



Relation between functional connectivity and rhythm discrimination in children who do and do not stutter



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ABSTRACT

Our ability to perceive and produce rhythmic patterns in the environment supports fundamental human capacities ranging from music and language processing to the coordination of action. This article considers whether spontaneous correlated brain activity within a basal ganglia-thalamocortical (rhythm) network is associated with individual differences in auditory rhythm discrimination. Moreover, do children who stutter with demonstrated deficits in rhythm perception have weaker links between rhythm network functional connectivity and rhythm discrimination? All children in the study underwent a resting-state fMRI session, from which functional connectivity measures within the rhythm network were extracted from spontaneous brain activity. In a separate session, the same children completed an auditory rhythm-discrimination task, where behavioral performance was assessed using signal detection analysis. We hypothesized that in typically developing children, rhythm network functional connectivity would be associated with behavioral performance on the rhythm discrimination task, but that this relationship would be attenuated in children who stutter. Results supported our hypotheses, lending strong support for the view that (1) children who stutter have weaker rhythm network connectivity and (2) the lack of a relation between rhythm network connectivity and rhythm discrimination in children who stutter may be an important contributing factor to the etiology of stuttering.

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1. Introduction

The ability to perceive and produce rhythmic patterns in the environment is fundamental to a number of human capacities including music and language processing, temporal control of attention, and coordination of purposeful action (Large and Jones, 1999; McAuley and Jones, 2003; Patel, 2006; Dilley and McAuley, 2008). Perception and production of auditory rhythms has been shown to engage a network of sub-cortical and cortical brain areas, including the basal ganglia, supplementary motor area (SMA), premotor cortices, auditory cortex, and cerebellum (Schubotz et al., 2000; Mayville et al., 2002; Lewis et al., 2004; Chen et al., 2006; Grahn and Brett, 2007; Chen et al., 2008; Bengtsson et al., 2009; Karabanov et al., 2009; Schwartz and Kotz, 2015).

Previous studies combining behavioral methods with functional magnetic resonance imaging (fMRI) have shown that better rhythm skills are associated with increased activity within regions of the rhythm network, including the SMA and pre-motor regions (Grahn and McAuley, 2009). Moreover, trained musicians with extensive

experience perceiving and producing rhythms have been shown to have greater task-related functional connectivity between auditory-motor areas within the rhythm network (Grahn and Rowe, 2009). Individuals with Parkinson Disease (PD), in contrast, (for whom the basal ganglia, a major rhythm network region is affected) exhibit worse same-different rhythm discrimination compared to age-matched controls (Grahn and Brett, 2009).

Developmental stuttering is a speech disorder with a growing body of research suggesting a possible core deficit in rhythm processing. As a disorder, developmental stuttering is characterized by impaired rhythmic flow of speech (World Health Organization, 2004). Stuttering can be remarkably, albeit transiently, alleviated even in the most severe cases by providing individuals with an external pacing signal, such as an auditory metronome. This fluency inducing effect of a rhythmic pacing signal is similar to the effect of auditory pacing signals on symptom alleviation in PD. In one of the most direct examinations of a general rhythm perception deficit in developmental stuttering, Wieland et al. (2015) showed that children who stutter perform significantly worse on an auditory same-different rhythm discrimination task compared to typically developing children. Moreover, in a separate resting-state fMRI (rsfMRI) study, children who stutter exhibited attenuated functional connectivity within regions of the rhythm network relative to typically developing children (Chang and Zhu, 2013). Taken together,

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there is increasing evidence that individuals who stutter have aberrant function of the cortical-subcortical network that supports rhythm processing. One question that emerges from this work is whether there is a relation between functional connectivity within the rhythm network and rhythm perception and if so, how this relationship might be altered for children who stutter.

Previous studies have shown that temporally correlated, intrinsic neural activity measured using resting state fMRI (rsfMRI) offers a glimpse into intrinsic connectivity networks that often recapitulates task-related functional connectivity of the same networks (Hampson et al., 2002; Thomason et al., 2008; Koyama et al., 2010; Thomason et al., 2011; Allen et al., 2014). Moreover, individual differences in spontaneous cortical activity assessed with rsfMRI has been shown to reliably predict individual differences in learning a visual-motor task (Baldassarre et al., 2012). No studies to date, however, have examined whether strength of intrinsic functional connectivity within the rhythm network predicts behavioral performance in a rhythm perception task.

Toward this end, the current study investigated the relation between spontaneous fluctuations in children's intrinsic functional connectivity using rsfMRI and individual differences in the ability to make same vs. different judgments about auditory rhythms in typically developing children and children who stutter. We hypothesized that for typically developing children, intrinsic functional connectivity in the rhythm network during rsfMRI would correlate with individual variation in the performance of an auditory rhythm discrimination task. In contrast, given past data showing an attenuated and different pattern of functional connectivity in the rhythm network in children who stutter (Chang and Zhu, 2013), as well as significantly worse performance on same-different auditory rhythm discrimination (Wieland et al., 2015), we expected that children who stutter would show a reduced, or possibly no relation between intrinsic functional connectivity in the rhythm network and rhythm discrimination performance.

