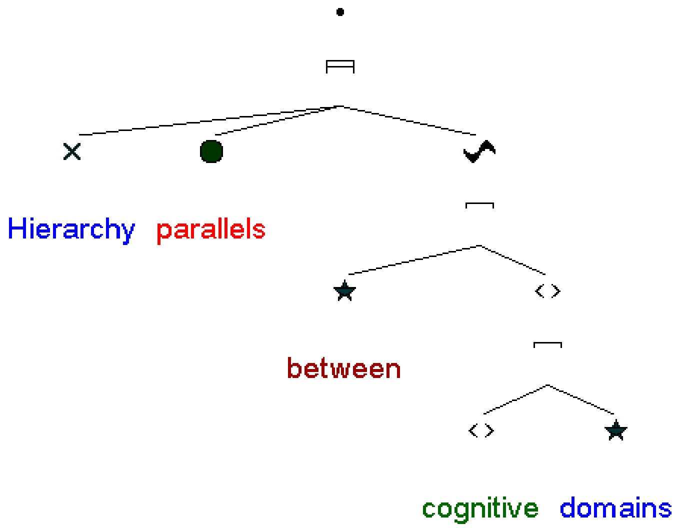

Figure 1.1. Hierarchical structure in language.

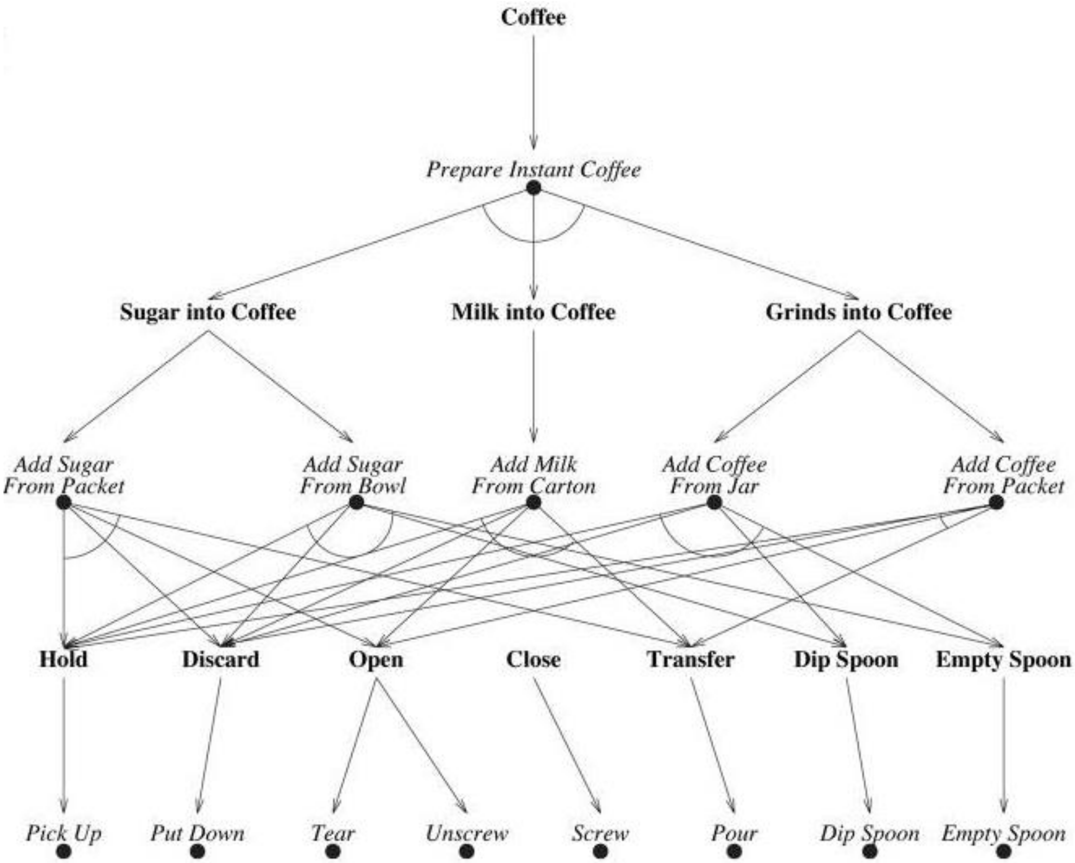

Figure 1.2. Hierarchical structure in action (Botvinick, 2008).

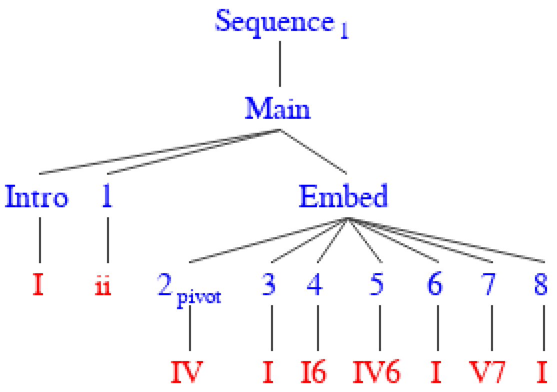

Figure 1.3. Hierarchical structure in music.

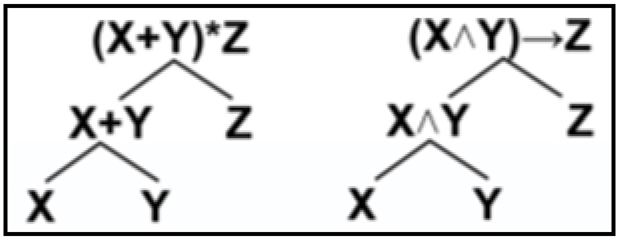

Figure 1.4. Hierarchical structure in algebra and deductive reasoning (Monti, 2017)

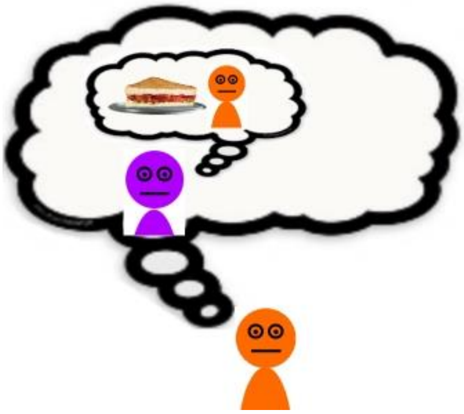

Figure 1.5. Hierarchical structure in mentalizing (Theory of Mind).

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Chapter 2

Bidirectional interference between language and music in a dual task experiment without syntactic violations

Abstract

In order to investigate potentially shared syntactic mechanisms between language and music, we conducted a novel adaptation of the dual task paradigm without syntactic violations to assess the degree of bidirectional interaction between the two domains. Participants listened to music progressions while reading natural language sentences and after were asked to provide, in randomized order, music closure judgments and language comprehension answers. We manipulated both language and music stimuli in terms of their syntactic structural complexity and syntactic working memory demands based on nonlocal dependencies between words or chords. We discovered a bidirectional pattern of cross-domain interaction whereby language and music interfered with each other to various degrees resulting mostly from syntactic structural complexity instead of syntactic working memory demands. We also found that cross-domain interactions occurred when syntactically critical words and keys temporally coincided across language and music sequences. These results of bidirectional interactions based on syntactic structural complexity and syntactically critical moments provide new evidence in support of theoretical models of shared resources between language and music.

Introduction

The structural parallels between language and music have been discussed for a long time (Fay, 1971; Lashley, 1951; Riemann, 1877). At the heart of both domains lies a combinatorial, generative process (i.e., syntax) for creating infinitely recursive sequences from discrete elements (e.g., sentences from letters, speech from phonemes, harmonic progressions from notes and chords) that unfold over time in hierarchical structures with superordinate and subordinate relations and with local and nonlocal dependencies (Chomsky, 1957; Fitch & Martins, 2014; Hauser, Chomsky, & Fitch, 2002; Lerdahl & Jackendoff, 1985; Patel, 2003; Rohrmeier, 2011).

Most discussions of shared vs independent resources in musicolinguistic processing focus on dependency processing across the two modalities. As detailed by Van de Cavey and Hartsuiker (2016), “dependency processing can be aligned with current structural processing theories in both tonal harmony and language” (p. 173). In language, prominent processing theories (e.g., Gibson, 1998, 2000) posit that incomplete structures need to be maintained active in memory and that incoming elements need to be integrated into this available structural ‘skeleton’. The longer the distance between two structurally-dependent elements, the higher the processing load on the mechanisms and resources for structural integration. Similarly, music has been described as a mixture of short-term, local relationships as well as a complex assortment of nested, nonlocal dependencies stretching over long ranges of musical passages (Lerdahl & Jackendoff, 1985), capable of creating tree-like structures. Processing demands – analogous to those described for language above – can be established between structural harmonic “heads” and the incoming elements of a progression which can be structured recursively (Rohrmeier, 2011).

Whether the hierarchical and syntactic similarities between language and music are substantial (i.e., based on shared neurocognitive resources or systems) or superficial (i.e., based on analogy only) is an important and unresolved question (Asano & Boeckx, 2015; Fedorenko & Varley, 2016; Peretz, Vuvan, Lagrois, & Armony, 2015) that reflects a broader debate surrounding the degree of interdependence between the structure-based operations of language and those of other forms of human thought (Boeckx, 2010; Fitch & Martins, 2014; Gleitman & Papafragou, 2013; Lashley, 1951; Monti, 2017; Rosenbaum et al., 2007). In the context of the relationship between language and music, the discussion is largely bound by two polar opposite positions.

On the one hand, there have been many neuropsychological observations of double dissociations between cases of amusia and aphasia (Ayotte et al., 2002; Luria et al., 1965; Marin & Perry, 1999; Peretz et al., 1994; Piccirilli et al., 2000)**.** Additionally, behavioral (e.g., Bonnel et al., 2001; Perruchet & Poulin-Charronnat, 2013) and neuroimaging evidence (e.g., Cheung, Meyer, Friederici, & Koelsch, 2018; Fedorenko, Behr, & Kanwisher, 2011) supporting modular independence has also been reported.

On the other hand, it has been proposed that language and music rely on common neurocognitive substrates, such as a “supramodal” mechanism for parsing structured hierarchies (i.e., supramodal hierarchical parser hypothesis, SHP; Fadiga, Craighero, & D’Ausilio, 2009; Tettamanti & Weniger, 2006), or a domain-*general* mechanism for online structural integration of domain-*specific* representations (i.e., shared syntactic integration resource hypothesis, SSIRH; Patel, 2003, 2012). These views account for behavioral data showing interference effects during dual processing (Fedorenko et al., 2009; Hoch et al., 2011; Kunert et al., 2016; Slevc et al., 2009), interactions between or co-localized electroencephalography (EEG) signal components (Koelsch et al., 2005; Sammler et al., 2013) as well as spatial overlap of blood oxygen-level dependent (BOLD) patterns in neuroimaging studies (Chiang et al., 2018; Koelsch et al., 2002). Some neuropsychological evidence on shared resources has also been reported (Patel, 2005; Patel, Iversen, Wassenaar, & Hagoort, 2008).

In a review of the available musicolinguistic literature, Fedorenko and Varley (2016) offered a reinterpretation of many studies that have been taken as evidence for shared domain-specific resources. Namely, they argue that syntactic violation paradigms often used in these studies might recruit attentional demands that are related to the saliency of the violation, rather than to the specifics of the syntactic manipulations. For example, they proposed that observed event-related potential (ERP) responses that are sensitive to syntactic violations (e.g., P600) are better thought of as signatures of error detection, as they have been observed in response to unexpected events in the absence of structural violations (see Fedorenko & Varley, 2016, p. 139-142 for further discussion).

Notably, however, some previous studies employing such violation paradigms have used a variety of attention-capturing or saliency controls (e.g., unexpected changes in timbre or volume) and have observed interactions between the modules in response to the syntactic violations but no interactions with the saliency controls (Fedorenko et al., 2009; Slevc et al., 2009). Furthermore, recent studies have manipulated music syntax using non-deviant chords in their progressions (i.e., less expected but in-key subdominant chords, rather than in-key tonic chords) and have found support for cross-modal syntactic interactions (Hoch et al., 2011; Kunert et al., 2016). Overall, the currently available data paint a rather mixed picture with respect to the relationship between musical and linguistic processing, particularly along structural parameters.

For the present study, we conducted a violation-free, bidirectional test of whether language and music interact and, if so, whether such interactions are preferentially due to syntactic structural complexity (SynSC) or shared syntactic working memory (SynWM) demands. Similar to Kunert et al. (2016), we employ a cross-modal, dual task design in which participants listened to music progressions of different structural complexity (and provided closure judgments of how well the final chords integrated with the previous chords) while reading natural language sentences of different structural complexity (and provided comprehension judgments).

Language syntactic complexity and working memory. See Figure 2.1 for schematics and Tables 2.1 and 2.2 for descriptions. A well-known example demonstrating processing complexity in English is the contrast between subject (SRC2) and object (ORC) relative clause (RC) filler-gap dependencies. In the ORC, the distance between the relative object *that* (*that = the man)* and its licensing verb (*saw)* is longer than the distance in the SRC between the relative subject *that (that = the soldiers)* and its predicate verb (*saw)*. Another example of sentence types with varying processing complexity (Figure 2.1), although less commonly studied, compares RCs that are center-embedded (SRC2) to ones that are right-branching (SRC1). SRC2 sentences introduce a nonlocal dependency between matrix subject (*the soldiers*) and verb (*fell*) that does not exist in SRC1 sentences. Thus, in both cases, according to dependency processing hypotheses (e.g., DLT: Gibson, 2000; SWM: Kljajević, 2010), the sentences with more nonlocal dependencies (ORC > SRC2 and SRC2 > SRC1) incur higher processing costs associated with storing, retrieving, and/or integrating non-local structural dependents. Because ORC has the same structure as SRC2 (i.e., center-embedded), yet incurs higher working memory costs due the distance between relativizer and verb, we compared these sentences as our syntactic working memory contrast (SynWM: ORC > SRC2). Because SRC2 has the same working memory costs (i.e., relativizer-verb distance) as SRC1 but has a more complex syntactic structure (i.e., center-embedded versus right-branching), we compared these sentences as our syntactic structural complexity contrast (SynSC: SRC2 > SRC1).

Music syntactic complexity and working memory. See Figure 2.1 for schematics and Table 2.2 for descriptions. Early empirical evidence suggested that highly hierarchical musical sequences are processed more efficiently (Deutsch, 1980) and that listeners' expectations towards global harmonic contexts within musical progressions could be manipulated with less expected but licit chords (e.g., a fourth harmonic degree following a full cadence, V-I-IV, as opposed to simply the more expected V-I authentic cadence) (Bigand & Pineau, 1997). In our study, we manipulated musical SynSC with different structures either resolving in an authentic cadence relative to the initial tonic context (first-key ending, i.e., Return) or the new context (second-key ending, i.e., Stay). Pivot chords (i.e., chords that are harmonically related to two keys) were used to establish new key contexts[1]; these were always the IV chord of the first key. Similarly, return chords that were used to reintroduce the original tonic context were always the V chord of the current (second) key. A sequence considered to resolve in the second key would have no return chord (i.e., Stay). Therefore, our SynSC contrast (Return > Stay) compared more complex (Return), similar to center-embedded sentences, to less complex (Stay) structures, similar to right-branching sentences. On the other hand, our syntactic working memory (SynWM) contrast (Pivot-Return distance) was defined within the same structure (Return only) comparing different distances between pivot and return chords, analogous to the linear-distance SynWM contrast in language. The point of embeddedness in music (i.e., pivot chord) occurred at either the 2nd, 3rd, or 4th chord. Return chords were also varied and could occur at the 6th, 7th, or 8th chord position. It is important to note that, for the SynSC contrast, although both structures contain key pivots, only Return structures contain key returns, so this creates a slight imbalance of working memory load between structures. However, in Return structures, the short and long distances are averaged together, so their differential effects should be minimized.

Research questions. The study was guided by two research questions. The first question was, do language and music interact bidirectionally in the absence of syntactic structural violations and to what degree are such potential interactions due to syntactic structural complexity (SynSC), syntactic working memory (SynWM), or both? To address this question, in both domains we manipulated SynSC and SynWM as

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[1] The pivot chord (IV) fits well with either the first or second key. As such, it serves as a transition point between clauses. Thus, it is the first chord immediately following the pivot chord that should be considered as part of the "second key" context.

described above (see Figure 2.1 and Table 2.1). We first assessed (Models 1 and 2) whether there were any general effects of processing both language and music domains simultaneously (dual task) versus separately (single tasks) and whether any cross-modal effects were bidirectional (i.e., language and music affect each other equally) or unidirectional (i.e., language influences music more, or vice versa). We then assessed, within the dual task only (Models 3 and 4), whether any cross-modal interference occurred preferentially at the level of SynSC or SynWM, or both.

The second research question was, do music and language interact at the junction of theoretically critical syntactic moments within the progressions and sentences? Theoretical accounts predict that language and music should interact at particular regions in which some unit (i.e., word or chord) is more structurally important than others (Fitch & Martins, 2014; Lashley, 1951; Patel, 2012). Specifically, we interpret critical points as the beginning of embedded phrases (the relativizer *that* in language; the pivot chord in musical progressions) and the end of embedded phrases (the main verb in language; the return chord in musical progressions) (see Figure 2.1 and Table 2.1). This question was addressed with Models 5 and 6, where we hypothesized that music and language judgments would be maximally impacted in trials where the critical points coincide across domains compared to when they do not coincide.

Methods

Participants

Fifty participants (n = 50) aged 18-45 (M = 21.20, SD = 4.60) were recruited via UCLA's SONA system. All participants identified English as their native language. Participants were compensated with course credit and given detailed informed consent. Planned sample size was determined with G*Power (Faul et al., 2007), using the *repeated measures, within factors* option (which assumes a mix of between-subjects and within-subjects effects, so therefore it is overconservative, but there is no option for completely within-subjects tests). We estimated power of 0.96 with sample size (n = 57) for a 3 x 3 repeated-measures ANOVA (the highest factorial model in our analyses) with the following parameters: effect size = 0.30 (considered medium ANOVA effect, Cohen, 1988), alpha = 0.01 (to adjust for multiple comparisons), power = 0.95, correlation among repeated measures = 0.50 (default), and nonsphericity correction = 1 (default). Thus, our obtained sample size (n = 50), given our fully within-subjects design, should have sufficed to observe relatively small effects with high power and high significance threshold, and it is also similar to that of a previous similar dual task experiments (Kunert et al., 2016, Experiment 1).

Stimuli

Language. Four types of sentences were used for the language task (see Figure 2.1 and Table 2.1). These included three types of structures with embedded relative clauses (RCs), two subject-extracted (SRC1, SRC2) and one object-extracted (ORC), as well as one sentence complement construction with no extractions (SE). All sentences were eight words long and used the same words in different order to control for low-level lexical differences across items. In general, sentences always had one level of embedding (signaled by the relativizer *that*), two noun (N) phrases, and two verb (V) phrases. The point of embedding (i.e., relativizer *'that'*) varied across sentence structure and could occur in the 3rd or 4th word position in the sentence[2]. The first verb in each sentence was ditransitive and semantically reversible, such that no noun-verb pair was more congruent than another. The second verb was transitive and accompanied by either an adverbial or nominal object. All subject nouns were semantically animate.

In sum, sentence structures were selected on the basis of two key criteria:

(a) embeddedness structure: whether the sentence was right-branching or center-embedded;

(b) distance of extraction: whether the sentence had no extraction, a subject-extraction, or object-extraction.

Music. The musical sequences used in this experiment were adapted and modified from those used in Kunert et al. (2016). See Figure 2.1 for schematic details. Sequences always had a fixed length of nine chords: one Intro tonal major chord (preceding the first word of a sentence) to establish the tonality of the first key, and eight chords to match the eight words of our sentences. For music, each sequence began with the tonic chord of a major key followed by several tonally related chords within that same key before pivoting keys. This new musical context was established by using the IV chord of the original key to pivot into a new key in which it acted as the I chord. For example, an F chord being the IV in the context of C major was used to pivot to the key

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[2] SRC1s had their point of embedding at the 6th position, rendering it ineligible for the present analyses.

of F major where it is the I and was followed by an A# chord which is the IV chord of F major but does not tonally fit in a C major context).

Thus, musical structures mimicked sentence structures in both the embedding and distance manipulations:

(a) embeddedness structure: whether the progression was right-branching (resolving in the second key) or center-embedded (resolving in the first key);

(b) distance of resolution: for progressions ending in the first/initial key, how many chords were in between the pivot and return locations.

Tasks

Task Type (Language, single task). Each sentence trial began with a fixation cross (1500ms) followed by a sentence presented word-by-word (750ms/word) on an otherwise blank screen. After each trial, participants saw one of two types of comprehension probes regarding the first (ditransitive) or second (transitive) subject-verb relationship (randomly selected and counterbalanced across sentence types) and were required to answer yes or no to whether the probe was congruent with the sentence. Participants were given up to six seconds to respond to the probe using a standard computer keyboard. Language performance was interpreted as a percent accuracy on the comprehension probes.

Task Type (Music, single task). At the start of each trial, participants were presented with an initial fixation cross accompanied by an initial (tonal major) chord (1500ms) used to establish the opening key for subsequent chords in the musical sequence. Participants then listened to the sequences chord-by-chord (750ms/chord) while only a fixation cross was displayed. At the end of each trial, participants were asked to give a closure judgment rating (i.e., how well the final chord/section of the sequence matched or closed the earlier sections, based on Kunert et al., 2016) on a numeric integer scale (1 = low closure; 4 = some closure; 7 = high closure). Participants were given up to six seconds to respond to each trial.

Task Type (Dual task). The dual task condition merged the two single tasks so that, on each trial, a word-by-word sentence and a chord-by-chord progression were simultaneously presented, requiring the participant to attend to and evaluate both. After each trial, participants were required to give comprehension answers and closure judgments in randomized order.

Task Blocks and Trials. Single and Dual tasks were each separated into three blocks (24 trials each, 72 trials in total) with the block order and trial order randomized. For language stimuli, 18 sentences of each type (72 total) were included per task and, for music stimuli, 36 progressions of each type (72 total) were included per task. All progressions were equally counterbalanced and nested for pivot and return place as well (12 trials per each pivot/return location). Finally, trials within each block were counterbalanced by all structural parameters varied in the stimuli designs.

Presentation*.* The experiment was designed using PsychoPy2 (Peirce et al., 2019) and experimentation was conducted in a quiet room. Visual stimuli were presented at a refresh rate of 60Hz and auditory stimuli were presented using over-ear headphones.

Practice session. After participants completed the Informed Consent procedure, they were given detailed task instructions and a practice session (with the exact same design used above) consisting of 16 unique trials in each of the three task conditions.

Participants were encouraged to ask questions about the task and repeat the practice trials, if necessary, to ensure complete understanding.

Analysis

Dependent variables (DVs). Linguistic processing was assessed with mean accuracy on the sentence comprehension probes. Music processing was assessed with mean closure judgments. Higher closure judgments either indicated better task performance, as interpreted by Kunert et al., 2016, or alternatively worse performance depending on the degree to which musical processing was impaired by concurrent language processing. Regardless of interpretation, any direction of change in closure judgments, in the presence of language, would be informative for hypothesized cross-domain interactions.

Independent variables (IVs)*.* The following independent variables were used in our Models: Task Type (Dual, Language, Music), Sentence Structure (SE, SRC1, SRC2, ORC), Music Structure (Return, Stay), Pivot Place (P2, P3, P4), Return Place (R6, R7, R8), and Pivot-Return Distance.

Specific Planned Contrasts. See Table 2.2 for summary. Syntactic structural complexity (SynSC) was specifically tested in language by comparing the more complex SRC2 structure to the less complex SRC1 structure and in music by comparing the more complex Return structure to the less complex Stay structure. Syntactic working memory (SynWM) was specifically tested in language by comparing the more SynWM-dependent ORC structure to the less SynWM-dependent SRC2 structure and in music with the Pivot-Return Distance as a continuous variable where higher distances between key pivots and returns indicate higher music SynWM demands.

Linear mixed models (LMM). All modeling was conducted in R (R Core Team, 2013). The advantages of linear mixed models (LMM) over general linear models (GLM) for within-subject designs include no assumption of sphericity, accurate modeling of crossed or nested factors, and mixing of fixed and random effects (Bates et al., 2014; Magezi, 2015; Nimon, 2012). For each model, we specified *subjects* as a random effect (note, models with *trials* as a random effect did not converge) and we conducted a model parsimony procedure (*RePsychLing* package in *R,* Bates et al., 2015) for each model to determine whether *subjects* should weight only the intercept term or also the slopes of IV main effects and/or interactions. Most models included *subjects* only on the intercept and none included *subjects* on the maximal model (Barr, Levy, Scheepers, & Tily, 2013). When language accuracy was the DV, generalized LMMs (GLMMs) were fit by maximum likelihood with a binomial logit function using the *glmer* function (*nmle4* package, Bates et al., 2014) and significance testing was conducted with the *mixed* and *emmeans* functions (with Tukey correction for multiple post hoc comparisons). When music closure was the DV, LMMs were fit by maximum likelihood with the *lmer* function (*nmle4* package, Bates et al., 2014) and significance testing was conducted with the *mixed* and *emmeans* functions (with Tukey correction).

