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EFFECTIVE CONNECTIVITY DURING AFFECTIVE PROSODY PROCESSING IN CHILDREN

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ABSTRACT

Affective prosody is defined as the paralingustic cues in the voice that convey emotions (Banse & Scherer, 1996). Before they are able to accurately label prosodies, infants and young children perceive and discriminate among them. It is likely that physical properties of the emotional environment, including affective prosodies, influence children's developmental outcomes. Yet little is known about children's neural processing of affective prosody cues as the majority of the neuroimaging studies examining the neural correlates of affective prosody processing has been conducted with adults, with the exception of a small body of literature on infants. Seeking to address this gap, this dissertation investigated neural processing of affective prosody in 6-to-10-year old children. It was hypothesized that affective prosody would be associated with effective connectivity among neural regions identified by two prominent neuroscience models. Furthermore, it was hypothesized that affective prosody would modulate effective connectivity. To investigate these questions data from a study utilizing functional magnetic resonance imaging were examined using effective connectivity analyses and graph theory measures. Results partially supported the hypotheses. At the group level, effective connectivity was observed only among regions identified by one of the neuroscience models. However, analyses revealed heterogeneity in effective connectivity at the individual level indicating that all regions were implicated in and functionally connected when children processed different prosodies. Moreover, analyses of graph theory metrics indicated that there were no differences in effective connectivity at the global network level, however there were differences in properties of specific nodes when children processed angry prosody relative to neutral prosody. These findings and implications for future studies are discussed.

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INTRODUCTION

The human voice is a salient feature of the auditory environment (Belin, Fecteau, & Bédard, 2004). Among other things, voices convey information about the emotional state of a speaker through nonlinguistic characteristics of speech referred to as affective prosody (Banse & Scherer, 1996). Accurately perceiving and interpreting these affective cues in the voice are critical for successful social interactions (Adolphs, 2002).

Prior to understanding the semantic content of utterances, infants appear to perceive differences in affective prosody (Fernald, 1993; Walker-Andrews & Grolnick, 1983) and by 12 months of age they appear to use prosodic cues to guide their actions (Vaish & Striano, 2004). As they age, behavioral research indicates that children's abilities to accurately discriminate among basic affective prosodies improves, though the evidence is mixed regarding when and how these changes occur (Nelson & Russell, 2011; Sauter, Panattoni, & Happi, 2013). Despite this mixed evidence, results from behavioral studies indicate that early in life humans perceive and differentiate between prosodies and that differentiating between these vocal cues appears to be meaningful for children prior to their abilities to label them.

It is likely that physical properties of the emotional environment, including expression of affective prosody, contributes to children's development. Indeed, at the behavioral level, studies have shown that exposure to heightened anger is associated with children's behavioral adjustment (Cummings & Davies, 2002). And even before behavioral outcomes are observed, exposure to an atypical emotional environment appears to influence children's neural functioning (Graham, Fisher, & Pfeifer, 2013; Shackman, Shackman, & Pollak, 2007). For example, one study found that hearing very angry relative to neutral prosody was associated with greater activation in rostral anterior cingulate cortex (ACC), caudate nucleus, and hypothalamus in

sleeping infants but only in infants from homes with higher levels of maternal-rated interparental conflict (Graham et al., 2013).

Despite preliminary evidence suggesting that the early environment may influence patterns of neural activation in response to affective prosody in young children, little is known about children's neural processing of these cues as the majority of neuroimaging studies, with the exception of few infant studies, have been conducted with adults. As a result, there exists a notable gap in our understanding of neural processing of affective prosody between infancy and adulthood. Ultimately, documentation of neural processing of affective prosody will increase our understanding of how children's early affective environments shape and influence neural processing of these cues. Thus, studies investigating the neural networks that support processing of affective prosody are necessary. To that end, the present study investigated affective prosody processing in typically developing 6-to 10-year old children. Two prominent neuroscience models guided this study. The first model described affective prosody processing in speech as part of a larger language processing research program (Schirmer & Kotz, 2006) whereas the second model identified neural regions and networks that play a key role in the processing of social information (Adolphs, 1999). It was proposed that regions identified by both models would be active when children heard affective prosody as these models were conceptualized as complementary, rather than competing.

Finally, there is a growing emphasis in neuroscience away from 1:1 mapping of cortical regions to specific psychological functions and towards the investigation of patterns of connectivity among neural regions (Cicchetti & Dawson, 2002). Thus, the present study investigated effective connectivity, defined as the influence that one neural region exerts over another (Friston, 2011), when children heard various prosodies. Given mixed evidence regarding

whether or not specific affective prosodies differentially modulate neural activation and/or connectivity (Lindquist et al., 2010; Vytal & Hamann, 2010), this study assessed whether hearing angry, happy, and neutral prosodies was related to differential modulation in effective connectivity.

Affective prosody and the early emotional environment

What is affective prosody? Defined as the suprasegmental features of speech that convey emotional states (Banse & Scherer, 1996; Schirmer & Kotz, 2006; Scherer, 1989) affective prosody cues include the tempo, pitch, quality, and amplitude of the voice (Banse & Scherer, 1996). Emotional states influence phonatory and articulatory muscles in the throat and mouth resulting in distinct acoustic patterns (Scherer, 1989). For example, anger is related to increases in vocal pitch and intensity whereas sadness is related to decreases in pitch and intensity (Scherer, 1989). In addition to conveying information about felt emotional states, affective prosody cues can also provide information about emotional states that feigned (Banse & Scherer, 1996). Moreover, these cues can capture attention and communicate information about the emotional state of a speaker even when an individual is not visually attending to a speaker (Shackman & Pollak, 2005) or is the intended recipient of such speech (e.g. a child hears a parent speaking in an angry voice to a sibling).

Children's early exposure to voices and affective prosody. That affective prosody need not be directed at an individual is an important factor when considering a child's early emotional environment. Exposure to emotional expressions begins in the family (Dunsmore & Halberstadt, 1997: Montague & Walker-Andrews, 2002). Even before birth, a human fetus hears voices as the inner ear begins to transduce sound during the second trimester (for review see Saffran, Werker, & Werner, 2006). Studies of fetal heartbeat reactivity have shown that fetuses

recognize and prefer their mother's voice to an unfamiliar female's voice suggesting that they are familiar with this voice after recurrent exposures (DeCasper, Lecanuet, Busnel, Granier-Deferre, & Maugeais, 1994; Kisilevsky et al., 2003; Kisilevsky et al., 2009). After birth, behavioral studies show that neonates recognize and prefer the voices of their mother and father (DeCasper & Fifer, 1980; Ockleford, Vince, Layton, & Reader, 1988) as well as their own language relative to a nonnative language (Moon, Cooper & Fifer, 1993). These postnatal preferences are theorized to result from sensitivity to the prosodic characteristics of speech that they have heard repeatedly (Aguert, Laval, Lacroix, Gil, & Bigot, 2013).

Across childhood, the voice is an important communicative tool for parents (Vaish & Striano, 2001). In infancy, parents use affective prosody cues to direct an infant's attention and to communicate interest (Fernald, 1985; Fernald & Simon, 1984). Following infancy, the toddlerhood period is characterized by children asserting themselves in ways that at times conflict with parental rules or are unsafe for the child resulting in the need for parents to set limits and discipline their newly autonomous children (Brownell & Kopp, 2007). These instances may result in parent's use of prosodic cues (e.g. angry tone or raised voice) as a tool to admonish children with the hope that this prevents the behavior in the future.

Though research on how parents use affective prosody as an associative tool for children is limited, it is evident that early in life infants and children are exposed to significant amounts of prosodic information. However these studies also reveal that infants and toddlers begin to use these prosodic cues to guide their own behaviors, we now present these results and discuss factors that may influence children's abilities to correctly identify these cues.

Children's behavioral responses to and knowledge of affective prosody. By five months of age, infants appear to differentially respond to paralinguistic cues in mothers' infant-

directed speech, as evidenced by infants' displays of positive affect in response to approvals and more negative affect in response to prohibitions (Fernald, 1993). And by 12 months of age, infants appear to use nonverbal affective cues – facial and/or vocal – to guide their behavior (Feinman & Lewis, 1983; Walden & Ogan, 1988). For example, one study found that maternal fearful vocal expressions were more likely to inhibit 12-month-olds' exploration of an ambiguous toy than did mothers' happy vocal and facial expressions. Moreover, maternal vocal fear was conveyed in meaningless utterances indicating that prosody, even without semantic information, influenced the degree to which infants approached the toy (Mumme et al., 1996). Additionally, in a series of studies, Repacholi and colleagues demonstrated that 18-month-olds were more hesitant to touch an object when an experimenter expressed negative vocal and facial emotions and words, particularly when they knew the experimenter could see them (Repacholi & Meltzoff, 2007; Repacholi, Meltzoff, & Olsen, 2008). Taken together, these results indicate that before they are able to speak, infants and toddlers differentiate among affective prosody cues and use these cues to inform their behaviors.

While behavioral studies show that very young children perceive and use differences in prosody to guide and inhibit behaviors, children are not able to reliably label different affective prosodies. Instead, this skill continues to improve as children age (Aguert et al., 2013; Baltaxe, 1991; Morton & Trehub, 2001; Sauter et al., 2013) though the evidence remains mixed regarding when children accurately label prosodies and how task conditions and demands influence these skills. It has been suggested that age-related improvements in these skills reflect decreasing reliance on semantic cues (Aguert et al., 2013; Morton & Trehub, 2001) as by age 10 children can accurately judge a speaker's emotional state from paralinguistic cues even in the presence of incongruent emotional speech (Friend, 2000).

Addressing these findings, it has been proposed that semantic information may dominate children's judgements about emotional communication. Consequently, as children are acquiring receptive language, it may be more difficult to integrate conflicting pieces of information (Friend & Bryant, 2000). This difficulty is likely related to children's executive functioning, defined as the higher order cognitive abilities that assist in goal-directed behaviors such as selective attention and mental flexibility (Zelazo et al., 2003). This theory helps to explain why children show difficulties interpreting conflicting affective cues while, paradoxically, studies have demonstrated that preschoolers accurately discriminate among basic affective prosodies in less demanding tasks, such as when speech that has been low-pass filtered or is spoken in a foreign language, (Baltaxe, 1991; Morton, Trehub, & Zelazo, 2003) and in the context of semantically neutral speech (Morton & Trehub, 2001).

Affective prosody processing at the neural level. Overall, there is significant evidence from the behavioral literature to suggest that early in life, children perceive, differentiate among, and use basic affective prosody cues. Furthermore, this work reveals that over time what improves as a result of cognitive maturation are children's abilities to correctly interpret affective prosody cues when they are spoken with conflicting and/or ambiguous semantic content. It follows then that at the neural level, before children are able to articulate the label or meaning of affective prosody, these cues are differentiated. Thus, hearing different affective prosodies should be related to differences in neural activation or interregional connectivity in young children. And, in fact, there is evidence to support this hypothesis as neuroimaging studies have demonstrated that as early as 7-months of age, differences in patterns of neural activation are observable when infants hear different prosodies (Blasi et al., 2011; Grossman, Striano, & Friederici, 2005).

In addition to findings from neuroimaging studies suggesting that early in life affective prosodies are differentiated at the neural level, there is preliminary evidence that the early emotional environment may influence this processing. It is well-documented that early experiences influence human development across multiple levels of functioning (Fox & Rutter, 2010) through continuous interactions between genes and the environment as experiences facilitate, maintain, and/or induce changes in achieved anatomical, physiological and behavioral states (Gottlieb, 1992). Across different homes, children are exposed to variability in emotional expression as parents differ in their levels of warmth and hostility as well as in the level of conflict in the marital relationship (Cummings, Davies, & Simpson, 1994; Katz & Gottman, 2009; Morris et al., 2002; Reuben et al., 2015). At the behavioral level, exposure to marital conflict is associated with differences in behavioral responses to angry incidents in the home in children as young as 1 to 2-years of age (Cummings, Zahn-Waxler, Radke-Yarrow, 1981). And as already mentioned, a neuroimaging study with infants found that exposure to interparental fighting was associated with differences in infants' processing of very angry voices (Graham et al., 2013). Though replication of findings are necessary, this study suggested that the emotional environment was associated with differences in neural processing of angry prosody early in development.

In sum, there is evidence that exposure to atypical emotional environments influence children's development across multiple levels. Yet if and how exposure to atypical affective prosody (e.g. high levels of anger) is related to these differences has not been isolated within studies examining the influence of the early environment on children's development. Though not a study of the environments' influence on affective prosody processing, the present study sought to begin addressing this question by examining response patterns in a neural network that was

active when typically-developing children heard angry, happy, and neutral prosodies. This work was guided by two leading neuroscience models discussed below.

Cognitive and social neuroscience models of neural processing of affective information

The two leading models that have organized affective prosody processing research emerged from the fields of cognitive neuroscience and social neuroscience. As each model provided key insights into the neural regions and network that are active when humans perceive and process affective prosody they were conceptualized as complementary. The strengths and limitations of each model as well as their implications for our understanding of affective prosody processing are discussed below.

Cognitive neuroscience model. The cognitive neuroscience model was proposed by Schirmer and Kotz (2006) to integrate conflicting findings from neuroimaging studies of lateralization in vocal emotional processing. This model proposed that affective prosody processing occurs across three stages. First, a stimulus is perceived and acoustic cues are processed in bilateral auditory cortex. Second, acoustic cues that convey emotional information are processed along a pathway from bilateral superior temporal gyrus (STG) to superior temporal sulcus (STS). Third, higher-order cognitive processing of emotional information occurs in inferior frontal gyrus (IFG) and orbitofrontal cortex (OFC). It is in the final stage of the cognitive neuroscience model, in these higher order processing regions, that emotions in the voice and verbal information are integrated thereby enabling evaluative judgments about emotional information and congruous/incongruous information (Schirmer & Kotz, 2006).

Significant support for the cognitive neuroscience model exists in the neuroimaging literature. Cognitive neuroscience research using fMRI, which has mainly involved adult participants, has established that regions in the temporal cortex, including STG, STS, and the

medial temporal gyrus (MTG) are sensitive to the human voice (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Mitchell, Elliot, Barry, Cruttenden, & Woodruff, 2003; Wildgruber , Ethofer, Kreifelts, & Grandjean, 2008). Further, multiple studies have found affective prosody processing engages a fronto-temporal network that includes frontal regions such as IFG and OFC (Bach, Grandjean, Sander, Hardener, Strik, & Seifritz, 2008; Buchanan et al., 2000; Frühholz & Grandjean, 2012; Ethofer et al., 2006a; Leitman et al., 2010; Wildgruber et al., 2008).