2. Materials and methods

2.1. Participants

Twenty-one children who stutter and 19 typically-developing children (hereafter controls) were recruited in this study. Four children who stutter (19%) and two controls (11%) were excluded due to severe head moments during rsfMRI. The final analyses included 17 children who stutter and 17 controls ranging from 6.08 to 11.42 years of age (8 F, 9 M in each group). The children were recruited through the Speech Neurophysiology Lab at Michigan State University. Many of these children also participated in the study reported in Wieland et al. (2015) with the exception of 6 children (3 controls, 3 children who stutter), who did not overlap in the two studies. Further, a total of 15 controls and 12 children who stutter (out of 17 in each group) overlapped between the current study and Chang and Zhu (2013). However, the fMRI data analyzed and reported in the current study were based on datasets that had little overlap with those reported in Chang and Zhu (2013). The participants included in both studies were recruited as part of a larger longitudinal study, and hence we were able to acquire fMRI datasets on multiple time points from each participant. For the current study, we selected the individual scans that were closest to the time when the rhythm discrimination experiment was conducted. As a result, fMRI datasets from only 5 controls and 1 stuttering child were those that were acquired in the same year in both studies. Namely, fMRI datasets from 12 controls and 16 children who stutter of the current study are distinct from those reported in Chang and Zhu (2013) study.

All children underwent careful screening to ensure normal speech and language development and typical developmental history except for the presence of stuttering in the stuttering group. Participants were monolingual, native speakers of English, with normal hearing, and without concomitant developmental disorders such as dyslexia,

ADHD, learning delay, or other confirmed developmental or psychiatric conditions. Parents also confirmed that no child was taking any medication affecting the central nervous system. Children who stutter and controls did not differ in chronological age or socioeconomic status (Hollingshead, 1975).

Research procedures were approved by the Michigan State University Institutional Review Board. Parents received nominal remuneration and children received small rewards (i.e., stickers) for their participation.

2.2. Speech, language, hearing, and cognitive evaluation

Prior to participation, all children were given a battery of standardized speech, language, and cognitive tests, audiometric hearing screening, oral-motor screening, and cognitive evaluations. Tests included the Peabody Picture Vocabulary Test (PPVT-4), Expressive Vocabulary Test (EVT-2), Goldman-Fristoe Test of Articulation (GFTA-2), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III, ages 3;0–7;0; or Wechsler Abbreviated Scale of Intelligence, WASI, ages 7;0–12;0) and receptive language test (subtests within the Test of Language Development, TOLD-P:3, ages 4;0–8;11; TOLD-I4, ages 9;0–12;0; or Test for Auditory Comprehension of Language, TACL-3, ages 4;0 to 8;11). Potential participants were excluded from the current study if their scores on any of these standardized tests were below two standard deviations of the mean.

Stuttering severity was assessed off-line by reviewing video recorded samples of speech, elicited through storytelling and conversational tasks with a certified Speech-Language Pathologist or a trained graduate student assistant. These speech samples were transcribed for further off-line analyses. The Stuttering Severity Instrument (SSI-4) was used to assess stuttering severity by considering percent frequency and duration of stuttering-like disfluencies, and physical concomitants associated with stuttering, derived from a minimum of 500 syllable speech sample recorded while the child engaged in conversations with a clinician. To be considered stuttering, children had to score at least very mild according to the total score on the SSI-4, stuttering judged to be present by a Speech-Language Pathologist, and the parent(s) had to express concern due to stuttering behavior. These measures were incorporated into a composite stuttering severity rating (SSI total score range: 8–29). To determine measurement reliability of the SSI score ratings, an intraclass correlation (ICC) coefficient was calculated based on the two independent judges' ratings of SSI on a larger sample of children, from which pool the current participants were recruited. The ICC based on 37 samples was very high, with Cronbach's alpha = 0.97 (absolute agreement; unadjusted). All children who stuttered were tested to be persistent at the time of behavioral testing. The average duration of stuttering was 5.14 years (range 2.1–8 years; SD 2.0).

2.3. MRI acquisition

Functional and anatomical MR images were acquired on a GE 3 T Signa® HDx MR scanner (GE Healthcare) with an 8-channel head coil. Functional images were acquired using echo-planar sequence with the following parameters: 38 contiguous 3 mm axial slices in an ascending, interleaved order, echo time = 27.7 ms, repetition time = 2500 ms, flip angle = 80°, field of view = 22 cm, matrix size = 64 × 64, ramp sampling. In total, 164 volumes were acquired during wakeful rest with subjects' eyes closed. Whole brain anatomical images were acquired using inversion recovery fast spoiled gradient recalled echo sequence with CSF suppressed, time of echo = 3.8 ms, time of repetition of acquisition = 8.6 ms, time of inversion = 831 ms, repetition time of inversion = 2332 ms, flip angle = 8°, field of view = 25.6 cm × 25.6 cm, matrix size = 256 × 256, slice thickness = 1 mm, and receiver bandwidth = ±20.8 kHz. During the scans, one staff member sat inside the scanner room next to the child at all times to monitor the child's comfort and to ensure cooperation during scanning.

2.4. Stimuli

Details regarding stimuli can be found in (Wieland et al., 2015). Briefly, stimuli were seven simple and seven complex auditory rhythms selected from a larger sample (Grahn and Brett, 2009). Rhythms were composed of a sequence of inter-onset-intervals (IOIs), where each interval was marked by the onset of a brief tone. Simple rhythms were comprised of a sequence of intervals with an explicit accent every four base IOIs, predicted to induce the strong perception of a periodic beat (Povel and Essens, 1985). In contrast, intervals comprising the complex rhythms were organized into a sequence so that the accents were not periodic, and thus not expected to induce the strong perception of a periodic beat. Each simple rhythm had a corresponding complex rhythm that was composed of the same intervals, but in a different order. Changes to the third presentation of the rhythm on different trials involved swapping the order of a pair of adjacent intervals (as in Grahn and Brett, 2009). The rhythm discrimination task was presented to participants using E-Prime v2.0 Professional (Psychology Software Tools, Inc.) running on a Lenovo Thinkpad laptop, Intel® Core™ i5 CPU with a 15-inch screen. Sounds were presented over a Logitech Compact Speaker System Z320 at a comfortable listening level, and responses were made by pressing marked buttons on the keyboard.