Results

Research Question 1

To address the first research question, whether language and music interact bidirectionally (i.e., whether the dual task imposes a cost on performance for each domain, compared to the single task) due to syntactic structural complexity (SynSC) or syntactic working memory (SynWM), we tested the following seven models.

Model 1: Task Type (Language, Dual) X Sentence Structure (SE, SRC1, SRC2, ORC)

See Figure 2.2 for the results of Model 1 (DV = language accuracy), which tested whether language processing was modulated by cross-domain interactions between language structure and musical interference. There was a significant interaction effect, $\chi^2(3) = 49.56$, $p < 0.0001$. There were interference effects such that language accuracy was lower in the Dual task compared to the single Language task for SE (ΔM = -7.74%, SE = 1.82%, $t(6285.75) = 4.26$, $p < 0.001$), SRC1 (ΔM = -8.28%, SE = 1.80%, $t(6285.25) = 4.60$, $p < 0.0001$), and SRC2 sentences (ΔM = -28.43%, SE = 1.81%, $t = 15.75$, $p < 0.0001$), but not for ORC sentences (ΔM = -3.53%, SE = 1.81%, $t(6285.44) = 1.95$, $p = 0.5163$). The interference effect was much larger in SRC2 (dropping to nearly chance accuracy) compared to SRC1 (ΔM = 20.15%, SE = 2.55%, $t(6285.36) = 7.91$, $p < 0.001$), SE (ΔM = 20.69%, SE = 2.56%, $t(6285.66) = 8.08$, $p < 0.0001$), and ORC (ΔM = 24.94%, SE = 2.55%, $t(6285.66) = 9.74$, $p < 0.0001$). There were no other significant differences of interference effect between SE, SRC1, and ORC (all $p > 0.24$).

For the language SynSC contrast, without music (Language task), the more syntactically complex SRC2 sentences were indeed, as hypothesized, more difficult to understand than the SRC1 sentences (ΔM = -12.02%, SE = 0.02%, $t(6285.14) = 6.71$, $p < 0.0001$). This difference increased drastically in the Dual task (ΔM = -32.17%, SE = 0.02%, $t(6285.45) = 17.74$, $p < 0.0001$) due to the large music interference effect on SRC2. For the language SynWM contrast, without music (Language task), the more

WM-dependent ORC was not more difficult to process than SRC2 (ΔM = -0.02%, SE = 0.02%, *t*(6285.16) = 0.63, *p* = 0.9985), contrary to our hypothesis, although both ORC and SRC2 were more difficult than SE and SRC1 sentences as expected. In the presence of music, SRC2 was much more difficult than ORC (ΔM = -23.77%, SE = 0.02%, *t*(6285.98) = 13.06, *p* < 0.0001), due to the large music interference effect on SRC2. All of these results indicate that the presence of music appeared to increase the difficulty of processing syntactic complexity of language (mainly via SRC2) but have no substantial effect on syntactic working memory demands of language (i.e., ORC was relatively spared).

Model 2a: Task Type (Music, Dual) X Music Structure (Return, Stay)

See Figure 2.3 for the results of Model 2a (DV = music closure), which tested whether music processing was modulated by cross-domain interactions between music structure (i.e., music SynSC: Return vs Stay) and language interference. There was a significant interaction, $\chi^2(1) = 29.71$, *p* < 0.0001. Closure judgments were higher in the Dual task compared to the single Music task for the more complex Return structure (ΔM = 0.41, SE = 0.07, *t*(95.73) = 5.62, *p* < 0.0001) but were not different for the less complex Stay structure (ΔM = -0.03, SE = 0.07, *t*(64.50) = 0.35, *p* = 0.9851). In other words, there was an interaction of language interference with the music SynSC contrast such that Return structures were lower than Stay structures without language (Music task), ΔM = -1.12, SE = 0.08, *t*(65.38) = 13.61, *p* < 0.0001, and this difference decreased in the presence of language (Dual task), ΔM = -0.69, SE = 0.08, *t*(82.59) =

8.32, $p < 0.0001$. These results indicated that the presence of language appeared to interfere with the processing of music syntactic complexity.

Model 2b: Task Type (Music, Dual) X Music SynWM (Pivot-Return Distance)

Model 2b (DV = music closure) tested whether music processing was modulated by interactions between music syntactic working memory (SynWM) and language interference (Dual vs Music). There was a significant interaction, $\chi^2(1) = 6.74$, $p < 0.01$. In the Music task, there was a significant effect of music SynWM, $b = -0.35$, $t(1738.46) = -2.60$, $p < 0.01$, such that closure judgments decreased as the distance between key pivots and returns increased. In the Dual task, this effect was increased, $b = -0.47$, $t(560.06) = -10.05$, $p < 0.0001$. Thus, the effect of language appeared to increase the working memory demand of music syntax.

Model 3a: Sentence Structure (SE, SRC1, SRC2, ORC) X Music Structure (Return, Stay)

See Figure 2.4 for the results of Model 3a (DV = language accuracy). Within only the Dual task, this model tested if language processing was modulated by cross-domain interactions between Sentence Structure (SE, SRC1, SRC2, ORC) and Music Structure (i.e., music SynSC: Return vs Stay), while controlling for music Pivot Place. There was no significant interaction, $\chi^2(3) = 4.94$, $p = 0.176$, and no significant main effect of Music Structure, $\chi^2(1) = 2.99$, $p = 0.084$. There was a significant main effect of Sentence Structure, $\chi^2(3) = 135.96$, $p < 0.0001$, due to SRC2 sentences being more difficult to understand than SE ($\Delta M = -34.07\%$, SE = 0.02%, $t(3268) = 16.84$, $p < 0.0001$), SRC1

(ΔM = -32.04%, SE = 2.02%, *t*(3268) = 15.99, $p < 0.0001$), and ORC sentences (ΔM = -23.32%, SE = 2.00%, *t*(3268) = 11.55, $p < 0.0001$). ORC sentences were also more difficult to understand than SE (ΔM = -23.32%, SE = 2.02%, *t*(3268) = 11.55, $p < 0.0001$) and SRC1 sentences (ΔM = -10.75%, SE = 2.03%, *t*(3269) = 5.30, $p < 0.0001$), with no significant difference between SE and SRC1 (p = 0.742). These results indicate that language comprehension was not affected by interactions between syntactic structures of music and language, but rather only by syntactic complexity manipulations of language as expected (via SRC2).

Model 3b: Sentence Structure (SE, SRC1, SRC2, ORC) X Music Structure (Return, Stay)

See Figure 2.5 for the results of Model 3b (DV = music closure). Within only the Dual task, this model tested if music processing was affected by cross-domain interactions between Sentence Structure (SE, SRC1, SRC2, ORC) and Music Structure (i.e., music SynSC: Return vs Stay), while controlling for music Pivot Place. There was a significant interaction, $\chi^2(3) = 65.13$, $p < 0.0001$. Closure judgments were lower for the more complex Return compared to the less complex Stay structures during SE (ΔM = -0.42, SE = 0.12, *t*(112.91) = 3.64, $p < 0.01$), SRC2 (ΔM = -1.28, SE = 0.11, *t*(116.65) = 11.40, $p < 0.0001$), and ORC sentences (ΔM = -0.95, SE = 0.11, *t*(390.95) = 8.48, $p < 0.0001$), but not during SRC1 sentences (ΔM = -0.16, SE = 0.11, *t*(110.70) = 1.48, $p = 0.818$). This music SynSC effect was greater for SRC2 sentences compared to SRC1 (ΔM = 1.12, SE = 0.15, *t*(200.09) = 7.63, $p < 0.0001$) and SE sentences (ΔM = 0.86, SE = 0.15, *t*(202.26) = 5.74, $p < 0.0001$), but not ORC sentences (ΔM = 0.33, SE = 0.15, *t*(342.84) = 2.28, *p* = 0.105). The music SynSC effect was also greater for ORC sentences compared to SRC1 (ΔM = 0.79, SE = 0.15, *t*(375.31)= 5.40, *p* < 0.0001) and SE sentences (ΔM = 0.53, SE = 0.15, *t*(356.38) = 3.55, *p* < 0.01), with no difference between SE and SRC1 sentences (ΔM = 0.26, SE = 0.15, *t*(183.06) = 1.78, *p* = 0.288). These results indicate that, when making musical closure judgments in the presence of language, language SynSC interacts with music SynSC such that the more complex SRC2 sentences show larger music structural effects when compared to the less complex SRC1 sentences. However, language SynWM does not interact with music SynSC since the more SynWM-dependent ORC sentences showed similar music structural effects as the less SynWM-dependent SRC2 sentences.

Model 4a: Sentence Structure (SE, SRC1, SRC2, ORC) X Music SynWM (Pivot-Return Distance)

Within only the Dual task, Model 4a (DV = language comprehension) tested if language processing was affected by cross-domain interaction between music SynWM (Pivot-Return Distance) and Sentence Structure (SE, SRC1, SRC2, ORC), either due to language SynSC (SRC2 vs SRC1) or SynWM (ORC vs SRC2). There was a significant interaction effect, $\chi^2(3) = 13.65$, *p* < 0.01. There was a trend-level effect of music SynWM for only SE sentences, *b* = -0.33, *t* = -1.95, *p* = 0.051, such that language accuracy tended to decrease as the distance between key pivots and return increased. The other sentences showed nonsignificant effects (all *p* > 0.11). For the specific contrast of language SynWM, there was no difference in the music SynWM effect between ORC and SRC2 (Δ*b* = 0.07, *t* = 0.45, *p* = 0.968). For the specific contrast of language SynSC, there was no difference in the music SynWM effect between SRC2 and SRC1 (Δ*b* = 0.33, *t* = 2.15, *p* = 0.137). These results indicate that when making language judgments in the presence of music, increased syntactic working demands of music had minimal effects and did not interact strongly with either language syntactic complexity or syntactic working memory.

Model 4b: Sentence Structure (SE, SRC1, SRC2, ORC) X Music SynWM (Pivot-Return Distance)

Within only the Dual task, Model 4b (DV = music closure) tested if music processing was affected by cross-domain interaction between music SynWM (Pivot-Return Distance) and Sentence Structure (SE, SRC1, SRC2, ORC), either due to language SynSC (SRC2 vs SRC1) or SynWM (ORC vs SRC2). There was a trend-level significant interaction effect, $\chi^2(3) = 13.65$, $p < 0.01$. There was a significant effect of music SynWM for only ORC sentences, $b = -0.39$, $t = -5.13$, $p < 0.0001$, such that closure judgments decreased as the distance between key pivots and return increased. The other sentences showed nonsignificant effects (all $p > 0.15$). For the specific contrast of language SynWM, there was no difference in the music SynWM effect between ORC and SRC2 (Δ*b* = -0.06, *t* = -0.59, *p* = 0.936). For the specific contrast of language SynSC, there was no difference in the music SynWM effect between SRC2 and SRC1 (Δ*b* = 0.069, *t* = 0.74, *p* = 0.88). These results indicate that, when making music judgments concurrent with language, musical syntactic working memory did interact with language syntactic working memory (via ORC, which has the highest working memory demand), but this effect was not reliably different from that of the other sentences.

Research Question 2

To address the second research question, whether language and music interact bidirectionally at syntactically critical moments within the progressions and sentences, we tested the following four models:

Model 5a: Sentence Structure (SE, SRC2, ORC) X Pivot Place (P2, P3, P4)

See Figure 2.6 for the results of Model 5a (DV = language comprehension). Within only the Dual task and controlling for Music Structure (Return Stay), this model tested if language processing was modulated by interactions between the critical syntactic moments of music (the key pivots, i.e., Pivot Place: P2, P3, P4) and language (when the pivots coincided with the relativizer *that* at the start of embedding for all sentences except SRC1, which did not coincide with key pivots). There was a significant interaction, $\chi^2(6) = 24.05$, $p < 0.001$. For SRC2, the critical interaction at pivot P3 produced lower accuracy than P2 ($\Delta M = -19.45\%$, $SE = 3.93\%$, $t(125.45) = 4.95$, $p < 0.0001$) and P4 ($\Delta M = -22.08\%$, $SE = 3.91\%$, $t(77.97) = 5.65$, $p < 0.0001$), but no difference between P2 and P4 moments ($\Delta M = 2.62\%$, $SE = 3.42\%$, $t(152.79) = 0.78$, $p = 0.999$). There were no other significant differences (all $p > 0.83$). These results indicate that language syntactic processing (for only SRC2 sentences) was affected by cross-modal interaction at the syntactically critical moment.

Model 5b: Sentence Structure (SE, SRC2, ORC) X Pivot Place (P2, P3, P4)

See Figure 2.7 for the results of Model 5b (DV = music closure). There was a significant interaction, $\chi^2(6) = 24.05$, $p < 0.001$. For SE, closure judgments at the critical P4 were lower than P3 (ΔM = -0.58, SE = 0.13, $t(76.41) = 4.40$, $p < 0.01$) but not P2 (ΔM = -0.34, SE = 0.13, $t(139.55) = 2.69$, $p = 0.244$), along with no difference between P2 and P3 (ΔM = -0.24, SE = 0.13, $t(144.43) = -1.86$, $p = 0.782$). For SRC2, closure judgments at critical P3 were higher than P2 (ΔM = 0.52, SE = 0.13, $t(132.69) = 4.03$, $p < 0.01$) but not P4 (ΔM = 0.35, SE = 0.13, $t(69.99) = 2.75$, $p = 0.225$), along with no difference between P2 and P4 (ΔM = 0.17, SE = 0.13, $t(128.82) = -1.36$, $p = 0.968$). For ORC, closure judgments at critical P3 were higher than P2(ΔM = 0.80, SE = 0.13, $t(721.49) = 6.21$, $p < 0.0001$) and P4 (ΔM = 0.46, SE = 0.13, $t(534.44) = 3.54$, $p = 0.022$), along with no difference between P2 and P4 (ΔM = 0.34, SE = 0.13, $t(854.32) = 2.77$, $p = 0.195$). These results indicate that music processing was affected by cross-modal interaction at critical moments for all three sentences.

Model 6a: Sentence Structure (SRC1, SRC2, ORC) X Return Place (R6, R7, R8)

See Figure 2.8 for the results of Model 5a (DV = language comprehension). Within only the Dual task and controlling for Pivot Place, this model tested if language processing was modulated by interactions between the critical syntactic moments of music (the key returns, i.e., Return Place: R6, R7, R8) and language (when the key returns coincided with the word that closed the embedding structure for all sentences except for SE). There was a significant interaction, $\chi^2(6) = 33.15$, $p < 0.0001$. For SRC2, language accuracy at the critical R7 was lower than R6 (ΔM = -23.82%, SE = 5.15%, *t*(242.11) = 4.62, *p* < 0.001) but not R8 (ΔM = 15.71%, SE = 5.79%, *t*(63.03) = 2.71, *p* = 0.245), along with R6 higher than R8 (ΔM = 39.53%, SE = 6.56%, *t*(127.48) = 6.02, *p* < 0.0001). No other differences were significant (all *p* > 0.82). These results indicate that language syntactic processing (for only SRC2 sentences) was affected by cross-modal interaction at the critical moment.

Model 6b: Sentence Structure (SRC1, SRC2, ORC) X Return Place (R6, R7, R8)

See Figure 2.9 for the results of Model 6b (DV = music closure). There was a significant interaction, $\chi^2(6) = 74.96$, *p* < 0.0001. For SRC1, closure judgments at the critical R6 were higher than R8 (ΔM = 1.32, SE = 0.18, *t*(84.53) = 6.32, *p* < 0.0001) but not R7 (ΔM = 0.25, SE = 0.18, *t*(84.50) = 1.39, *p* = 0.961), and R7 was higher than R8 (ΔM = 1.07, SE = 0.24, *t*(101.29) = 4.41, *p* < 0.01). For SRC2, closure judgments at the critical R7 were lower than R6 (ΔM = -1.47, SE = 0.20, *t*(149.93) = 7.38, *p* < 0.0001) but not R8 (ΔM = 0.14, SE = 0.22, *t*(88.90) = 0.64, *p* = 0.999), and R6 was higher than R8 (ΔM = 1.61, SE = 0.21, *t*(133.60) = 7.67, *p* < 0.0001). For ORC, closure judgments at the critical R7 were lower than R6 (ΔM = -1.61, SE = 0.17, *t*(326.21) = 9.21, *p* < 0.0001) but not R8 (ΔM = 0.14, SE = 0.20, *t*(217.80) = 1.34, *p* = 0.973), and R6 was higher than R8 (ΔM = 1.33, SE = 0.21, *t*(310.18) = 6.40, *p* < 0.0001). These results indicate that music processing was affected by cross-modal interaction at syntactically critical moments for all three sentences.

Discussion

Summary of Experiment. We designed this study to contribute new evidence to the ongoing debate about the relation between language syntax and music syntax – whether they share or do not share the same computational resources – which nestles into the larger unresolved mystery surrounding the potential interdependence between language and other hierarchically-structured forms of thought (Monti, 2017). Based on Kunert et al. (2016), we used a cross-modal, dual task paradigm in which participants listened to music progressions while reading natural language sentences. In a novel approach, we manipulated both domains in terms of their syntactic structural complexity (SynSC) and syntactic working memory (SynWM) in order to better understand which aspects, if any, of syntactic integration or processing may be shared across domains. The language SynSC contrast (SRC2 > SRC1) compared the more complex SRC2 sentences to the less complex SRC1 sentences (which have equivalent SynWM demands) while the language SynWM contrast (ORC > SRC2) compared the more WM-dependent ORC sentences to the less WM-dependent SRC2 sentences (which have equivalent SynSC). The music SynSC contrast compared the more complex Return structures (which resolve in their initial key) to the less complex Stay structures (which resolve in the new/second key), which differ minimally in their SynWM demand, while the music SynWM contrast was based on the linear distance between key pivots and returns in Return structures only, thus avoiding any SynSC confound. Our novel design required responses for both music closure and language comprehension in Dual trials to assess any degree of bidirectional interference between domains. We also compared performance on the Dual task to performance on single tasks involving only music or language. In line with previous dual task paradigms on this topic, we reasoned that the degree of cross-modal interference, as measured by a change in closure or comprehension scores, reflects the degree of shared computational mechanisms due to limited allocation of resources for processing competing stimuli. Importantly, neither language or music tasks contained any syntactic violations, in order to avoid potential confounds of attentional demands related to the saliency of the violation instead of the specific syntactic manipulations.

Summary of Results. Our first research question concerned whether language and music interact bidirectionally due to modulations of SynSC or SynWM. Models 1 and 2 compared language and music performance between the Dual task (simultaneous language and music) and Single tasks (either language or music alone). There was an overall pattern of bidirectional interference effect such that the intrusion of music during sentence reading modulated language comprehension (for all sentence structures except for ORC, although the numerical trend was present) and the intrusion of language during music listening modulated closure judgments (for all music structures).

This bidirectional interference effect then unraveled into an unbalanced pattern across domains depending on SynSC or SynWM. The intrusion of music modulated the language SynSC contrast (SRC2 > SRC1) more than the SynWM contrast (ORC > SRC2) based on the results of Model 1, which showed that language accuracy was especially impaired during the more syntactically complex SRC2 sentences but was relatively spared during the more WM-dependent ORC sentences. In contrast, the intrusion of language interacted with both music SynSC (Model 2a, closure ratings were modulated during only the more complex Return structures) and music SynWM (Model 2b, closure ratings were increasingly modulated by the key pivot-return distance). This unbalanced interference pattern was further evident in the Dual task: (i) music SynSC did not seem to affect language processing in general and did not interact with language SynSC or language SynWM (Model 3a); (ii) language SynSC did affect music processing in general and did interact with music SynSC (Model 3b); (iii) music SynWM mostly did not affect language processing and did not interact with language SynSC or SynWM (Model 4a); and (iv) language SynWM did not affect music processing and did not interact with music SynSC (Model 4b) or music SynWM (Model 3b). These results indicate that language and music interact bidirectionally due to general cross-domain interference (i.e., the dual task effect) that seemed mainly due to specific interactions of structural complexity.

Interestingly, although bidirectional, much of the cross-domain syntactic interference appeared to be unbalanced with manipulations of language structures exerting more influence over music rather than vice versa. This pattern of results could potentially indicate that shared syntactic resources are disproportionally allocated across language and music domains (perhaps dependent on task demands, or trial-by-trial fluctuations in attention).

Our second research question concerned whether any cross-domain interactions occurred specifically when syntactically critical moments in both language (start and end of embedding) and music (key pivots and returns) coincided temporally, or more generally across the entire dual stream of words and chords. An unbalanced bidirectional pattern of interference emerged such that music processing was affected by every junction of critical moments, for every relevant sentence and regardless of whether it involved a key pivot (Model 5b) or return (Model 6b), whereas language processing was affected strongly by critical junctions only during SRC2 sentences (Model 5a and 6a). These results indicate that language and music seem to interact at syntactically critical moments, particularly for the more syntactically complex sentences (SRC2 and ORC). This interesting phenomenon has not been investigated much in the literature, which has largely been focused on the question of whether and to what degree language interferes with music or vice versa. That we were able to observe such effects given our subtle experimental manipulations and coarse measures of language comprehension and musical closure judgments (of the entire sentence and chord progression, respectively) could indicate the potential for these focal interactions to at least partially account for language-music interference effects. Future research with more time-sensitive measures (e.g., event-related potentials using EEG or MEG) would be necessary for more complete investigation.

To summarize: first, it appears that music and language interact at a level above and beyond a general processing effect of engaging in a dual task; second, this effect is unbalanced as the effects of language on music were more predominant than the effects of music on language; third, the interaction between music and language seems to be primarily driven by processing demands associated with more complex (center-embedded) structures, even when controlling for intra-sentential working memory demands; fourth, and separately, the interaction between music and language appears to be maximal when structurally critical moments coincide in both domains. Taken together, these bidirectional interactions between language and music provide novel evidence consistent with theoretical accounts of shared syntactic computations, such as shared domain-specific resources and/or representations of musical and linguistic structures.

General Discussion. The observed pattern of bidirectional influence between language and music supports the notion of shared computational resources between domains and also is consistent with the idea of shared neural resources or systems underlying such shared syntactic computation. Although dual task paradigms do not directly address the latter issue, cross-domain interference effects could result from a form of competition between simultaneously active neural networks which rely on the same neural components (i.e., regions, sub-networks) that support syntactic processing. Alternatively, interference effects could reflect shared cognitive control and working memory demands rather than shared syntactic resources (Oechslin et al., 2013; Rogalsky et al., 2011; Rogalsky et al., 2008; Slevc et al., 2013; Slevc & Okada, 2015), or perhaps some mixture of both syntax-specific and syntax-nonspecific processes ongoing simultaneously.

An ongoing challenge for uniting language and music, and for cognitive neuroscience in general, concerns identifying specific neural structures that cause specific cognitive functions (Price & Friston, 2005). Some theories propose that Broca's area may support such cross-domain integration of syntactic processing (Fadiga et al., 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Jeon, 2014; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012). However, a more refined model of shared neural systems would need to account for functional heterogeneity of regions like the LIFG (e.g., dissociations between spatial clusters that appear more language-specific or more domain-general; Blank et al., 2014; Fedorenko et al., 2012; Mineroff et al., 2018), widely distributed syntactic networks including other frontal and temporal areas (Blank et al., 2016), complex interactions between (core) language and nonlanguage (e.g., multiple-demand) networks depending on task contexts (Fedorenko & Thompson-Schill, 2014), complex local and global network dynamics across the brain (Bullmore & Sporns, 2009; Roland, 2017), as well as large-scale, parallel configurations of cortical and white matter subcircuits that underlie different language functions (Duffau, 2018; Duffau et al., 2014; Teichmann et al., 2015).

It is important to note that both our syntactic complexity (SynSC: SRC2 > SRC1) and our syntactic working memory (SynWM: ORC > SRC2) contrasts involved the SRC2 sentence structure, which showed the largest effects of musical interference on language (Models 1, 5a, and 6a). This was expected for our SynSC contrast, given that SRC2 is more syntactically complex than SRC1. However, it was surprising for our SynWM contrast, given that ORC has more SynWM demand than SRC2. One possible explanation for these results is that SRC2 (e.g., *The man that saw the soldiers fell down*) differed from the others in that both verbs (e.g., *saw*, and *fell down*) link to the subject noun (*man*). Although both ORC and SRC2 are center-embedded, in SRC2 the final verb requires resolving a nonlocal dependency with the main noun, otherwise a strictly linear reading of the sentence would lead to an incorrect interpretation that *the soldiers fell down*. Given this peculiarity and the linear format of our comprehension probes (e.g., *the soldiers fell down*), it's possible that the enhanced musical interference on SRC2 comprehension accuracy could be due to participants applying more heuristic interpretation strategies that are based on minimal efforts (i.e., strictly linear reading) to resolve local syntactic ambiguity given the global semantic interpretation rather than engaging in complex syntactic integration (i.e., the 'Good Enough' parsing hypothesis; Ferreira et al., 2002; Ferreira & Patson, 2007). If this was the case, then participants' comprehension for SRC2 should have been similarly impaired on both of the misleading comprehension probes (e.g., *soldiers fell down*, *soldiers saw man*) that required nonlocal syntactic integration. However, we found that although the first probe had low accuracy (M = 66.83%, SE = 2.37%) the second probe had much higher accuracy (M = 90.09%, SE = 2.52%, $t(3516.22) = 8.36$, $p < 0.0001$). Thus, it appears that the heuristic hypothesis cannot fully account for the specific music interference on SRC2 sentences, since there was evidence that participants were engaged in appropriate syntactic parsing for at least the second probe. Although given that the first type of misleading probe yielded strong impairment of comprehension, we cannot rule out the possibility that participants utilized heuristic strategies at least some of the time.

