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Reproducing speech intervals in the sub-hundred millisecond (ms) range with a translocation in 7q31.

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Abstract

THERE IS INCREASING EVIDENCE, gathered from human and animal studies, that mutations in the transcription factor* FOXP2 *impairs sensorimotor responses at the brain level [1,2,3].

How some gene interactions produce afferent-efferent circuits involving gabaergic and glutamergic populations of cells in different parts of the CNS is unclear. It is known that* FOXP2 *is expressed in a sensorimotor dopaminergic circuit, comprising the striatum, thalamus, deep cerebral cortical layers, the inferior olive and Purkinje cells of the cerebellum [4, 5,14]; see FIG 1.

Here we focus on a case of a subject A with speech and language disorders who has a chromosomal translocation t[7;11] affecting 7q31, the locus of* FOXP2 *[6,7,8]; see FIG 2.

Since there is substantial evidence that the neural basis for interval timing of fast movement changes, crucial for speech and language, may be regulated by these sensorimotor dopaminergic circuits [9,10,20], we focus here on how interval timing in the ms range is reproduced by A compared to the tutor, and a control C matched for sex, age, languages and education.

It is found that A reproduces non-word sequences with significantly fewer dynamic changes than C. We discuss these findings relating them to the debatable hypothesis that the cerebellum may be more involved in the perception and production of sub-second intervals.

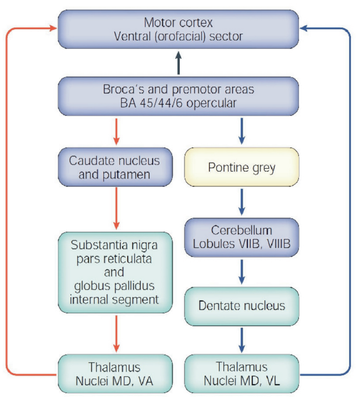
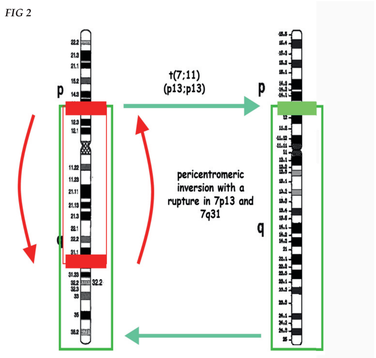


FIG 1 - Proposed circuit for FOXP2*-dependent speech and language (taken from [14]). Red arrows, inferior frontal-basal ganglia loop; blue arrows, inferior frontal-cerebellum loop. Blue and green boxes indicate structures that express* FOXP2*; blue boxes indicate the structures that have been found, using neuroimaging, to be abnormal either structurally, functionally, or both in affected KE family members. Besides the structures shown here, other components of the basal ganglia circuit that express* FOXP2 *include the subthalamic nucleus and the ventral medial, centromedian and parafascicular nuclei of the thalamus; similarly, other cerebellum-related structures that express this gene include the inferior olivary complex and the red nucleus. BA, Brodmann areas; MD, medial dorsal thalamic nucleus; VA, ventral anterior thalamic nucleus; VL, ventral lateral thalamic nucleus.*

FIG 2



Introduction

IN THE LAST YEARS, many lines of research have been conducted to disentangle the neurobiological underpinnings of human language, including the search for genes that control the growth and function of neural substrates involved in auditory-motor association learning. In humans the non-functionality of *FOXP2*, due to point mutations,[16,17] translocations, [11] or deletions [18], has been found to cause deficits at this level. [1,3]

Although time interval processing is involved in most (if not all) sensorimotor functions, including language [9,15], no time interval measurements of speech have been applied to these pathological cases in order to evaluate their neural bases.

Many lines of research point to the hypothesis that processing of time in millisecond and second intervals may depend on different neural networks and there is now considerable evidence to suggest that these intervals are possibly produced by different brain mechanisms [12]. For instance, repetitive Transcranial Magnetic Stimultation (rTMS) over the lateral cerebellum impairs time perception in a short interval millisecond range (400-600ms) only, whereas rTMS of right prefrontal cortex impairs timing of supra-, not sub-second durations.[10,19] Moreover activation has been found in the basal ganglia (putamen) during a 1-s duration discrimination task but not in the cerebellum.[13]

In a previous perceptual-production experiment applied to this case, it was found that A did not deviate significantly in the time interval comprising the whole sequence compared to that of the tutor or C, but did significantly deviate in the interval timing of the vocalizations from the control making them longer.[7] In a subsequent perceptual experiment, it was found that there was a significant correlation between not perceiving sub-200 ms word intervals and failing on the integration of supra-200 ms word intervals.[8] Based on that evidence, we hypothesize that auditory-motor time interval changes in the ms range are at risk of being impaired. We investigate here that question using an Acoustic Dynamics Analysis.