2.5. Procedure

On each trial, children heard two successive presentations of a standard rhythm and judged whether a third (comparison) rhythm was the same or different from the standard. The same-different discrimination task was presented in the context of a computer game, where on each trial “Randy Drummer” played a standard rhythm two times and then either the same rhythm played back to Randy by his twin brother “Sandy Same,” or a different rhythm played back by his friend “Doggy Different.” Children indicated whether the third rhythm was being played by Sandy Same (who played the same rhythm) or Doggy Different (who played a different rhythm) by pressing the respective button on the keyboard, which was marked with a visual representation of the two different characters (see Fig. 1). The IOI between presentations of each rhythm was 1100 ms, the child was given an unlimited response time and the next trial began immediately after a response. Response side-associations were counterbalanced across participants.

The experiment started with four practice trials, consisting of same and different variants of one simple rhythm and one complex rhythm, which were not used during the test trials. The practice was followed by 28 test trials where children heard same and different variants of seven simple and seven complex rhythms. Correct/Incorrect feedback was provided after each practice trial, but not during the test trials.

During the experiment, six short breaks were given after every fourth trial, during which children were told that they were doing well and had earned a sticker. The frequency of the tones marking the rhythms also varied randomly from trial to trial and took on one of six values: 294, 353, 411, 470, 528, or 587 Hz. The entire experiment lasted approximately 20 min.

2.6. Data analysis

2.6.1. Behavioral task

Performance on the rhythm discrimination task was assessed using a signal detection analysis to distinguish between participants' ability to discriminate same and different rhythms from any general tendency to respond same or different (Macmillan and Creelman, 2004). Responding ‘different’ on trials when the comparison was different from the standard was treated as a ‘hit’ and responding ‘different’ on trials when the comparison was the same as the standard was treated as a ‘false alarm’. Hit rates (HR's) and false alarm rates (FAR's) were then used to calculate d' (a measure of sensitivity). Sensitivity, d' , is determined by $z(\text{HR}) - z(\text{FAR})$. Values of $d' = 0$ correspond to chance performance, with larger values corresponding to better discrimination. A 2 (Group: children who stutter, controls) \times 2 (Rhythm Type: simple, complex) ANOVA's was conducted on d' with Group as a between-subjects factor and Rhythm Type as within-subject factor.

2.7. MRI data analysis

2.7.1. fMRI data preprocessing

fMRI data preprocessing was conducted using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). After discarding the first four volumes, functional images of each subject were corrected for acquisition timing and spatially realigned to the first volume. Motion-related artifacts were removed using an automatic de-noising procedure, which uses independent component analysis (ICA) to separate noise sources from signals originated from neuronal activity (Xu et al., 2014). Individual anatomical images were then aligned to the first volume of the functional image and normalized to the MNI space using DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) algorithm implemented in SPM12. The deformation flow field estimated from DARTEL was used to normalize the ICA de-noised functional images to the MNI space. The normalized functional images were resampled to 3 mm^3 voxel size, spatially smoothed with a 6 mm FWHM kernel and band-pass filtered with cutoff frequencies at 0.01 and 0.1 Hz. Time-series of voxels located in the white-matter were averaged and regressed out from the signals of each voxel. Although the ICA-based de-noising procedure should

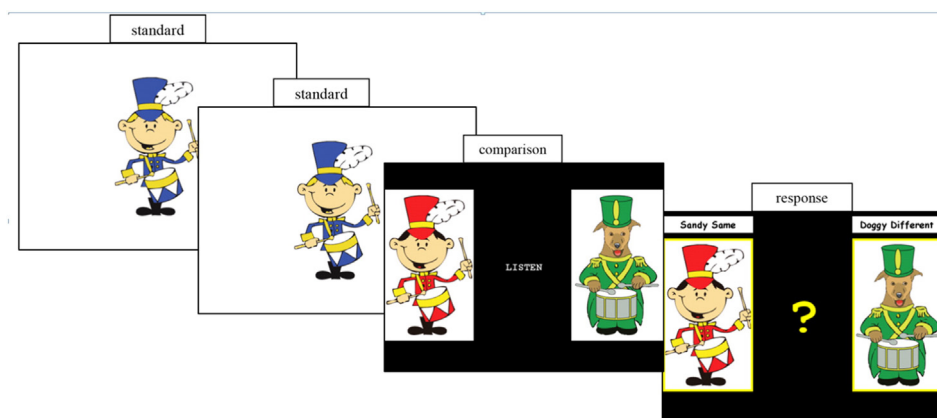


Fig. 1. Schematic of the same-different rhythm discrimination task presented to children as a computer game. Children heard a standard rhythm played twice by Randy the drummer. They then heard a comparison rhythm that were either the same or different as the standard rhythm. On same trials, the same rhythm was played by Sandy Same, Randy's twin brother. On different trials, the different rhythm was played by Doggy Different.

effectively remove motion-related artifacts, to further reduce potential adverse effects of abrupt head movements, a volume censoring technique, called image scrubbing was employed to remove volumes associated with abrupt head movements (Power et al., 2012). Framewise displacement (FD), an empirical sum of movements in the six motion directions between each consecutive volume was calculated. Volumes with FD larger than 0.5 mm were removed from the individual functional images. If >20% of the total volumes were removed in a subject, both imaging and behavioral data of that subject was excluded from all the analyses.