Limitations. First, we did not include non-syntactic manipulations, such as arithmetic or semantic garden-path sentences (Kunert et al., 2016; Poulin-Charronnat et al., 2005), to measure for potential interactions unrelated to syntactic processing, which is the basis of alternative theoretical accounts of music-language interactions (Large & Jones, 1999; Perruchet & Poulin-Charronnat, 2013b). However, we chose instead to focus on structural manipulations in the absence of violations, with the rationale that resulting cross-domain interactions between these carefully controlled syntactic manipulations would not likely be due to general attentional resources. If that were the case, then all manipulations should have generated robust interference effects in both domains; instead, we observed a pattern of bidirectional interference in the dual task that was both relatively unbalanced between language and music and was based more on syntactic complexity than syntactic working memory demands. However, we acknowledge that general interference effects comparing between dual and single tasks are consistent with attentional resources accounts, but these results were not the main focus of our study.

Second, although we experimentally manipulated structures based on syntactic structural complexity (SynSC) and syntactic working memory (SynWM), we acknowledge that both processes mutually intertwine during syntactic integration, thereby precluding a pure dissociation between them. This could be considered analogous to the synergy between syntax and semantics in English and many other languages (i.e., changes to one subprocess necessarily invoke changes to the other subprocess) which cannot be completely dissociated from each other in natural language involving complex sentence processing, although they can be richly studied. With this caveat in mind, we attempted to tease out and interpret differential effects between SynSC and SynWM based more on relative differences rather than absolute separations. The pattern of bidirectional interference between domains that we observed seemed to emerge mostly from interactions based more on SynSC (in both language and music) and less on SynWM. However, we suspect that both SynSC and SynWM subprocesses are interacting during cross-domain interference in complex ways too intricate to be observed with the current experimental methodology.

Conclusion. In conclusion, this novel adaptation of a dual task paradigm without syntactic violations provides preliminary evidence for bidirectional interactions between language and music along domain-specific lines. These results support theoretical models of shared syntactic resources for processing language and music (Koelsch, 2012; Lashley, 1951; Patel, 2012). Future research with neuromodulation could help to test theoretical predictions that such shared syntactic resources also reflect shared neural resources.

Figures

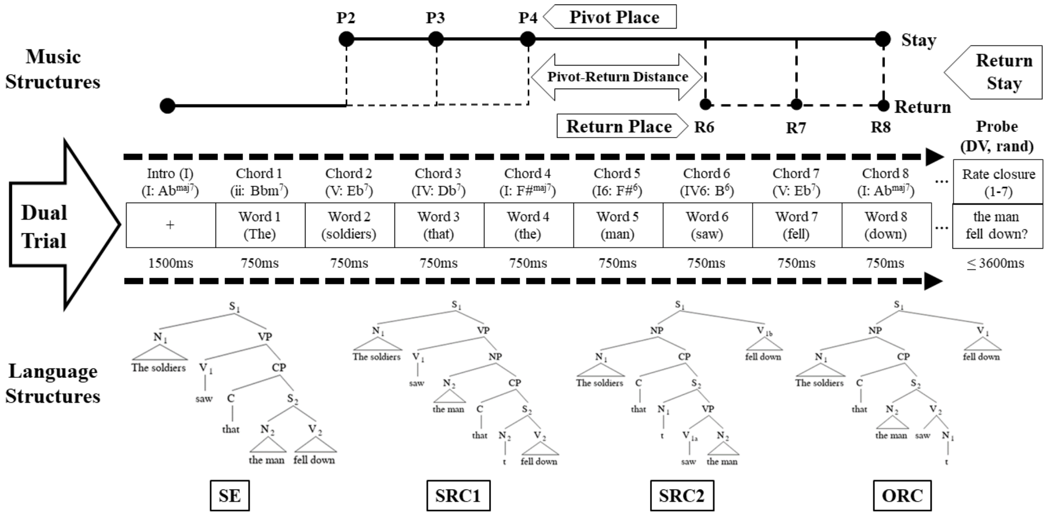

Figure 2.1. Example of dual task trial with schematics of language and music manipulations. Each dual trial consisted of an Intro chord (to establish the opening key), followed by eight word/chord pairs, followed by two probes (for dependent variable, DV) presented in randomized order (closure rating for music, comprehension question for language). Pivot Place (P2, P3, P4) refers to legal musical key change at one of three locations. Return Place (R6, R7, R8) refers to legal musical key return at one of three locations (for Return trials only). ReturnStay refers to whether the key returned to original Intro key, or stayed in new (second) key. Pivot-Return Distance refers to the linear distance between key pivots and returns. For language, SE refers to simple embedded sentences, SRC1 refers to subject-extracted relative clause (right-branching), SRC2 refers to subject-extracted relative clause (center-embedded), and ORC refers to object-extracted relative clause (center-embedded).

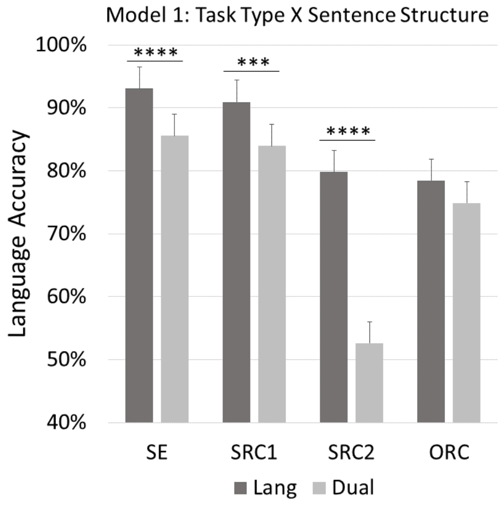

Figure 2.2. Results for Model 1, which tested the interaction effect of Task Type (Dual, Language) by Sentence Structure (SE, SRC1, SRC2, ORC) on language accuracy. SE = simple embedded structure. SRC1 = subject-extracted relative clause (right-branching). SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

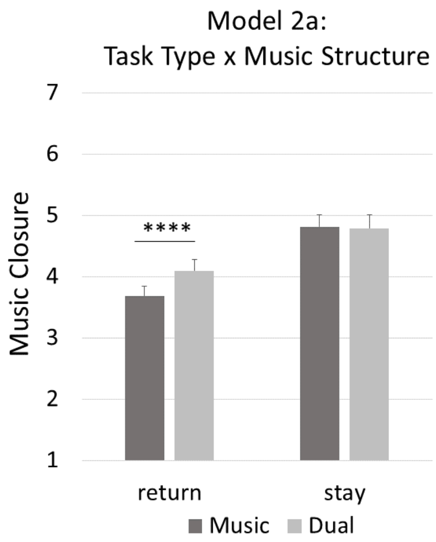

Figure 2.3. Results for Model 2a, which showed an interaction effect between Task Type (Dual, Language) and Music Structure (Return, Stay) on music closure judgments. Music Structure is synonymous with the music syntactic structural complexity contrast (music SynSC: Return vs Stay). Return = final chords return to initial key after pivot (more syntactically complex). Stay = final chords stay in new key after pivot (less syntactically complex). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

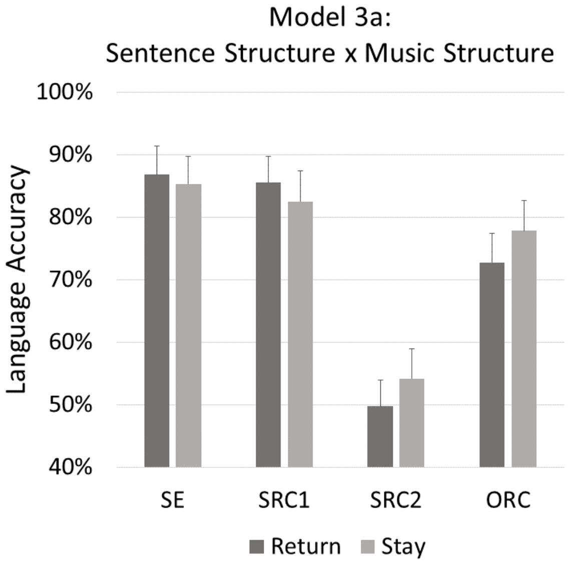

Figure 2.4. Results for Model 3a, which did not produce an interaction effect between Sentence Structure (SE, SRC1, SRC2, ORC) and Music Structure (i.e., music SynSC: Return vs Stay) on language accuracy (in Dual task only). Music Structure is synonymous with the music syntactic structural complexity contrast (music SynSC, Return vs Stay). SE = simple embedded structure. SRC1 = subject-extracted relative clause (right-branching). SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

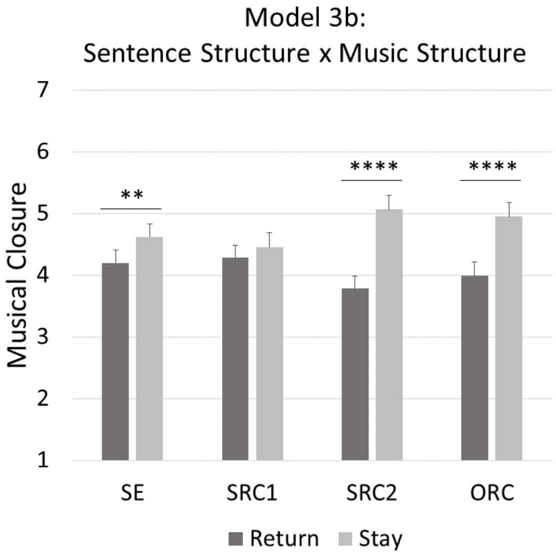

Figure 2.5. Results for Model 3b, which produced an interaction effect between Sentence Structure (SE, SRC1, SRC2, ORC) and Music Structure (i.e., music SynSC: Return vs Stay) on closure judgments (in Dual task only). SE = simple embedded structure. SRC1 = subject-extracted relative clause (right-branching). SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

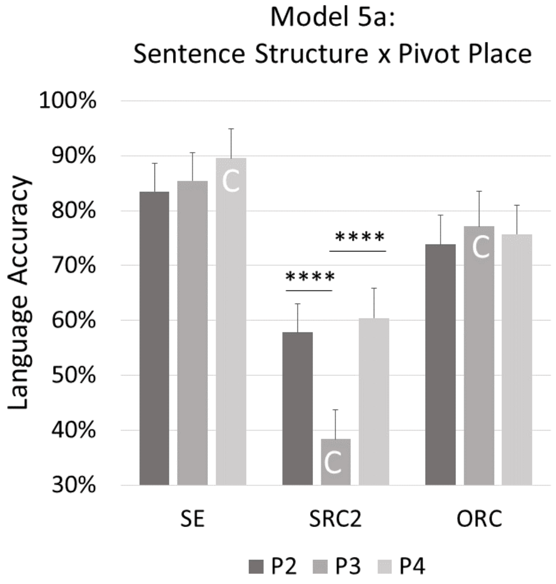

Figure 2.6. Results for Model 5a which tested for cross-domain interactions at syntactically critical moments (indicated by "C"). There was an interaction effect between Sentence Structure (SE, SRC2, ORC) and music Pivot Place (P2, P3, P4) on language accuracy (in Dual task only). SE = simple embedded structure. SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). P2 = key pivot at 2nd chord/word. P3 = key pivot at 3rd chord/word. P4 = key pivot at 4th chord/word. Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

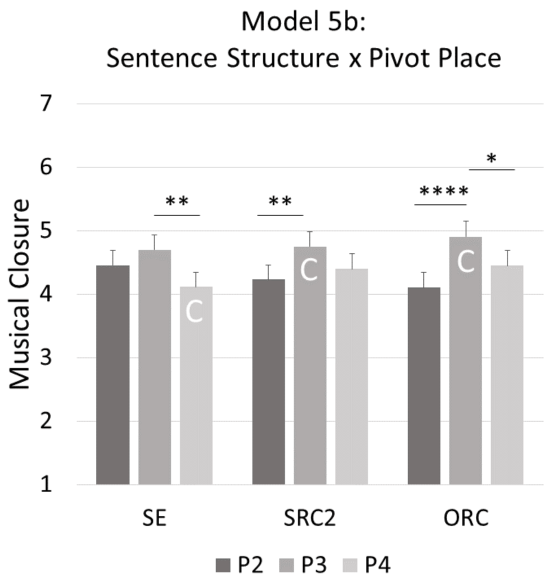

Figure 2.7. Results for Model 5b which tested for cross-domain interactions at syntactically critical moments (indicated by “C”). There was an interaction effect between Sentence Structure (SE, SRC2, ORC) and music Pivot Place (P2, P3, P4) on music closure judgments (in Dual task only). SE = simple embedded structure. SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). P2 = key pivot at 2nd chord/word. P3 = key pivot at 3rd chord/word. P4 = key pivot at 4th chord/word. Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

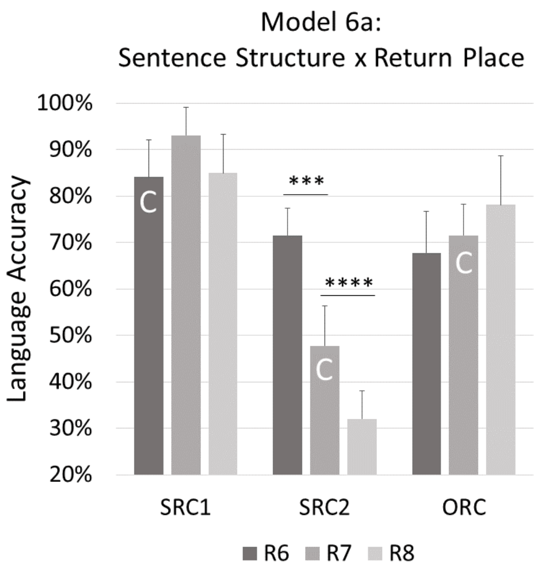

Figure 2.8. Results for Model 6a which tested for cross-domain interactions at syntactically critical moments (indicated by “C”). There was an interaction effect between Sentence Structure (SE, SRC2, ORC) and music Return Place (R6, R7, R8) on language comprehension (in Dual task only). SE = simple embedded structure. SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). R6 = key return at 6th chord/word. R7 = key return at 7th chord/word. R8 = key return at 8th chord/word. Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

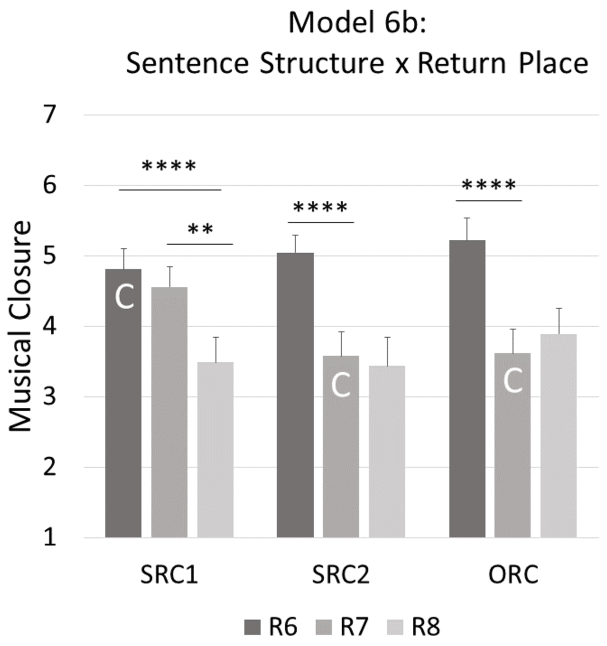

Figure 2.9. Results for Model 6b which tested for cross-domain interactions at syntactically critical moments (indicated by “C”). There was an interaction effect between Sentence Structure (SE, SRC2, ORC) and music Return Place (R6, R7, R8) on language comprehension (in Dual task only). SE = simple embedded structure. SRC2 = subject-extracted relative clause (center-embedded). ORC = object-extracted relative clause (center-embedded). R6 = key return at 6th chord/word. R7 = key return at 7th chord/word. R8 = key return at 8th chord/word. Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

Tables

Sentence	Example	Critical words	SynSC type	SynWM type
SE	The soldiers (N1) saw (Va) that the man (N2) fell down (Vb)	4 (that)	low (right-branching)	absent (no distance)
SRC1	The soldiers (N1) saw (Va) the man (N2) that fell down (Vb)	6 (that)	low (right-branching)	low (short distance)
SRC2	The soldiers (N1) that saw (Va) the man (N2) fell down (Vb)	3(that), 7(fell)	high (center-embedded)	low (short distance)
ORC	The soldiers (N1) that the man (N2) saw (Va) fell down (Vb)	3(that), 7(fell)	high (center-embedded)	high (long distance)

Table 2.1. Description of language stimuli. SE = simple embedded structure. SRC1 = subject-extracted relative clause. SRC2 = subject-extracted relative clause. ORC = object-extracted relative clause. Critical words = syntactically critical moments. SynSC type = degree of syntactic structural complexity (surface structure). SynWM type = degree of syntactic working memory type (based on distance between relativizer *that* and the licensing verb).

Domain	Contrast	Variables
Language	SynSC	SRC2 > SRC1
	SynWM	ORC > SRC2
Music	SynSC	Return > Stay
	SynWM	Pivot-Return distance

Table 2.2. Description of statistical contrasts used to test for cross-modal interactions between language and music. SynSC refers to syntactic structural complexity. SynWM refers to syntactic working memory. For language SynSC, SRC2 has higher SynSC than SRC1 (center-embedded vs right-branching structures) but equivalent SynWM (same distance between relativizer and licensing verb). For language SynWM, ORC has higher SynWM than SRC2 (same distance) but equivalent SynSC (center-embedded). For music SynSC, Return has higher SynSC than Stay (key returns after initial pivot vs key stays after initial pivot). For music SynWM, Pivot-Return Distance refers to the linear distance between key pivots and returns (for Return structures only).

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Chapter 3

Broca's area and hierarchical processing: Bayesian meta-analysis of neurostimulation literature

Abstract

Language and many other cognitive domains involve computation of hierarchical or syntactic structures (i.e., hierarchical/syntactic processing) for generating complex sequences from finite elements (e.g., sentences from letters, harmonies from keys, equations from numbers and symbols, complex actions from simple movements). An ongoing debate concerns whether this computational parallel derives from shared neural resources, with possibly Broca's area (the left inferior frontal gyrus, LIFG; BA 44 and BA45) as a domain-general network hub across language and other hierarchically structured cognitive domains. To explore this idea, we conducted a Bayesian inferential meta-analysis on data from published neurostimulation studies that used hierarchical or syntactic processing tasks to investigate six cognitive domains: action, artificial grammar, language, logical reasoning, math, and music. Frequencies of statistical test results reported by those studies were analyzed with Bayesian probabilities of forward inferences, P(Effect|Cause), and reverse inferences, P(Cause|Effect), in different models to assess the potential specificity of Broca's area (versus other regions) for linguistic (versus nonlinguistic) hierarchy or syntax. We discovered that Broca's area, based mostly on stimulation of the pars opercularis (BA 44), does not appear highly specific for language syntax but rather more domain-general across hierarchically-structured cognition. However, the inferential results depended strongly on

hypothesized prior beliefs about the degree to which the chosen task engaged the cognitive process or how successfully the stimulation procedure modulated the neural region. The present study takes a small step forward towards illuminating the mysterious relation between language and thought by demonstrating, for the first time, that Bayesian inferential meta-analysis of neurostimulation literature can potentially enhance causal reasoning about shared resources across cognition.

Introduction

The relation between language and thought seems to involve a fundamental feature of human cognition, the ability to create infinitely recursive sequences from finite elements (e.g., ideas from concepts, sentences from letters, music from keys and beats, math from symbols, complex actions from simple movements) via a combinatorial, generative process (i.e., syntax) for integrating relations between elements within hierarchical structures which depend on locality, order, and movement (Fitch & Martins, 2014; Hauser et al., 2002; Lashley, 1951; Spelke, 2003). To illustrate in natural language, one can understand the complex sentence *The mouse that the cat chased escaped* and how it differs in meaning from *The cat that the mouse chased escaped.* Such hierarchical or syntactic processing seems to be a cornerstone of language (Chomsky, 1957; Hauser et al., 2002), as well as musical cognition (Koelsch et al., 2013; Lerdahl & Jackendoff, 1985), action planning and understanding (Botvinick, 2008; Lashley, 1951; Pulvermüller, 2014; Rosenbaum et al., 2007), artificial grammar processing (Bahlmann et al., 2008; Friederici, 2004), deductive reasoning (Monti & Osherson, 2012), complex math like algebra (Chomsky, 1997; Ernest, 1987), problem solving (Dehaene & Changeux, 1997), mentalizing within Theory of Mind (Gallese, 2007; Oesch & Dunbar, 2017), and even computer programming (Fitch et al., 2005).

Whether or not the computational parallels between language and nonlanguage domains are based on shared neural mechanisms has been a vibrant area of research and debate. On one side, many researchers have championed the classical language region of "Broca's area" (i.e., the left inferior frontal gyrus, LIFG; pars opercularis, BA 44, and pars triangularis, BA45) as a domain-general region at the intersection of neural networks for language, music, action, and possibly other hierarchically structure-dependent cognition (Fadiga et al., 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Jeon, 2014; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012). The LIFG has been associated with language syntax based on neuropsychological (Grodzinsky, 2000; Zurif et al., 1993), functional Magnetic Resonance Imaging (fMRI) (Ben-Shachar et al., 2003; Fiebach et al., 2005; Friederici, 2011; Pallier et al., 2011; Uddén & Bahlmann, 2012), and neurostimulation research (Kuhnke et al., 2017; Sakai et al., 2002). Similar research has also linked the LIFG to the hierarchical or syntactic processing of action cognition (Clerget et al., 2013; Fadiga, Craighero, & D'Ausilio, 2009; Fiebach & Schubotz, 2006; Koechlin & Jubault, 2006), music cognition (Chiang et al., 2018; Koelsch et al., 2002), deductive reasoning (Goel et al., 1997, 1998; Knauff et al., 2003; Reverberi et al., 2007; Tsujii et al., 2010), arithmetic and algebraic cognition (Chochon et al., 1999; Dehaene et al., 1999; Friederici et al., 2011; Maruyama et al., 2012; Stanescu-Cosson et al., 2000), artificial grammar processing (Friederici et al., 2011; Uddén et al., 2008; Uddén & Bahlmann, 2012), and Theory of Mind (Molenberghs et al., 2016; Spreng et al., 2008; Van Overwalle & Baetens, 2009).

On the other side of the debate, there is much evidence of functional dissociations between language and other domains including music (Ayotte et al., 2002; Luria et al., 1965; Marin & Perry, 1999; Piccirilli et al., 2000), math (Delazer et al., 1999; Varley et al., 2005), and deductive reasoning (Monti & Osherson, 2012). Previous fMRI studies have not found involvement of language regions such as the LIFG in math (Amalric & Dehaene, 2017; Fedorenko et al., 2011; Monti et al., 2012; Zago et al., 2001), deductive reasoning (Coetzee & Monti, 2018; Goel & Dolan, 2001; Monti et al., 2007, 2009; Parsons & Osherson, 2001), and music (Fedorenko et al., 2011; Rogalsky et al., 2011). Recently, more rigorous fMRI studies (using functional localizers for single-subject analysis) have revealed robust dissociations between a core language network and peripheral, domain-general networks such as the multiple demand (MD) frontoparietal network responsible for cognitive control and working memory (Blank et al., 2014; Blank & Fedorenko, 2017; Fedorenko & Thompson-Schill, 2014). Blank et al. (2014) also showed substantial functional heterogeneity within the LIFG such that it comprises both language-specific (mostly the pars triangularis) and domain-general zones (surrounding the pars triangularis, often including pars opercularis). Moreover, these core language and peripheral networks have been shown to interact depending on the task context (Fedorenko & Thompson-Schill, 2014), indicating that cross-network dynamics may complicate questions about shared versus distinct mechanisms. Even within the language system alone, linguistic syntax appears to engage a widespread and predominantly left-lateralized network (Blank et al., 2016) including the IFG, middle frontal gyrus, and temporal areas such as the posterior superior temporal gyrus (pSTS), another region also widely associated with language syntax (Bornkessel et al., 2005; Grewe et al., 2007; Xiao et al., 2015; Zaccarella et al., 2017).

From a different perspective, Fedorenko & Varley (2016) offered a reinterpretation of many studies that have used syntactic violation tasks to test for shared resources. They argued that such paradigms recruit attentional demands (e.g., working memory, cognitive control) that are related to the saliency of the violation instead of the specific syntactic processing. Similarly, when comparing language and music, others have argued for shared cognitive control and working memory demands rather than shared syntactic resources (Oechslin et al., 2013; Rogalsky et al., 2011; Rogalsky et al., 2008; Slevc et al., 2013; Slevc & Okada, 2015). However, it has also been proposed that the long-distance operations of syntactic integration recruiting Broca's area or the language network in general are distinct from working memory even if partly dependent on it (Bahlmann, Schubotz, & Friederici, 2008; Fiebach, Schlesewsky, Lohmann, von Cramon, & Friederici, 2005; Friederici, 2004).