There is also evidence that neural regions identified by the cognitive neuroscience model are active when infants hear affective prosodies. Infant studies have used various neuroimaging methods, including MRI, electroencephalography (EEG), and near infrared spectroscopy (NIRS), and have provided evidence for a specialization for voice processing in frontal and temporal regions similar to those seen in adults in infants as young as 7 month of age (Blasi et al., 2011; Grossman, Oberecker, Koch, & Friederici, 2010). Results from these studies also suggest that these regions differentiate among affective prosodies early in life (Blasi et al., 2011; Cheng, Lee, Chen, Wang, & Decety, 2012; Grossman et al., 2005). For example, using event related potentials (ERP), Grossman and colleagues (2005) found that 7-month-old infants showed positive slow waves over temporal electrodes for both happy and angry prosodies but not for neutral. And an MRI study found that sad vocalizations compared to neutral modulated activation in OFC and insula in 3- through 7-month-olds (Blasi et al., 2011).

In addition to those regions identified by the cognitive neuroscience model, adult neuroimaging studies have also shown that perceiving and processing affective prosody is associated with significant activation in subcortical regions including the basal ganglia (e.g. putamen, caudate nucleus, nucleus accumbens; Bach et al., 2008; Morris, Scott & Dolan, 1999), ACC, insula (Bach et al., 2008; Johnstone et al., 2006), cuneus and precuneus (Leitman et al.,

2010; Mitchell et al., 2003; Sander et al., 2005). Furthermore, these studies reveal the complexity of this processing as activation in response to affective prosody is modulated by task demands (Bach et al., 2008; Frühholz, Ceravolo, & Grandjean, 2011; Mitchell et al., 2003; Sander et al., 2005), stimuli salience (Leitman et al., 2010), emotional intensity (Ethofer et al., 2006a), and the number of stimulus presentations (Wiethoff, Wildgruber, Grodd, & Ethofer, 2009). Finally, variations in activation are not solely structure-specific. A meta-analysis revealed a widespread network of superior temporal cortex regions that were responsive to affective prosody but found that stimulus factors including attentional focus, valence, and paraverbal versus nonverbal expressions influenced functional connections among temporal and frontal regions (Frühholz & Grandjean, 2012).

In sum, there is ample support that perceiving and processing affective prosody is related to activation in temporal and frontal regions identified by the cognitive neuroscience model. However, evidence also suggests that there are additional regions in the underlying neural architecture that supports this processing. Furthermore, though the cognitive neuroscience model proposes that lower order regions encode information and project to higher order processing regions, there is no articulation of if and how various affective prosodies may modulate connection presence, strength, or direction. Based on these limitations, a social neuroscience model was also reviewed. It was proposed that this additional model would augment the understanding of affective prosody processing provided by the first model.

Social neuroscience model. The social neuroscience model was originally proposed as a discrete set of brain structures whose activity enabled humans to make inferences about the intensions, thoughts, and feelings of others (Adolphs, 2009; Brothers, 1990). Originally, this model included STG, OFC, the amygdala, the temporal poles, and the temporo-parietal junction

(TPJ) (Brothers, 1990). Since then, neuroimaging studies have identified additional neural regions that support social cognitive processes including ventromedial prefrontal cortex (vmPFC), paracingulate cortex, insula, and the fusiform face area (FFA). As a result, the social brain model now proposes that this widespread network of cortical and subcortical regions interact to enable a diverse set of social cognitive processes including characterizing, understanding, and flexibly responding to social cues (Adolphs, 1999; Blakemore, 2008; Kennedy & Adolphs, 2012; Lieberman, 2007).

Research stimulated by this model guided the present study in two ways. First, this model identified neural regions that likely support children's processing of affective prosody and that were not included in the cognitive neuroscience model. One area of research that contributed to the theory that specific neural regions are critical for social cognition has been the study of how brain lesions are related to deficits in social and emotional tasks (Adolphs, 1999). These studies have shown that lesions in the right insula, and right frontal and temporal pole cortices are associated with lower recognition scores on emotional prosody rating tasks (Adolphs, Damasio, & Tranel, 2002), that lesions in bilateral amygdalae are associated with impaired recognition of anger and fearful prosody (Scott et al., 1997), that lesions in the basal ganglia and insula are most frequently seen in aprosodic syndromes (Cancelliere & Kertesz, 1990), and that lesions in left basal ganglia are associated with impaired evaluation of emotional prosody (Paulmann, Pell, & Kotz, 2008). Finally, patients with ventromedial prefrontal cortex (vmPFC) damage show difficulties interpreting complex social information (Beer et al., 2003), reductions in empathy for others (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2005), and deficits in theory of mind tasks (Leopold et al., 2012; Shamay-Tsoory et al., 2005). This last finding is particularly relevant to the current study as theory of mind refers to the abilities that enable representations of one's

own and another's mental state and in predicting the emotions and behaviors of others (Adolphs, 2009; Frith & Frith, 2001). In sum, lesion studies have provided evidence that social brain regions including the insula, temporal poles, basal ganglia, and vmPFC are important for accurately interpreting emotional cues and states. Thus it is highly probable then that these regions are important for accurately interpreting affective prosody cues.

In addition to identifying neural regions that likely support affective prosody processing in children, a major contribution of research stimulated by the social neuroscience model, particularly for the present study, has been the focus on investigating how individual differences in neural connectivity are associated with deficits in social cognition. This work has primarily been conducted with individuals with Autism Spectrum Disorder (ASD), a neurodevelopmental disorder associated with deficits in social communication and cognition (Adolphs, 1999). It has been theorized that atypical neural connectivity is associated with social cognitive deficits observed in individuals with ASD. Interestingly, results from these studies have been mixed with evidence of both functional hyperconnectivity across multiple brain subsystems (Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013; Supekar et al., 2013) and selective decreases in connectivity among limbic-related brain regions (e.g. vmPFC, left amygdala, regions within temporal cortex (Gotts et al., 2012; DiMartino et al., 2009). Though more work is necessary to further clarify the ontogeny of these aberrant neural systems in individuals with ASD, this research program provides evidence that atypical interregional connectivity among social brain regions are associated with social cognitive deficits. Thus, it is likely that typical variability in connectivity among these regions supports processing of social and emotional cues; this fact, in conjunction with study findings discussed, highlights the importance of documenting both typical and atypical development of neural networks.

In sum, research stimulated by the social neuroscience model provided insight into cortical and subcortical neural regions that are likely involved in the processing of affective prosody. Moreover, research stimulated by this model, which has increasingly focused on documenting typical and atypical development of neural systems, has increased our understanding of how differences in functioning in these systems is related to social cognitive deficits. As a result of the contributions of the cognitive and social neuroscience models, these models were not conceptualized as competing, but, rather as complementary. To that end, the present study predicted that hearing angry, happy, and neutral prosodies would be related to activation within regions identified by both of these models. Additionally, it was also expected that hearing affective prosody would be associated with functional coupling among these regions. To test this theory, connectivity analyses were conducted as these methods allow for characterization of the functional relations between regions within a network. These methods, and the specific hypothesis about the affective prosody processing network, are now discussed.

Connectivity analyses for fMRI data

It is well documented that the brain is a dynamic system comprised of segregated cortical regions that are anatomically and functionally connected (Rubinov & Sporns, 2010; Smith, 2012; Van Den Heuvel & Pol, 2010). Advances in data analytic techniques for neuroimaging data within the past two decades have improved our abilities to study multiple levels of connectivity thereby permitting us to answer questions about the topology of brain networks (Minati, Varotto, D'Incerti, Panziva, & Chan, 2013; Sporns, 2011). Briefly, there exist three different types of connectivity (structural, functional, and effective) and though these terms have at times been used interchangeably in the neuroimaging literature, they provide unique information about neural architecture and function (Friston, 2011). Structural connectivity refers to the anatomical

connections (axons) between segregated brain regions (Rubinov & Sporns, 2010; Sporns, 2011) whereas functional connectivity refers to the temporal co-activation of cortically segregated regions (Friston, 1994; Friston, 2011; Poldrack et al., 2011). Based on Hebbian learning theory (Hebb, 1949), which has been simplified to the idiom "neurons that fire together, wire together" (Keysers & Perrett, 2004), functional connectivity methods infer dependencies based on correlations between changes in the blood oxygenation level-dependent (BOLD) signal in discrete neural regions obtained from fMRI data (Friston, 2011; Jolles, Van Buchem, Crone, & Rombouts, 2011).

Functional connections among neural regions give rise to and support complex thoughts and behaviors (Friston, 2011; Goldenberg & Galván, 2015; Stephan, Li, Iglesias, & Friston, 2015). These connections, though constrained by anatomical connectivity, are dynamic and variable (Sporns, 2012) and are "changing on time scales of milliseconds and in ways that reflect changing patterns of endogenous or stimulus-driven processing (Sporns, 2011, p. 2). Yet functional connectivity is limited in that it does not characterize the causal influence of activation in one region on another (Poldrack et al., 2011). To address this limitation, analytic methods were created to examine effective connectivity, which refers to the direct and indirect influences that one neural region exerts over another (Goldenberg & Galván, 2015; Rubinov & Sporns, 2010). Both dynamic and task-dependent, effective connectivity reveals the changing functional architecture among regions in a network as a result of experimental manipulations (Friston, 2011; Goldenberg & Galván, 2015).

Effective connectivity methods. Multiple data analytic approaches for studying effective connectivity exist. One of the most frequently used methods, dynamic causal modeling (DCM), was developed to be a biologically plausible model for fMRI data (Scherf, 2015). This method

compares numerous models within the same data using Bayesian model comparison (Friston, 2011). DCM is limited, however, as it is a confirmatory approach that restricts the number of nodes that can be included within a model (Smith, 2012) and that requires that connections within the network are specified *a priori* to model selection (Poldrack et al., 2011). Furthermore, DCM does not provide information about contemporaneous connections between regions as this method was designed to model lagged connections (Friston, Harrison, & Penny, 2003; Smith, 2012).

Other effective connectivity methods, such as path analyses approaches like structural equation modeling (SEM), address these limitations. SEM models contemporaneous relations among BOLD signals as well as the directional relations between regions; however, this method is not exhaustive and therefore does not search for all possible network connections (Gates, Molenaar, Hilary, & Slobounov, 2011). Furthermore, SEM assumes statistical independence of observations, an assumption that cannot be made with fMRI time-series data (Kim, Zhu, Chang, Bentler, & Ernst, 2007). To address the issue of dependence in time-series data unified SEM (uSEM) was developed. This method is a two-step algorithm that analyzes multivariate times-series data for individual subjects and models both contemporaneous and longitudinal relations among regions (Kim et al., 2007). Longitudinal relations were defined as connections that exist between brain regions at different time points (Kim et al., 2007). To further develop this method, the extended unified SEM method was proposed (euSEM; Gates et al., 2011). EuSEM added to uSEM's ability to model lagged and contemporaneous connections in fMRI data by estimating the effect of experimental manipulations on the BOLD signal and connectivity among regions (Gates et al., 2011).

Most recently, Gates and colleagues proposed the Group Iterative Multiple Model Estimation (GIMME) method. GIMME is a data driven analytic approach that estimates both uSEM and euSEM. This approach models lagged and contemporaneous directional connections without *a priori* specifications about these components at both the group and individual subject levels (Gates & Molenaar, 2012). This is accomplished across multiple steps. In the first step, the best fitting group model is identified. Beginning with a null model, an iterative procedure adds and removes parameters. Based on Lagrange modification indices, pathways are freed at the group level if they improve model fit for a specified number of subjects (Gates & Molenaar, 2012; Hilary, Medaglia, Gates, Molenaar, & Good, 2014). All potential pathways are examined and evaluated for whether or not they improve the model fit for the majority of subjects and pruned it they do not. Once the best fitting group model is identified, individual models are conducted for each subject. Beginning with the group model, pathways are freed and significant and nonsignificant pathways for that subject are opened or trimmed respectively (Gates & Molenaar, 2012).

Effective connectivity with children. The GIMME approach is particularly well-suited for neuroimaging studies with children as it examines connectivity at both the group and individual subject level. Across the lifespan, both gray and white matter densities in the brain undergo extensive and heterogeneous changes as a result of processes such as synapse formation, pruning, and myelination and neuronal migration (Belsky & de Haan, 2011; Collin & Van Den Heuvel, 2013; Giedd et al., 1999; Sowell et al., 2003). Across development interregional neural systems become increasingly complex as a result of interactions between biological and environmental factors (Goldenberg & Galván, 2015; Menon, 2013).

Changes in network complexity occur at the structural level, however both functional and effective connectivity also show age-related changes. In a seminal study of the development of neural networks, Supekar and colleagues (2009) showed that though the global functional architecture of children's brain and many of the gross measures of network topology were similar to those in adults by the time children were 7 years of age, children showed "significantly weaker connectivity between paralimbic, association, and limbic areas" compared to adults (Supekar et al., 2009, p. 9). A subsequent study found that three prominent independent functional networks were identifiable in children as young as two years of age but that children showed weaker functional connectivity among regions. Furthermore, across development into young adulthood there were considerable changes in connectivity strength and node distribution (for review see Menon, 2013). Similar to findings of functional connectivity, studies investigating effective connectivity have also shown differences in children and adults. For example, Hwang and colleagues (2010) found that effective connectivity strength was greater in adults relative to children in a network believed to underlie inhibitory control. Moreover, two separate studies found evidence suggesting a continuous neural tuning of effective connectivity in the core face processing network (He et al., 2015; Kadosh, Kadosh, Dick, & Johnson, 2016). These results reveal a developmental reconfiguration and refinement of neural networks which likely reflects the continuous interactions and contributions of both brain maturation and experiences (Cicchetti & Dawson, 2002; Gottlieb & Halpern, 2002).

In sum, there is evidence to suggest that there may exist differences in the functional properties of the network that supports affective prosody processing not only across development but within a sample of children of different ages. Indeed, one of the studies described above found significant variability in 3- to 6-year olds effective connectivity in the face processing

network resulting in the best fitting model only characterizing 47% of their sample (He et al., 2015). Unfortunately the extant neuroimaging literature on affective prosody processing has been conducted primarily with adults. Though the present study did not evaluate developmental changes in connectivity as data were only collected from children, this study took two important steps in furthering our understanding of normative variability in connectivity during affective prosody processing in children. First, informed by previous findings of heterogeneity in connectivity across children, this study utilized a method that is sensitive to individual differences. By modeling effective connectivity at the group and individual subject levels, the GIMME method permitted the documentation of normative variability in connectivity in the neural network examined. Secondly, the present study investigated connectivity in a sample of typically developing children. Neuroimaging studies with typically children have the potential to provide a fuller understanding of the full range of typical variability in neural processing and connectivity (Cuthbert & Insel, 2012). Ultimately fuller documentation of this variability and the development of the functional architecture of the brain can improve our understanding of when and how pathological processes develop (Cuthbert & Insel, 2012).