2.7.2. Modulatory effect of d' on functional connectivity

The seed regions, the left and right putamen were defined according to the WFU PickAtlas (Maldjian et al., 2003). Putamen was selected as the seed region for the functional connectivity calculations based on the fact that the putamen is: 1) a core area associated with rhythm perception (Grahn and McAuley, 2009; Grahn and Rowe, 2009); 2) reduced in functional connectivity in people who stutter with other cortical areas (Lu et al., 2010; Chang and Zhu, 2013), and shows different activity patterns during rest and speech relative to controls, which is normalized during paced (i.e., with a metronome) speech (Toyomura et al., 2011); 3) identified as an input region that receives cortical efference copies of motor planning from the motor cortex that allows timely initiation and termination of speech sound sequences, posited to be deficient in a neuro-computational model of stuttering (Bohland et al., 2010; Civier et al., 2013). The putamen has also been shown to modulate auditory-motor interaction critical for rhythm processing via beta oscillations (Bartolo and Merchant, 2015), suggested to be deficient in stuttering (Etchell et al., 2014a, 2014b, 2016).

For each subject, the time-series of the voxels in each seed region (left and right putamen) were averaged and correlated with the time-series of each voxel in the whole brain. The correlation coefficient at each voxel was converted to Fisher's z scores, generating a functional connectivity map for each subject. Individual functional connectivity maps were entered into a general linear model (GLM) to determine the modulatory effect of d' on functional connectivity with the left putamen at each voxel. The GLM included functional connectivity of each subject as the dependent variable and group as a factor and d' as a covariate. Additionally, sex, age, intelligence quotient, socioeconomic status based on education level of subject's mother, and a head movement measure (i.e., number of volumes removed by the image scrubbing procedure) were included as independent variables to capture the effects of no interest. At the group level, two-sample t -tests were used to compare the individual estimates of d' , that is, the modulatory effects on functional connectivity, between CWS and controls. Voxels in the white-matter areas defined by PickAtlas (Maldjian et al., 2003) were excluded from the group analysis. Unless otherwise stated, the significance threshold was set at $p < 0.01$ and cluster size $k > 91$, corresponding to $p < 0.01$, corrected for multiple comparisons. This cluster size threshold for correcting multiple comparisons was determined by AFNI's program 3dClustSim (March 2016 version).

To further illustrate the relation between functional connectivity and rhythm discrimination performance, we plotted the individual functional connectivity measures of each region (i.e., the inputs for the whole brain analysis) against combined d' . Specifically, based on the contrast between CWS and controls in the modulatory effect of rhythm discrimination performance (d'), we extracted individual functional connectivity measures (Fisher's z) between the putamen and the significant clusters in the LPMV, LSTG, SMA (i.e., the core rhythm network), left cerebellum (LCBM), right cerebellum (RCBM) and left inferior temporal gyrus (LITG) for both groups. For each cluster, Fisher's z in the voxels within a 5-mm-radius sphere centered at the peak coordinates were extracted and averaged. Similar to the whole-brain GLM analysis, sex, age, IQ, socioeconomic status were removed from functional connectivity using linear regression.

3. Results

3.1. Behavioral data

Based on a signal-detection analysis using d' as an unbiased measure of discrimination, children who stutter (CWS) showed worse rhythm discrimination performance than controls (CWS: $M = 1.16$, $SD = 0.95$; Control: $M = 2.06$, $SD = 0.85$), $F(1,32) = 8.52$, $MSE = 1.61$, $p = 0.006$). Moreover, consistent with previous research, children showed a beat-based advantage whereby simple rhythms with an explicit periodic accent were better discriminated than complex rhythms without tones marking each on the beats (simple, $M = 1.79$, $SD = 1.03$; complex, $M = 1.41$, $SD = 1.14$), $F(1,32) = 6.97$, $MSE = 0.35$, $p = 0.013$). There was also a reliable rhythm type by group interaction, $F(1,32) = 4.18$, $MSE = 0.35$, $p = 0.049$, whereby poorer discrimination by CWS (compared to controls) was more evident for complex rhythms (Control: $M = 2.01$, $SD = 0.97$; CWS: $M = 0.82$, $SD = 1.00$) than for simple rhythms (Control: $M = 2.10$, $SD = 0.96$; CWS: $M = 1.49$, $SD = 1.02$) (Fig. 2). The correlation between stuttering severity and d' was not significant: the Pearson correlation coefficient (r) between SSI4 scores and the combined d' was 0.28 ($p = 0.27$). Because the correlation between individual simple and complex discrimination performances was very high for both groups (Control: $r = 0.67$, CWS: $r = 0.53$), we calculated a composite measure of rhythms discrimination that combined simple and complex trials for the purposes of analyzing the relation between functional connectivity and behavioral performance.

3.2. Relation between intrinsic functional connectivity within rhythm network and rhythm discrimination performance

We first examined the extent of functional connectivity of the putamen with the rest of the brain in each group. The results obtained from the left and right putamen were very similar. For controls, there was significant functional connectivity across much of the rhythm network regions of interest (seed area defined in the left putamen). In contrast, the overall functional connectivity between the left putamen and regions in the rhythm network was weaker in children who stutter relative to controls (Fig. 3). When comparing functional connectivity with the left putamen directly between groups, children who stutter showed attenuated functional connectivity in the supplementary motor area, extending to the cingulate cortex and the precuneus (MNI coordinate: $-3, -15, 57$; peak z value: -4.13 ; size: 289 voxels). This result is consistent with our previous study (Chang and Zhu, 2013).