In a meta-analysis of an fMRI database, Poldrack (2006) demonstrated that Bayesian probability theory could inform hypothesis testing about inferences of potentially causal relations between language (or any cognitive process) and neural activity of the LIFG (or any brain region or network) as measured by blood oxygen level dependent (BOLD) signal. The forward inference – the degree to which the LIFG is active given that language was engaged by a task, or P(LIFG|Lang) – seems more deductively plausible because it moves from a relatively known cause (i.e., participant was engaged in language during the task) to an observed effect (i.e., participant's LIFG showed reliable BOLD changes). In contrast, the reverse inference – the degree to which language was engaged by the task given that the LIFG is active, or P(Lang|LIFG) – seems less deductively plausible because it moves from the observed effect to the relatively unknown cause. The probability of either inference can be formulated with Bayes Theorem, as demonstrated for the reverse inference in Figure 3.1.

In other words, the reverse inference – or P(Lang|LIFG), known as the posterior probability – depends on the specificity of the activation of LIFG to the presence of language, P(LIFG|Lang), versus the absence of language, P(LIFG|~Lang), and it also depends on the prior belief that language was engaged, P(Lang), or not engaged, P(~Lang), by the experimental task chosen (note that technically the prior should be calculated as P(Lang|Task), see Hutzler (2014) for an expanded demonstration). Therefore, the reverse inference increases in probability with increasing specificity of the LIFG-language relation – as P(LIFG|Lang) increases and P(LIFG|~Lang) decreases – and with increasing specificity of the language-task relation – as P(Lang) increases and P(~Lang) decreases.

With this Bayesian procedure, Poldrack (2006) found that the probability of the reverse inference P(Lang|LIFG) was 0.69, indicating some moderate probability that an observed BOLD activation in the LIFG means that language was engaged (versus not engaged) by the chosen task. The strength of evidence for this inference was calculated with the Bayes Factor (BF), a model comparison procedure (see Methods). The BF for the reverse inference was around 2.3, which by one standard convention (Jeffreys, 1961; Kass & Raftery, 1995) can be interpreted as positive but not substantial evidence. Alternatively, Bayes Theorem applied to the forward inference of P(LIFG|Lang) yielded a probability of 0.65 with a corresponding BF of 1.85, indicating positive but not substantial evidence for a moderate probability that LIFG is activated by language processing during a task. Taken together, one can tentatively conclude from these results that the specificity of the LIFG for language compared to nonlanguage domains, as determined by fMRI meta-analysis of published studies, seems potential but rather unlikely. However, it is crucial to emphasize that, in Bayesian analysis, the prior belief is fundamental and could drastically alter results and interpretations (see Methods and Results for more details).

The present study adapts the Bayesian inferential meta-analysis with two novel aims. The first aim was to focus on the specificity of the LIFG for linguistic versus nonlinguistic hierarchical or syntactic processing. The purpose was to directly address the ongoing debate reviewed above regarding the degree to which the LIFG functions specifically for the language network instead of as a shared neural resource across hierarchically-structured cognitive domains. Note that this study was not designed to address the related and important issue of the specificity of the LIFG to syntactic versus non-syntactic processing (such as semantics, working memory, etc), although future research could also leverage the Bayesian meta-analysis for that purpose.

The second aim was to focus the investigation on the underexplored literature of cognitive neurostimulation (i.e., neuromodulation, including techniques such as transcranial magnetic stimulation, TMS, and transcranial direct or alternating current stimulation, tDCS or tACS). In comparison to behavioral, neuropsychological, and neuroimaging research, relatively few neurostimulation studies have assessed syntactic or hierarchical processing of language (e.g., Cattaneo et al., 2009; Kuhnke et al., 2017; Sakai et al., 2002) and other domains such as complex action (e.g., Clerget et al., 2013;

Kang & Paik, 2011; Verwey et al., 2002), music (e.g., Andoh et al., 2008; Rosen et al., 2016), logic (e.g., Ragni et al., 2016; Tsujii et al., 2010, 2011), or artificial grammar (Savic et al., 2017; Uddén & Bahlmann, 2012). It's unclear if any neurostimulation study has ever directly addressed the issue of shared neural mechanisms between linguistic and nonlinguistic hierarchy. And to our knowledge, this is the first study to meta-analytically investigate this topic within the neurostimulation literature. Neurostimulation techniques can contribute uniquely important information about neurocognitive relations because, unlike neuroimaging, they have potential for direct causal manipulation (i.e., increasing or decreasing cortical excitability) of specific regional or network dynamics and causal inference about their proposed cognitive functions (Bestmann & Feredoes, 2013; Silvanto & Pascual-Leone, 2012; Tanaka & Watanabe, 2009). However, the degree of causal inference from stimulation (the Cause) to observed cognitive behavior within a task (Effect) seems to depend on several potential confounds or sources of variance such as inaccurate targeting and subthreshold stimulation (Oliver et al., 2009), local and remote effects of stimulation (Bestmann & Feredoes, 2013; Sack, 2006), complex network dynamics (Bassett et al., 2006; Bullmore & Sporns, 2009; Roebroeck et al., 2011), null results (de Graaf & Sack, 2011), ineffective controls for placebo and expectation effects (Davis et al., 2013; Duecker et al., 2013; Palm et al., 2013), and state dependency (Silvanto et al., 2008, 2017). Although outside the scope of the present study, these myriad issues caution a strong causal interpretation of cognitive neuromodulation.

With this caveat in mind, the present study contributes a fresh perspective of brain-behavior relations, based on neuromodulation research, to the ongoing debate over the potentially shared neural resources of language and other hierarchically-structured cognition. To accomplish both aims, we conducted a thorough review of the neurostimulation literature (given that no neuroimaging database exists to our knowledge) within the specific context of syntactic or hierarchical processing of six cognitive domains: action, artificial grammar, language, logic, math, and music. Reported statistical tests across all studies were analyzed with the Bayesian procedure of forward (i.e., cause to effect) and reverse (i.e., effect to cause) inferences in order to assess the specificity of Broca's area (versus other regions) for language versus nonlanguage syntax.

Methods

Database Searches

The PubMed, PsycINFO, and Google Scholar databases were used to search for peer-reviewed, published studies (for all years up to 2018) which were relevant to the six domains of action, artificial grammar, language, logic, math, and music. All permutations of the following keywords were searched within each respective domain: 1) Action (*action, chunking, motor, sequence, syntax, syntactic*); 2) Artificial grammar (*artificial, grammar, sequence, syntax, syntactic*); 3) Language (*language, syntax, syntactic*); 4) Logic (*deductive, logic, reasoning*); 5) Math (*algebra, algebraic, math, syntax, syntactic*); 6) Music (*harmony, harmonic, melody, melodic, music, musical, syntax, syntactic*). The following neurostimulation techniques were included in the search: 1) transcranial magnetic stimulation (TMS) – which includes single-pulse or repetitive TMS (rTMS), and patterned TMS such as continuous or intermittent theta burst stimulation (cTBS and iTBS, respectively); 2) transcranial electrical stimulation (TES) – which includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). The keyword *transcranial* was used to search for these techniques in combination with the cognitive keywords above.

Inclusions and Exclusions: Tasks and Studies

The action domain included complex, hierarchical motor sequences and action perception tasks, while excluding simple forms (lacking hierarchical structure) of such tasks. The artificial grammar domain included any tasks involving hierarchical sequences or sentences of artificial grammar, while excluding any single-word, or non-syntax-dominant, or verb-noun matching tasks. The language domain included any task involving complex syntactic processing, such as picture-sentence matching or sentence manipulation, while excluding any non-syntax-dominant, or verb-noun matching tasks. The logic domain included analytical Raven’s Matrices and syllogisms and deductive reasoning tasks, while excluding figural Raven’s Matrices and other non-deductive reasoning tasks. The math domain included tasks using algebraic equations and multi-digit calculations, while excluding tasks of numerosity (magnitude, sign) or single-digit calculations. The music domain included melodic or harmonic processing tasks involving hierarchical structures, while excluding nonsyntactic tasks such as pitch or tone discrimination.

No invasive stimulation studies involving preoperative patients (e.g., direct brain stimulation, DBS, direct electrical or cortical stimulation, DES or DCS) were included because they have a categorically different method of reporting results (i.e., not based on statistical tests but rather successful stimulation events for each patient) which did not enable the statistical procedure of our meta-analysis (for a separate review of noninvasive studies on language syntax, see Zanin et al., 2017).

Inclusions and Exclusions: Statistical Contrasts

Included contrasts involved any interactions, main effects, simple main effects, post hoc tests, and correlations or regressions that were conducted or reported by a study which were relevant to testing for a present or absent effect of neurostimulation. In other words, an included contrast must have involved a test of some neurostimulation factor, condition, or parameter (e.g., stim on or off, stim high or low, tDCS vs tACS, etc), such as a test between neurostimulation sites (e.g., LIFG vs RIFG, BA 22 vs BA 40, etc) or a test between sample groups (e.g., stim group vs sham group, TMS group vs tDCS group, etc). Each contrast was coded with 1 for a statistically significant effect or with a 0 for a statistically nonsignificant effect, with significance determined by the methods of the corresponding study. Frequencies of statistical contrasts across studies were reported in 2 x 2 contingency tables for different models of interpretation (see Bayesian Inference Models section below).

Neurostimulation Targets

Within the context of the six tasks, any study involving stimulation to any brain region was included in our search. Stimulation of Broca's area or the left IFG (StimLIFG) was defined as including either the left pars opercularis (BA 44) or pars triangularis (BA 45), or both simultaneously, in contrast to stimulation of any other regions (StimOther).

Bayesian Probability Theory

Bayesian inferences. Similar to cognitive neuroimaging, cognitive neurostimulation can involve two inferences. With the forward inference, i.e., P(ΔCog|StimROI), one infers an observed effect of cognitive change (i.e., ΔCog) from a potential cause of stimulation of some region or network (i.e., StimROI). In other words, what is the probability that the stimulation of some region or network caused a change in some cognitive process? Conversely, with the reverse inference, i.e., P(StimROI|ΔCog), one infers the potential cause from the observed effect. In other words, what is the probability that an observed cognitive change was caused by the stimulation? Importantly, the cognitive process depends on the task used, i.e., P(ΔCog|Task), and the stimulation also assumes that the neural function was successfully modulated, i.e., P(ΔROI|StimROI), although for simplicity of analysis these technicalities are set aside for now, yet they could be included as additional prior information or nested inferences in more complicated analyses.

The Bayes Theorem represents how a prior belief in a model or hypothesis should change probabilistically to account for the relevant evidence available. It can be applied to both forward and reverse inferences (see Figures 3.2 and 3.3, and Appendix 3.1 for more detail).

With this Bayesian method, the forward inference depends on the selectivity of the specific regional stimulation (and resulting network changes) for a specific cognitive process versus any cognitive process (or the absence of that process). The reverse inference depends on the selectivity of the specific cognitive process to a specific region/network stimulation versus stimulation of any region/network (or the absence of the stimulation).

Bayesian sensitivity analysis. It is crucial to note that each Bayesian inference depends on the prior belief of the hypothesis before any evidence is assessed. For the forward inference, the prior belief, P(ΔCog), is the overall (i.e., marginal) probability of the specific cognitive process changing due to any possible cause (e.g., what task is used, what the person is doing, etc). For the reverse inference, the prior belief, P(StimROI) or approximately synonymous with P(ΔROI), is the overall probability of the specific neural activity changing due to any possible cause (e.g., what the person is doing, interactions of other neural dynamics, etc). We began our analysis by assuming a change prior ($P = 0.50$), similar to Poldrack (2006). We then conducted a procedure known as Bayesian sensitivity analysis, by plotting the inference outcomes (the posterior probabilities) across the range (0-1) of prior probabilities, in order to assess the reliability of the inference probabilities.

Bayes Factor (BF). The strength of evidence for either inference can be computed with the Bayes Factor (BF), a model comparison procedure representing a ratio between two model likelihoods, which are formulated in Figures 3.4 and 3.5. For either inference, if $BF = 1$, then both models seem equally likely given their respective data. The more that $BF > 1$, the more likely the first (numerator) model seems compared to the second (denominator) model, and vice versa for $BF < 1$. Although a continuous distribution without arbitrary thresholds, the BF is often interpreted by the following convention (Jeffreys, 1961): a BF between 1-3 means positive but not substantial or unnoteworthy evidence (i.e., the first model is less than 3x more likely than the second model), a BF between 3-10 means substantial evidence (i.e., the first model is between 3x to 10x more likely than the second model), and a BF > 20 means strong evidence (i.e., the first model is more than 10x likely than the second model).

It is important to note that the original formulation of the Bayes Factor, from which the above BF formula can be derived (see Appendix 3.2), includes the prior information (as the ratio of the posterior odds to the prior odds). However, in the case of tests between simple hypotheses (e.g., ΔCog or StimROI equals a single value or ratio) as opposed to tests between complex hypotheses (e.g., ΔCog or StimROI equals a range of values or ratios), the priors algebraically cancel out, thereby reducing the BF to the same likelihood ratio test in frequentist statistics (Gelman et al., 2013). Consequently, during the Bayesian sensitivity analysis when the prior values are adjusted, only the posterior probabilities (and not the corresponding BF values) of the forward and reverse inferences change.

True positive (TPR) and true negative rates (TNR). In the present neurostimulation context, the TPR (as known as sensitivity or hit rate), calculated as Σ(ΔCog & StimROI)/Σ(StimROI), estimates the proportion of contrasts involving stimulation of a specific region (StimLIFG) which showed the hypothesized cognitive outcome (ΔCog). The TNR (as known as specificity or selectivity), calculated as Σ(~ΔCog & ~StimROI)/Σ(~StimROI), estimates the proportion of contrasts which did not stimulate the region (~StimROI) and did not find the hypothesized cognitive outcome (~ΔCog). See Appendices 3.3, 3.4, and 3.5 for TPR and TNR formulae for each meta-analysis model.

Bayesian Inferential Models

Model fMRI. The 2 x 2 contingency table reported in the original fMRI meta-analysis (Poldrack, 2006), along with Bayes Theorem, was used to calculate the forward inference – the degree to which the LIFG showed differential BOLD activity given that language was engaged by a task, or P(LIFG|Lang) – and the reverse inference – the degree to which language was engaged by the task given that the LIFG showed differential BOLD activity, or P(Lang|LIFG). For all formulae of this model, see Appendix 3.3.

Model 1 (Within-language syntax specificity of LIFG). A 2 x 2 contingency table, based on neurostimulation, was constructed with all statistical contrasts, within only the language domain, that showed either a significant (ΔSynLang) or nonsignificant (~ΔSynLang) effect of stimulation applied to either the LIFG (StimLIFG) or to another brain region (StimOther). Model 1 compares between present and absent effects within only language in order to assesses the language syntax specificity of the LIFG versus other regions. The forward inference is P(ΔSynLang|StimLIFG), which was computed with Bayes Theorem as the probability of a change (versus no change) in language syntax given that the LIFG (versus another region) was stimulated. The reverse inference is P(StimLIFG|ΔSynLang), which was computed with Bayes Theorem as the probability that the LIFG (versus another region) was stimulated given an observed change (versus no change) in language syntax. For all formulae of this model, see Appendix 3.4.

Model 2 (Cross-domain syntax specificity of LIFG). A 2 x 2 contingency table, based on neurostimulation, was constructed with only the statistically significant contrasts in either language (ΔSynLang) or nonlanguage domain (ΔSynOther) involving stimulation to either the LIFG (StimLIFG) or to any another brain region (StimOther). Unlike Model 1, which is limited to the language domain but compares significant to nonsignificant effects, Model 2 compares only significant effects across language and nonlanguage domains in order to assess cross-domain syntax specificity of the LIFG compared to other regions. For all formulae of this model, see Appendix 3.5.

Results

Search Results. See Table 3.1 for a list of total recorded contrasts from all studies within each cognitive domain. See Table 3.2 for a list of how many studies conducted each neurostimulation technique in each domain. The language domain included 383 contrasts across 11 studies (7 TMS, 1 TBS, 3 tDCS), and nonlanguage domains together provided 684 contrasts across 33 studies (16 TMS, 3 TBS, 9 tDCS, 2 tACS, 3 tRNS). It is interesting to note that, of the language studies that targeted the LIFG, most studies (5/7) exclusively targeted the pars opercularis, one study targeted both pars opercularis and triangularis simultaneously, and one study targeted both separately. Of the nonlanguage studies that targeted the LIFG, about half (5/11) exclusively targeted the pars opercularis, about half (4/11) targeted both pars opercularis and triangularis simultaneously, two studies targeted the pars triangularis only, and one study targeted both separately.

There was substantial variability of methodologies across all studies included in the meta-analysis. Out of all the TMS studies including single-pulse, rTMS, and TBS (27 total), 25 studies used a figure-eight coil, one study used a cone coil, and one study did not report this specific information. All TBS studies used an intensity of 80% of active motor threshold (aMT). Of the 23 single-pulse TMS and rTMS studies, seven studies used 110% of resting motor threshold (rMT), six studies used 90% rMT, three studies used 100% rMT, and the remaining studies varied between 50-75% rMT. The TMS targeting procedures included the following: 23 studies used neuronavigation (MR structural image) for targeting, three studies used the EEG 10-20 system, and one study did not report this information. All transcranial electrical stimulation (17 total tES studies: including tDCS, tACS, and tRNS) used the EEG 10-20 system for targeting. There was also high variability of methods used for controls. Of the 27 TMS studies, five studies used a control group receiving stimulation of a different region (usually the vertex), five studies used a control group receiving either no stimulation or sham stimulation, six studies used a control site (within-subjects), five studies used a control stimulation (within-subjects, either sham or no stimulation), five studies did not use any controls (only a within-subjects design), and one study used both a control group (different region stimulation) and a control stimulation (sham, within-subjects). Of the 17 tES studies, seven studies used a control stimulation of sham (within-subjects), six studies used a control group of sham stimulation, two studies used a control group (different region), one study used no control (within-subjects only), and one study used both a control group (different region) and control group (sham).

Model fMRI (Poldrack, 2006). The 2 x 2 contingency table is shown in Table 3.3**,** the inference results in Table 3.4, and the Bayesian sensitivity analysis in Figure 3.6. The forward inference, P(ΔLIFG|Lang), or the probability that the LIFG was active (as measured by a reliable change in BOLD signal) given that language was engaged, was not high (P = 0.65) at a chance prior (i.e., P(ΔLang) = 0.50). The corresponding BF (1.85) indicated positive but unsubstantial evidence in support of the inference. The Bayesian sensitivity analysis showed that the forward inference, (i.e., posterior probability), fluctuated drastically with the prior. In other words, the specificity of the language-LIFG relation strongly depended on the specificity of the language-task relation (i.e., the belief that the task engaged language syntax). The reverse inference, P(Lang|ΔLIFG), or the probability that language was engaged given that the LIFG was active, was not high (P = 0.69) at a chance prior (i.e., P(ΔSynLang) = 0.50). The corresponding BF (2.30) indicated positive but unsubstantial evidence. The Bayesian sensitivity analysis showed that the reverse inference posterior fluctuated drastically with the prior. In other words, the specificity of the language-LIFG relation strongly depended on the degree to which LIFG would be activated at any time (during task or rest). For the entire model, the true positive rate was low (0.19), indicating that most contrasts in language studies did not find reliable LIFG activation, and the true negative rate was high (0.92), indicating that most contrasts in nonlanguage studies also did not find reliable LIFG activation.

Model 1 (Within-language syntax specificity of LIFG). The 2 x 2 contingency table is shown in Table 3.5**,** the inference results in Table 3.4, and the Bayesian sensitivity analysis in Figure 3.7. The forward inference, P(ΔSynLang|StimLIFG), or the probability of a change (versus no change) in language syntax given that the LIFG (versus another region) was stimulated, was not high (P = 0.60) at a chance prior (i.e., P(ΔSynLang) = 0.50). The corresponding BF (1.50) indicated positive but unsubstantial evidence in support of the inference. The Bayesian sensitivity analysis showed that the forward inference (i.e., posterior probability) fluctuated drastically with the prior. In other words, the specificity of the language-LIFG relation strongly depended on the specificity of the language-task relation (i.e., the belief that the task engaged language syntax). The reverse inference, P(StimLIFG|ΔSynLang), or the probability that the LIFG (versus another region) was stimulated given an observed change (versus no change) in language syntax, was also not high (P = 0.64) at a chance prior (i.e., P(ΔSynLang) = 0.50). The corresponding BF (1.78) indicated positive but unsubstantial evidence. The Bayesian sensitivity analysis showed that the reverse inference posterior also fluctuated drastically with the prior. In other words, the specificity of the language-LIFG relation strongly depended on the neuromodulation effect (i.e., the belief that the stimulation successfully modulated neural activity). For the entire model, the true positive rate was low (0.35), indicating that most contrasts involving LIFG stimulation did not find a change in language syntax, and the true negative rate was high (0.80), indicating that most contrasts involving stimulation of another brain region also did not find a change in language syntax.

Model 2 (Cross-domain syntax specificity of LIFG). The 2 x 2 contingency table is shown in Table 3.6, the inference results in Table 3.4, and the Bayesian sensitivity analysis in Figure 3.8. The forward inference, P(ΔSynLang|StimLIFG), or the probability of a change in language syntax (versus nonlanguage syntax) given that the LIFG (versus another region) was stimulated, was moderate but not high (P = 0.69) at a chance prior (i.e., P(ΔSynLang) = 0.50). The corresponding BF (2.25) indicated positive but unsubstantial evidence. The Bayesian sensitivity analysis showed that the forward inference (i.e., posterior probability) fluctuated drastically with the prior. In other words, similar to Model 1, the specificity of the language-LIFG relation strongly depended on the specificity of the language-task relation. The reverse inference, P(StimLIFG|ΔSynLang), or the probability that the LIFG (versus another region) was stimulated given an observed change in language syntax (versus nonlanguage syntax), was moderate but not high (P = 0.72) at a chance prior (i.e., P(ΔSynLang) = 0.50). The corresponding BF (2.56) indicated positive but unsubstantial evidence. The Bayesian sensitivity analysis shows that the reverse inference posterior fluctuated drastically with the prior. In other words, the specificity of the language-LIFG relation strongly depended on the neuromodulation effect. For the entire model, the true positive rate was not high (0.48), indicating that around half of contrasts involving LIFG stimulation did not show a change in language syntax, and the true negative rate was high (0.81), indicating that most contrasts involving non-LIFG stimulation did not show a change in language syntax.

Discussion

In the present study, we investigated the specificity of the left inferior frontal gyrus (LIFG; specifically Broca's area, BA 44/45) for linguistic versus nonlinguistic syntactic or hierarchical processing (Aim 1) by conducting a novel application of a Bayesian meta-analysis based on a literature review of neurostimulation experiments (Aim 2) involving the domains of action, artificial grammar, language, logic, math, and music. We included only neurostimulation studies using only syntactic/hierarchical tasks, in contrast to the original meta-analysis (Poldrack, 2006) involving only fMRI studies and including all language tasks. Bayesian probability theory was used to estimate the degree and strength of forward (i.e., from cause to effect) and reverse (i.e., from effect to cause) inferences within two different neurostimulation models and also the original fMRI model (Poldrack, 2006).

Both Model 1 and Model 2 assessed the syntax specificity of the LIFG (versus other brain regions) based on neurostimulation data, although Model 1 compared between significant and nonsignificant effects within language and Model 2 compared significant effects between language and nonlanguage domains. When the prior probability was assumed at chance (P = 0.50), the results of both models closely resembled the result of the fMRI model, in terms of both the forward and reverse inferences with only moderate probabilities (posteriors ranging from 0.60-0.72) and positive but unsubstantial strength of evidence (BF ranging from 1.49-2.56), and in terms of the true positive (ranging from 0.19-0.48) and true negative rates (ranging from 0.80-0.96). In other words, the specificity of the LIFG (i.e., Broca's area) for language syntactic/hierarchical processing, without considering any prior information about the task or neural dynamics (i.e., assuming chance prior, P = 0.50), seems potential but not highly probable. Therefore, these neuromodulation results provide some support for theoretical models of Broca's area (LIFG; BA 44/45) as a cross-domain network hub for syntactic integration, rather than specific to the language domain (Fadiga et al., 2009; Fiebach et al., 2005; Fitch & Martins, 2014; Jeon, 2014; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012).

However, the Bayesian sensitivity analyses indicated that the forward and reverse inferences about the language selectivity of Broca's area appear unstable and change drastically with large changes in the prior belief that the chosen task engaged language syntax or that the chosen stimulation procedure successfully modulated neural activity. High prior probabilities yielded high posterior probabilities of forward and reverse inferences, and low priors yielded low inferences. These alternative results paint quite different pictures. On the one hand, low prior beliefs might arise from knowledge of improper or uncertain methods (e.g., task involves too many nonspecific or interacting cognitive processes, inaccurate or subthreshold stimulation, etc) which would call into question or invalidate the resulting inferences of low probability of any relation between language syntax and the LIFG. On the other hand, high prior beliefs could indicate high certainty of the task or stimulation procedure. In such situations, the resulting inferences would indicate high specificity of the LIFG for language syntax, which would support the notion of nonshared or dissociable neural mechanisms between language and many cognitive domains (Blank et al., 2014; Fedorenko & Varley, 2016; Monti, 2017). This apparent paradox could be interpreted as exemplifying the potential influence of experimental methodology (particularly, chosen tasks and neuroscience methods) on experimental observations and subsequent interpretations. Such methodological differences may be artefactually contributing, directly or indirectly, to the accumulation of polar evidence on either side of the debate regarding the potential interdependence between language and thought (i.e., other cognitive domains).