Neural differentiation among affective prosodies

Finally, there exists an ongoing debate in the emotion processing and neuroimaging literatures as to whether or not different emotions have discrete physiological and neural correlates (Vytal & Hamann, 2010). On one side of this argument, it has been proposed that basic emotions are produced by activity within specific neural regions (Ekman, 1999) or similar underlying neural networks (Izard, 2009). In contrast, the psychological constructionist approach argues that different emotional states, cognition, and perceptions are “not respected by the brain” but, rather, that they emerge from the meaning that individuals make out of sensory

information based on their environment and previous experiences (Lindquist et al., 2010). The evidence is contradictory as to whether or not different emotions are processed in discrete neural locations. For example, one meta-analysis found that experiencing and processing different emotions (fear, anger, sadness, disgust, and happiness) was correlated with significant activation in specific neural regions (Vytal & Hamann, 2010). The authors argued that these findings supported Ekman's discrete emotion theory. However, these findings may have been impacted by the inclusion of studies with a wide range of emotional tasks and experimental paradigms (e.g. viewing facial expressions & emotional pictures, hearing emotional voices; Vytal & Hamann, 2010). In contrast, another meta-analysis found no evidence for the discrete emotion theory, rather findings suggested that there existed a set of neural regions that were important for and interacted with one another to engender emotions, cognitions, and perception (Lindquist et al., 2010).

Evidence from the affective prosody processing literature is also complex as studies have found evidence that various affective prosodies are related to increases in activation in specific neural regions and differences in network connectivity patterns. For example, greater activation in middle STS (Grandjean et al., 2005) and bilateral STG, insula, OFC, IFG, and the amygdala has been observed for angry relative to neutral prosody (Ethofer et al., 2009). However, activation in OFC was more pronounced during the first exposure indicating that this region may actually be modulated by *novel* emotional stimuli (Ethofer et al., 2009). Yet another study found increased activation in the OFC when subjects were attending to angry prosody explicitly; increased activation in the right amygdala and bilateral mSTC were seen for angry>neutral irrespective of attention (Sander et al., 2005). With respect to happy prosody, greater activation has been observed in right mid STG for happy>neutral and in aMTG, pMTG, and rIFG for

happy>angry prosody (Johnstone et al., 2006). Similarly, a study using event related potential (ERP) found that the N3 amplitude was greater in frontal electrode sites in adults for happy compared to angry suggesting greater effortful processing of happy prosody (Iredale, Rushby, McDonald, Dimovska-DiMarco, & Swift, 2013).

At the network level, studies of effective connectivity during affective prosody processing in adults exist. Using DCM, the first study showed that the best-fitting model of the network that supported judging affective prosody was one in which right posterior temporal cortex served as the input region and projected activation to bilateral inferior frontal cortex (Ethofer et al., 2006b). A follow up study revealed that activity in the mid STG was modulated by hearing affective prosody and that an emotional voice area could be identified within this region (Ethofer et al., 2011). Using the PPI approach, this study found that hearing affective prosody enhanced the connections of this emotional voice area with a network of regions including bilateral posterior thalamus, left middle frontal gyrus, right putamen, and right cerebellum suggesting that relative to neutral voices (Ethofer et al., 2011).

Taken together, there is evidence that hearing emotional voices may enhance functional coupling between a widely distributed network of neural regions. Building on this work, the present study investigated effective connectivity during affective prosody processing in a network of regions identified by the two neuroscience models explicated above. This work was largely exploratory due to the limited number of studies that have examined connectivity in the affective prosody processing literature, however, based on findings from the study conducted by Ethofer and colleagues (2011) and the behavioral literature reviewed suggesting that children differentiate among affective prosodies, it was hypothesized that the three prosodies that children heard (happy, angry, and neutral) would differentially modulate effective connectivity.

The present study. The present sought to address a gap in the neuroimaging literature as, to date, there exist no studies of children's affective prosody processing. This dissertation had two specific aims. Using the Group Iterative Multiple Model Estimation (GIMME) approach, the first aim was to investigate effective connectivity within a network of cortical and subcortical neural regions when typically developing 6-to-10 year old children heard happy, angry, and neutral prosodies. It was hypothesized that this network would include neural regions identified by a cognitive neuroscience model and a social neuroscience model as it was proposed that these are complementary rather than competing models. The GIMME analytic method for modeling effective connectivity was utilized in the present study as this method permits examination of effective connectivity at both the group and individual subject level and may thus be sensitive to individual differences in connectivity across children.

The second aim of this dissertation was to examine whether different affective prosodies (e.g. angry, happy, neutral) significantly modulated effective connectivity within this identified network. Differences in effective connectivity were quantified both by testing for significant differences in the strength of connections between neural regions and in differences in global and nodal network properties across affective prosody conditions. There is conflicting evidence from the neuroscience literature regarding whether or not processing different affective prosodies should result in differences in neural activation or connectivity. However, evidence from behavioral studies reveals that as early as infancy, children are differentiating among and using affective cues to inform their behaviors. There is therefore a basis to hypothesize that at the neural level hearing different affective prosodies may modulate effective connectivity. Thus this study was built on solid theoretical foundation and was exploratory in nature.

METHOD

Participants

Data for this dissertation were taken from the Processing Emotions in the Environment Project (PEEP). Families with a child between the ages of 6y, 0m to 10y, 11m were identified through a community database maintained by The Pennsylvania State University Child Study Center. Additional criteria for inclusion (not recruiting) were that the children spoke and understood English, and had no condition that would preclude them participating in a scanning visit. Exclusionary criteria included the presence of medical devices that would make scanning unsafe and/or that the child did not understand English. As a result of this recruitment strategy, 40 families initially enrolled in the study. Of these, imaging data were collected from 32 children as three children declined to participate, three stopped participating during scanning, and two were excluded due to screening procedures.

Of the 32 children who participated in scanning, data from five children could not be used due to experimenter error. As a result, 27 children provided neuroimaging data. There were no significant differences in age, $t(38) = -.107$, $p = .92$, or gender $t(38) = 1.47$, $p = .15$, between children who provided imaging data and those who did not.

The average age of the 27 children (15 female) who completed a scanning visit was 95.00m (*SD* = 15.57, range = 72 – 123m). Children were identified by their mothers as Caucasian (n=23, 85.20%) or biracial (n=4, 14.80%). Average family income was $83,407.41 (*SD* = $39,252.89, range = $8,000 - $160,000).

Due to motion greater than 3mm during scanning, data from 12 of the 27 children from whom imaging data were collected had to be removed. As a result, data analyses were conducted on fMRI data from 15 children. The average age of the 15 children who provided usable data

was 95.20m (*SD* = 14.99, range = 73-123m). There were no significant age, $t(25) = .073$, $p = .94$, gender, $t(25) = 1.29$, $p = .21$, or family income differences, $t(25) = 1.59$, $p = .12$, between children included in analyses and those removed due to motion.

Procedures

This study was approved by the Penn State Institutional Review Board (IRB#34090). Families completed three visits. The first and last visits occurred at the family's home. The scanning visit took place at the Penn State Social Life and Engineering Sciences Center (SLEIC).

Visit 1. After written consent and assent were obtained, children participated in an orientation designed to familiarize them with MRI scanning procedures. Children then completed a standardized assessment of receptive and expressive language. Mothers completed questionnaires about their child's temperament.

Over the course of data collection, a training protocol was developed to improve the rate of MRI data acquisition. The new protocol was conducted during the first visit. Children practiced lying still in a play tunnel that approximated the size of the MRI bore as they listened to MRI scanning sounds. Children completed progressively longer timed-trials. Staff provided verbal feedback and positive reinforcement during trials.

Visit 2. At SLEIC, all children participated in a mock scanner session prior to scanning. This session was altered during the study to include the presentation of scanner sounds and timed-trials similar to those that children completed during the home visit. Children were then accompanied into the MRI room by a familiar staff member and the MRI technician.

Prior to scanning children were informed that they would hear someone speaking while in the scanner. On in the scanner, staff checked in with children throughout the scanning session. Functional data were collected during a passive listening task.

Visit 3. As parents completed additional questionnaires, children rated the affective intensity of the stimuli. Initially, children were asked open-ended questions about each script (e.g. “How do you think this person is feeling?”), however, this generated a wide range of responses. This task was therefore altered to constrain children’s answers. Children were provided with two sets of emotional faces that ranged from neutral to very angry (1-4) and neutral to very happy (1-4). They were asked to rate the degree to which each script was both angry and happy.

Scripts were recorded by a professional sound engineer at The Pennsylvania State University Public Broadcasting radio station (WPSU). Visual inspection of spectrographic data indicated that scripts spoken in one prosody had similar acoustic profiles and that scripts spoken in different prosodies had different acoustic profiles. To control for differences in loudness across prosodies scripts were Root Mean Square (RMS) normalized using Sound Forge 10. Silence was interspersed between each 2s utterance so that each script was 15s in duration.

Functional affective prosody listening task. A block design was used in this study. Eight distinct run orders were generated. Each run contained 12 blocks (4 scripts spoken in 3 prosodies) with one additional neural script added at the end of the run end to ensure that a run did not conclude with an angry voice. Blocks were pseudorandomized and separated by 15s of silence. As a result, each run lasted 6 minutes and 54s. Two functional runs were collected from each child.

MRI data acquisition. Neuroimaging data were collected using a Siemens 3T Magnetom Trio using a 12 channel head coil. Total scan time was 24 min, 43 sec. An anatomical MPRAGE was first acquired followed by two functional scans and a resting state scan. Subjects 001-003 completed one functional run; following these visits all subjects completed two

functional runs. Anatomical images were acquired using a 3D-MPRAGE pulse sequence with 160 slices collected (TR/TE/TI= 1640, 2.01, 820 ms; voxel size = 1mm^3, FOV = 256). EPI were acquired aligned with AC-PC in descending order (TR/TE = 3000, 20ms, FOV = 200, flip angel = 80, voxel size = 2.5 mm^3).

Raw fMRI data were preprocessed using BrainVoyager QX v2.3 (Brain Innovation, Masstricht, The Netherlands). Anatomical MPRAGE images were normalized and transformed using AC-PC alignment. PreporFunctional images were 3-D motion corrected, spatially smoothed (5mm) and temporal filtering of low-frequencies (GLM Fourier basis 5 cycle). Resulting translational motion parameters were examined and subjects with movement greater than 2.9mm in any of the six axes were excluded from subsequent analyses.

Measures

The following assessment measure was not included in analyses of fMRI data. These measures were used to characterize the study sample and determine study eligibility.

Language assessment. During the first home visit children completed four subtests of the Clinical Evaluation of Language Fundamentals, 4th edition (CELF-4; Semel et al., 2003). The CELF-4 is a well validated measure of children's language abilities and test-retest reliability measures ranging from .88 to .92 for composite scores based on a standardization population (Semel et al., 2003). Standard procedures were followed to generate a Core Language Score (CLS) for each child. CLS standard scores are based on norms for children of similar age, with a mean of 100 and a standard deviation of 15. Scores ranging from 86-114 are in the Average range, and scores ranged from 116-130 are in the Above Average range. Based on their performance on selected subtests of the CELF, two children were not included in subsequent analyses. In both of these instances parents were provided feedback about their children's

performance. As a group children's performances were characterized as Average (n = 15; M = 111.73, SD = 8.98). Similarly, for the 10 children included in the final analyses below, the mean CLS score fell within the Average range (M = 113.5, SD = 7.53).

Data Analysis

fMRI Data. Raw fMRI data were preprocessed using BrainVoyager QX v2.3 (Brain Innovation, Maastricht, The Netherlands). Functional images were 3-D motion corrected, spatially smoothed (5mm FWMHW) and temporally filtered for low-frequencies up to 5 cycles. Participants with motion greater than 2.9mm in any of the six directions for any TR were excluded from subsequent analyses. Data from functional runs of two participants were recovered by removing TRs in which high motion occurred and then re-preprocessed.

Data from at least one functional run were available for 15 children as three children provided only Run1 data and two children provided only Run2 data. Of these 15 children, data from both functional runs were available for 10 children. For each participant and run, the time series images for each brain volume were analyzed for emotion differences in a fixed-factor GLM. Each emotion was defined as a separate predictor and modeled with a box-car function adjusted for the delay in hemodynamic response. Time series images were spatially normalized into Talairach space, which is common practice in pediatric neuroimaging research.

Creating Regions of Interest. To determine the set of regions that were active when while children processed emotional voices, we computed a whole-brain voxel-wise mixed-model ANOVA including emotion as a fixed factor and subject as a random factor using only the images from run 1 (n=13). The network of regions was defined by the balanced contrast [(Happy + Angry + Neutral) - 3*Silence]. The group level map was corrected at the whole brain level for false positive activations using the False Discovery Rate procedure with a $q < .10$ (Genovese,

Lazar, & Nichols, 2002). Table 1 shows the size and Talairach coordinates for each of the group-defined ROIs.

Group level region of interest (ROI) analyses. Individual participant regions of interest were defined in a two-step process. First, broad regions of interest were extracted from the significant activation within the group level map based on brain structure and functional anatomy reported in the adult literature (Buchanan et al., Talairach, 1988). Second, to optimize the signal within each of these regions for each individual participant in each run, the peak positive voxel within this region (separately for each run) was identified. If the peak positive value was a negative *t* value, as was the case for 54 ROIs across subjects, across runs, the values for each voxel from the original ROI were extracted and sorted using Excel. Using the corrected peak values, individual ROIs were defined as a 6mm sphere of activation centered on these peak voxels.

Correcting ROIs. Each individually-defined 6mm ROIs was visually examined to assess 1) if there existed overlapping voxels among different ROIs and 2) if voxels had been placed on skull. Overlapping ROIs are problematic as they result in the same voxels being included for different ROIs thereby including the same information in two ROIs time-series data. This issue results in poor model estimation (Smith et al., 2011). Twenty-two overlapping regions were identified ranging in size from 1 to 609 voxels. Of note, a 6mm ROI has 925 voxels. Based on these findings, individual ROIs were re-defined as a 4mm sphere around the peak positive voxel.