Methods

Design of the perception and production experiment

Subjects: N=2. Sex=Female.

At the time of the test: Age A=10 years 4 months; C=10 years. Both were drug free and with no auditory dysfunctions. Their school and socioeconomic level and their languages (Valencian and Castilian) were the same. Subjects were sitting 2m in front of the tutor unable to see the tutor's lips to preclude interference between auditory and lip visual inputs. Nonsensical sequences were produced by the tutor N=255 (A) and N=252(C). Temporal production times of utterances from tutor: Max=2s Min=110ms.

Sequence structures: V;VC;VCV;C;CVC;CV. The maximum sequence had 6 time intervals with 5 movement changes or shifts. $V^2C^2V^2$;$C^2V^2C^2V^2$. Laryngeal and supra-laryngeal movements were required to produce vocalizations used in their languages (automated vocalizations N=10) and new ones (non automated vocalizations N=3). The test targets the ability to respond with automated and non automated auditory-motor associations and the ability to reproduce the order of these associations in a sequence.

A PRAAT sound analyser and a camcorder were used. Each sequence was kept in a wav. form.

Analysis of Acoustic Dynamics

Multi-Step AFI (MAFI) chooses frames which can be interpolated via Acoustic Flow to reproduce a complete spectrogram with little error [21]. For example, MAFI can identify a phonetic 'glide' as a single segment, without any prior knowledge of what that segment might represent. A number of parameters could be extracted from the MAFI analysis, but for simplicity we have concentrated on just two: segment duration and dynamics per unit time.

MAFI quantifies the number and abruptness of acoustic changes as well as the rapidity of formant transitions, thereby determining the nature and degree of distortion in phonetic realisation. Thus we can extrapolate information about both the phonological structure of an utterance and its phonetic realisation. By comparing such properties with those in normal speech, we can characterise some of the dynamic properties of a particular speech impairment and identify a set of salient and robust acoustic indicators.

Hence the dynamics of the data was matched as closely as possible, dividing each audio into 100ms or less segments by setting a low MAFI threshold. This close match of the data allowed the dynamics of the features in the spectrogram within each of these segments to be measured more accurately.

Results

FIGS-3-6 show the total dynamics in all the data produced by each child and the respective target. The x-axis in the plots represent spectral feature movements per ms within each segments of 100ms or less, produced by MAFI. These graphs show the number of times quantities of spectral movement (per 100ms or less) occur.

FIG 3

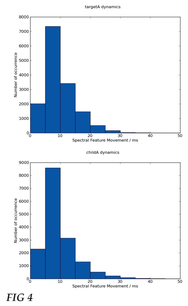


FIG 4

FIG 5

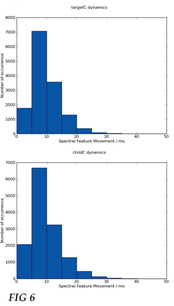


FIG 6

Conclusion

Observation of segments of 100ms or less that are produced by MAFI shows that child A has fewer dynamics (i.e. spectral movement per 100ms or less) in her production than her Target A, Child C or Target C.

Discussion

These findings on the poor dynamics of speech in A are consistent with previous results for this subject which show overestimation of interval timing changes in a perception-production task [7] and failure to respond to under 200ms word intervals in a perception task [8]. All together these findings suggest that rapid changes in the auditory-motor association circuit in the ms range may be at risk. Further trimming of the audio data may allow the Acoustic Dynamics Analysis to detect which specific time interval ranges are most at risk in our subject. These future temporal analyses coupled with fMRI analyses and investigation into the functionality of *FOXP2* may help to answer whether the involvement of the inferior olive, which sends via the contralateral inferior cerebellar peduncle climbing fibers to the Purkinje cells in the cerebellum, is facilitating auditory-motor association intervals in the ms range to a greater extent than the rest of the auditory-motor circuit. It will also contribute to gaining a better insight into the role of *FOXP2* on auditory-motor association learning, and eventually into the role of *FOXP2* on time interval processing in language production and comprehension.

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