The present study has some limitations. First, in the Bayesian sensitivity analysis, the range of probabilities for the prior beliefs (i.e., that the task engaged language, or that the neurostimulation technique successfully modulated the neural response) was based on simulations instead of acquired data (because none of the studies reported such information). Therefore, it is unclear to what extent the present findings about the high variability of inferences dependent on the priors would change if study-specific priors were used instead. It is interesting to note, however, that the use of Bayesian sensitivity analysis in cognitive neurostimulation for causal inferences about brain-behavior relations could represent a type of counterfactual reasoning (i.e., how would our inferential results change if we had different prior beliefs?) that could enhanced causal inferences (Pearl & Mackenzie, 2018).

Second, we only included peer-reviewed, published studies. Publication bias has been shown to influence meta-analytic results (Rothstein et al., 2006). Although we were unable to assess this issue here, it seems probable that many experimental studies that did not find significant effects have not been published, which would likely bias our analyses. To reduce this potential bias, the meta-analysis included all statistical tests reported in each study that were relevant to a test of potential neurostimulation effects, rather than simply coding each study in a simple binary fashion (i.e., the study found a significant effect on language or not). Because most studies reported both significant and nonsignificant effects, we hope that this captured variability offsets some of the potential publication bias.

Third, we were unable to assess regional differences between the pars opercularis (BA 44) and pars triangularis (BA 45) because most language and nonlanguage studies which stimulated the LIFG specifically targeted BA 44. It appeared that most studies' rationale for this decision was based on previous fMRI evidence for the selective role of this subregion in syntax (e.g., Fiebach et al., 2005; Friederici, 2018;

Vigneau et al., 2006). In other words, the results we report here of the relatively unspecific role of the LIFG for language syntax are based mostly on the pars opercularis region of the LIFG. In contrast to previous research, more recent fMRI studies based on single-subject analyses have demonstrated alternative evidence, despite individual differences in spatial profiles, for the language-specific syntactic role of the pars triangularis and the domain-general role of the pars opercularis in nonlanguage domains such as working memory, cognitive control, action, music, and algebra (Blank et al., 2014; Fedorenko et al., 2012; Mineroff et al., 2018). They have argued that much of the previous research showing selectivity of the LIFG (and pars opercularis in particular) for language syntax were potentially confounded by task designs that did not sufficiently isolate language syntactic effects from more general effects of working memory, cognitive control, or task difficulty (Fedorenko & Varley, 2016; Mineroff et al., 2018). This issue may have affected many neurostimulation studies as well, which may explain our present findings that the LIFG (pars opercularis in most studies) does not appear highly specific to language syntax, which is consistent with evidence for the domain-general role of the pars opercularis.

Lastly, because of the paucity of neurostimulation studies, we were constrained to assess language specificity at a regional level. A network-level analysis would have been a more informative test of the proposed interdependence between language and nonlanguage domains given previous evidence for the widely distributed processing of language syntax (Blank et al., 2016), evidence from invasive stimulation of large-scale, parallel configurations of cortical and white matter subcircuits that underlie different language functions (Duffau, 2018; Duffau et al., 2014; Teichmann et al., 2015), and evidence of complex local and global network dynamics across the brain (Bullmore & Sporns, 2009; Roland, 2017). Unfortunately, we did not find enough language syntax studies (using complex tasks of sentence or phrase level) that stimulated other regions in the purported language network to allows us to conduct a network-level analysis.

In conclusion, the present study discovered that Bayesian inferential meta-analysis can be successfully applied to neurostimulation literature in order to test causal inferences about brain-behavior relations. The results showed that Broca's area (based mostly on pars opercularis) did not seem highly specific to language syntax, when compared to other brain regions and other cognitive domains, given that both forward and reverse inferences about the specific relation between Broca's area and language syntax showed only low to moderate probabilities (posteriors between 0.60 to 0.72) with corresponding low strength of evidence (Bayes Factors less than 3). These findings appear to support theoretical predictions of Broca's area as a shared neural resource for hierarchical processing across cognition. However, prior beliefs about cognitive tasks and successful stimulation can drastically change the results and subsequent interpretations. Therefore, the present results should be considered as tentative and preliminary pending future research on this topic to fully account for the variability of experimental methodologies.

Figures

$$P(\text{Lang} \mid \text{LIFG}) = \frac{P(\text{LIFG} \mid \text{Lang})P(\text{Lang})}{P(\text{LIFG} \mid \text{Lang})P(\text{Lang}) + P(\text{LIFG} \mid\sim \text{Lang})P(\sim \text{Lang})}$$

Figure 3.1. Bayes Theorem for reverse inference in fMRI (Poldrack, 2006).

$$P(\Delta\text{Cog} \mid \text{StimROI}) = \frac{P(\text{StimROI} \mid \Delta\text{Cog})P(\Delta\text{Cog})}{P(\text{StimROI} \mid \Delta\text{Cog})P(\Delta\text{Cog}) + P(\text{StimROI} \mid\sim \Delta\text{Cog})P(\sim \Delta\text{Cog})}$$

Figure 3.2. Bayes Theorem for forward inference in cognitive neurostimulation.

$$P(\text{StimROI} \mid \Delta\text{Cog}) = \frac{P(\Delta\text{Cog} \mid \text{StimROI})P(\text{StimROI})}{P(\Delta\text{Cog} \mid \text{StimROI})P(\text{StimROI}) + P(\Delta\text{Cog} \mid\sim \text{StimROI})P(\sim \text{StimROI})}$$

Figure 3.3. Bayes Theorem for reverse inference in cognitive neurostimulation.

$$BF = \frac{P(\text{StimROI} \mid \Delta\text{Cog})}{P(\text{StimROI} \mid\sim \Delta\text{Cog})}$$

Figure 3.4. Bayes factor (BF) for forward inference in cognitive neurostimulation.

$$BF = \frac{P(\Delta\text{Cog} \mid \text{StimROI})}{P(\Delta\text{Cog} \mid\sim \text{StimROI})}$$

Figure 3.5. Bayes factor (BF) for reverse inference in cognitive neurostimulation.

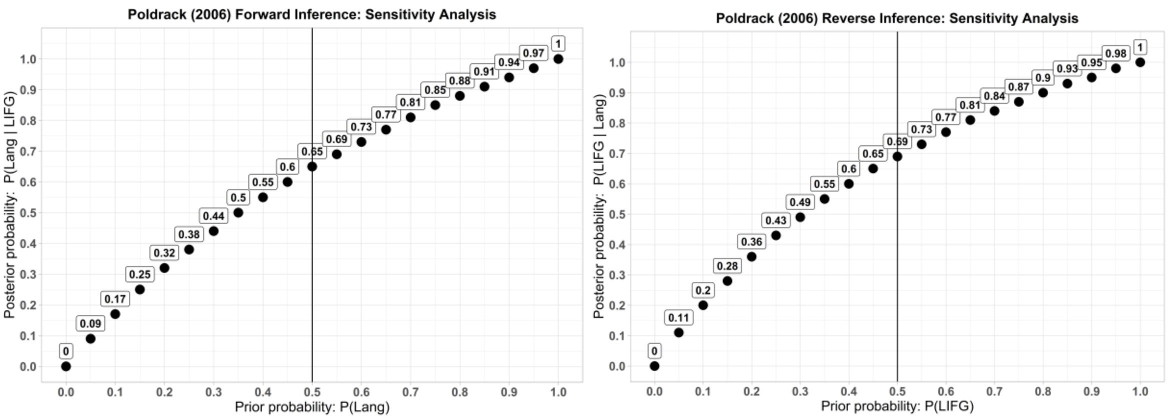


Figure 3.6. Results of Bayesian sensitivity analysis for forward (left panel) and reverse (right panel) inferences for the fMRI model (Poldrack, 2006). P(ΔLang) refers to the prior probability that language was engaged by the experimental task. P(LIFG) refers to the prior probability of LIFG being active. The vertical lines indicate a change prior (P = 0.50) which was initially chosen to compute the forward and reverse inferences and then was systematically adjusted with intervals of 0.05 across the full range from 0 to 1 (x-axis). The resulting posterior probabilities for the respective inference are shown on the y-axis.

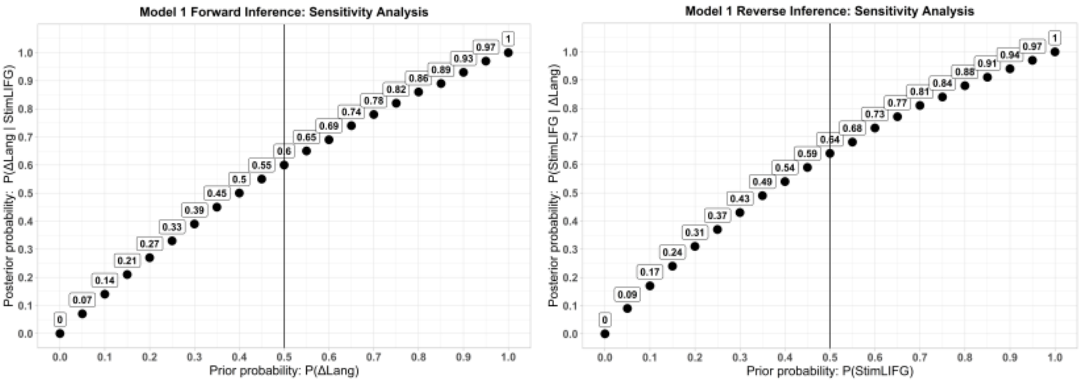


Figure 3.7. Results of Bayesian sensitivity analysis for forward (left panel) and reverse (right panel) inferences for neurostimulation Model 1. P(ΔLang) refers to the prior probability that language was engaged by the experimental task. P(StimLIFG) refers to the prior probability of a successful neurostimulation effect. The vertical lines indicate a change prior (P = 0.50) which was initially chosen to compute the forward and reverse inferences and then was systematically adjusted with intervals of 0.05 across the full range from 0 to 1 (x-axis). The resulting posterior probabilities for the respective inference are shown on the y-axis.

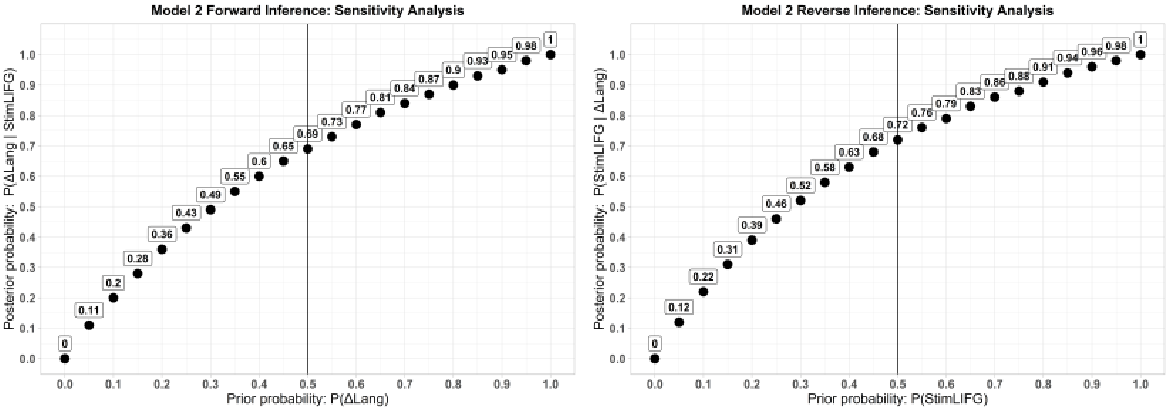


Figure 3.8. Results of Bayesian sensitivity analysis for forward (left panel) and reverse (right panel) inferences for neurostimulation Model 2. P(ΔLang) refers to the prior probability that language was engaged by the experimental task. P(StimLIFG) refers to the prior probability of a successful neurostimulation effect. The vertical lines indicate a change prior (P = 0.50) which was initially chosen to compute the forward and reverse inferences and then was systematically adjusted with intervals of 0.05 across the full range from 0 to 1 (x-axis). The resulting posterior probabilities for the respective inference are shown on the y-axis.

Tables

	Contrasts	Studies
Action	184	11
AG	84	4
Logic	135	6
Math	237	9
Music	44	3
Language	383	11
Other	684	33
Totals	1067	44

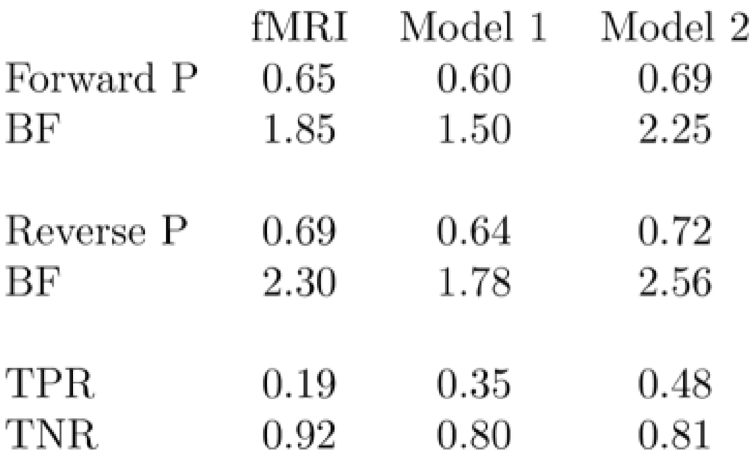
Table 3.1. List of all reported contrasts, relevant to the potential effects of neurostimulation, by studies in different cognitive domains. *AG* refers to artificial grammar. *Other* refers to sum total of all non-language domains. These contrasts were used to construct the 2 x 2 contingency tables for the different models.

	Language	Other	Total
TMS	7	16	23
TBS	1	3	4
tDCS	3	9	12
tACS	0	2	2
tRNS	0	3	3

Table 3.2. Frequencies of studies using different neurostimulation techniques.

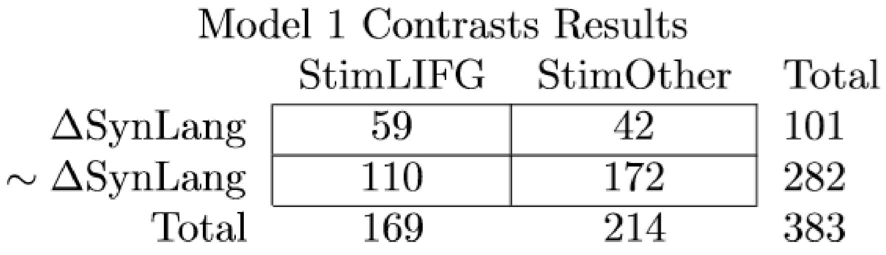
	Lang	∼Lang	Total
ΔLIFG	166	199	365
∼ΔLIFG	703	2154	2857
Total	869	2353	3222

Table 3.3. For the fMRI model (Poldrack, 2006), the 2 x 2 contingency table of frequencies of statistical tests reported by the included studies. Lang refers to contrasts from language studies. ~Lang refers to contrasts from nonlanguage studies. ΔLIFG refers to a reliable BOLD signal change in the left inferior frontal gyrus. ~ ΔLIFG refers to the absence of a reliable BOLD signal change in the LIFG.



	fMRI	Model 1	Model 2
Forward P	0.65	0.60	0.69
BF	1.85	1.50	2.25
Reverse P	0.69	0.64	0.72
BF	2.30	1.78	2.56
TPR	0.19	0.35	0.48
TNR	0.92	0.80	0.81

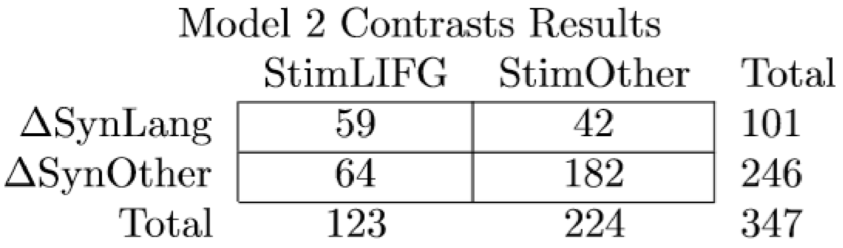
Table 3.4. Results summary: the forward inference probability (Forward P) with corresponding Bayes Factor (BF), the reverse inference probability (Reverse P) with corresponding BF, and the true positive and true negative rates (TPR, TNR) for each of the models. fMRI refers to the model from the original fMRI analysis (Poldrack, 2006). Models 1 and 2 refer to the neurostimulation analyses in this study.



Model 1 Contrasts Results

	StimLIFG	StimOther	Total
ΔSynLang	59	42	101
$\sim \Delta$SynLang	110	172	282
Total	169	214	383

Table 3.5. For neurostimulation Model 1, the 2 x 2 contingency table of frequencies of statistical tests reported by the included studies. StimLIFG refers to stimulation of the left inferior frontal gyrus. StimOther refers to stimulation of any other region. ΔSynLang refers to a statistically significant effect of change in language syntax. ~ΔSynLang refers to a statistically nonsignificant effect of change in nonlanguage domains.



Model 2 Contrasts Results

	StimLIFG	StimOther	Total
ΔSynLang	59	42	101
ΔSynOther	64	182	246
Total	123	224	347

Table 3.6. For neurostimulation Model 2, the 2 x 2 contingency table of frequencies of statistical tests reported by the included studies. StimLIFG refers to stimulation of the left inferior frontal gyrus. StimOther refers to stimulation of any other region. ΔSynLang refers to a statistically significant effect of change in language syntax. ΔSynOther refers to a statistically significant effect of change in nonlanguage domains.

Appendix 3.1

All formulae (Cognitive Neurostimulation examples)

Bayes Theorem (Forward Inference)

$$P(\Delta\mathrm{Cog} \mid \mathrm{StimROI}) = \frac{P(\mathrm{StimROI} \mid \Delta\mathrm{Cog})P(\Delta\mathrm{Cog})}{P(\mathrm{StimROI} \mid \Delta\mathrm{Cog})P(\Delta\mathrm{Cog}) + P(\mathrm{StimROI} \mid \sim \Delta\mathrm{Cog})P(\sim \Delta\mathrm{Cog})}$$

Bayes Theorem (Reverse Inference)

$$P(\mathrm{StimROI} \mid \Delta\mathrm{Cog}) = \frac{P(\Delta\mathrm{Cog} \mid \mathrm{StimROI})P(\mathrm{StimROI})}{P(\Delta\mathrm{Cog} \mid \mathrm{StimROI})P(\mathrm{StimROI}) + P(\Delta\mathrm{Cog} \mid \sim \mathrm{StimROI})P(\sim \mathrm{StimROI})}$$

Bayes Factor (Forward Inference)

$$BF = \frac{P(\mathrm{StimROI} \mid \Delta\mathrm{Cog})}{P(\mathrm{StimROI} \mid \sim \Delta\mathrm{Cog})}$$

Bayes Factor (Reverse Inference)

$$BF = \frac{P(\Delta\mathrm{Cog} \mid \mathrm{StimROI})}{P(\Delta\mathrm{Cog} \mid \sim \mathrm{StimROI})}$$

True Positive Rate (TPR)

$$TPR = \frac{\Delta\mathrm{Cog} \cap \mathrm{StimROI}}{\mathrm{StimROI}}$$

True Negative Rate (TNR)

$$TNR = \frac{\sim \Delta\mathrm{Cog} \cap \sim \mathrm{StimROI}}{\sim \mathrm{StimROI}}$$

Appendix 3.2

Bayes Factor derivation (Cognitive neurostimulation example)

$$BF = \frac{P(\Delta\mathrm{Cog} \mid \mathrm{StimROI})}{P(\sim \Delta\mathrm{Cog} \mid \mathrm{StimROI})} \Big/ \frac{P(\Delta\mathrm{Cog})}{P(\sim \Delta\mathrm{Cog})}$$

$$= \frac{P(\mathrm{StimROI} \mid \Delta\mathrm{Cog}) P(\Delta\mathrm{Cog})}{P(\mathrm{StimROI} \mid \sim \Delta\mathrm{Cog}) P(\sim \Delta\mathrm{Cog})} \Big/ \frac{P(\Delta\mathrm{Cog})}{P(\sim \Delta\mathrm{Cog})}$$

$$= \frac{P(\mathrm{StimROI} \mid \Delta\mathrm{Cog})}{P(\mathrm{StimROI} \mid \sim \Delta\mathrm{Cog})}$$

Appendix 3.3

All formulae (fMRI model, Poldrack, 2006)

Bayes Theorem (Forward Inference)

$$P(\text{Lang} \mid \text{LIFG}) = \frac{P(\text{LIFG} \mid \text{Lang})P(\text{Lang})}{P(\text{LIFG} \mid \text{Lang})P(\text{Lang}) + P(\text{LIFG} \mid\sim \text{Lang})P(\sim \text{Lang})}$$

Bayes Theorem (Reverse Inference)

$$P(\text{LIFG} \mid \text{Lang}) = \frac{P(\text{Lang} \mid \text{LIFG})P(\text{LIFG})}{P(\text{Lang} \mid \text{LIFG})P(\text{LIFG}) + P(\text{Lang} \mid\sim \text{LIFG})P(\sim \text{LIFG})}$$

Bayes Factor (Forward Inference)

$$BF = \frac{P(\text{LIFG} \mid \text{Lang})}{P(\text{LIFG} \mid\sim \text{Lang})}$$

Bayes Factor (Reverse Inference)

$$BF = \frac{P(\text{Lang} \mid \text{LIFG})}{P(\text{Lang} \mid\sim \text{LIFG})}$$

True Positive Rate (TPR)

$$TPR = \frac{\text{Lang} \cap \text{LIFG}}{\text{LIFG}}$$

True Negative Rate (TNR)

$$TNR = \frac{\sim \text{Lang}\cap \sim \text{LIFG}}{\sim \text{LIFG}}$$

Appendix 3.4

All formulae (Neurostimulation Model 1)

Bayes Theorem (Forward Inference)

$$P(\Delta\text{SynLang} \mid \text{StimLIFG}) = \frac{P(\text{StimLIFG} \mid \Delta\text{SynLang})P(\Delta\text{SynLang})}{P(\text{StimLIFG} \mid \Delta\text{SynLang})P(\Delta\text{SynLang}) + P(\text{StimLIFG} \mid\sim \Delta \text{ SynLang})P(\sim \Delta\text{SynLang})}$$

Bayes Theorem (Reverse Inference)

$$P(\text{StimLIFG} \mid \Delta\text{SynLang}) = \frac{P(\Delta\text{SynLang} \mid \text{StimLIFG})P(\text{StimLIFG})}{P(\Delta\text{SynLang} \mid \text{StimLIFG})P(\text{StimLIFG}) + P(\Delta\text{SynLang} \mid \text{StimOther})P(\text{StimOther})}$$

Bayes Factor (Forward Inference)

$$BF = \frac{P(\text{StimLIFG} \mid \Delta\text{SynLang})}{P(\text{StimLIFG} \mid\sim \Delta\text{SynLang})}$$

Bayes Factor (Reverse Inference)

$$BF = \frac{P(\Delta\text{SynLang} \mid \text{StimLIFG})}{P(\Delta\text{SynLang} \mid\sim \text{StimOther})}$$

True Positive Rate (TPR)

$$TPR = \frac{\Delta\text{SynLang} \cap \text{StimLIFG}}{\text{StimLIFG}}$$

True Negative Rate (TNR)

$$TNR = \frac{\sim \Delta\text{SynLang} \cap \text{StimOther}}{\text{StimOther}}$$

Appendix 3.5

All formulae (Neurostimulation Model 2)

Bayes Theorem (Forward Inference)

$$P(\Delta\text{SynLang} \mid \text{StimLIFG}) = \frac{P(\text{StimLIFG} \mid \Delta\text{SynLang})P(\Delta\text{SynLang})}{P(\text{StimLIFG} \mid \Delta\text{SynLang})P(\Delta\text{SynLang}) + P(\text{StimLIFG} \mid \Delta\text{SynOther})P(\Delta\text{SynOther})}$$

Bayes Theorem (Reverse Inference)

$$P(\text{StimLIFG} \mid \Delta\text{SynLang}) = \frac{P(\Delta\text{SynLang} \mid \text{StimLIFG})P(\text{StimLIFG})}{P(\Delta\text{SynLang} \mid \text{StimLIFG})P(\text{StimLIFG}) + P(\Delta\text{SynLang} \mid \text{StimOther})P(\text{StimOther})}$$

Bayes Factor (Forward Inference)

$$BF = \frac{P(\text{StimLIFG} \mid \Delta\text{SynLang})}{P(\text{StimLIFG} \mid\sim \Delta\text{SynOther})}$$

Bayes Factor (Reverse Inference)

$$BF = \frac{P(\Delta\text{SynLang} \mid \text{StimLIFG})}{P(\Delta\text{SynLang} \mid\sim \text{StimOther})}$$

True Positive Rate (TPR)

$$TPR = \frac{\Delta\text{SynLang} \cap \text{StimLIFG}}{\text{StimLIFG}}$$

True Negative Rate (TNR)

$$TNR = \frac{\Delta\text{SynOther} \cap \text{StimOther}}{\text{StimOther}}$$

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Chapter 4

Do language and algebra share neural resources for hierarchical processing? A neuromodulation exploration

Abstract

Language and algebra resemble each other in their dependence on hierarchical structures and for expressing relations between elements in complex sequences. Whether these computational similarities reflect shared neural networks remains an unresolved question and relates to the deeper mystery of the relation between language and thought. In this randomized within-subjects design, linguistic and algebraic syntactic tasks were given to participants before and after transcranial magnetic stimulation (TMS; specifically, continuous theta burst stimulation) of either the left inferior frontal gyrus (LIFG; specifically, the pars opercularis), a presumed language syntax region or a cross-domain network hub, and the right intraparietal sulcus (RIPS), a presumed network node for numeric and algebraic cognition. We discovered that stimulation of either region modulated performance on both cognitive tasks. These results appear consistent with the cross-domain interpretation of Broca's area (specifically the pars opercularis), a perspective potentially extending to the RIPS as well. Future replication studies will be necessary to ascertain the reliability of these preliminary findings.