After the 4mm sphere ROIs were created, ROIs were again assessed for overlapping voxels. For those overlapping regions found, multiple steps were taken to correct this issue. First, a new ROI that included the overlapping region was created and both the centroid of the overlapping region and the number of overlapping voxels were documented (see Table 2). The

sizes of the overlapping regions ranged from 2 to 125 voxels. A decision regarding which ROI the overlapping voxels would be given to was made based on brain structure and ROI coordinates reported in fMRI studies of affective prosody processing in adults. Using Matlab, overlapping voxels were identified and then removed from the original volume-of-interest (VOI) files. Time-series data were then extracted from each corrected ROI, for each run, for each subject.

ROIs were also examined to determine if any voxels were on the subjects' skull. To correct this issue, the peak voxel text file for that ROI was extracted. Voxels were sorted by their *t* values to identify the highest positive *t* value. The voxel coordinates that corresponded with the highest *t* value that would move the entire sphere to an acceptable placement on the brain was identified (see Table 3). As a final step, all ROIs were redefined by placing 4mm spheres around the corrected peak values. Time-series data were extracted from each ROI, for each run, for each subject.

Effective connectivity analyses. Using the extracted time-series data, task-related regressors were calculated for each condition (happy, angry, and neutral). This strategy is informed by the PPI approach. To calculate the regressor, the raw time course vectors for each condition were obtained. Raw time course vectors for all regions, for all subjects, across each condition were then mean-centered using custom MATLAB scripts. The centered time-series data were deconvolved using a double gamma function to estimate the hemodynamic response function (HRF) in AFNI (Gold et al., 1998). The deconvolved time-series data were then multiplied by a condition vector coded for the condition of interest (e.g. happy = 1, all other = 0). The resulting time course vector therefore only included time-series data for the specific

condition of interest. Finally, the condition-specific time-series data were reconvolved with the HRF.

The final reconvolved time-series data for each affective prosody (Angry, Happy, and Neutral) were then separately submitted to the GIMME program. As discussed earlier, GIMME first conducts an iterative procedure that identifies common pathways at the group level (Gates & Molenaar, 2012). Based on modification indices, if a pathway significantly improves the model fit for a specified number of subjects this pathway is freed for all subjects. Originally, the modification index was set to 75%. However, when these analyses were conducted, GIMME was unable to identify common group level paths and had difficulties converging on a common group map for any of the prosody conditions. Based on recommendations made by Smith and colleagues (2011) the modification index was then reduced to 51%. As a result, if a pathway significantly improved the model fit for six subjects this pathway was freed for all subjects. This change was sensitive to the fact that when data from Run1 and Run2 were combined, each prosody condition had approximately 2 minutes of time-series data.

Once the common group model was identified GIMME continued in a semi-confirmatory manner by beginning a search for individual subject level maps. Beginning with the group map, GIMME iteratively evaluated if opening additional pathways improved model fit for the individual subject (Gates & Molenaar, 2012). Five indices for the individual subject level models were produced. These included root mean square error of approximation [RMSEA], non-normed fit index [NNFI], comparative fit index [CFI], and standardized root mean-square residual [SRMR]; Gates & Molenaar, 2012). Fit indices and acceptable fit can be found in Brown (2006). The fifth index produced by GIMME is the result of a chi-square test, however a nonsignificant chi-square does not reveal if a model is the best or true fit (Poldrack et a., 2011) and this statistic

has extreme limitations, the first of which is that it is extremely sensitive to sample size (Hooper, Coughlan, & Mullen, 2008). Following the direction of Gates and Molenaar (2012), model fit was evaluated based on whether or not the criteria for two of the four (RMSEA, NNFI, CFI, & SRMR) fit indices were met. When a models failed to meet two of these four indices it indicated that there were no additional pathways that when freed would improve model fit for that specific subject (Gates & Molenaar, 2012).

Testing differences in effective connectivity. Models of effective connectivity are expressed as path diagrams in which brain regions (nodes) are linked by connections (edges; Poldrack et al., 2011). Differences in connectivity strength were first tested on identical pathways identified in the group-level maps across the prosody conditions used paired-samples *t*-tests and repeated-measures one-way analyses of variance (ANOVA). Graph theory metrics were then estimated to derive multiple measures of network organization at the global and node levels (Sporns, Chialvo, Kaiser, & Hilgetag, 2004). These measures characterize functional segregation, defined as the ability of densely interconnected nodes to engage in specialized processing and functional integration defined as the combination of specialized information across these interconnected regions (Rubinov & Sporns, 2010). The present study investigated five measures of global network organization. These included: 1) global efficiency, which estimates distances between remote nodes in a network as the inverse of the shortest path length, 2) network density, which conveys the number of edges in the graph that is proportional to the possible number of edges, 3) the clustering coefficient, which represents the number of possible connections between closely spaced nodes as a proportion of the possible number of connections, 4) the shortest path length, which is a commonly used measure of the average length between all pairs of nodes in a network and 5) centrality, which refers to the overall cohesion of connections

and communication with a network as it measures distances among various nodes in a graph (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010).

We investigated four indices of node connectivity. These included: 1) the clustering coefficient, 2) the total strength of the node, which quantified the number of pathways in and out of that node, 3) modularity, which represents the number of clearly delineated and non-overlapping groups of nodes and 4) the centrality of a node, which conveys how many of the shortest pathways between all nodes pass through pairs of this node (Rubinov & Sporns, 2010).

Graph theory metrics were conducted in MATLAB. To test if there were significant differences in these global network or node metrics, we conducted repeated-measures one way analysis of variance (ANOVA) with a Bonferroni correction.

RESULTS

Behavioral ratings of speech stimuli

In the final home visit, children rated the happy scripts as significantly more happy than angry, $t(14) = 8.00$, $p < .001$ and the angry stimuli as significantly more angry than happy, $t(14) = 8.83$, $p < .001$. As the children engaged in passive listening during the scanning, these findings support the view that the children were capable of perceiving differences in affective prosody during scanning.

Group and individual level ROI analyses

Whole brain voxel-wise analyses on Run1 revealed that children exhibited significant activation in response to human speech [(Happy + Angry + Neutral) - 3*Silence] in regions identified by both the cognitive and social cognitive neuroscience models. These regions included bilateral posterior and anterior auditory cortex, bilateral STG, bilateral caudate, bilateral IFG, bilateral OFC, left vmPFC, and left insula (see Figure 1).

Effective connectivity analyses

Connectivity analyses with run1 data. Initially, only the reconvolved time series data extracted from the 14 corrected, individually-defined ROIs from Run1 were submitted to the GIMME program (n=13). The decision to exclude subjects with only Run2 data (n=2) reflected findings that multiple ROIs showed significant adaptation in the BOLD signal across Run1 and Run2 for different prosodies and variability in adaptation across ROIs across prosodies may have included findings. Additionally, the fifth neutral block of time series data for the Neutral condition was removed so that the amount of time series data was constant across conditions.

When time-series data from the 14 ROIs were submitted to GIMME, the program was unable to identify any common group level pathways for any of the prosody conditions and multiple subjects across each condition failed to meet fit indices criteria. Thus a decision was made to reduce the number of ROIs based on findings from adaptation analyses. As adaptation in neural activation indicates that a region is "tuned to the processing of a specific stimulus attribute" (Bestelmeyer, Maurage, Rouger, Latinus, & Belin, 2014, p. 8098) only regions that were sensitive to affective prosody (i.e. that showed significant adaptation) were included in the connectivity analyses. To investigate adaptation in the BOLD response, the averaged beta weights for each ROI, for each prosody, were submitted to Wilcoxon signed-ranked tests.

Results from the adaptation analyses indicated that there were different but overlapping regions for which the signal was modulated by Happy and Angry prosodies. Angry prosody modulated activity in right anterior auditory cortex, $Z = -2.19$, $p = .028$, right posterior auditory cortex, $Z = -2.50$, $p = .013$, left STG, $Z = -2.40$, $p = .017$, right caudate, $Z = -2.09$, $p = .037$, left OFC, $Z = -2.80$, $p = .005$, right OFC = $Z = -2.80$, $p = .005$, whereas Happy prosody modulated activation in right anterior auditory cortex, $Z = -1.99$, $p = .047$, right OFC, $Z = -2.40$, $p = .017$,

left IFG, $Z = -2.50$, $p = .013$, right IFG, $Z = -1.99$, $p = .047$, left insula, $Z = -2.40$, $p = .007$, and left vmPFC, $Z = -2.19$, $p = .028$.

To reduce the number of ROIs in the connectivity analyses, right STG and left posterior auditory cortex were initially removed as these regions did not show significant adaptation to either Happy or Angry prosodies. Unfortunately, trimming the number of ROIs did not enhance the GIMME program's ability to detect common group pathways for the Angry and Happy conditions, and the model failed to converge at the group level for the Neutral condition. Thus data from two additional ROIs, left anterior auditory cortex and left caudate, were removed as both of these regions only showed marginally significant adaptation to Angry prosody ($p < .08$) but did not show adaptation to Happy or Neutral prosodies.

Data from the 10 remaining ROIs were submitted to GIMME program, however, no common group pathways were identified and individual subject maps failed to meet fit criteria. Finally, the modification index was reduced from 75% to 51% based on suggestions made by Smith and colleagues (2011) when conducting connectivity analyses with smaller amounts of time-series data. Once again, the model failed to converge at the group level across prosody conditions.

Connectivity analyses with run1 & run2 data. To avoid trimming the number of ROIs further, time-series data from Run2 was included in these analyses. Including Run2 increased subjects' data from four blocks to eight for each prosody condition thereby increasing GIMME's ability to detect effects. The fifth Neutral condition block was excluded again to ensure that the three conditions had an equivalent number of time-series data blocks. Only subjects for whom both Run1 and Run2 data were available were included in these analyses thus decreasing the number of subjects from 13 to 10.

The same steps described above were taken to investigate effective connectivity in the combined Run1 and Run2 time-series data. Time-series data from 14 ROIs and then 12 ROIs were submitted to the GIMME program for each prosody condition. Across prosody conditions these maps failed to converge for multiple subjects. When the time-series data from 10 ROIs (right anterior and right posterior auditory cortex, left STG, bilateral OFC, bilateral IFG, right caudate, left insula, & left vmPFC) were submitted to the GIMME program, multiple common pathways were identified at the group level across the three prosody conditions. The effective connectivity group maps for the Angry, Happy, and Neutral conditions are presented in Figure 2.

At the group level, hearing different affective prosodies was associated with effective connectivity between regions identified by the cognitive neuroscience model including auditory cortex, left STG, OFC, and IFG. All conditions (Angry, Happy, & Neutral) include pathways in which right anterior auditory cortex exerted an effect on left STG and in which right OFC exerted an effect on left OFC. Furthermore, when children heard Happy and Angry prosody, right IFG exerted an effect on right OFC, however, the direction of influence was reversed when children heard neutral prosody. Similarly, left OFC exerted an effect on left IFG when children heard Happy and Angry prosodies, yet the opposite effect was observed when children heard Neutral prosodies. Interestingly, there were no common lagged connections at the group level. Moreover, the cognitive neuroscience model predicts that information is directed from STG to frontal regions for higher order processing. However, in the present study only when children heard Happy prosody was the STG functionally connected to left IFG and the direction of this connection was opposite of what the model would predict.

At the individual subject level, criteria for at least two of the four fit indices were met for each subject, across each prosody condition. Individual subject maps for the Angry, Happy, and

Neutral conditions are presented in Figures 3, 4, and 5 respectively. Visual inspection of these models shows heterogeneity in effective connectivity across the prosody conditions as well as across subjects within the same condition. To illustrate the within condition heterogeneity Figure 6 shows the Angry, Happy, and Neutral maps from three randomly selected subjects.

In sum, individual subject-level connective maps indicate that hearing different prosodies was associated with contemporaneous and lagged connections among cortical and subcortical regions identified by both the cognitive and social neuroscience models. However, due to the heterogeneity in the presence and direction of connections across subjects, pathways were not identified at the group level as the requisite number of children (6 in the case of the 51% modification index) did not have the same pathways.

Testing differences in effective connectivity across prosody conditions. To test for differences in the strength of the common pathways in the group maps across the three prosody conditions, the beta weights and standard errors from the individual subject maps were submitted to repeated measures t-tests and one way analyses of variance (ANOVA) were conducted. These tests revealed no significant differences in path strength across any of the prosody conditions.

To investigate if there were significant differences in network topology across affective prosody conditions, graph theory metrics were calculated using MATLAB (2012). These global network level statistics were then submitted to repeated-measures ANOVA. Mauchly's test indicated that the assumption of sphericity was not violated in any tests conducted. Tests revealed no statistically significant differences in global efficiency, density, centrality, modularity, or clustering across the group maps for the Angry, Happy, and Neutral conditions.

Tests were then conducted for individual nodes (ROIs). A significant effect of prosody was observed for right OFC centrality, $F(2,18) = 5.019$, $p=.019$. Post hoc tests using the

Bonferroni correction revealed that right OFC was more centralized in the Angry condition (M=15.48, SD=3.30) compared to the Neutral (M=4.72, SD =2.10) condition. Similarly, results were obtained for right posterior auditory cortex, F(2,18) = 4.278, p = .03. Post hoc tests using the Bonferroni correction revealed that this region was more central in the Angry (M=11.54, SD=3.56) relative to the Neutral (M=2.65, SD =1.98) condition. These results indicate that more short pathways passed through these regions in the Angry condition compared to the Neutral condition. Similarly, right OFC had a significantly higher clustering coefficient, F(2,18) = 6.09, p = .01) in the Angry condition (M=.18, SD = .05) compared to the Neutral condition (M = .049, SD = .02), indicating that there were more connections between right OFC and its neighboring nodes in the Angry condition. Only one region, the right posterior auditory cortex, showed a statistically significant effect of prosody on diversity, F(2,18) = 3.76, p < .043. However, post hoc tests using the Bonferroni correction failed to reach statistical significance for each of the three contrasts. Finally, the total strength of each of the nodes was tested. A significant effect of prosody was found for left STG, F(2,18) = 7.10, p = .005. Post hoc analyses revealed that this region had significantly fewer connections directed in and out in the Angry Condition (M = 2.40, SD = .34) than in both the Happy (M = 3.80, SD = .33) and Neutral (M = 3.60, SD = .40) conditions. In contrast, and similar to results for clustering and centrality, right posterior auditory cortex had significantly higher total strength, F(2,18) = 4.64, p = .02 in the Angry (M = 4.20, SD = .47) relative to the Neutral (M = 2.80, SD = .29) condition.

Effective connectivity in a combined affect condition. To increase GIMME's power to detect effects within the data, time series data from the Happy and Angry conditions were combined into a Combined Affect condition (CAC). Thus the number of blocks of data increased from 8 to 16 (8 Happy & 8 Angry). Of note, due to motion in Run2, one subject only had nine

blocks of time series data for the Neutral condition as the final block was clipped from the analyses to remove TRs that included motion>3mm. The data was clipped prior to preprocessing and the additional TRs were removed during the convolution and reconvolution steps so that additional 0s were not included in the time-series data in this step.