Next, we examined the relation between resting-state functional connectivity and individual variation in combined discrimination performance of both simple and complex rhythms (d') for controls and children who stutter. We first calculated the Pearson correlation

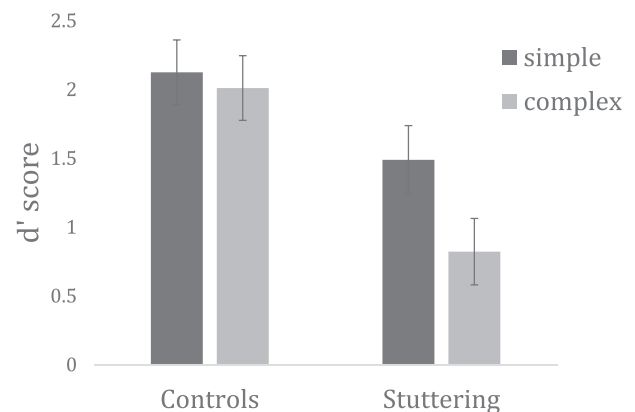


Fig. 2. Rhythm discrimination performance (d') comparing simple and complex rhythms for controls and children who stutter ("Stuttering"). Error bars show mean \pm SEM.

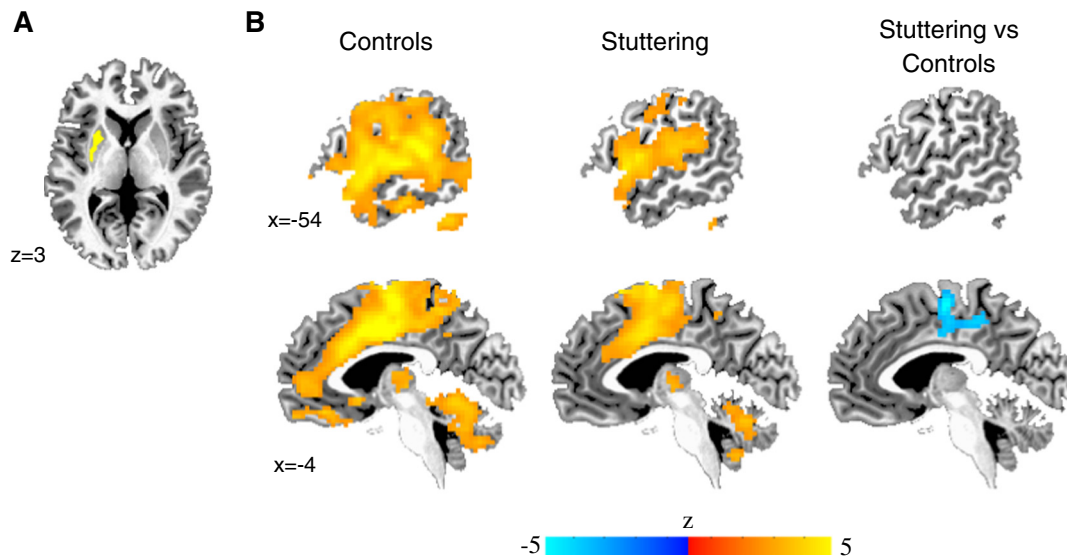


Fig. 3. Attenuation of function connectivity with the left putamen seed in children who stutter. (A) The left putamen, the seed region used in our analyses, is indicated in yellow. (B) Functional connectivity with the left putamen in controls (left panel) and children who stutter (mid panel). Consistent with our previous study (Chang and Zhu, 2013), the right panel shows that functional connectivity between the left putamen and the supplementary motor area was attenuated in children who stutter compared with children who do not stutter ($p < 0.05$, corrected). Results of the functional connectivity are overlaid on the structural image of a single subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

coefficients between each of the seed regions (left and right putamen) and every voxel in the whole brain, generating a functional connectivity map for each participant.

The relation between functional connectivity and rhythm discrimination performance at the group level were analyzed using the general linear model with group as a factor and d' as a covariate. The model also included sex, age, IQ, socioeconomic status, and a head motion measure to capture effects of no interest. This whole brain analysis showed that functional connectivity between the left putamen and areas in the rhythm network, including the left vPMC, SMA, STG, were specifically and positively correlated with rhythm discrimination performance in controls, but not in children who stutter (Fig. 4, Table 1). The results were virtually identical for the right putamen (Supplementary Fig. 1) and hence we present results primarily based on left putamen seed (Table 1, Figs. 4 and 5).

4. Discussion

In this study, we compared the strength of spontaneous correlated brain activity (i.e., functional connectivity) in the putative rhythm network in children who do and do not stutter. We also examined how functional connectivity was associated with behavioral performance on a same-different auditory rhythm discrimination task in both groups. The rhythm network comprises the putamen, supplementary motor area (SMA), premotor cortex (PMC), and auditory areas in the bilateral superior temporal gyrus (STG). There were three main findings. First, typically-developing children (controls) showed robust spontaneously correlated activity within the rhythm network. Second, consistent with Chang and Zhu (2013), children who stutter showed attenuated connectivity between the putamen and SMA compared to controls. Third, there was a robust positive correlation between intrinsic functional connectivity and behavioral performance on the rhythm discrimination task for controls, but not for children who stutter.

Previous fMRI studies have shown that a wide variety of behavioral tasks that assess different aspects of timing and temporal processing activate an overlapping network of regions that includes the SMA, basal ganglia (BG), cerebellum, parietal and prefrontal cortices. Of these, the SMA and BG have been proposed to constitute a core timing network that interacts with other neural structures to support domain specific timing (e.g., somatosensory, motor, auditory, visual timing) (see

Merchant et al., 2013) for a review). Consistent with this view, fMRI studies that have specifically focused on rhythm processing reveal that the SMA, ventral premotor area, inferior frontal gyrus, auditory cortices, and BG (particularly the putamen) are engaged during both rhythm perception and production, and are also more active in musicians than in non-musicians (Grahn and McAuley, 2009; Grahn and Rowe, 2009; Grahn et al., 2011). The putamen, SMA, PMC and STG appear to show greater involvement when rhythm processing involves the internal generation of a beat.