Introduction

Like natural language, complex mathematical cognition such as algebra can be described as hierarchically structure-dependent such that complex sequences (e.g., equations, formulae) can be created from finite elements (i.e., numbers, symbols, operations) via a computational process for integrating relations between elements which depend on locality, order, and movement (Chomsky, 1997; Ernest, 1987). For example, compare the sentences “dog bites man” and “man bites dog” to the arithmetic expressions “5–3” and “3–5”: different orderings of the same tokens produce different results (Monti, 2017). According to Chomsky, algebra might be thought as an abstraction of natural language (Chomsky, 1988), relying on the same recursivity mechanisms (Hauser, Chomsky, & Fitch, 2002).

Whether the hierarchical similarities between language and math are substantial (i.e., based on shared neurocognitive mechanisms) or superficial (i.e., based on analogy only) is an ongoing debate that reflects a broader topic of the potential interdependence between the structure-based operations of language and those of other cognitive domains (Boeckx, 2010; Fitch & Martins, 2014; Gleitman & Papafragou, 2013; Lashley, 1951; Monti, 2017; Rosenbaum et al., 2007).

On one side of the debate, many studies have demonstrated a close link between language and math. Using a relatively simple arithmetic task, Dehaene, Spelke, Pinel, Stanescu, & Tsivkin (1999) reported that exact calculations recruited the LIFG (although outside the traditional Broca’s area as noted by Fedorenko and Varley, 2016) whereas approximate calculations recruited bilateral intraparietal cortex, a result replicated in a subsequent study (Stanescu-Cosson et al., 2000). In a cross-cultural behavioral study, Spelke & Tsivkin (2001) demonstrated that exact calculations involving two-digit numbers, but not approximate numbers, were more efficiently processed in the same language in which participants were previously trained – similar to previous studies showing that bilinguals are better at arithmetic in their first language.

In a lesion overlap study, Baldo & Dronkers (2007) found that left hemisphere stroke patients had correlated language and arithmetic performance and that some patients with language and arithmetic problems had lesions that included the LIFG. However, as noted by Fedorenko and Varley (2016), that study also found some evidence of dissociation between some patients' language and arithmetic abilities. Other lesion or fMRI studies have also observed association of the LIFG with arithmetic and algebraic processing (Chochon et al., 1999; Friederici et al., 2011; Maruyama et al., 2012; Rickard et al., 2000; Tohgi et al., 1995). These results are consistent with the notion that the classical language region of "Broca's area" (i.e., the left inferior frontal gyrus, LIFG; pars opercularis, BA 44, and pars triangularis, BA45) may function instead as a domain-general region for syntactic processing at the intersection of language, music, action, and possibly any other hierarchically structure-dependent cognition (Fadiga et al., 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Jeon, 2014; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012). Although, this relation may depend entirely on individual differences of functional heterogeneity within the LIFG, given recent evidence for both language-specific and domain-general subregions (Blank et al., 2014, 2016; Fedorenko et al., 2012).

On the other side of the debate, many cross-cultural, lesion, or neuroimaging studies have provided evidence to refute the claim of shared computational or neural processes between language and mathematical cognition (whether arithmetic or algebraic). Two lesion studies demonstrated dissociations such that aphasiac patients with lesions in language-relevant regions were able to perform exact arithmetic and even advanced algebraic processing involving embedded structures (Klessinger, Szczerbinski, & Varley, 2007; Varley et al., 2005). Some developmental studies have indicated the separable trajectories of linguistic and mathematical thinking (Butterworth, 2005; Butterworth et al., 2008). In a review of fMRI and intracranial studies, Amalric & Dehaene (2017) concluded no substantial neural overlap in language-related perisylvian regions between mathematical and nonmathematical thinking. This conclusion was also supported by an early positron emission tomography (PET) study of exact arithmetic involving two-digit numbers (Zago et al., 2001). In a clever fMRI and magnetoencephalography (MEG) study comparing different levels of increasing algebraic complexity in either syntactically correct or incorrect parsing, Maruyama, Pallier, Jobert, Sigman, & Dehaene (2012) found a major role of the horizontal section of the intraparietal sulcus (hIPS) in processing syntactically correct and increasingly complex algebraic expressions. However, despite the predominant role of the hIPS, they also discovered some evidence of association of specific language-relevant regions (the pars triangularis and pars orbitalis of the LIFG, posterior STS, and putamen) with increasing algebraic syntactic complexity. The authors suggested that this surprising result may partially support theoretical hypotheses of the cross-domain role of the LIFG. At least two other neuroimaging studies showed nonshared neural resources between language and math. Fedorenko, Behr, & Kanwisher (2011) reported that exact arithmetic processing did not engage language-relevant regions including the LIFG. In a novel fMRI study directly comparing between language and algebraic syntax processing, Monti et al. (2012) discovered dissociations such that algebraic reasoning preferentially engaged bilateral hIPS along with other parietal regions, the left middle frontal gyrus, and medial precuneus whereas linguistic reasoning preferentially engaged classical language regions of the LIFG (BA 44, 45), posterior superior temporal gyrus/sulcus (pSTG/pSTS), angular and supramarginal gyri, and middle temporal gyrus (MTG).

On this topic, most prior research has utilized neuroimaging techniques (e.g., fMRI) which provide only correlational evidence brain-behavior relations. Neurostimulation techniques can contribute uniquely important information about brain-behavior (i.e., neurocognitive) relations because, unlike neuroimaging, they have potential for direct causal manipulation (i.e., increasing or decreasing cortical excitability) of specific regional or network dynamics and their consequent cognitive functions (Bestmann & Feredoes, 2013; Silvanto & Pascual-Leone, 2012; Tanaka & Watanabe, 2009). However, relatively few neurostimulation studies on arithmetic or algebraic cognition have been conducted so far. Göbel, Rushworth, & Walsh (2006) showed that repetitive Transcranial Magnetic Stimulation (rTMS) on left or right hIPS (anterior and posterior segments) impaired double-digit addition. Andres, Pelgrims, Michaux, Olivier, & Pesenti (2011) demonstrated that TMS on either left or right hIPS, but not bilateral posterior superior parietal lobule (PSPL), obtained from peak activations in an fMRI subtraction and multiplication task resulted in decreased performance (increased reaction time, increased errors). Hauser, Rotzer, Grabner, Mérillat, & Jäncke (2013) reported that anodal transcranial Direct Current Stimulation (tDCS) over left posterior parietal cortex (PPC), but not right PPC, enhanced number comparison and subtraction performance. Pope, Brenton, & Miall (2015) found that anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) improved arithmetic processing, verbal working memory, and attention. Sarkar, Dowker, & Kadosh (2014) showed that tDCS over bilateral DLPFC modulated arithmetic processing. Grabner, Rütsche, Ruff, & Hauser (2015) demonstrated that tDCS over left PPC modulated arithmetic learning. Two different studies reported improved performance from a five-day arithmetic training program due to transcranial Random Noise Stimulation (tRNS) over bilateral DLPFC (Popescu et al., 2016; Snowball et al., 2013) or over bilateral PPC (Popescu et al., 2016). The overall pattern of modulated arithmetic processing by stimulation of the hIPS (when using the more spatially focal technique of TMS) or stimulating the larger PPC (when using the less spatially focal tDCS or tRNS techniques) is consistent with the neuroimaging evidence for the prominent role of the hIPS and associated PPC as network hubs for arithmetic or algebraic cognition (Amalric & Dehaene, 2016, 2017; Maruyama et al., 2012; Monti et al., 2012). The identified role of DLPFC in mathematical reasoning is also similarly consistent across the neuroimaging and neurostimulation literature. Curiously, it seems that no neurostimulation study has yet to specifically investigate the question of arithmetic or algebraic dependence on purported language-relevant regions.

The present study leverages a neurostimulation paradigm to specifically investigate the potentially shared neural basis for the computational parallel of hierarchical, structure-dependent processing between language and algebra. In a within-subjects design, we compared participants' performance on language and algebraic tasks (involving complex hierarchical operations) both before and after TMS stimulation (with the cTBS protocol) to the pars opercularis subregion of the LIFG and to the right hIPS (RIPS), in randomized order. We used an offline TMS protocol known as continuous theta burst stimulation (cTBS) to modulate cortical activity for an extended duration while we tested task performance (Huang et al., 2015; Stagg et al., 2009; Suppa et al., 2016; Wischnewski & Schutter, 2015; Xu et al., 2013). Our primary hypothesis, based on prior evidence for the functional and neural dissociations between language and math, was a functional dissociation such that cTBS stimulation of the LIFG should modulate only language and cTBS stimulation of the RIPS should modulate only algebra. However, given theoretical accounts for the pivotal role of Broca's area (LIFG) in cross-domain hierarchical processing and prior evidence for functional associations between language and math, we anticipated that cTBS stimulation of the LIFG may alternatively modulate both language and algebra.

Methods

Participants

Twenty-six participants aged 18-28 (M = 20.81, SD = 2.70) were recruited via UCLA's SONA system. All participants identified English as their native language. Participants were recruited from UCLA campus via flyers. Participants were screened for risk factors (see Inclusion/exclusion criteria below) and given detailed informed consent. Participants were paid $25/hour. Three participants dropped out of the study (two due to scheduling conflicts, the other due to general discomfort reported during the first 10 seconds of the first stimulation session). Another participant was excluded because we could not reliably estimate their active motor threshold (a necessary procedure for calibration of the stimulation intensity). Two more participants were excluded from the statistical analysis because of chance accuracy (close to 50%)

indicating insufficient task performance. Therefore, the final sample size (n = 20) for the statistical analysis excluded six participants in total.

Power calculations for sample size*.* Planned sample size was determined with G*Power (Faul et al., 2007), using the “repeated measures, within factors” option (which assumes a mix of between-subjects and within-subjects effects, so therefore it is overly conservative, but there is no option for completely within-subjects tests). We estimated power for a 2 x 2 repeated-measures ANOVA with the following parameters: effect size = 0.40 (considered large ANOVA effect, Cohen, 1988), alpha = 0.05, power = 0.95, correlation among repeated measures = 0.50 (default), and nonsphericity correction = 1 (default). The predicted sample size was n = 24 (actual power = 0.96). Given that this G*Power procedure is overly conservative for crossed within-subjects designs, our obtained sample size (n = 20) was sufficient to observe relatively large effects with high power.

Inclusion/exclusion criteria. Inclusion criteria included the following: 1) right-handed; 2) young to middle-aged adults (between the ages of 18-50); 3) English as native/first language. Exclusion criteria included the following: 1) history of neurological disorders, 2) history of seizures in the individual or in any of their first-degree relatives, 3) currently taking any medications that increase the risk of seizures, 4) current use of psychoactive medication or illicit drugs (increases risk of seizures), 5) presence of metallic or electronic implants in head, 6) heavy alcohol use (increases risk of seizures), and 7) pregnancy (for extra safety precaution). Screening took place via a phone call in a private room after potential participants first contacted our lab, with the option of speaking with a qualified neurologist at any point during the study.

Additional tests*.* Participants were tested on the backwards version of the Digit Span (subtest of the WAIS-III, Wechsler, 1997), as a measure of their working memory (WM), before and after each stimulation session in order to assess potential stimulation effects nonspecific to language or math syntax, as well as to determine if individual WM variability interacts with stimulation effects of hierarchical processing. Visual imagery ability was measured with the Visual Vividness Imagery Questionnaire (VVIQ; Marks, 1973), which we included to determine if individual differences in visual imagery interacted with potential stimulation effects on language or math. Participant expectations about the potential effects of neuromodulation on their cognition and/or brain function were measured with the Expectations Assessment Survey (EAS; Rabipour, Davidson, et al., 2018; Rabipour, Wu, et al., 2018), both at the start and end of the study, in order for us to assess any change in their expectations as a result of their experience of the neurostimulation and whether such change may interact with any stimulation effects.

Language Task

The language task was adapted from the behavioral study in Chapter 2 comparing language and music. Two of the sentence structures (SRC1 and SRC2) were chosen for this study because they comprise the syntactic structural complexity (SynSC) contrast (SRC2 > SRC1) given that SRC2 has the same working memory costs (i.e., relativizer-verb distance) as SRC1 but has a more complex syntactic structure (i.e., center-embedded versus right-branching), based on dependency processing theories (e.g., DLT: Gibson, 2000; SWM: Kljajević, 2010). We defined SRC1 (i.e., Low) and SRC2 (i.e., High) as the two levels of our task Difficulty condition. An example of SRC1 is *The dealer noticed the gambler that won money*, and an example of SRC2 is *The dealer that noticed the gamblers won money*. For each sentence type, four different comprehension probes were created, two that related both subjects with the first verb (e.g., for SRC2, *The dealer noticed the gambler*, or *The gambler noticed the dealer*) and two that related either subject with the second verb (e.g., for SRC2, *The dealer won money*, or *The gamblers won money*). As such, half of the probes were congruent and the other half were incongruent with the sentence. Six stimulus sets were created, two sets for the practice session and four sets for the experimental sessions. Each stimulus set contained 96 trials (48 trials for each of Low/SRC1 and High/SRC2 difficulty) presented in randomized order for each subject. Each set had all unique sentences that were constructed from the same nouns and verbs used across all sets, in order to control for any stimuli differences confounding potential effects of stimulation. The order of stimuli sets across stimulation sessions was also randomized for each subject. All stimuli were pilot tested before the experiment began to ensure task feasibility and effect of difficulty manipulation.

Each trial began with a fixation cross (1000ms) followed by both a sentence (either SRC2 or SRC1, in randomized order) and a corresponding comprehension probe (one of the four possible probes, in randomized order) presented on the screen at the same time (sentence above probe). Participants were instructed to read the sentence and respond to the comprehension probe (with a keyboard button press, either “Yes”/congruent or “No”/incongruent) as quickly and accurately as possible. Trial duration was set for each subject according to their previous practice performance so that the task was neither too easy nor too difficult. Accuracy and response time (RT) were logged on every trial.

Algebra Task

The algebra task was adapted from a previous fMRI study (Monti et al., 2012). The modified design involves making a congruency judgment between a Cue inequality statement (e.g., $X – Y > Z$) and a Target inequality statement of either low-level difficulty (i.e., Low) that correctly matches the Target (e.g., $X > Z + Y$) or does not match the Target (e.g., $X > Z –$ Y), or a target of high-level difficulty (Level 2) that either correctly matches (e.g., $Y < -Z + X$) or does not correctly match (e.g., $Y < Z + X$). The Low difficulty condition does not require the participant to manipulate any complex hierarchy of the algebraic statement and involves only one short step (e.g., a linear movement of one of the variables across the inequality symbol). However, the High difficulty requires manipulation of the higher-order structure involving two or more movements and a reflection of the statement around the inequality that must be performed in a specific embedded order. These difficulty levels (from low to high degree of hierarchical complexity) were specifically designed to parallel the syntactic difference in the language task (SRC1 low, SRC2 high). All trials were created from this design by permuting all possible locations of the three letters (X, Y, Z), by permuting different arithmetic operations (divide, multiply, add, subtract), and by permuting flips of the inequality sign (in High level only). Importantly, the algebraic task does not involve any numerical arithmetic calculations, in order to specifically engage higher-level hierarchical operations of algebraic cognition. All stimuli were pilot tested before the experiment began to ensure task feasibility and effect of difficulty manipulation.

Equivalent to the language task, each trial began with a fixation (1000ms) followed by simultaneous presentation of the Cue and Target inequality statements on the screen. Six stimuli sets were created, two sets for the practice session and four sets for the experimental sessions. Each stimulus set contained 96 trials (48 trials for each of Low and High difficulty) presented in randomized order for each subject. Each set had all unique inequality statements that were constructed from the same symbols used across all sets, in order to control for any stimuli differences confounding potential effects of stimulation. The order of stimuli sets across stimulation sessions was also randomized for each subject. Trial duration was set for each subject according to their previous practice performance so that the task was neither too easy nor too difficult.

Magnetic Resonance Imaging (MRI)

After MRI safety screening, a high-resolution T1-weighted image (MPRAGE, TR = 1900ms, TE = 2.26ms, 1mm^3 voxel size) was acquired for each participant from a 3 Tesla Siemens Prisma MRI scanner at the Staglin IMHRO Center for Cognitive Neuroscience at UCLA. The T1-weighted image was used for enhanced target placement and neuronavigation.

Transcranial Magnetic Stimulation (TMS)

Targets and neuronavigation. All TMS procedures were conducted with a MagStim Rapid^2 stimulator (The MagStim Company LTD), using a figure-eight flat coil (double 70mm) within the Neuromodulation Lab of the Ahmanson-Lovelace Brain Mapping Center at UCLA. TMS stimulation was neuronavigated with each participant’s T1-weighted image by using BrainSight (Rogue Research). The T1 image for each participant was registered to the MNI 1mm template using ANTs nonlinear registration (Avants et al., 2011) and the inverse warp transformations were used to move (i.e., backproject) the target masks in MNI space into native brain space (and were visually checked for accuracy). Four target locations were marked on each participant's brain image. The hand region (or "hand knob") of the motor area in each hemisphere was based on neuroanatomical features (Yousry et al., 1997) or, when not feasible, based on the backprojected MNI coordinates of the hand region in left (MNI: x = -33, y = -23, z = 67) or right hemisphere (MNI: x = 37, y = -23, z = 67). For the language target, the pars opercularis (BA 44) was identified as part of the LIFG based on neuroanatomical features (Duvernoy, 1999). The algebra target was defined based on the MNI coordinates of the cluster peak voxel (MNI: x = 44, y = -44, z = 52) from the Algebra > Language contrast in Monti et al. (2012) which corresponded to the anterior segment of the horizontal IPS and was approximately consistent spatially with results from other math-relevant studies (Dehaene et al., 2003; Göbel et al., 2006).

Motor thresholding. Each TMS session began with an active motor thresholding (aMT) procedure. The aMT was defined as the minimum stimulation intensity sufficient to elicit a motor-evoked potential (MEP, > 50 microvolts in amplitude) in the contralateral first dorsal interosseous muscle (FDI; connecting to index finger) on 50% of single TMS pulses to the contralateral hand knob of the motor cortex while the participant flexed the muscle laterally at approximately 15-20% of their maximum strength (as they were instructed, although the flexing strength was not measured). The Signal software (Cambridge Electronic Design Ltd) was used to automatically deliver a single TMS pulse every 10 seconds (with 20% jitter) and to visualize MEP outputs from the FDI electrode. The program Adaptive PEST (Sen et al., 2017; Borckardt et al., 2006) was used to facilitate iterative adjustment of TMS intensity after each pulse depending on whether or not an MEP was observed.

TMS protocol. A protocol of patterned TMS known as continuous Theta Burst Stimulation (cTBS) was used for stimulation of experimental targets (LIFG or RIPS). Neurostimulation with cTBS was chosen because of substantial prior evidence that it can induce long-lasting cortical inhibition in motor cortex for at least 15-20 minutes or even up to 60 minutes (Gamboa et al., 2011; Huang et al., 2004, 2010; Stagg et al., 2009; Wischnewski & Schutter, 2015). Decreased performance following cTBS, suggesting inhibitory effects, have also been observed in nonmotor regions such as the prefrontal cortex (Drummond et al., 2017; Lowe et al., 2018). Parameters for cTBS included the following: intensity (80% of active motor threshold), burst frequency (5 Hz), overall frequency (50 Hz), burst of 3 pulses, 200 bursts in a single cycle totaling 600 pulses for a total stimulation duration of 40 seconds. cTBS was administered at an intensity of 80% of the aMT as recommended for safety and effectiveness (Rossi et al., 2009). Pain and discomfort ratings on a scale from 0 (nothing) to 10 (most ever felt) were collected from each participant after each cTBS stimulation. Average ratings showed relatively good tolerability of cTBS stimulation, although pain and discomfort ratings were both higher on average for LIFG stimulation (see Figure A4.1.1 in Appendix 4.1), which was expected given its sensitive location on the frontotemporal area. Paired-sample t-tests indicated that participants rated LIFG stimulation as more painful ($t(21) = 3.81$, $p < 0.001$) and more uncomfortable ($t(21) = 4.39$, $p < 0.001$) than RIPS stimulation.

TMS sessions*.* The experiment involved three sessions on separate days separated by at least 24 hours and up to 1 week. Session 1 involved informed consent, questionnaires, and task practice only (no TMS). Sessions 2 and 3 involved the following: (i) an initial baseline test of both language and math tasks (preTMS), followed by (ii) the aMT procedure and then cTBS to either the LIFG or the RIPS (randomized), followed by (iii) a post-stimulation test (postTMS) on both tasks.

Analysis

Independent variables (IVs). The following IVs were used: Site (LIFG, RIPS) indicating which brain region was stimulated; Task (Language, Math) corresponding to language and algebra tasks; Difficulty (Low, High) corresponding respectively to SRC1 and SRC2 in the language task and unembedded vs embedded inequality statements in the algebra task; and TMS (preTMS, postTMS) indicating test sessions before and after cTBS stimulation. All IVs were fully crossed in the within-subjects design.

Dependent variables (DV). Accuracy (ACC) and reaction time (RT) were collected on each trial, with higher ACC and lower RT indicating better performance. The ACC and RT data were analyzed in Model 1 (described below). All missed trials were excluded from the data, and the RT data included only accurate trials that were not outliers (i.e., either <250ms to avoid guesses or > 3*SD to avoid extremely slow trials). Change scores were calculated as the difference in the mean ACC (ΔACC) and median RT (ΔRT), across all trials, between TMS sessions (postTMS – preTMS). The change scores were analyzed with Model 2 (described below). An additional DV of RT change normalized by ACC change (ΔRT/ΔACC), based on the classic inverse efficiency score (Hughes et al., 2014; Townsend et al., 1983), was included in Model 2 to account for potential speed-accuracy trade-offs. Lower ΔRT/ΔACC values indicate better performance.

Hypotheses. The primary hypothesis was a 2 (Site: LIFG, RIPS) x 2 (Task: Language, Math) x 2 (TMS: preTMS, postTMS) interaction involving the following nested effects. First, given the prior evidence for cTBS (TMS) stimulation having inhibitory effects on neural activity (Huang et al., 2015; Stagg et al., 2009; Suppa et al., 2016; Wischnewski & Schutter, 2015), we hypothesized an inhibitory TMS effect (postTMS – preTMS) such that task performance would decline for postTMS compared to preTMS sessions. Second, if the LIFG is specific for language syntax and does not support algebraic syntax, then LIFG stimulation should yield a TMS effect for language but not algebra. However, if the LIFG plays a pivotal role for syntactic processing across hierarchically structured cognitive domains, then LIFG stimulation should yield a TMS effect for both language and algebra. Third, if the RIPS is specific for algebraic but not language syntax, then RIPS stimulation should yield a TMS effect for algebra but not language. In addition to the primary hypothesized model, we also hypothesized a main effect of task Difficulty (High condition would yield lower ACC and higher RT than the Low condition) and possible interactions with other factors (in the simplified Model 2 analyses).

Statistics. We used two different types of analysis to test the various hypotheses. **Model 1** comprised the following IVs: the full 2 (Site: LIFG, RIPS) x 2 (Task: Language, Math) x 2 (TMS: preTMS, postTMS) interaction as well as Difficulty (High, Low) as a main effect. Separate generalized linear mixed models (GLMM) were conducted for ACC and RT data (using all trials, rather than means) using the *glmer* function (*nmle4* package, Bates et al., 2014) in R (R Core Team, 2013) as well as the *GAMLj* package (Gallucci, 2019) in jamovi (The jamovi project, 2019). GLMMs enabled appropriate modeling of our fully crossed factorial within-subjects design (Magezi, 2015) by including participants as a random factor influencing the intercept term. Unfortunately, we did not have a large enough sample size to weight the random factor of participants on the slopes of the main or interaction effects or to include the random factor of trials (none of these models converged). GLMM also enabled accurate modeling of the untransformed trial data of ACC (binomial distribution with the logit link function, which gives the log of the odd of ACC=1 over ACC=0) and RT (gamma distribution with the identity link function, which appropriately models the skewed distribution of RT data; Lo & Andrews, 2015). Significance testing (i.e., *p* values) was conducted with parametric bootstrapping (10,000 samples). GLMM assumptions of normally distributed residuals, linear relations, and no substantial outliers were tested and confirmed prior to analysis. The model fit (AIC) of each GLMM was also confirmed to be substantially lower than the model fit of the equivalent alternative general linear model (GLM), thereby justifying inclusion of participants as a random factor. Planned comparisons without multiple comparison correction, instead of post hoc comparisons with correction, were conducted given our a priori, theory-driven hypotheses about variable TMS effects across sites and tasks. We also iteratively tested inclusion of the participant variables of working memory (WM), visual imagery (VVIQ), and expectations as covariates.