The previously described model with 10 ROIs was submitted to GIMME with the modification index set at 51%. GIMME identified 12 common pathways in the group map (see Figure 7). Effective connectivity was observed between cortical and subcortical regions identified by both neuroscience models and each ROI had at least one pathway directed in or out of the region. Furthermore, as predicted by the cognitive neuroscience model, connectivity was observed within the auditory correct and left STG exerted an effect on right OFC. Interestingly, left IFG exerted an effect on left STG. All connections were contemporaneous.

As previously found in the separate prosody conditions, subject level maps showed heterogeneity in the direction and number of pathways in regions identified by both models. Figure 8 shows the individual subject effective connectivity maps for the Combined Affect condition.

Finally, when time-series data from the Neutral condition were submitted to the GIMME program eight common pathways at the group level were identified. These pathways were the same as identified in earlier analyses of effective connectivity with fewer Neutral time-series blocks. However, with the addition of the two additional blocks of data, GIMME identified a pathway in which left STG influenced right OFC and a pathway from right posterior auditory cortex to left vmPFC. Interestingly, the direction of influence of left OFC and left IFC was reversed in these analyses. Results at the individual subject level were similar to those reported for the Neutral condition with fewer time-series blocks (see Figure 9). Heterogeneity across

subjects was observed in both lagged and contemporaneous connections and these pathways were observed across all regions included within the network. Of note, at the individual subject level, GIMME was unable to identify a map that met criteria for two of the four fit indices for one subject. As a result, graph theory measures were conducted and tested for differences for global network properties but not for nodal properties.

Testing differences in effective connectivity across conditions. Paired samples t-tests revealed no significant differences in the strength of the six connections that were present in both the Combined Affective and Neutral conditions. Once again, graph theory measures were calculated in MATLAB and paired samples t-tests were conducted to test for significant differences in global and nodal properties across the two conditions. Statistically significant differences were observed between the Combined Affect and Neutral conditions at the global network level, but not for individual nodes. Specifically, global efficiency for the Combined Affect condition was significantly higher (M = .49, SD = .04) than for the Neutral condition (M = .40, SD = .07; $t(9) = 4.26$, $p = .002$). Similarly, Centrality was significantly higher for the Affective Prosody condition (M = 130.50, SD = 33.03) than for the Neutral condition (M = 79.50, SD = 33.03; $t(9) = 4.01$, $p = .003$).

DISCUSSION

The human voice is a salient feature of the auditory environment. Through paralinguistic cues the voice can convey important about a speaker's emotional state (Belin et al., 2004). Behavioral studies of young children reveal that children perceive differences in affective prosody cues at a young age, yet how they process these cues at the neural level has received limited attention. As a result, there exists a gap in our knowledge of the neural processing of affective prosody in children as well as how the early emotional environment influences this

processing. To address this gap, the present study investigated effective connectivity in a neural network in 6-to-10-year-old children when they heard angry, happy, and neutral prosodies. It was hypothesized that hearing affective prosody would engage a network of cortical and subcortical regions identified by two leading neuroscience models of emotional voice processing and social stimuli processing respectively.

This study utilized a data analytic approach that permitted investigation of effective connectivity at both the group and individual subject levels. Results indicated that there were significant differences in properties of individual nodes but not in global network properties across the three prosody conditions. In contrast, when Happy and Angry prosodies were combined into one condition, significant differences in global network measures between this Combined Affect condition and the Neutral condition were observed. We discuss results and implications of these results as well as strengths and limitations of the current study.

Effective connectivity during affective prosody processing in children

Effective connectivity during affective prosody processing in the group. At the group level, hearing happy, angry, and neutral prosodies was associated with effective connectivity between regions primarily identified by the cognitive neuroscience model (Schirmer & Kotz, 2006). Across all three prosody conditions right anterior auditory cortex exerted an effect on left STG. The direction of this pathway was consistent with the cognitive neuroscience model prediction, as well as with previous studies findings, that anterior auditory cortex is sensitive to all sounds whereas STG is important for “perceptual analysis of voices” (Ethofer et al., 2009, p 1262) and is sensitive to linguistic features of speech (Binder et al., 2000). Furthermore, though pathways were directed towards and away from bilateral OFC, a region identified by both

neuroscience models, there were no common group level pathways to or from subcortical regions identified by the social neuroscience model (e.g. vmPFC, insula; Adolphs, 1999).

One interesting finding was that at the group level connectivity was not observed between left STG and inferior frontal regions. This was surprising given predictions from the cognitive neuroscience model and evidence for this pathway in a previous study using effective connectivity analyses (Ethofer et al., 2006b; Schirmer & Kotz, 2006). On the contrary, hearing happy prosody was associated with a pathway directed from left IFG to left STG. Also notable were findings of effective connectivity between bilateral OFC, from right IFG to right OFC, left OFC to left IFG, and from left IFG to left OFC. Though these findings were not unexpected as IFG has been linked to emotion recognition and emotional empathy (Shamay-Tsoory, 2011; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009) and that activity in OFC is associated with decision making (for review see Bechara, Damasio, & Damasio) they built on the cognitive neuroscience model by providing evidence of connectivity among the frontal regions identified by the model. Moreover, it is notable that even though each group map had the same pathways between regions, the directional patterns of connectivity between the OFC and IFG were more similar across the two affective prosody conditions (Angry and Happy) relative to the neutral condition.

Effective connectivity at the subject level. Though findings at the group level were unexpected, at the subject level a different pattern in effective connectivity was evident as connectivity was observed among cortical and subcortical identified by both neuroscience models. Specifically, effective connectivity was now present, across the three prosody conditions, between all regions of interest including vmPFC, left insula, and right caudate.

These results revealed noteworthy heterogeneity across children in effective connectivity among these regions in the different prosody conditions. These findings were similar to findings from studies of the face processing network that show differences in effective connectivity across children (He et al., 2015) and supported Gates and Molenaar (2012)'s concerns that other methods for modeling effective connectivity may fail to accurately describe connectivity in individuals. Pooling time-series data across subjects may lead to conclusions about patterns of connectivity that are not representative of any one particular subject in a group as the beta weights, directions of connections, and network coupling may vary across subjects (Gates & Molenaar, 2012; Poldrack et al., 2011). Nonetheless, these findings are indicative that hearing angry, happy, and neutral prosodies was related to the recruitment of a widespread network of neural regions implicated in processing of emotional stimuli in this sample of children.

Modulation of effective connectivity by prosody. A second aim of the present study was to investigate whether or not hearing different affective prosodies significantly modulated global and nodal properties of the network of regions examined. Though it was hypothesized that hearing different prosodies would modulate effective connectivity this aim was largely exploratory. This was due the fact that only two adult studies had investigated effective connectivity during affective prosody processing as well as the ongoing debate regarding whether or not processing of emotions is related to discrete physiological and neural correlates (Vytal & Hamann, 2010). Graph theory was used to probe measures of global network and node properties.

At the network level, tests revealed no significant differences in any of the five network measures examined (e.g. global efficiency, density, centrality, modularity, or the clustering coefficient). However, at the node level, significant differences in these graph theory measures

were found. Though interpretations of these findings were made *post hoc* they reflect that hearing angry prosody relative to neutral prosody may involve increased connectivity among specific neural regions. The first finding was that the centrality and clustering coefficient metrics were significantly larger in right OFC when children heard angry prosody compared to when they heard neutral prosody. In a previous study OFC showed increased activation in response to angry relative to neutral prosody (Ethofer et al., 2009). Our results suggest that this region plays an important role in children's decoding of angry prosody as nodes with high centrality are considered hubs of activity as they are "powerful distributors of information" (Power et al., 2013, p. 798) and therefore are critical for efficient communication within a network (Bullmore & Sporns, 2009).

Activity in OFC has been related to numerous processes including recognizing emotions and controlling emotional expressions, decision making, and evaluating outcome expectancies (Hornak, Rolls, & Wade, 1996; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009). Yet this region is an extensively connected region that projects information from multiple modalities (e.g. visual, auditory, gustatory) and is therefore in "an ideal position to provide information to other neural regions about the external environment" (Rempel-Clowner, 2007, p. 73). Based on our findings, it is possible that right OFC may be especially important for the processing of angry prosody through its facilitation of communication among other regions.

Additional findings were that right posterior auditory cortex had significantly higher centrality and number of total connections (total strength) when children heard an angry voice compared to when they heard a neutral voice. In contrast, the opposite was found for left STG; this region had more connections directed out to and in from other regions when children heard the neutral voice. These findings are interesting given evidence that right auditory cortex is

implicated in pitch processing in speech and music (Zatorre, 1988; Zatorre, Belin, & Penhune, 2002; Zatorre, Evans, Meyer, 1994) and that the left auditory cortical areas, specifically posterior left STG, are associated with speech sound processing and speech production (Binder et al., 2000). Moreover, these findings are in line with results from studies of affective prosody processing in adults conducted by Ethofer and colleagues. These studies found that right posterior auditory cortex was the input region in an effective connectivity map during affective prosody processing (2011) and that activation in STG was not influenced by task demands suggesting that this region plays an early role in perceptual analysis (Ethofer et al., 2008). In sum, these results suggest that angry and neutral prosodies may differential modulate effective connectivity.

Effective connectivity in the combined affective condition. Finally, post hoc analyses were conducted to examine if concatenating time-series data from the two affective prosody conditions (Angry and Happy) increased our power to detect effects. Results suggested that this was the case and provided a different picture of effective connectivity within the neural network of the same 10 ROIs. In this Combined Affect condition, not only were more connections observed among regions in the group map, but effective connectivity was observed between cortical and subcortical regions identified by the cognitive and social neuroscience models. Additionally, the pathway discussed earlier from STG to a region in the frontal cortex that was predicted to be present by the cognitive neuroscience model was present in this group map.

Unlike findings when the Angry and Happy conditions were investigated separately, when compared to connectivity in the neutral condition, significant differences were observed in the global efficiency of effective connectivity in the Combined Affect condition compared to the neutral condition. In graph theory, global efficiency provides information about how efficiently

information is shared among nodes in the network (Krackhardt, 1994). This finding implies that information is more easily shared among discrete regions when the voice contains affective prosody relative to neutral prosody. Though these analyses were conducted *post hoc* and were exploratory, they reveal that at the group level, increasing the amount of time-series did increase our abilities to detect effective connectivity among regions identified by the two neuroscience models thus supporting that processing of affective prosody cues recruit cortical and subcortical regions.

In sum, results from the present studied indicated that children recruit a widespread network of temporal and frontal regions when processing angry, happy, and neutral prosodies that was more apparent at the individual subject level. Furthermore, the use of graph-based analyses revealed differences in node properties for the angry and neutral conditions suggesting that there may be meaningful differences in functional architecture in this network when children process angry relative to neutral stimuli.

Limitations of the current study

Several limitations of the current study must be noted. First as increasing the amount of time series data into a combined prosody condition resulted in the identification of additional common group level pathways, it is possible that the smaller sample size and the limited blocks of time series data for each affective prosody condition impacted our abilities to detect effects within these data (Button et al., 2013). Smaller sample sizes can lower statistical power which can in turn decrease the likelihood that effects found reflect true effects and/or lead to overestimation of the magnitude of effects (Button et al., 2013). It is therefore necessary to interpret and consider the results found in the present study with caution until they can be replicated or challenged in a larger sample of children.

Understanding the limitations of small amounts of data, the present study did take steps in ensure that data were properly corrected for the number of tests that were conducted to circumvent interpreting results that were not significant. First, when group level ROIs were defined, the group map was corrected at the whole-brain level using the False Discovery Rate procedure as this method is more sensitive to the number of voxelwise tests statistics that are performed than standard procedures (Genovese et al., 2002). Furthermore, in post hoc analyses, results were corrected for multiple comparisons and only differences that survived these corrections were reported.

The present study was largely exploratory and future studies with larger sample sizes will be necessary to determine if these results are replicable. Future studies would benefit from implementing protocols that increase researcher's abilities to successfully collect imaging data from children as there are limited appropriate approaches to cleaning data with high movement. In the present study successful data acquisition increased significantly with the introduction of two structured and lengthy training sessions that occurred prior to children entering the scanner. These sessions included showing children pictures of the scanner, exposing them to the scanner sounds, and timed trials during which children practiced laying still while staff members provided *in vivo* feedback on their performance and positive reinforcement (e.g. stickers). It is recommended that future studies develop similar protocols that increase children's comfort with the scanning environment and abilities to stay still for the prolonged period of time necessary to acquire data. Additional suggestions for training can be found in a paper by Scherf and colleagues (2016; under review).

A second limitation of the present study was that children's affective environment was not measured directly thus we could not investigate if individual differences in connectivity were

related to differences in children's environments. New methods have become available that permit recording of the auditory affective environment (Mehl & Pennebaker, 2003). For example, Electronic Activation Recording (EAR) is a recording device that records snippets of sound throughout the day (Mehl & Pennebaker, 2003). This method has primarily been used to evaluate the linguistic content of natural conversations, however new programs permit the evaluation prosodic cues of the voice. The use of such methods will enhance our understanding of children's daily exposure to affective prosody and both typical and atypical variability in parents' use of affective prosody.

Finally, though not a limitation but rather a caveat of the study methods is that children were not asked to complete a task (e.g. identify or rate valence/intensity) in the scanner but rather listened passively to the stimuli. It was assumed that they were attending to these prosodies and all children confirmed that they had heard voices; however the lack of a behavioral response in the scanner may have led to differences in children's level of attention towards the stimuli. However previous studies have shown that task demands can influence patterns of neural activation (Ethofer et al, 2009). Furthermore, the present study was interested in investigating differences in neural processing of affective prosody that more closely approximated overhearing these cues in their environment. Thus the decision to have children listen passively to the stimuli reflected this aim.

Implications and future directions of the present study

Despite these limitations, this was the first known study of effective connectivity during affective prosody processing in children. A strength of the research design in the present study was the use of scripts that more closely approximated children's everyday exposure to affective prosody. In the studies discussed in the introduction, the affective prosody stimuli included

single words (Ethofer et al., 2011), pseudo-words (Bach et al., 2008; Grandjean et al., 2005), or short, one sentences phrases (Johnstone et al., 2006; Leitman et al., 2010). And, as reported, these studies found that hearing affective prosody was associated with significant activation within multiple neural regions. However, in their daily lives children hear and are learning to interpret affective prosody in the context of speech. Thus the use of ecologically valid stimuli may have more closely approximated and studied children's experiences.