The ability to generate an internal beat (i.e., a periodic timing signal) is also critical for successful speech perception and production; the cortical-subcortical network engaged in rhythm perception provides temporal structure to optimize perception, and production through precise timing of speech movements (Kotz and Schwartz, 2010). For efficient segmentation of the continuous speech signal into meaningful units, patterns of stressed and unstressed syllables provide rhythmic and (quasi-) periodic cues to segmentation (Lehiste, 1977; Selkirk, 1984; Patel, 2010); these rhythmic expectations provide temporal structure to enable efficient perceptual prediction of upcoming sounds (Dilley and Pitt, 2010; Morrill et al., 2014; Kotz and Schmidt-Kassow, 2015), and also allows for precise timing of movements for speech production. Robust connectivity among the cortical-subcortical rhythm network regions thus likely provides scaffolding for the internal timing of sound sequences that is critical for both speech perception and fluent speech production.

Although our functional connectivity analyses were based on rsfMRI data and not task-based fMRI data, we showed a strong relation between strength of resting-state functional connectivity within the rhythm network and rhythm discrimination performance in typically developing children. Our findings are consistent with previous studies that have demonstrated that functional connectivity between task-related regions during resting-state recapitulates that observed during task performance (Hampson et al., 2002; Thomason et al., 2008; Koyama et al., 2013; Allen et al., 2014). Even though our participants were not performing a rhythm perception task during rsfMRI, the resting-state functional connectivity between the regions involved in rhythm processing in the control participants were correlated with their performance of a rhythm discrimination task conducted outside the scanner. This indicates that strength of resting-state functional connectivity within regions of the rhythm network, particularly with the

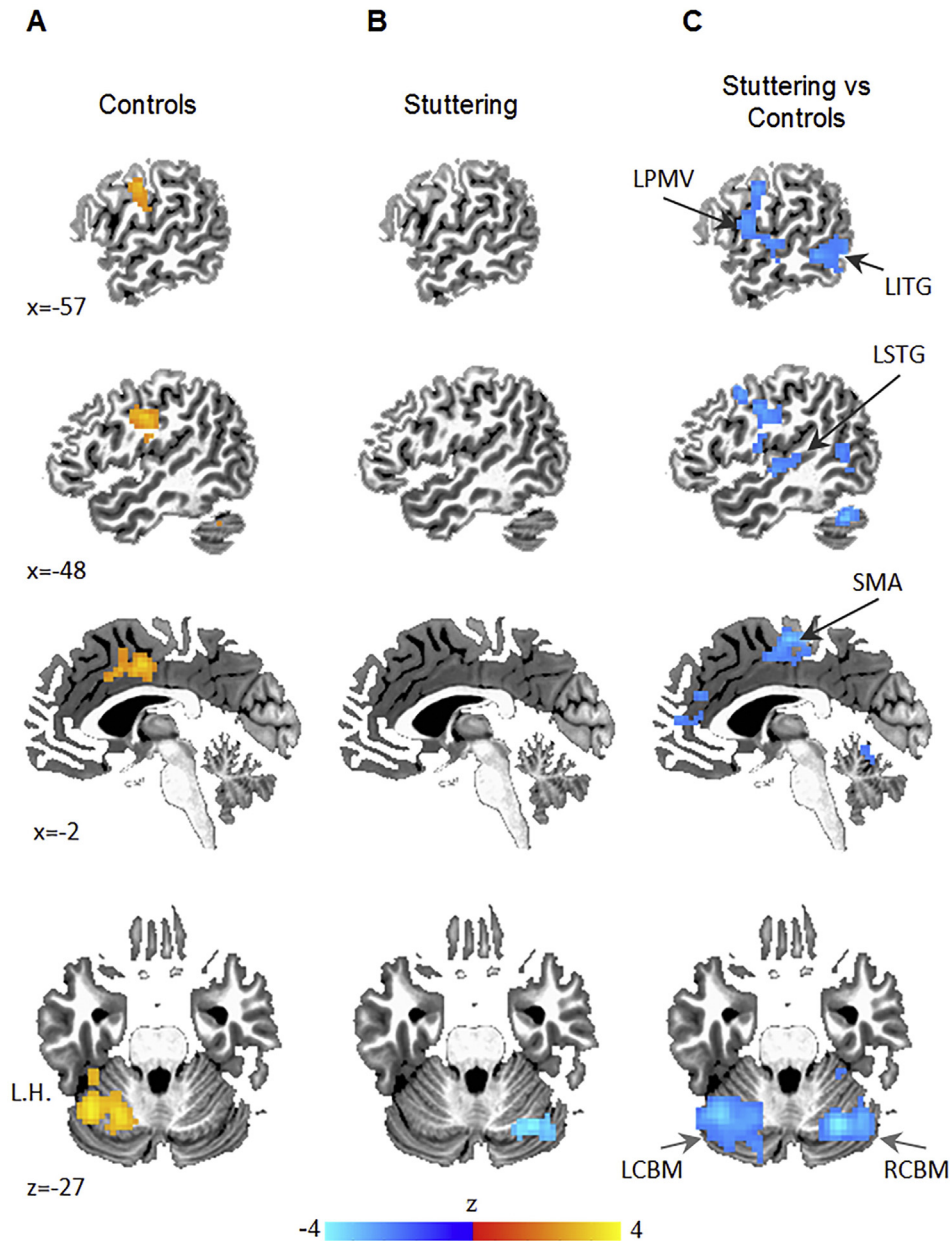


Fig. 4. Relation between functional connectivity with the left putamen and rhythm discrimination performance (d'). (A) Brain regions where functional connectivity with the left putamen were positively correlated with d' in controls (indicated in orange). (B) In contrast, this relation between functional connectivity and d' was not found in children who stutter (“Stuttering”). (C) Compared with controls, children who stutter exhibited attenuated relation between functional connectivity and d' in the bilateral motor and auditory areas as well as cerebellum (indicated in blue). The results of the group contrast were rendered on the anatomical image of a single subject. The results of the group contrast were rendered on the anatomical image of a single subject. LPUT: left putamen, LPMV: left ventral premotor area; SMA: supplementary motor area, LITG: left inferior temporal gyrus, LSTG: left superior temporal gyrus, LCBM: left cerebellum, and RCBM: right cerebellum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