The second analysis, **Model 2**, used TMS change scores (ΔACC, ΔRT, and ΔRT/ΔACC) to reduce model complexity without the TMS factor and to increase statistical power, thereby enabling estimation of the 2 (Site: LIFG, RIPS) x 2 (Task: Language, Math) x 2 (Difficulty: High, Low) interaction for each DV. Change scores were separately analyzed with linear mixed models (LMM; *nlme4* in R, and *GAMLj* in jamovi) with participant as random factor weighting the intercept. All assumptions were checked for violations. Similar to Model 1, we conducted planned, hypothesis-driven comparisons and also tested for participant covariates.

Results

Visual imagery, working memory, and expectations. Working memory (WM), as measured by backwards Digit span (see Figure A4.2.1 in Appendix 4.2 for more detail), did not reliably change before and after TMS stimulation to either LIFG or RIPS. Student's paired t-tests and Bayesian paired t-tests indicated that the TMS effect (postTMS – preTMS) on WM was not reliable for LIFG ($t(19) = 1.17$, $p = 0.258$, $d = 0.26$, $BF_{10} = 0.42$) or for RIPS although there was some trend present ($t(19) = 1.88$, $p = 0.076$, $d = 0.420$, $BF_{10} = 1.35$). Participants' expectations about stimulation-induced changes in brain or cognition (see Figure A4.3.1 in Appendix 4.3 for more detail) also did not seem to change before and after study completion. Nonparametric Wilcoxon signed-rank tests and the Bayesian equivalent both indicated no reliable changes in participants' expectations about their brain ($W = 59.50$, $p = 0.337$, $BF_{10} = 0.35$) or cognition changing from stimulation ($W = 20.50$, $p = 0.280$, $BF_{10} = 0.39$). Visual imagery ability, as measured by VVIQ (see Figure A4.4.1 in Appendix 4.4) showed substantial variability across participants. None of these measures significantly correlated with any of the IVs in Models 1 or 2 (all p's > 0.20).

Model 1a (ACC). See Figure 4.1 for results. The GLMM on accuracy (ACC) data indicated that the 2 (Site) x 2 (Task) x 2 (TMS) interaction was not significant, AIC = 6804.33, $\chi^2(1) = 0.04$, $p = 0.850$. Planned comparisons with odds ratios (ORs) indicated that algebra accuracy was 1.41 times more likely to increase after TMS stimulation to LIFG (SE = 0.19, $Z = 2.56$, $p = 0.011$) and 1.55 times more likely to increase after TMS stimulation of RIPS (SE = 0.21, $Z = 3.21$, $p = 0.001$), but language accuracy was not likely to change from either LIFG (OR = 0.99, SE = 0.15, $Z = 0.04$, $p = 0.970$) or RIFG stimulation (OR = 1.19, SE = 0.16, $Z = 1.29$, $p = 0.199$). In a reduced model without the three-way interaction, there was a significant 2 (Task) x 2 (TMS) interaction, AIC = 6701.11, $\chi^2(1) = 4.48$, $p = 0.034$. Algebra accuracy was 1.48 times more likely to increase after TMS stimulation to either region, SE = 0.14, Z = 4.11, $p < 0.001$, but language accuracy was not likely to change, OR = 1.12, SE = 0.11, Z = 1.04, $p = 0.300$. There was also a significant main effect of participants' expectation about their cognition and brain being changed by stimulation, $\chi^2(1) = 5.46$, $p = 0.019$, $b = 0.22$ (SE = 0.09), 95% CI (0.04, 0.40), indicating that as participant prior expectation increased so did their overall accuracy (but it did not interact with any IVs). There was also a main effect of task Difficulty as hypothesized, $\chi^2(1) = 100.97$, $p < 0.001$, such that accuracy was higher for Low conditions of SRC2 and algebraic embedding (M = 96.30%, SE = 4.36%, 95% CI [95.30, 97.00%]) versus High conditions of SRC1 and algebraic non-embedding (M = 92.70%, SE = 7.82%, 95% CI [91.00, 94.10%]). However, task difficulty did not substantially interact with other factors (all *p*'s > 0.48).

Model 1b (RT). See Figure 4.2 for results. The GLMM on reaction time (RT) data indicated that the 2 (Site) x 2 (Task) x 2 (TMS) interaction was not significant, AIC =

40229, $\chi^2(1) = 1.68$, $p = 0.194$. Language RT decreased (i.e., performance increased) after stimulation of LIFG (M = -0.06, SE = 0.02, Z = -3.14, p = 0.002) and RIPS (M = -0.09, SE = 0.02, Z = -4.61, p < 0.001). Math RT decreased after stimulation of RIPS (M = -0.14, SE = 0.05, Z = -3.21, p = 0.001) but did not change after LIFG stimulation (M = -0.03, SE = 0.05, Z = -0.62, p = 0.540). In a reduced model without the three-way interaction (AIC = 39915), there was a trend-level 2 (Site) x 2 (TMS) interaction, $\chi^2(1) = 2.59$, $p = 0.108$. RT on both tasks became faster after TMS stimulation to LIFG (M = -0.06, SE = 0.02, Z = -3.12, p = 0.002), and RT on both tasks became even faster after RIPS stimulation (M = -0.10, SE = 0.02, Z = -5.40, p < 0.001). There was a main effect of TMS, $\chi^2(1) = 35.85$, $p < 0.001$, such that RT was faster after stimulation in general. There was also a main effect of task Difficulty, $\chi^2(1) = 310.29$, $p < 0.001$, such that the Low condition was faster than the Hard condition for both tasks, but Difficulty did not interact with any other factors (all *p*'s > 0.38).

Model 2a (ΔACC). The LMM (AIC = 478.26, $R^2 = 0.07$) on the change score for accuracy (ΔACC) indicated that the full 2 (Site) x 2 (Task) x 2 (Difficulty) interaction was not significant, F(1,133) = 0.67, p = 0.414, there was no main effect of Difficulty, F(1,136) = 0.45, p = 0.505, and Difficulty did not interact with either Site or Task (all *p*'s > 0.14). The 2 (Site) x 2 (Task) interaction was also not significant, F(1,133) = 0.04, p = 0.845. However, the main effect of Task was significant, F(1,133) = 4.13, p = 0.044, such that the TMS-induced change of increased algebra accuracy (M = 2.27%, SE = 0.61%) was much higher than that of language accuracy (M = 0.60%, SE = 0.61%). None of the participant variables were significant as covariates (all *p*'s > 0.65). Overall, these results are consistent with the ACC results of Model 1a, with the exception of the lack of task Difficulty effect.

Model 2b (ΔRT). The LMM (AIC = 131.84, R^2 = 0.23) on the change score for reaction time (ΔRT) indicated that the full 2 (Site) x 2 (Task) x 2 (Difficulty) interaction was not significant, F(1,133) = 0.67, p = 0.668, there was no main effect of Difficulty, F(1,137) = 0.23, p = 0.631, and Difficulty did not interact with either Site or Task (all *p*'s > 0.18). The 2 (Site) x 2 (Task) interaction was also not significant, F(1,133) = 0.19, p = 0.661. However, the main effect of Site was trend-level significant, F(1,133) = 3.10, p = 0.080, such that the TMS-induced change in RT after RIPS stimulation (M = -0.18, SE = 0.05) was higher than the change in RT after LIFG stimulation (M = -0.09, SE = 0.05). None of the participant variables were significant as covariates (all *p*'s > 0.47). Overall, these results are consistent with the RT results of Model 1b, with the exception of the lack of task Difficulty effect.

Model 2c (ΔRT/ΔACC). See Figure 4.3 for results. The LMM (AIC = 314.29, R^2 = 0.19) on the change score for speed-accuracy trade-off (ΔRT/ΔACC) indicated that the full 2 (Site) x 2 (Task) x 2 (Difficulty) interaction was not significant, F(1,133) = 0.03, p = 0.859, there was no main effect of Difficulty, F(1,137) = 1.23, p = 0.270, and Difficulty did not interact with either Site or Task (all *p*'s > 0.77). The 2 (Site) x 2 (Task) interaction was also not significant, F(1,133) = 0.25, p = 0.620. However, the main effect of Task was significant, F(1,137) = 5.45, p = 0.021, such that the TMS-induced change of increase in algebra performance (M = -0.38, SE = 0.08) was higher than that of language performance (M = -0.17, SE = 0.08), given that lower ΔRT/ΔACC scores indicate better performance. There was also a trend-level main effect of Site, F(1,137) =

2,79, p = 0.097, such that the TMS-induced performance change after RIPS stimulation (M = -0.35, SE = 0.09) was higher than the change after LIFG stimulation (M = -0.20, SE = 0.09), but for each Site the difference between language and math was not significant (all *p*'s > 0.132), although math was numerically higher than language in both cases. Overall, these results of changes in speed-accuracy trade-off induced by TMS are mostly consistent with the results from Model 1 and Model 2, with the exception of the lack of task Difficulty effect.

Discussion

In this study, we used a behavioral paradigm of linguistic and algebraic hierarchical tasks (with low and high difficulty conditions of structural complexity) as well as TMS neurostimulation (specifically, cTBS) to investigate potentially shared neural resources underlying the computational similarities of hierarchical processing between natural language and algebra. We targeted Broca's area (LIFG; specifically, the pars opercularis, BA 44), given prior evidence for its role in syntactic processing of language (Friederici, 2018) and other hierarchically structured cognitive domains (Fadiga, Craighero, & Alessandro, 2009; Jeon, 2014; Tettamanti & Weniger, 2006). We also targeted the horizontal section of the right IPS (RIPS), given prior evidence for its role as a network hub for arithmetic and algebraic cognition (Amalric & Dehaene, 2016, 2017; Maruyama et al., 2012; Monti et al., 2012). With a fully crossed within-subjects design, our primary hypothesis was a functional dissociation such that cTBS stimulation of the LIFG would modulate task performance of language but not math, whereas cTBS stimulation of the RIPS would modulate math but not language. We measured task performance with accuracy (ACC), reaction time (RT), and a metric of speed-accuracy trade-off (RT/ACC). We tested different statistical models with untransformed (using GLMMs on all trials) and transformed task measures (using LMMs on mean-based change scores before and after TMS sessions).

Contrary to our primary hypothesis, none of the task measures yielded a significant interaction of TMS effects between brain regions and cognitive domains. Planned comparisons demonstrated quite an unexpected pattern of results. Overall, both LIFG and RIPS stimulation produced some increase in language performance (due to faster response times, despite minimal change in accuracy) but much more increase in algebraic performance (due to higher accuracy and sometimes faster responses). This pattern also appeared in the combination of observed results of differential TMS effects across tasks (for accuracy and speed-accuracy trade-off) and across sites (for reaction time and speed-accuracy trade-off). Additionally, although there were significant effects of task difficulty as hypothesized, such that the condition of high complexity was more difficult than low complexity for both tasks, task difficulty did not interact with TMS stimulation or other factors, indicating that TMS seemed to equally affect, or not affect, both difficulty conditions regardless of task or brain region stimulated.

Given that previous research usually demonstrates inhibitory effects of cTBS stimulation (Huang et al., 2015; Stagg et al., 2009; Suppa et al., 2016; Wischnewski & Schutter, 2015), the consistent pattern of increased performance on either task that we observed after cTBS stimulation of either region warrants examination of some potential alternative explanations. It’s possible that the increased performance was due to practice effects on the tasks over time, given the within-subjects design. We attempted to reduce potential practice effects with two features of our design. In an initial behavioral session which occurred at least one day before the first stimulation session, participants were given one hour of practice on the tasks and, for each person, we adjusted the max trial duration separately for language and math tasks so that it was neither too easy nor too difficult (to avoid ceiling and floor effects, respectively). However, despite this preemptive strategy, the mean accuracies for the different conditions (see Figure 4.1) indicated overall relatively high performance. It seems possible that most participants experienced some learning effects. The overall high accuracies (even for the high difficulty condition, although it showed lower accuracy than the low difficulty condition) may have prevented TMS stimulation from effectively modulating cognitive behavior, given that TMS seems to preferentially engage more difficult tasks. The second design feature to minimize practice effects was our inclusion of a baseline task session before each TMS stimulation (preTMS) which was compared to the task session after TMS stimulation (postTMS). Thus, the TMS effect (calculated as postTMS – preTMS) for each brain region specifically adjusted for this baseline, with the logic that practice and learning effects over time should increase performance in both preTMS and postTMS sessions. Although there were some practice effects in the baselines, the significant TMS effects in our results indicate that postTMS sessions improved even more than the preTMS sessions, which might indicate a stimulation specific effect.

It's possible that participants had prior expectations about positive outcomes of brain stimulation which caused their performance to increase. Participant expectations about stimulation-induced brain and cognition changes were assessed both at the start and end of study participation. However, participant expectations did not reliably change across the study and did not interact with any of the TMS effects. Another possibility is that the relative unpleasantness of the cTBS stimulation contributed to an alerting or arousing effect inducing better performance after stimulation. However, if this were likely, then cTBS over LIFG should have shown substantially greater increased performance effects, given than participants rated LIFG stimulation as more painful and more uncomfortable than RIPS stimulation.

It’s possible that inaccurate targeting or subthreshold stimulation contributed to the results. For targeting, we used a sophisticated procedure to reduce the risk of inaccuracy (see Methods). However, one limitation of our study is that the targets were based on neuroanatomy (pars opercularis for LIFG) and fMRI-BOLD contrasts based on group activation (for RIPS). A more accurate procedure would be to define the targets based on functional localizers of language and math tasks for each participant, given that this procedure has been shown to provide more accurate subject-specific BOLD activation results (Blank et al., 2014; Blank & Fedorenko, 2017). Regarding stimulation threshold, we used a standard procedure of cTBS applied at 80% of active motor threshold. It’s possible that the motor cortex threshold does not apply to nonmotor cortices given that recent work has discovered differences and variability across cortices and detection methods (e.g., MEP vs TMS-induced EEG responses, Rocchi et al., 2018).

Another limitation of our study was that the interval between stimulation sessions across brain regions was often very short (24-48 hours) for many participants due to scheduling feasibility as compared to a longer duration (1 week) for other participants.

Although each region was only stimulated once, it's possible that metaplasticity effects could have occurred in these short time periods across brain networks and contributed to an accumulation of stimulation effects or learning effects with unpredictable outcomes for network functions (Abraham & Bear, 1996; Galanis & Vlachos, 2020; Müller-Dahlhaus & Ziemann, 2014; Rioult-Pedotti et al., 2007). Given that the two targets (LIFG and RIPS) are on opposite hemispheres, such metaplasticity would have to involve long range network dynamics between these particular regions that are not normally associated together as part of the same cognitive or neural networks.

Potential metaplasticity effects were tested with additional GLMM analyses on accuracy (ACC) and reaction time (RT) data. There was a marginally significant interaction of Session (TMS1, TMS2) X TMS (preTMS, postTMS) for accuracy (ACC: $\chi^2 = 3.32$, $p = 0.068$) and for reaction time (RT: $\chi^2 = 3.46$, $p = 0.063$). Post hoc tests indicated that, in the first TMS session (where Site was counterbalanced across participants), ACC increased ($z = 3.99$, $p < 0.001$) and RT decreased ($z = 3.32$, $p = 0.068$), whereas in the second TMS session (Site counterbalanced), there was no change in ACC ($z = 4.13$, $p < 0.001$) and only a trend decrease in RT ($z = 1.84$, $p = 0.066$). There were no additional three-way interactions with Site, Task, or Difficulty conditions for either ACC (all *p*'s > 0.11) or RT (all *p*'s > 0.23). The potential interaction between Session and TMS indicates differential TMS effects across repeated TMS stimulations equivalent for different regions, tasks, and difficulty levels. However, given that performance always increased (see Models 1 and 2 as well), it remains unclear whether such interaction would result from cross-network metaplasticity (larger TMS effect in the first session) of cTBS (which is typically interpreted as inhibitory) or more simply due to task learning effects (more learning in the first session). Future experiments could further investigate the issue of metaplasticity by including additional repeated stimulations for each targeted region in order to separate within region/network effects from cross region/network effects and also by including different stimulation protocols (e.g., cTBS and iTBS) in order to compare potential excitatory versus inhibitory effects.

Another complication for TMS research is that it seems likely that neural plasticity and other dynamics of regions or networks that are being stimulated could react and adapt to, or compensate for, the stimulation effect in order to maintain function (Chung et al., 2017; Graaf & Sack, 2011; Pascual-Leone et al., 2000; Sack, 2006). This phenomenon could partly account for the well-known high interindividual variability in responses and cognitive outcomes from TMS and TBS to both motor and nonmotor regions (Acheson & Hagoort, 2013; Guerra et al., 2020; Hinder et al., 2014; Jannati et al., 2017, 2019; Ji et al., 2017; Rocchi et al., 2018; Suppa et al., 2016; Viejo-Sobera et al., 2017; Xu et al., 2013), which may have also contributed to the variable effects across participants in the present study.

Another limitation is that no control region (to compare to the LIFG and RIPS sites) or control group (to compare stimulation to no stimulation) was included. Adding a control region or group would have substantially increased the statistical complexity of the design and analysis (given a relatively small sample size of 20 participants). However, such controls would have allowed a more rigorous test of the specificity of the LIFG or RIPS for language and math hierarchical processing.

Given all of the potential caveats mentioned above, a few tentative conclusions can be drawn from the results of this study. First, modulation of both language and algebra hierarchical processing from stimulation of the LIFG seems consistent with previous evidence of the functional associations between language and math as well as theoretical models of Broca's area as a cross-domain hub for language, music, action, and possibly other hierarchically structured cognition (Fadiga, Craighero, & D'Ausilio, 2009; Jeon, 2014; Tettamanti & Weniger, 2006; Uddén & Bahlmann, 2012). However, the result seems inconsistent with other research demonstrating functional dissociations between language and math (and other cognitive domains), particularly including evidence from fMRI studies that linguistic and algebraic hierarchical processing do not spatially overlap in the LIFG (Fedorenko et al., 2011; Maruyama et al., 2012; Monti et al., 2012). Second, the modulation of algebraic processing after stimulation of the RIPS was consistent with previous evidence and theoretical models of this region as a major hub for mathematical cognition (Amalric & Dehaene, 2016, 2017; Maruyama et al., 2012; Monti et al., 2012). Notably, at least two previous TMS studies on the RIPS have demonstrated algebraic effects (Andres et al., 2011; Göbel et al., 2006), although they found decreased performance instead of the increased performance observed in the present study. Third, the effect of RIPS stimulation modulating language, albeit less than algebra, is difficult to interpret due to limited prior evidence for the relation between the RIPS and language. At least one previous study has tested language hierarchical processing associated with cTBS applied to the RIPS, reporting a nonsignificant effect yet showing a numerical decrease in accuracy (Carreiras et al., 2012). The surprising result observed in the present study could reflect something anomalous about the current study or it could reflect a potential association requiring replication by future studies. Similar to the LIFG, perhaps the RIFG also potentially participates in a larger syntactic network which may interact with language networks, although this remains speculative at present.

It is important to emphasize that we specifically targeted the pars opercularis region of the LIFG, given that much previous research has focused on the pars opercularis as a crucial network node for language syntactic processing (e.g., Fiebach et al., 2005; Friederici, 2018; Vigneau et al., 2006). In the neuromodulation research, it appears that most studies on syntactic or hierarchical processing have also targeted this region (see Chapter 3). However, recent fMRI studies based on single-subject analyses have demonstrated alternative evidence, despite substantial individual differences in spatial profiles, for the language-specific syntactic role of the pars triangularis instead of the pars opercularis, the latter of which appears to have a more domain-general role underlying working memory, cognitive control, action, music, and math (Blank et al., 2014; Fedorenko et al., 2012; Mineroff et al., 2018). This new perspective of the pars opercularis seems consistent with the present study's results of changes in both language and algebra after stimulation of that subregion. These cross-domain results may also derive from the potential role of the LIFG in general as a coordinator and conflict controller between task-specific networks (Hsu et al., 2017). For the time being, it seems that the functional heterogeneity of the LIFG, depending on different subregions and task contexts, has likely been a major source of variability throughout the rich history of research on Broca's area for language and other cognitive domains. Unfortunately, some prominent theoretical models of Broca's area as a cross-domain hub do not yet sufficiently account for such functional heterogeneity in their predictions (Fadiga et al., 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Jeon, 2014; Tettamanti & Weniger, 2006).

Another crucial point is that the effects of TMS have been demonstrated by dual TMS-fMRI studies to spread to contralateral or other distant regions that are structurally or functionally connected to the target region (Bestmann & Feredoes, 2013; Hartwigsen et al., 2013; Michael et al., 2003; Nahas et al., 2001; Sack, 2006), which may not be surprising given evidence for complex local and global network dynamics across the brain (Bullmore & Sporns, 2009; Roland, 2017). With regard to language function, recent fMRI research indicates a widely distributed network for language syntax (Blank et al., 2016), which appears highly correlated internally but does also interact with other nonlanguage networks (Fedorenko & Thompson-Schill, 2014), and recent evidence from invasive stimulation techniques (direct cortical stimulation) supports a framework of large-scale, parallel configurations of cortical and white matter subcircuits that underlie different language functions (Duffau, 2018; Duffau et al., 2014; Teichmann et al., 2015). Therefore, such network-level phenomena likely complicate interpretations of any specific regional effects of stimulation, particularly when involving subregions of a brain area like the LIFG which appears to be a densely connected hub in the brain (Achard et al., 2006; Hsu et al., 2017; Xu et al., 2016).

In conclusion, contrary to the hypothesized dissociation between language-LIFG and algebra-RIPS relations, the present study demonstrated that both LIFG and RIPS stimulation modulated performance in both language and algebra. These results appear inconsistent with prior evidence of dissociations between language and math yet partially consistent with evidence and theories of cross-domain associations. However, given the predominant interpretation of inhibitory effects of cTBS stimulation (although some variability has been observed depending on task contexts, neurobiology and other factors; Gentner et al., 2008; Suppa et al., 2016; Viejo-Sobera et al., 2017; Xu et al., 2013), the pattern of increased performance from cTBS observed here may instead reflect potential limitations of the present study as discussed above, such as learning or cross-network metaplasticity effects. Future replication efforts will be necessary to ascertain the reliability of these results. Importantly, although several previous neurostimulation studies have assessed mathematical cognition associated with other brain regions, the present study appears to be the first to test the relation of the LIFG with complex math as well as the first to directly compare the neural bases of language and math in the same experiment. Because neurostimulation confers the advantage of increased potential for testing causal neurocognitive relations, future neuromodulation research on this topic will be necessary to provide a more complete understanding of potentially shared or nonshared neural resources between language and math (and other cognitive domains).