Secondly, this study represented a first step towards a fuller understanding of children's neural processing of affective prosody and how the early environment shapes and influences this processing. As Gottlieb (1992) cogently stated "genes in and of themselves cannot cause development any more than stimulation in itself can cause development." In essence, though the brain is substantially shaped by genes, this development is impacted by experience such that "each person's brain comes to reflect, at least in part, his or her unique experiential history" (Belsky & de Haan, 2011, p. 413). As reviewed earlier, the brain undergoes significant changes overtime that increase our abilities to integrate information and that facilitate higher order cognitions (Collin & van den Heuvel, 2013). And as a result of these changes, exposure to atypical levels of affective prosody, in particular anger, may have implications both for children's processing of affective prosody as well as neural development. Indeed, as discussed, two studies examining these relations found that exposure to higher levels of parental conflict was related to differences in patterns of neural activation in infants for very angry > neutral speech (Graham et al., 2013) and that childhood physical abuse was related to 7- to 12-year-olds allocating greater neural resources to processing angry voices (Shackman et al., 2007).

A full understanding of the significance of these differences for children's functioning will necessitate studies of typically developing children with normative levels of affective

prosody exposure. Information gathered from typical samples will provide a context and baseline for recognizing what is considered deviant from the norm (Bruck, 1997) and can help inform our conceptualizations of what differences in patterns of activation and connectivity signify in these cases. Ultimately, results such as those found by the two studies above bolstered by additional evidence that early exposure to anger does indeed lead to significant differences in the functional architecture of children's brains can be used to teach about the potential implications of exposure to high levels of anger, a lesson that may be particularly important for high-risk parents.

Future directions. To further our abilities to understand neural network topology, in addition to the information provided by graph theory metrics, analytic methods are now being developed that are sensitive to differences in changes in the patterns of effective connectivity in a network (Elbich, Molenaar, & Scherf, in prep). The use of such methods may further our understanding of interregional communication in a network during affective prosody processing as these methods are more sensitive to patterns of connections and will allow for better characterization of the topology of a network.

TABLES

Table 1

Size and Talairach Coordinates of Group Regions of Interest

	Brodmann's Area	X	Y	Z	# of Voxels
L					
Anterior Auditory Cortex		-43	-26	10	1248
Posterior Auditory Cortex		-54	-39	8	865
Superior Temporal Gyrus		-61	-22	3	1078
Caudate		-8	7	5	171
Inferior Frontal Gyrus	44/45	-55	21	14	1065
Orbitofrontal Cortex	47	-46	26	-3	528
vmPFC		-1	49	-12	59
Insula		-35	8	-13	59
R					
Anterior Auditory Cortex		43	-24	10	1470
Posterior Auditory Cortex		44	-36	6	153
Superior Temporal Gyrus		60	-17	4	568
Caudate		9	6	8	849
Inferior Frontal Gyrus	44/45	45	26	7	1166
Orbitofrontal Cortex	47	47	24	-2	941

Note. Regions of interest (ROI) defined based on whole brain group level map activation for Happy + Angry+ Neutral > silence contrast in Run1. The group map was corrected at the whole brain level using the FDR procedure at $q < .10$. The size and location of each ROI are reported. X,Y,Z coordinates in Talairach space. L = left hemisphere, R = right hemisphere.

Table 2.

Talairach Coordinates of Individual Regions of Interests' Original and Redefined Peak Voxels

Subject	Region of Interest	Original Peak Voxel	New Peak Voxel
1	Right IFG	(56, 22, 4)	(55, 2, 4)
2	Left IFG	(-55, 19, 25)	(-54, 19, 25)
3	Left IFG	(-59, 19, 21)	(-52, 17, 24)
4	Left IFG	(-55, 25, 9)	(-50, 25, 10)
4	Left IFG	(-58, 25, 19)	(-50, 23, 15)
5	Right OFC	(55, 28, 1)	(47, 25, 1)
5	Left OFC	(-50, 24, -6)	(-49, 25, -6)
6	Left IFG	(-58, 22, 12)	(-56, 22, 12)
6	Left IFG	(-58, 29, 0)	(-55, 19, 9)
7	Right OFC	(55, 25, 0)	(50, 31, 1)
8	Left OFC	(-50, 29, -3)	(-47, 30, 0)
8	Left IFG	(-57, 22, 21)	(-54, 20, 23)
8	Right IFG	(54, 27, 4)	(49, 25, 4)
8	Left IFG	(-52, 25, 9)	(-51, 26, 9)

Note. Table shows individual level ROIs that were redefined because placing a 4mm sphere around the original peak voxel identified from the group-level ROI resulted in part of the ROI being placed on the child's skull. Numbers in the subject column refer to individual children, the repetition of subject numbers shows children for whom multiple ROIs had to be corrected. IFG = Inferior frontal gyrus. OFC = Orbitofrontal cortex.

Table 3.

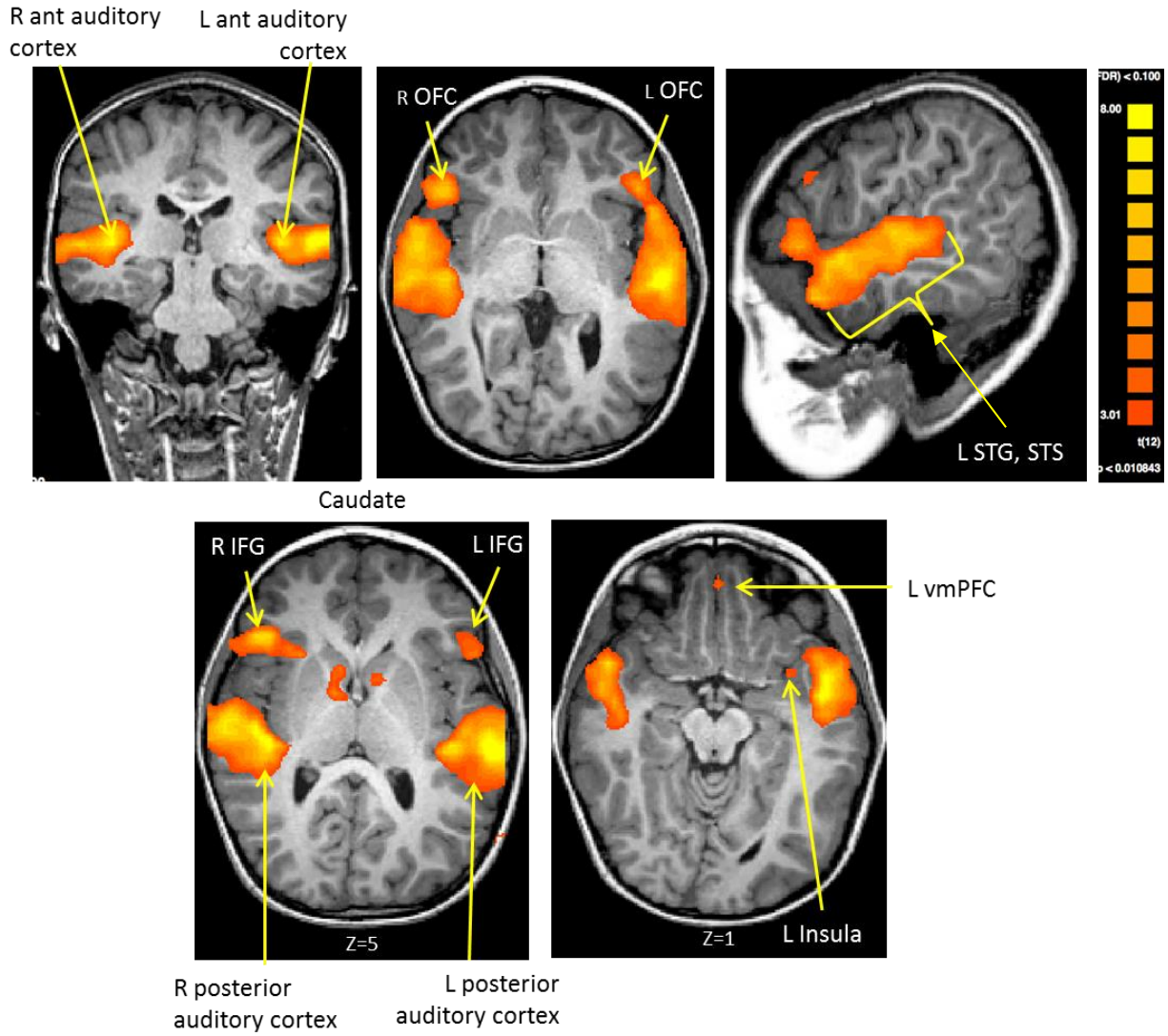
Description of Shared Voxels among Individually Defined Region of Interests and the Size of the Redefined Nonoverlapping Region of Interests

Subject	Overlapping Regions	# of Voxels	Centroid of Overlap	Region voxels Taken From	Size of new ROI
1	Left OFC & Right IFG	56	(-51, 21, 2.5)	OFC	201
1	Right OFC & IFG	94	(55.5, 23, 2.5)	OFC	163
2	Right Anterior & Posterior AC	21	(50, -33, 10)	Posterior AC	236
2	Left Anterior & Posterior AC	2	(-52, 34.5, 9)	Posterior AC	255
3	Right IFG & OFC	42	(45.5, 31.5, 2)	OFC	215
4	Right Anterior AC & STG	125	(52, -17, 7)	Posterior AC	132
5	Right IFG & OFC	118	(53, 28, 2.50)	OFC	139
6	Left Anterior & Posterior AC	23	(-49, -32, 9)	Posterior AC	234
7	Right IFG & OFC	44	(47, 23.5, 2)	OFC	213
8	Right IFG & OFC	24	(44, 23.5, 3.5)	OFC	233

Note. Table shows ROIs that included overlapping voxels, the size of the region that overlapped, and the Talairach coordinates of the centroid of the overlap. The centroid of the overlapping region was used to inform which ROI the voxels belonged to. The volume of interest file were edited to remove the overlapping voxels from the regions indicated in the “taken from” column. Finally, table shows the size of the new ROI after voxels were removed. Numbers in the subject column refer to individual children, the repetition of subject numbers shows children for whom multiple ROIs had to be corrected. IFG = Inferior frontal gyrus. OFC = Orbitofrontal cortex. AC = Auditory cortex. STG = Superior temporal gyrus.

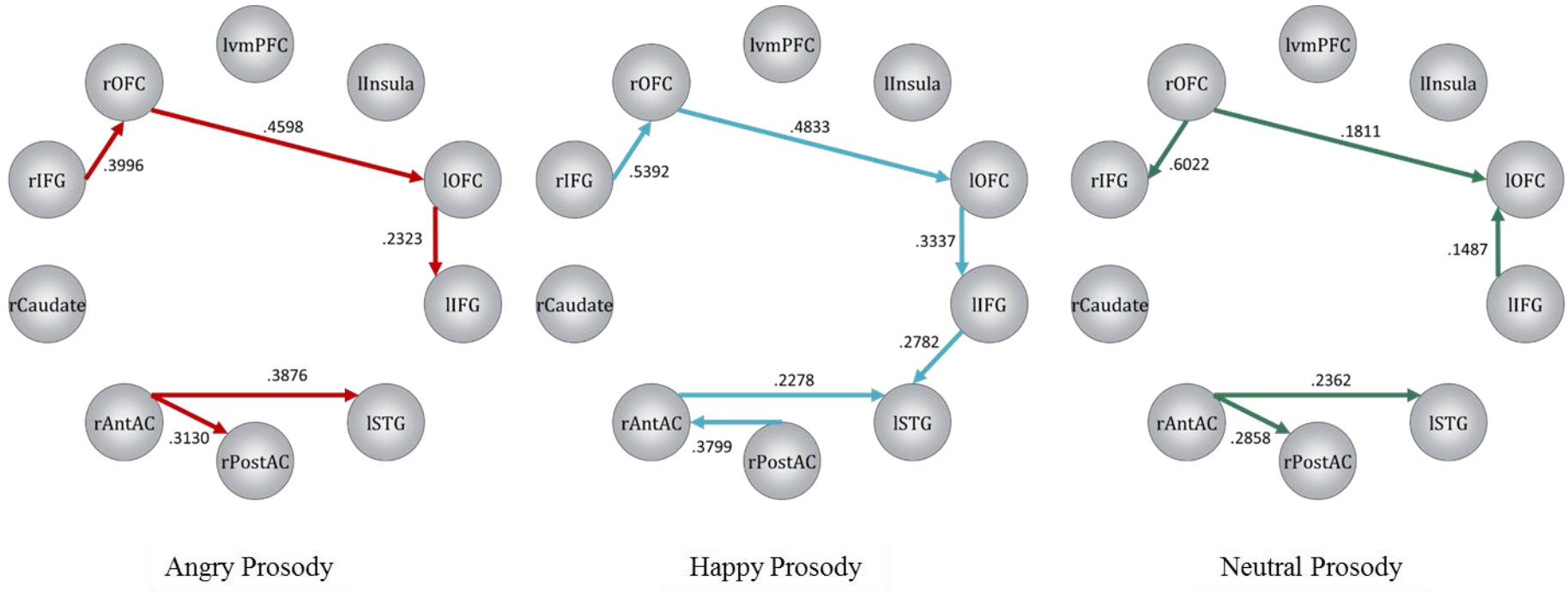
FIGURES

Figure 1. Regions of Interests Defined at the Group Level based on Functional Activation in Run1