putamen, can be viewed as a predisposition of the ability to successfully discriminate rhythms (Baldassarre et al., 2012). Our selection of the putamen as seed region for functional connectivity analysis was based on strong empirical support for its role in rhythm perception, as well as accumulating evidence of its pathophysiological relevance in stuttering (as reviewed in previous sections). However, we cannot rule out whether other parts of the striatum would also exhibit aberrant connectivity as it relates to rhythm perception in stuttering children.

For children who stutter, no significant relation was found in the whole brain analysis between intrinsic functional connectivity within the rhythm network and rhythm discrimination performance. However, the exploratory scatter plots (Fig. 5) illustrate a negatively trending correlation for children who stutter between putamen-cerebellum

functional connectivity and d' . The cerebellum has been shown to be overactive during stuttered speech (Fox et al., 2000; Budde et al., 2014), and successful stuttering therapy associated with decreased activity in the cerebellum (De Nil et al., 2003). On the other hand, cerebellum is suggested to serve a compensatory mechanism for a deficient core timing network (Kotz and Schwartz, 2010; Kotz and Schmidt-Kassow, 2015) that comprises the putamen and other cortical regions. This may be because of the cerebellum’s role in event timing (Ivry and Schlerf, 2008) and fine-tuning skilled movements via an efferent copy mechanism that integrates motor planning and sensory prediction. Although speculative, the negative correlation observed in children who stutter between putamen-cerebellum functional connectivity and performance on the rhythm discrimination task suggests

Table 1
Clusters exhibiting significant correlation between functional connectivity and rhythm discrimination (d').

Region	Side	x	y	z	t	No. of voxels
<i>Children who stutter</i>						
<i>Typically developing children (controls)</i>						
Precentral gyrus	L	-45	-12	33	4.0	125
	R	51	-18	18	4.0	600
Cerebellum	L	-36	-60	-30	4.0	214
Cingulate cortex/supplementary motor area	L/R	3	6	39	3.7	139
<i>Children who stutter vs. Controls</i>						
Cerebellum	L	-36	-60	-30	-5.1	466
	R	27	-69	-27	-4.9	360
Precentral gyrus/superior & middle temporal gyrus	L	-63	-3	12	-4.3	404
Precentral gyrus/superior temporal gyrus	R	63	-3	30	-3.8	436
Supplementary motor area	L/R	-3	-15	57	-4.3	293
Posterior inferior temporal gyrus	L	-57	-48	-6	-3.5	172
Superior frontal gyrus	L	-24	45	30	-3.9	148

that children who stutter (compared to controls) may use different and variable strategies/mechanisms (and associated neural substrates) to perform the rhythm-discrimination task. Consistent with this possibility, a number of researchers have made a distinction between beat-based and interval-based timing mechanisms that rely on different neural substrates with beat-based timing linked to the rhythm network (Grube et al., 2010; Grahn and McAuley, 2009; McAuley and Jones, 2003). If children who stutter rely to a greater extent on an interval-based timing mechanism to discriminate rhythms, then this would be

expected to reduce (or even potentially eliminate) the relation between functional connectivity within the rhythm network and performance on the rhythm discrimination task. Moreover, with variable strategies, the relation between functional connectivity within the rhythm network and d' will vary substantially among children who stutter and reduce the chance to detect the effect at the group-level analysis. In addition, while most of the stuttering children who participated in this study are likely to persist in stuttering (given the duration of stuttering at the time of their participation), there is a chance that we included some children who will eventually recover from stuttering. It is possible that children who recover from stuttering may show rhythm network development that is more similar to controls, or show distinct growth that is compensatory, which allows them to recover. In future studies, we will be able to conduct a retrospective analysis based on children who have recovered versus persistently stuttering children, which may help elucidate some of these issues. In sum, further studies are warranted to confirm and extend the results reported here; specifically to elucidate the basis for an overall lack of correlation found between functional connectivity and d' found in children who stutter.

Accumulating evidence has suggested that a core deficit of developmental stuttering is associated with deficient interaction among cortical and subcortical regions (Wu et al., 1997; Lu et al., 2010; Chang and Zhu, 2013; Wieland et al., 2015) involved in both rhythm and speech processing. These findings largely support theoretical perspectives that have implicated the role of timing-related neural circuits in stuttering (Alm, 2004; Etchell et al., 2014a, 2014b). The current findings, where children who stutter show 1) worse rhythm discrimination, 2) attenuated functional connectivity, and 3) no relation between intrinsic functional connectivity and rhythm discrimination performance, supports this hypothesis. Moreover, the differences between children who