Figures

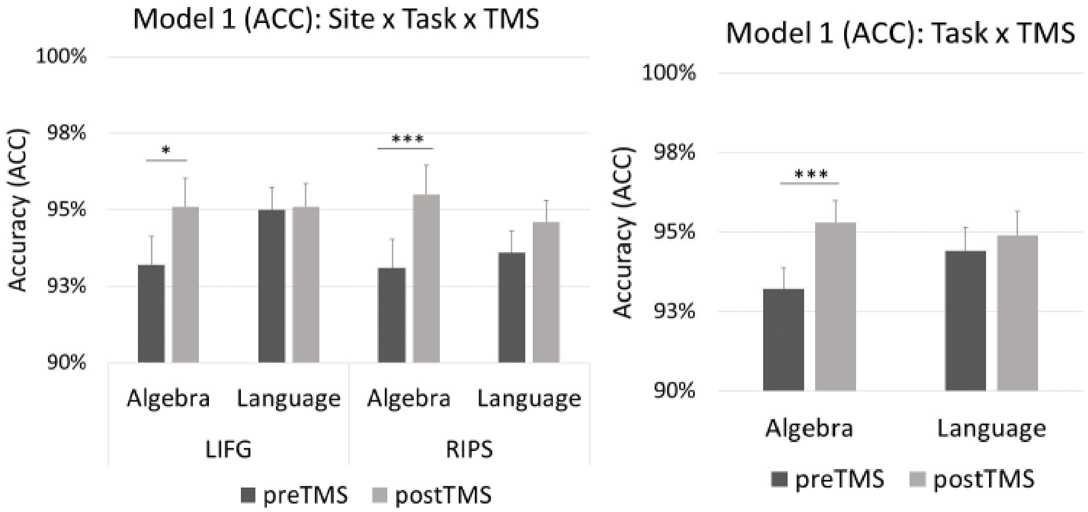

Figure 4.1. Results for Model 1a on accuracy (ACC) data, showing the nonsignificant Site x Task x TMS interaction and the significant Task x TMS interaction (both with planned comparisons). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

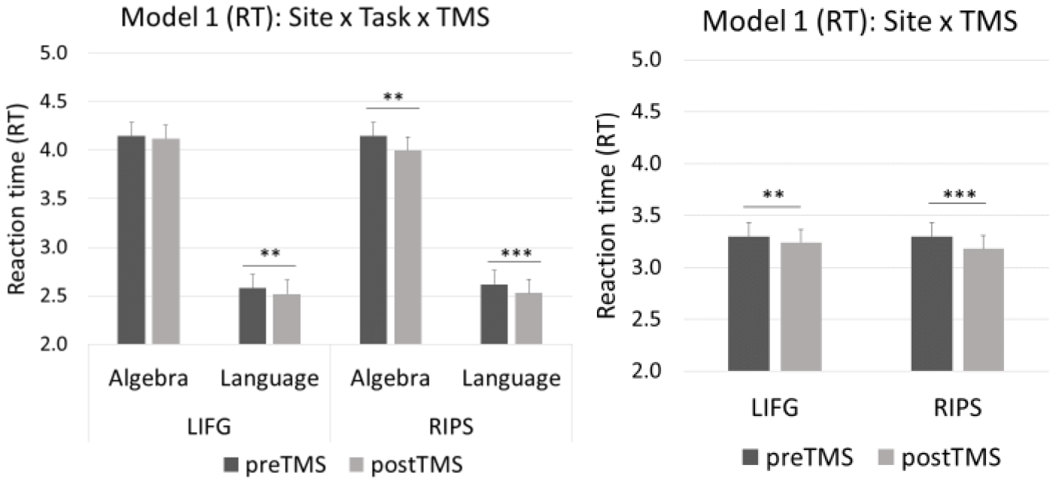

Figure 4.2. Results for Model 1b on reaction time (RT) data, showing the nonsignificant Site x Task x TMS interaction and the trend-level Site x TMS interaction (both with planned comparisons). Asterisks for p values of differences from planned pairwise t-tests: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001.

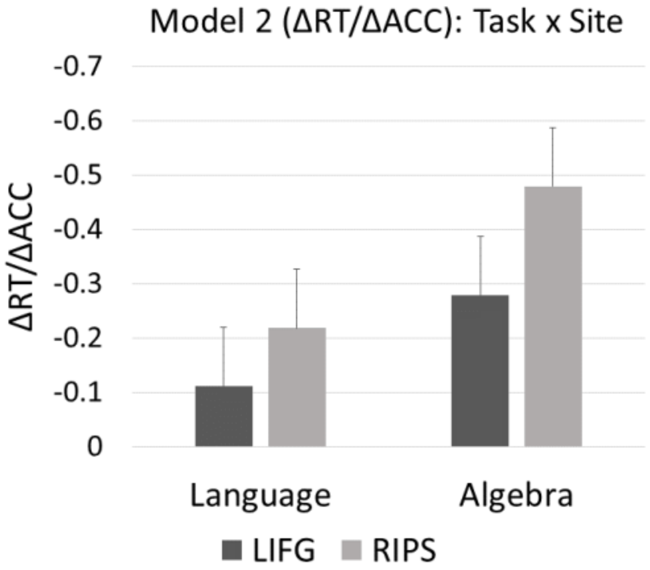

Figure 4.3. Results for Model 2c on the speed-accuracy trade-off (ΔRT/ΔACC) data, showing the nonsignificant Task x Site interaction, although there was a significant main effect of Task (Math > Language) and a trend-level main effect of Site (RIPS > LIFG). Higher (i.e., more negative) RT/ACC values indicate better performance because ΔRT/ΔACC is a difference score (postTMS – preTMS) and RT decreased (indicating faster performance).

Appendix 4.1

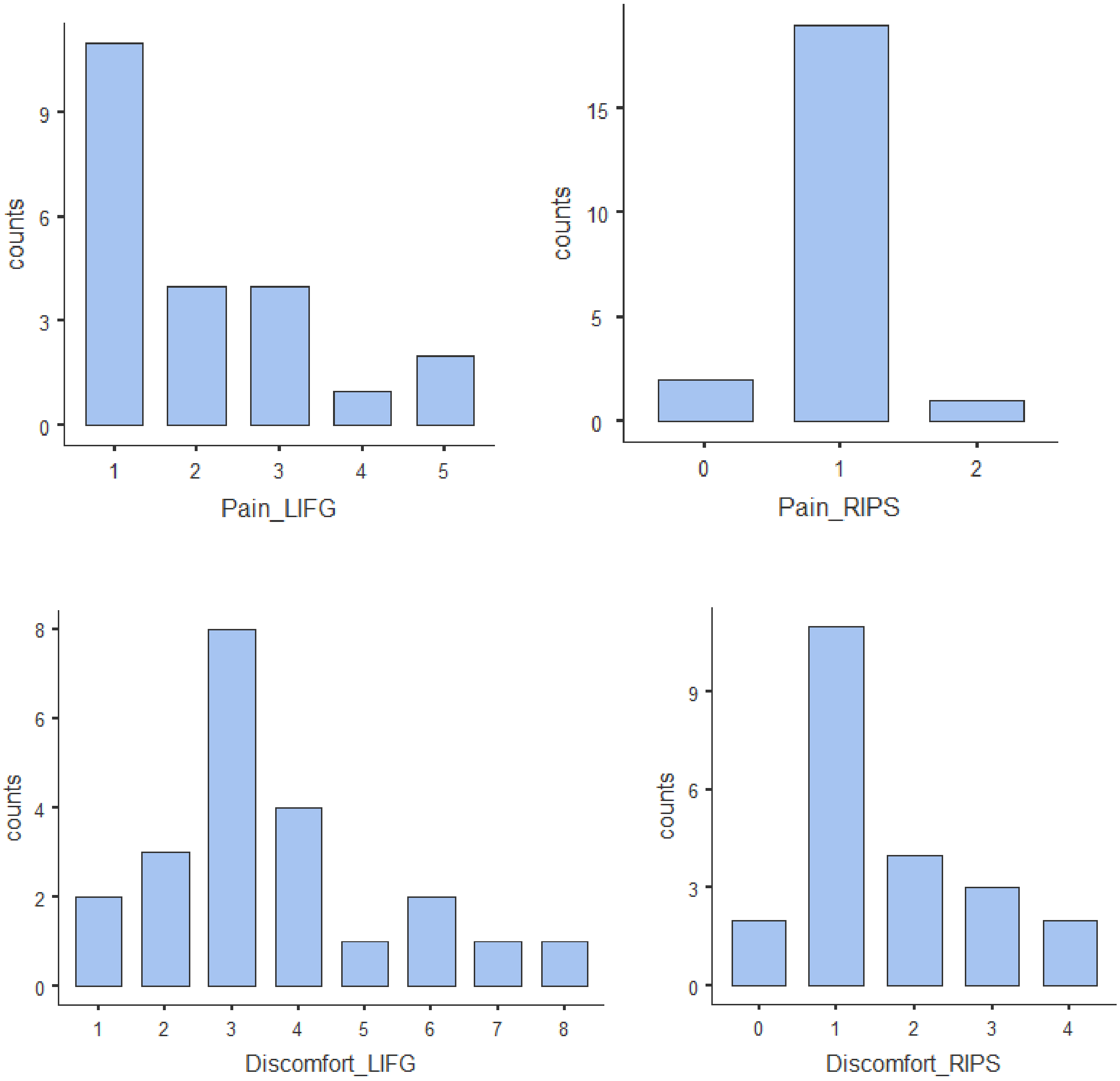

Figure A4.1.1. Histograms of participants' Pain and Discomfort ratings after cTBS stimulation of the pars opercularis subregion of the left inferior frontal gyrus (LIFG) and the horizontal segment of the right intraparietal sulcus (RIPS).

Appendix 4.2

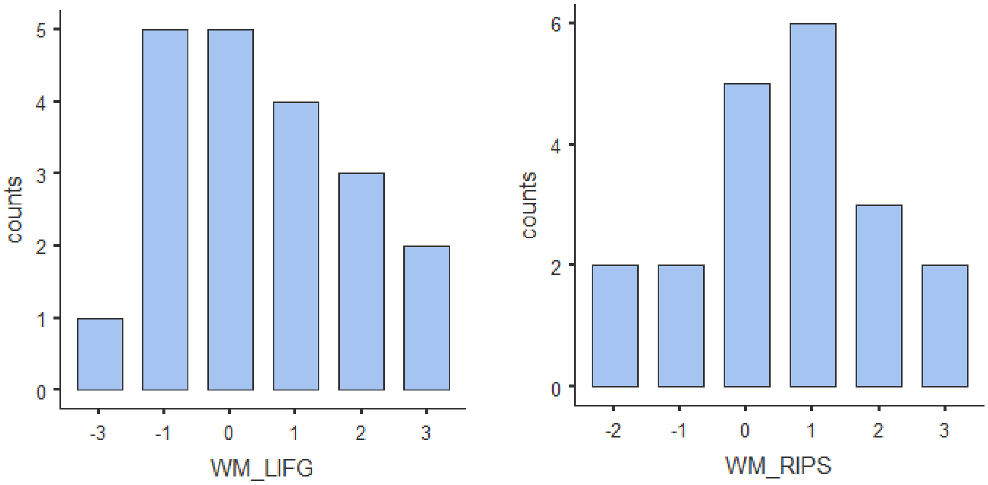

Figure A4.2.1. Histograms for the change scores (postTMS – preTMS) of the backwards Digit Span measure of working memory (WM) for each Site (LIFG, RIPS).

Appendix 4.3

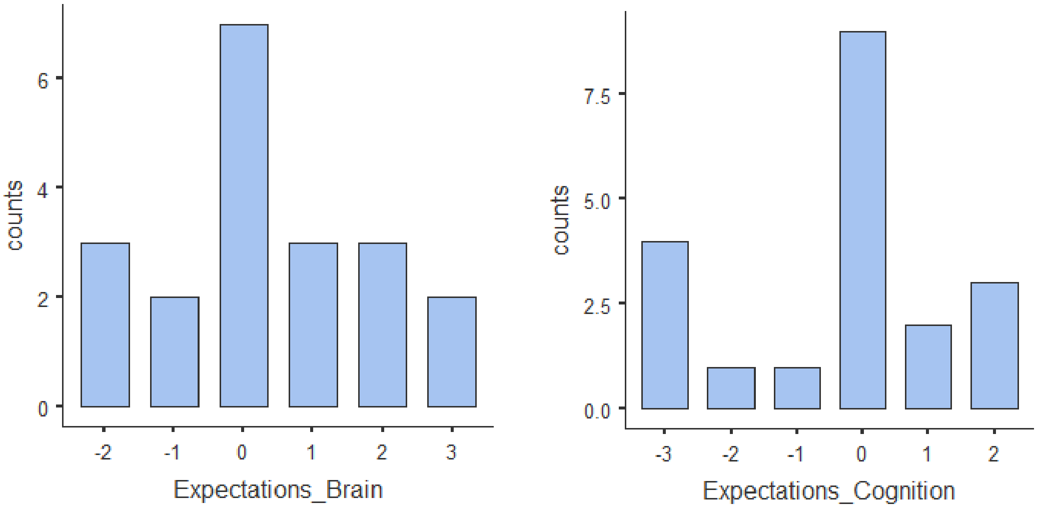

Figure A4.3.1. Histograms for the change scores (study end – study start) of participant's expectations about TMS-induced brain changes (Expectations_Brain) and cognitive changes (Expectations_Cognition), taken from the Expectations Assessment Survey (EAS). A value of 0 indicates no change in expectations. Higher and lower values indicate expectations increased or decreased by the end of the study, respectively.

Appendix 4.4

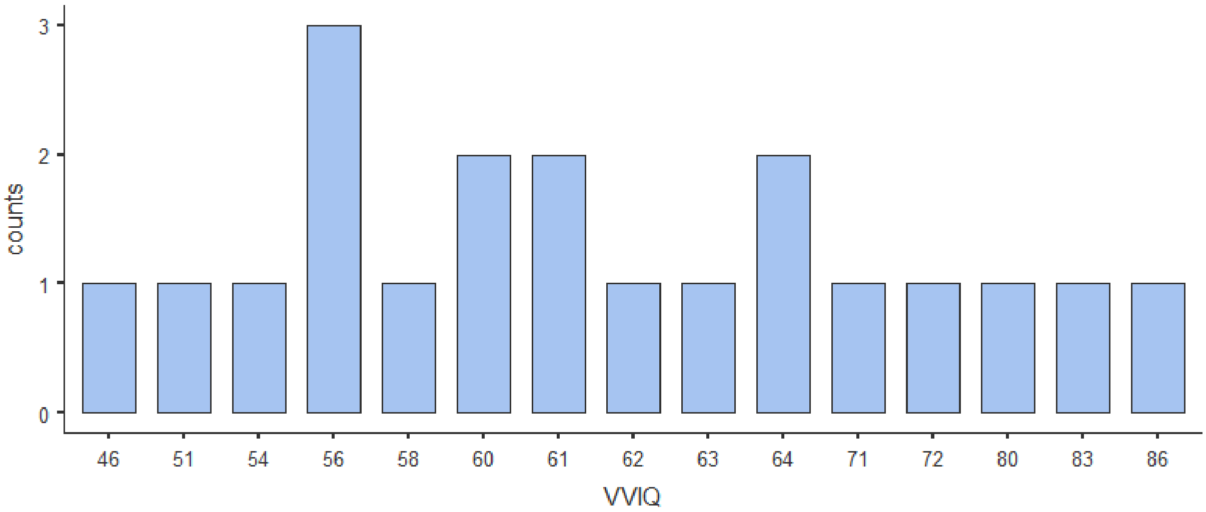

Figure A4.4.1. Histogram for participants' average scores on the visual imagery measure (Vividness of Visual Imagery Questionnaire, VVIQ).

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Chapter 5

General Summary and Discussion

Three different methodologies in this dissertation – a behavioral experiment, a meta-analysis, and a neuromodulation experiment – provided complementary evidence in support of theories which propose that hierarchical similarities between language and other cognitive domains reflect shared computational and neural resources.

In Chapter 2, a novel adaptation of a dual task paradigm without syntactic violations demonstrated bidirectional interactions between language and music which seemed driven mostly by syntactic complexity rather than syntactic working memory demands. Cross-domain interactions also preferentially occurred when syntactically critical words and keys temporally coincided across language and music sequences. These results add new evidence supporting the shared syntactic integration resource hypothesis (SSIRH; Patel, 2012) which predicts shared syntactic resources between language and music. Future experiments on the topic of shared resources between language and music, or any other cognitive domain, could combine dual task and neuromodulation paradigms to more rigorously test the degree to which shared cognitive resources may depend on shared neural resources. For example, if dual task interference between language and music syntactic processing were to increase after inhibitory stimulation of Broca's area, this result would provide enhanced evidence of a potentially causal role of this region as a shared resource for domain-general syntactic integration of domain-specific syntactic representations in language and music, as predicted by the SSIRH.

The work described in Chapters 3 and 4 directly tested theoretical models of Broca’s area as a cross-domain network hub for hierarchical processing. In Chapter 3, a novel application of a Bayesian inferential meta-analysis on published neurostimulation studies spanning six cognitive domains – action, artificial grammar, language, logic, math, and music – was conducted in order to assess the potential specificity of Broca’s area for hierarchical processing of language. Bayesian probability theory was used in different models to test forward (i.e., cause to effect) and reverse (i.e., effect to cause) inferences about shared neural resources. The meta-analysis indicated that Broca’s area, based mostly on stimulation of the pars opercularis subregion, appeared more domain-general and less language-specific. This finding supports theoretical models of Broca’s area as a cross-domain hub for hierarchical processing (Fadiga, Craighero, & D’Ausilio, 2009; Fiebach & Schubotz, 2006; Fitch & Martins, 2014; Tettamanti & Weniger, 2006). Given that most studies in the meta-analysis stimulated the pars opercularis, the results also support previous fMRI evidence for the domain-general role of this subregion (Blank et al., 2014, 2016; Fedorenko et al., 2012; Mineroff et al., 2018).

An important caveat to note for Chapter 3 is that all inferences were highly susceptible to changes in prior beliefs about the degree to which the chosen task engaged the cognitive process or how successfully the stimulation procedure modulated the neural region. This instability potentially reflects the influence of methodological differences on experimental observations and subsequent interpretations about specific causal relations between cognitive processes and specific brain regions and networks. Future research could adopt similar Bayesian procedures as used in Chapter 3 in order to more directly estimate and account for the potential influence of these experimental uncertainties.

In Chapter 4, a novel experiment of cognitive neuromodulation was conducted to test whether hierarchical similarities between language and algebra derive from shared neural resources. TMS stimulation (using continuous theta burst stimulation, cTBS) of both the LIFG (specifically, pars opercularis) and the horizontal segment of the right intraparietal sulcus (RIPS) seemed to produce changes in both linguistic and algebraic performance. The result of LIFG stimulation modulating algebra performance seems contradictory to previous research of functional dissociations between language and algebra yet seems consistent with the notion that Broca's area, and the pars opercularis subregion in particular, functions as a domain-general hub for hierarchical processing (as also indicated by the findings in Chapter 3). The result of RIPS stimulation modulating algebra performance confirms previous research of the RIPS as a key network node for mathematical cognition. However, the modulation of language performance from RIPS stimulation was unexpected, potentially reflecting something anomalous about the current study methods, or more interestingly, a potential domain-general role of the RIPS as well. Above all, the result of cTBS stimulation consistently enhancing, instead of impairing, performance in language and algebra tasks was surprising given the presumed inhibitory nature of cTBS stimulation. As discussed in Chapter 4, this finding of improved performance may have resulted from effects of task learning, cross-network metaplasticity, or insufficient task difficulty which may have overridden any effects of neurostimulation. Alternatively, given previous evidence for variability of cTBS effects (e.g., Rocchi et al., 2018; Suppa et al., 2016; Viejo-Sobera et al., 2017; Xu et al., 2013), the observed facilitation may have resulted from the effects of neurostimulation, perhaps due to complex interactions of the stimulated regions with their participating networks. Although this possibility remains speculative at present, future research combining cTBS with fMRI or EEG could enable measurement of stimulation-induced modulations of network dynamics in order to more rigorously test theories of shared neural resources between cognitive domains.

It is important to emphasize that the degree of causal inference from stimulation of a specific region or network to observed cognitive behavior within a task seems to depend on several potential confounds or sources of variance such as inaccurate targeting and subthreshold stimulation (Oliver et al., 2009), local and remote effects of stimulation (Bestmann & Feredoes, 2013; Sack, 2006), complex network dynamics (Bassett et al., 2006; Bullmore & Sporns, 2009; Roebroeck et al., 2011), null results (de Graaf & Sack, 2011), expectation effects (Davis et al., 2013; Duecker et al., 2013; Palm et al., 2013), and state dependency (Silvanto et al., 2017; Silvanto et al., 2008). The neurostimulation experiment in Chapter 4 was able to account for some of these issues via the following methods: a neuronavigation procedure for more accurate targeting; a fully crossed within-subjects design to reduce the confound of differences between individuals and to facilitate interpretation of null results; stimulation of two regions (instead of just one region) to test for potential nonspecific effects of neurostimulation (although a third, control region would have been even more ideal); and measurement of participants' expectations about potential brain or cognitive changes. Other issues such as network dynamics and local/remote effects would require combined neuroimaging and neuromodulation experiments, an area of active research (Bestmann & Feredoes, 2013; Siebner et al., 2009).

A potential solution to the complex causal inferences involved in cognitive neurostimulation could come from development of an inferential framework (cf., Poldrack, 2006; Price & Friston, 2005) for assessing potentially causal relations between the major cognitive, neural, and methodological components of any experiment. For example, see Figure 5.1 for a causal diagram of an idealized representation of a typical cognitive neurostimulation experiment. In this example, experimental methods (Methods), such as choice of stimulation and task paradigms, determine the parameters of the stimulation procedure (Stim) and the task (Task). The stimulation (Stim) presumably causes (i.e., single arrow) a neurobiological change in one or more targeted regions (ΔRegion_r) which may lead to mutually interactive (i.e., double arrow) changes between the region and one or more networks ($\Delta\text{Network}_n$) which may subsequently cause a change in one or more cognitive processes ($\Delta\text{Cognition}_c$). The specific task (Task_t) also presumably changes $\Delta\text{Cognition}_c$ via a neuromodulatory effect on $\Delta\text{Network}_n$. The task also determines the behavioral variables ($\Delta\text{Behavior}_v$) used to measure $\Delta\text{Cognition}_c$. Finally, the participant's potential expectations about stimulation-induced brain changes ($^{S}\Delta\text{Brain}$) may modulate the effects of Stim and Task_t on $\Delta\text{Network}_n$ thereby also modulating $\Delta\text{Cognition}_c$ as measured by $\Delta\text{Behavior}_{v.}$

With this experimental framework, any causal inference in any cognitive neurostimulation experiment – such as the probability of a change in a cognitive process resulting from a change in a network and the subject's expectation, i.e.,

$P(\Delta\text{Cognition}_c \mid \Delta\text{Network}_n , {}^{S}\Delta\text{Brain})$ – could in principle, given sufficient and appropriate data, be estimated using Bayesian probability theory (similar to Chapter 3) or more rigorous causal analysis (Pearl & Mackenzie, 2018). This procedure could significantly advance understanding of the causal efficacy of neurostimulation techniques like TMS as well as enhance knowledge of specific brain-behavior relations.

In conclusion, the combined works of this dissertation demonstrate the benefits of a multi-pronged research approach for exploring the multidimensional issue of neurocognitive relations between language and thought. The behavioral dual task experiment discovered novel evidence that both language and music can simultaneously interact with each other, although to various degrees, based on the complexity and critical junctions of syntactic structures, which is consistent with theoretical predictions of shared syntactic resources. The Bayesian meta-analysis, applied to neurostimulation literature for the first time, provided nuanced evidence, depending on prior beliefs, in support of theories of Broca’s area (based mostly on the pars opercularis) as a shared neural resource for hierarchical processing across cognition. A novel neurostimulation experiment on linguistic and algebraic hierarchical processing also provided tentative evidence, depending on methodological issues, for the pars opercularis subregion of Broca’s area, and possibly also the right inferior parietal sulcus (RIPS), as a shared neural resource between language and math.

Potential implications of such shared cognitive and neural resources between language and thought extend into many practical and theoretical avenues. For example, neurostimulation therapy for traumatic brain injury, stroke, or dementia patients could specifically target cross-domain network hubs to more efficiently enhance multiple cognitive networks and behavioral outcomes simultaneously. In education, focused training of hierarchical processing abilities in students may further increase their learning or proficiency in multiple domains such as reading and writing (e.g., by honing their syntactic parsing skills), mathematical or logical reasoning (e.g., by improving their manipulation of algebraic or deductive statements), complex problem solving (e.g., by improving strategic planning of possible outcomes), abstract thinking (e.g., by enhancing synthesis of interrelated concepts), and musical training (e.g., by increasing their ability to construct more complicated chord structures or action sequences). Above all, a better understanding of the causal dependencies between language and other cognition may advance philosophical and scientific investigations of how the thinking, talking mind emerges from the brain.

Figures

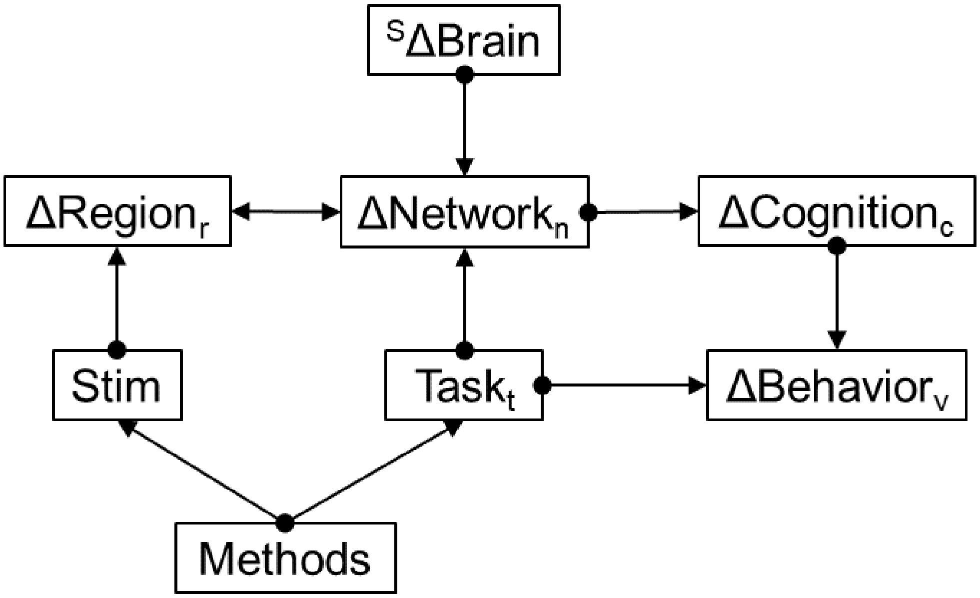

Figure 5.1. Causal diagram of an experimental ontology for cognitive neurostimulation.

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