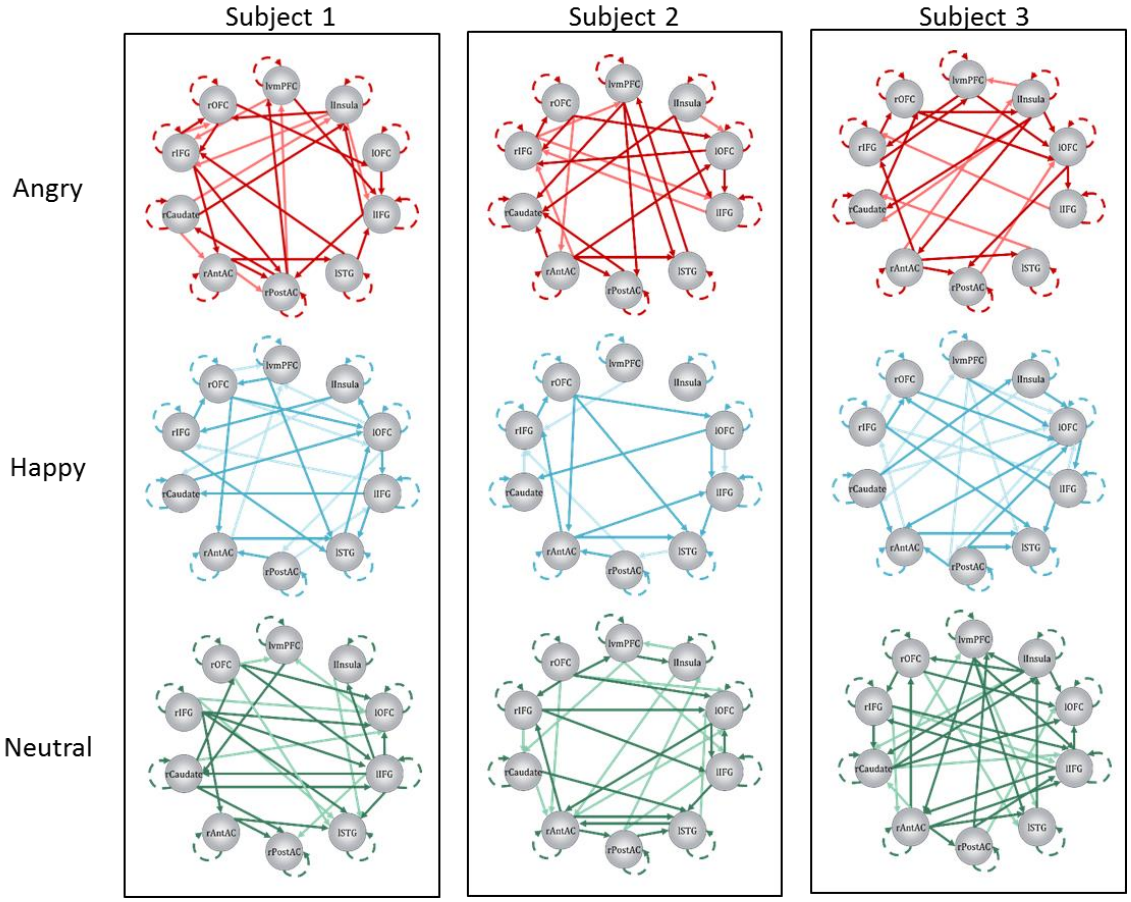
Note. Figure shows Regions of Interests defined at the group level, by functional activation in Run1 for the Happy+Angry+Neutral - 3Silence balanced contrast. Group level map was corrected at whole brain level using the False Discovery Rate Procedure with a q < .10. ROIs were mapped onto a representative subjects brain. Z coordinate shows position of each slice with respect to the Talairach atlas. IFG = Inferior Frontal Gyrus. OFC = Orbitofrontal Cortex, STG = Superior Temporal Gyrus. STS = Superior Temporal Sulcus.

Figure 2. Group Level Maps of Effective Connectivity during Processing of Angry, Happy, and Neutral Prosodies



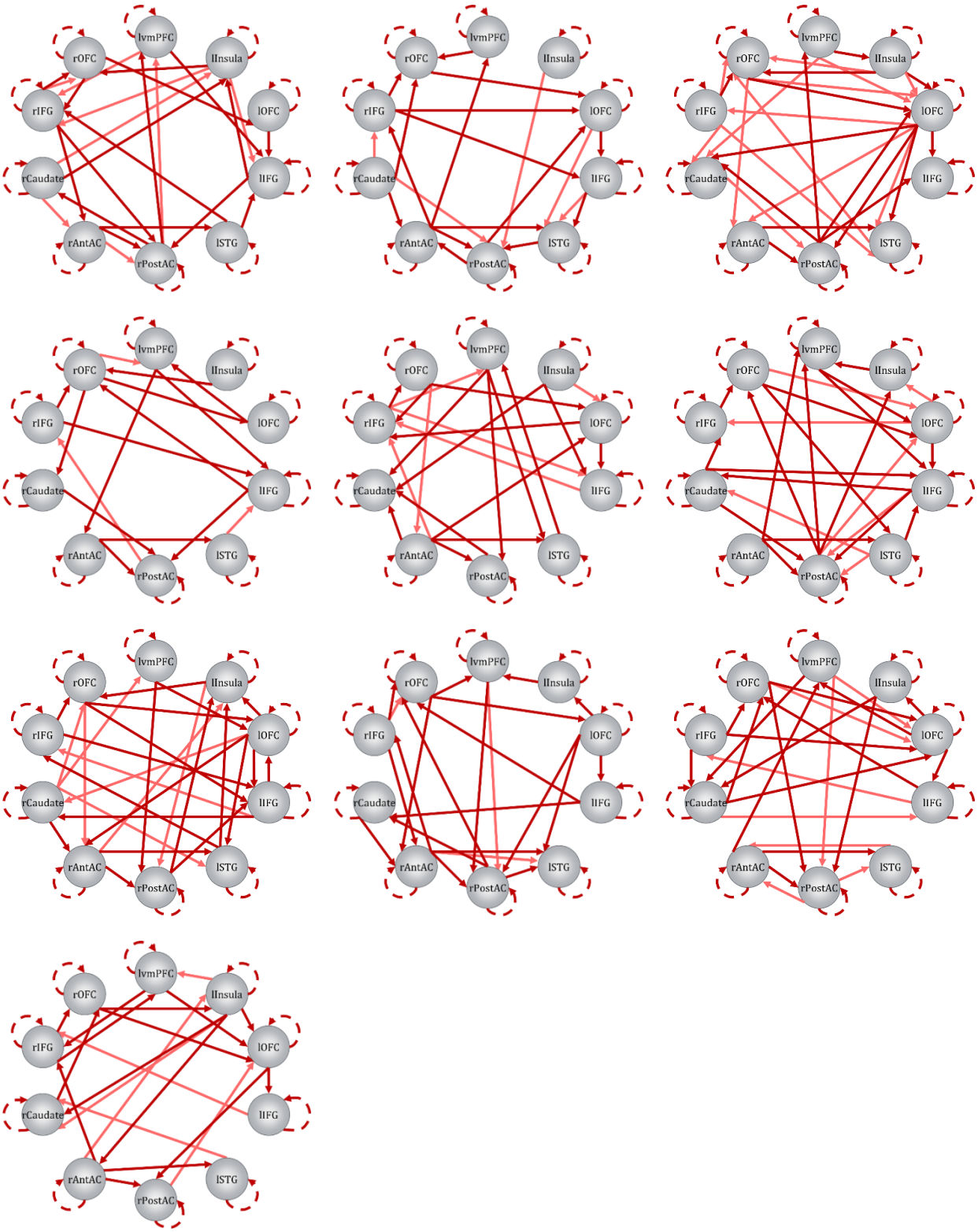
Note. Figure shows effective connectivity at the group level when children heard angry (red), happy (blue), and neutral (green) prosody. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. rAntAC = Right anterior auditory cortex, rPostAC = Right posterior auditory cortex IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 3. Effective Connectivity during processing of Angry, Happy, and Neutral Prosodies in Three Randomly Selected Subjects



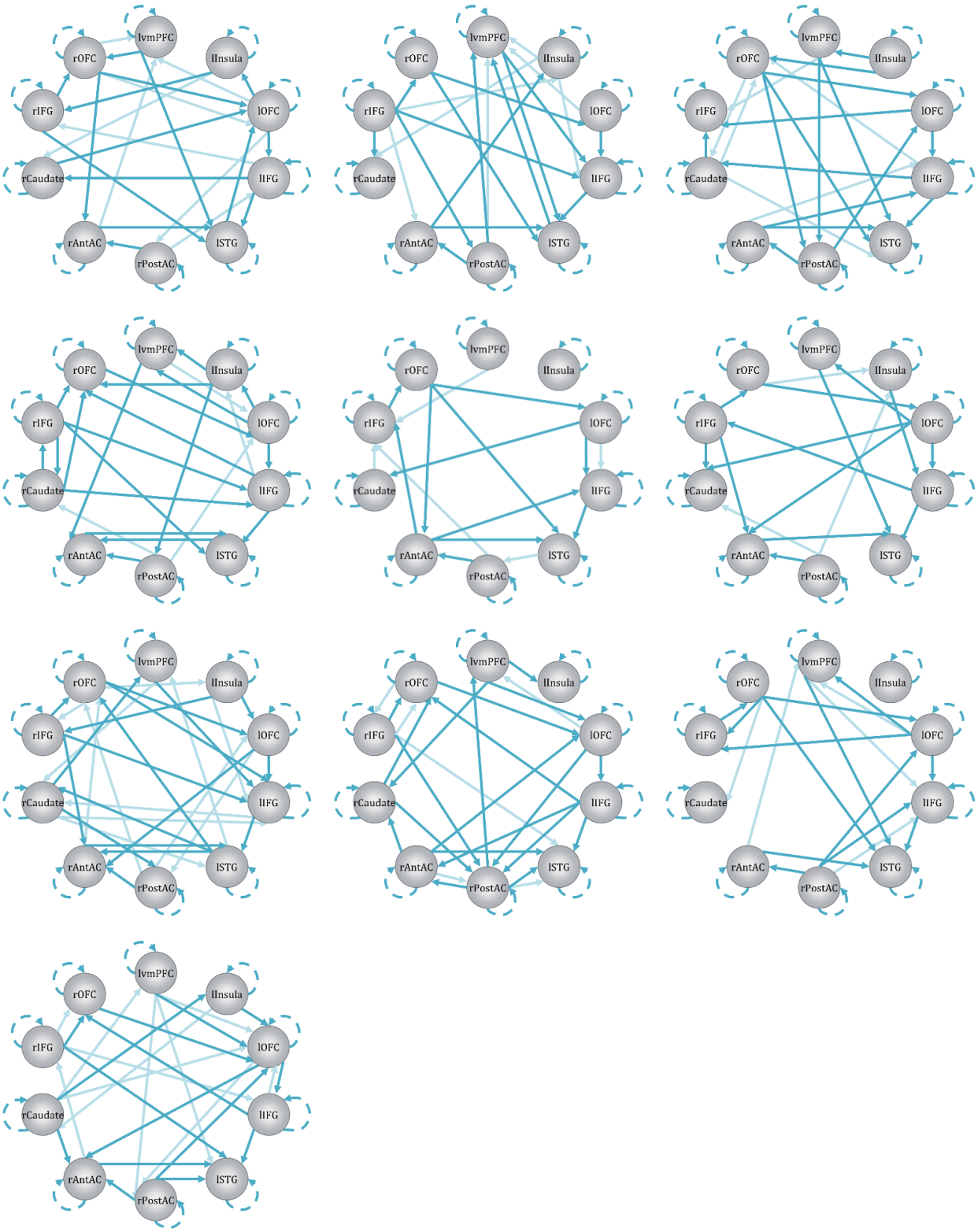
Note. Figure shows effective connectivity during processing of angry (red), happy (blue) and neutral (green) prosodies for three individual, randomly chosen subjects. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Darkly colored lines represent contemporaneous connections, lightly colored lines indicate lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 4. Individual Subject Maps of Effective Connectivity during Processing of Angry Prosody



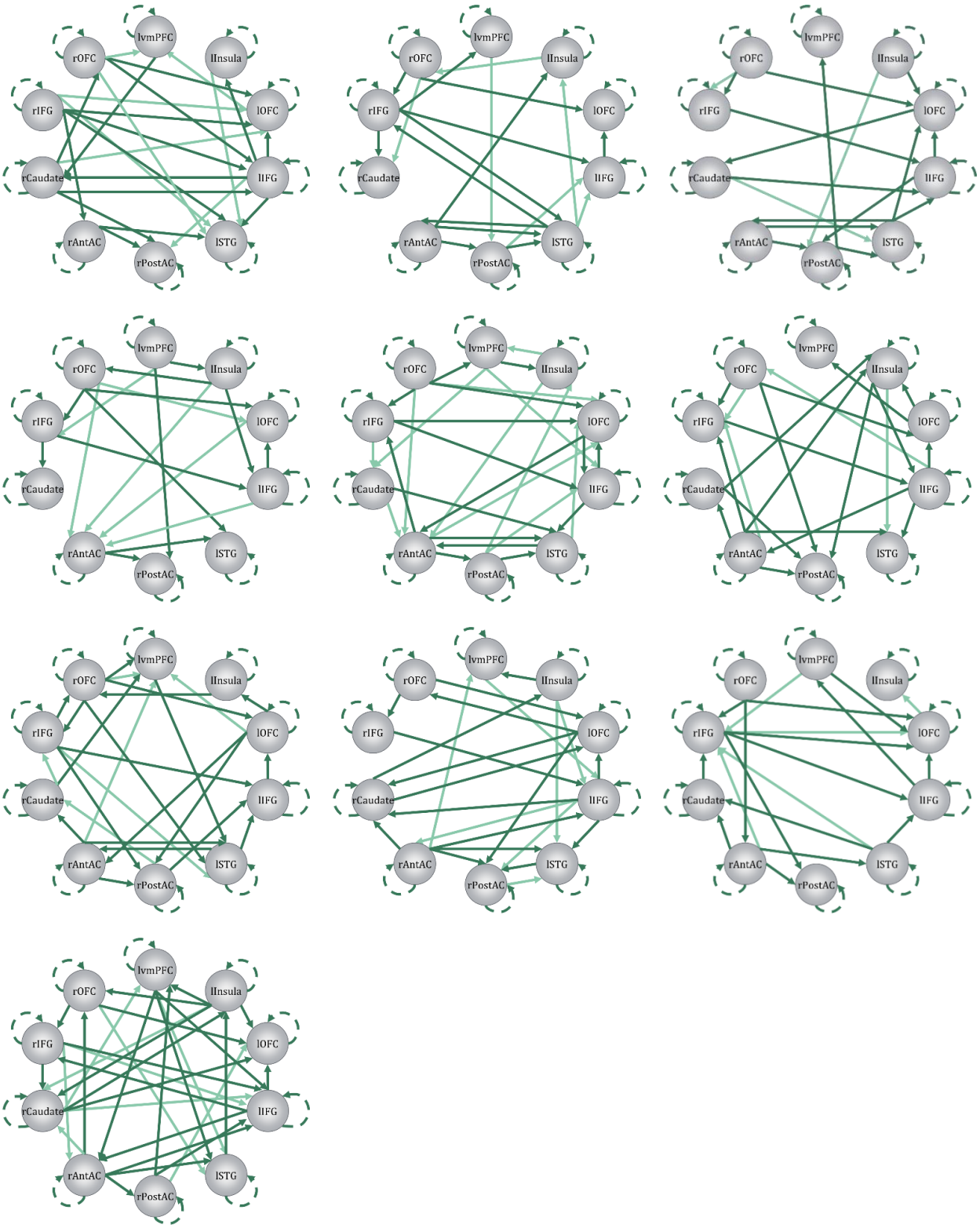
Note. Figure shows effective connectivity maps identified by GIMME during the processing of neutral prosody for each of the 10 subjects. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Dark red lines indicate contemporaneous connections between regions, light red lines show lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 5. Individual Subject Maps of Effective Connectivity during Processing of Happy Prosody