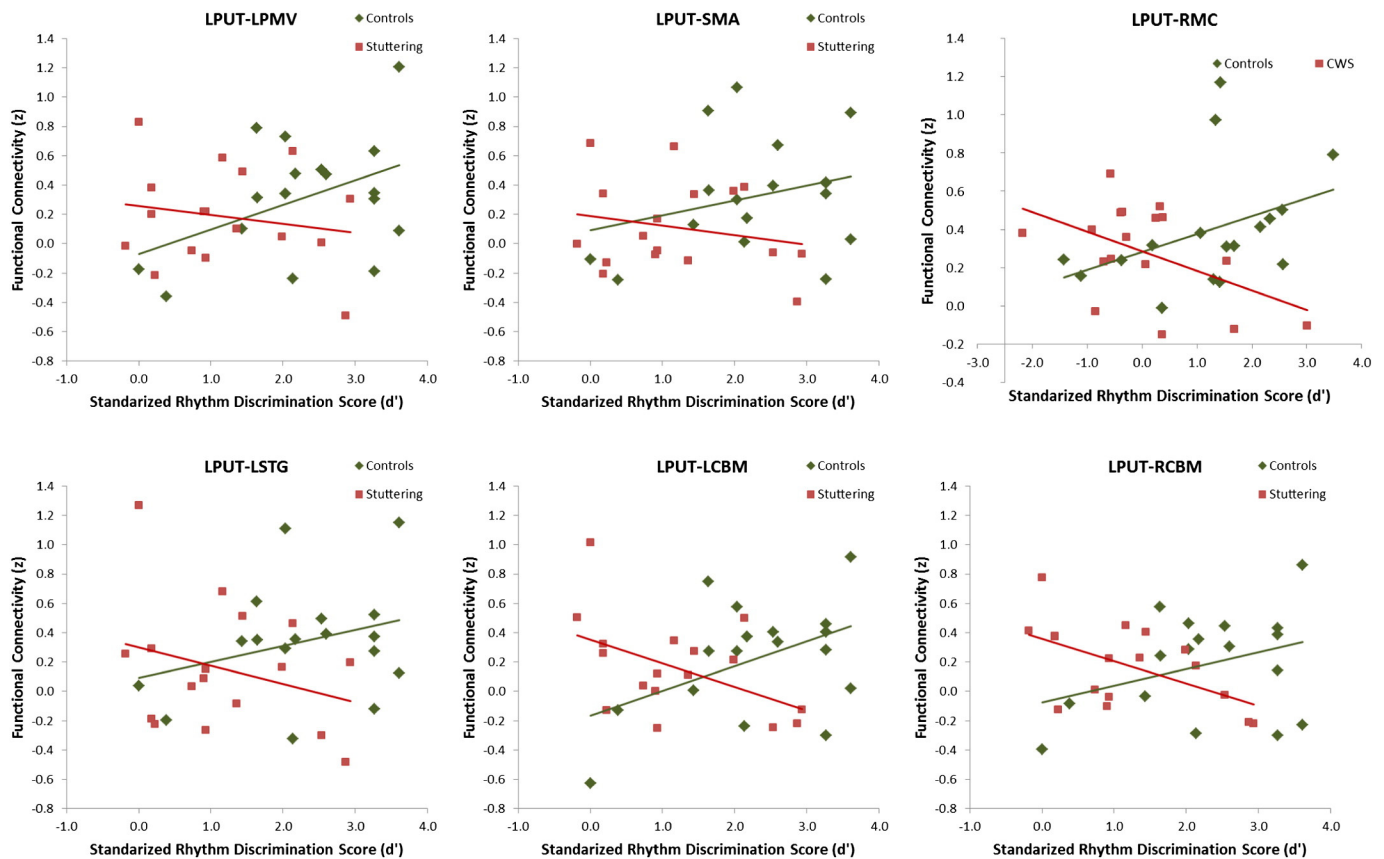


Fig. 5. Individual rhythm discrimination performance (d') plotted against functional connectivity (Fisher's z) between the left putamen (LPUT) and the left ventral premotor area (LPMV), supplementary motor area (SMA), right motor cortex (RMC), left superior temporal gyrus (LSTG), left cerebellum (LCBM) and right cerebellum (RCBM). Linear regression was used to remove the effects of socioeconomic status, IQ, age and gender from the raw functional connectivity between regions.

stutter and controls in d' (rhythm discrimination performance) and the differential relation to functional connectivity observed in this study between groups did not seem to be related to individual differences in cognitive ability, socioeconomic status or head movements during rsfMRI. When measures of these effects (IQ, socioeconomic status and head movements), together with d' , were included in the statistical model we found that they did not modulate group differences found in the relationship between functional connectivity and d' mentioned above.

To rule out the possibility that the effect of d' was a general effect on functional connectivity, and not specific to the regions in the rhythm network, we carried out the same analysis using a seed region in the left primary visual cortex (i.e., calcarine sulcus defined by WFU PickAtlas), a region unrelated to rhythm processing. In this post hoc analysis, as expected, we did not find any significant relationship between d' and functional connectivity in either children who stutter or controls, nor did we find any between group differences. These additional analyses provided confidence in our results that functional connectivity in the rhythm network exhibited a specific relation with rhythm discrimination performance.

In summary, the results of this study are the first to show a relation between strength of intrinsic functional connectivity in the rhythm network comprising the putamen and motor cortical areas and rhythm discrimination performance for typically developing children. In contrast, in children who stutter, strength of connectivity was dissociated from behavioral performance. This supports the view that children who stutter have a core deficit in rhythm processing associated with the ability to perceive temporally structured sound sequences, a skill that underlies rhythm perception as well as speech perception and production (Kotz and Schwartz, 2010). Results corroborate previous findings of subtle timing related deficits in people who stutter (Van Riper, 1982; Donald and Mackay, 1984; Kent, 1984; Caruso et al., 1994), and provide support for examining not only classical speech perception and production cortical networks, but also considering subcortical timing networks in understanding the pathophysiology of stuttering.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.nicl.2016.08.021>.

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