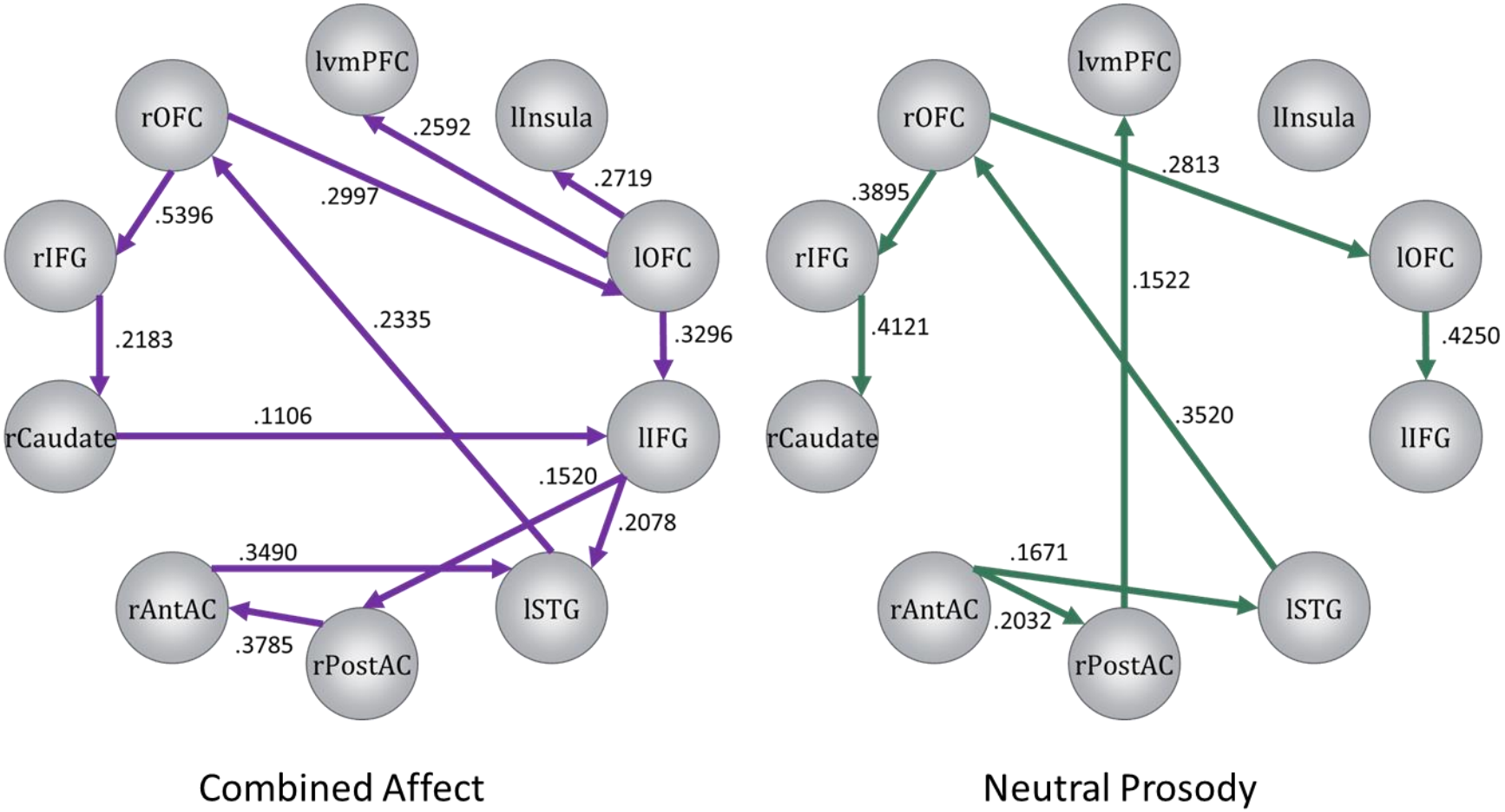
Note. Figure shows effective connectivity maps identified by GIMME during the processing of neutral prosody for each of the 10 subjects. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Dark blue lines indicate contemporaneous connections between regions, light blue lines show lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 6. Individual Subject Maps of Effective Connectivity during Processing of Neutral Prosody



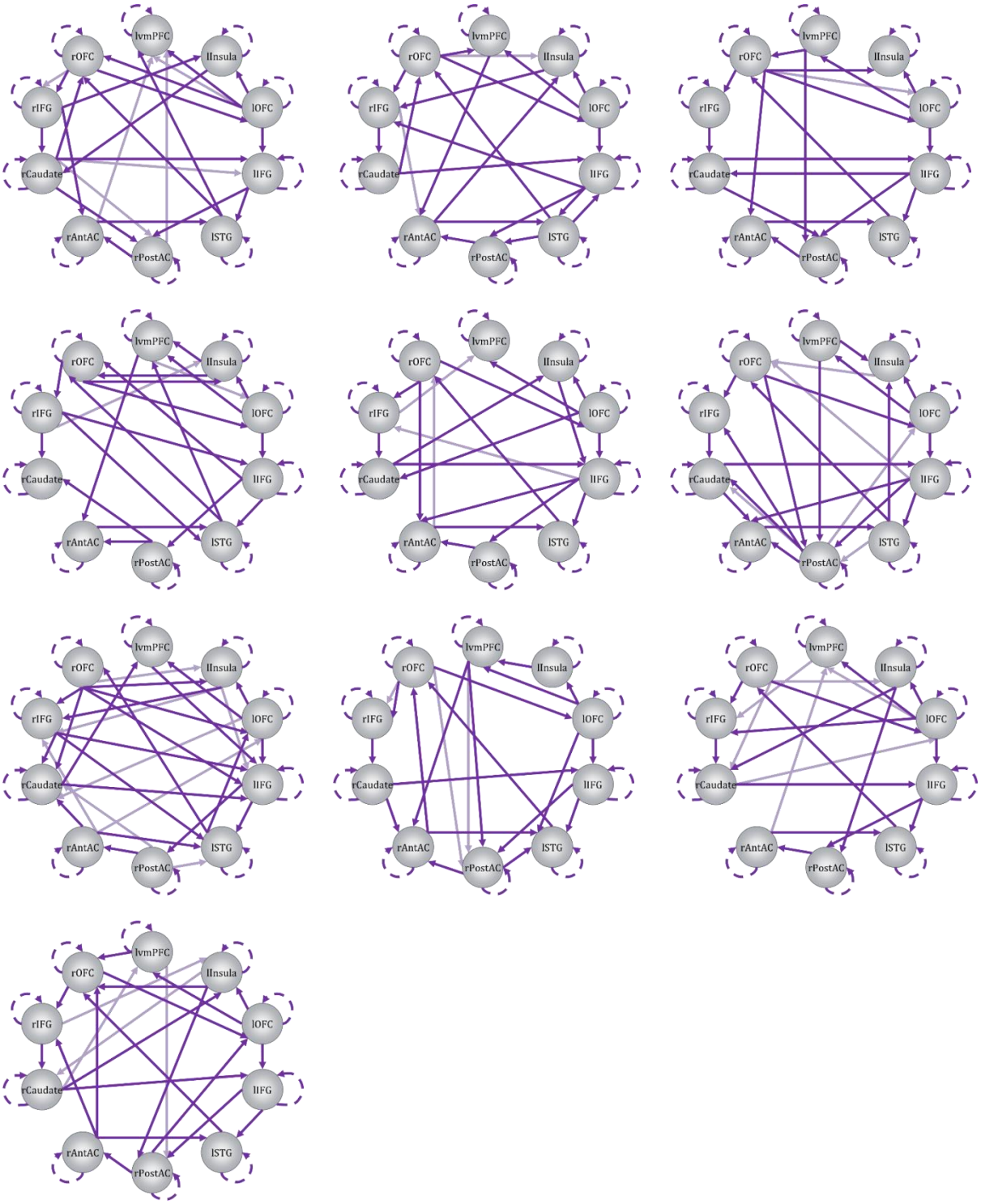
Note. Figure shows effective connectivity maps identified by GIMME during the processing of neutral prosody for each of the 10 subjects. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Dark green lines indicate contemporaneous connections between regions, light green lines show lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 7. Group Level Maps of Effective Connectivity during Processing of Combined Affective (Happy + Angry) and Neutral Prosodies



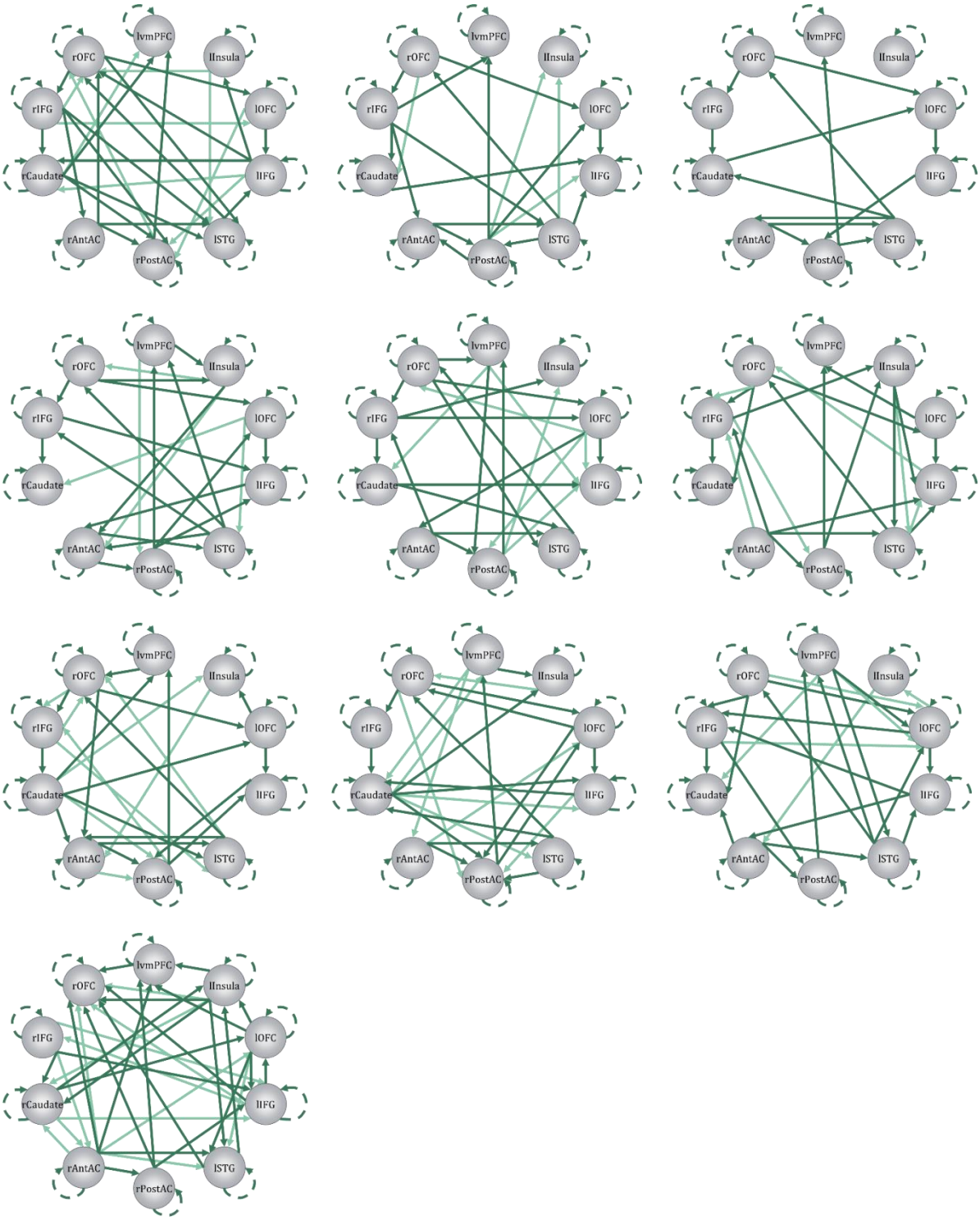
Note. Figure shows effective connectivity at the group level when children heard affective prosody (Happy + Angry prosodies; purple lines) and neutral (green) prosody. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 8. Individual Subject Maps of Effective Connectivity during Processing of Combined Affective Prosodies (Happy + Angry)



Note. Figure shows effective connectivity maps identified by GIMME during the processing of affective prosody (Happy + Angry prosodies) for each of the 10 subjects. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Dark green lines indicate contemporaneous connections between regions, light green lines show lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus.

Figure 9. *Individual Subject Maps of Effective Connectivity during Processing of Neutral Prosody with all Blocks of Time-Series Data Included.*



Note. Figure shows effective connectivity maps identified by GIMME during the processing of neutral prosody) for each of the 10 subjects. In these analyses, all time-series data (10 blocks) were included in the analyses. Circles represent discrete neural regions (nodes) and arrows represent effective connectivity among these regions (edges). Arrows indicate the direction of the influence exerted by one neural region to another. Dark green lines indicate contemporaneous connections between regions, light green lines show lagged connections. rAntAC = Right anterior auditory cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal cortex, lvmPFC = left ventromedial prefrontal cortex, STG = Superior temporal gyrus. * indicates that the map identified for this subject failed to converge and meet criteria for at least two of the fit indices.

APPENDIX

Natural speech scripts that children heard in the scanner.

Script 1	Content	Seconds
Woman:	Oh, hi, it's you.	02
	You'll be home soon.	02
	Dinner won't be ready.	02
	It takes an hour.	02
	I have lots to do.	02
	Fine, I'll fix dinner.	02
		12

Script 2	Content	Seconds
Woman:	Sorry you're tired.	02
	We should talk.	02
	About lots of things	02
	Money, the weekend	02
	Fine we won't talk now.	02
	OK, never mind.	02
		12

Script 3	Content	Seconds
Woman:	Hi, the checkbook's gone.	02
	You took it.	02
	I don't have it.	02
	You had it last.	02
	It's just not here.	02
	You'll have to find it.	02
		12

Script 4	Content	Seconds
Woman:	Hi, I hoped you'd call.	02
	You're running late.	02
	I need your help.	02
	There's too much to do.	02
	Just change your plans.	02
	See you when you get here.	02
		12

Note. Scripts were recorded by a woman in happy, angry, and neutral prosodies. Each functional run included each script, spoken in each prosody.

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