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Endophenotypes of FOXP2: Dysfunction within the human articulatory network

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ABSTRACT

The identification of the first gene involved in a speech-language disorder was made possible through the study of a British multi-generational family (the "KE family") in whom half the members have an inherited speech-language disorder caused by a *FOXP2* mutation. Neuroimaging investigations in the affected members of the KE family have revealed structural and functional abnormalities in a wide cortical-subcortical network. Functional imaging studies have confirmed dysfunction of this network by revealing abnormal activation in several areas including Broca's area and the putamen during language-related tasks, such as word repetition and generation. Repeating nonsense words is particularly challenging for the affected members of the family, as well as in other individuals suffering from idiopathic developmental specific language impairments; yet, thus far the neural correlates of the nonword repetition task have not been examined in individuals with developmental speech and language disorders. Here, four affected members of the KE family and four unrelated age-matched healthy participants repeated nonsense words aloud during functional MRI scanning. Relative to control participants, repetition in the affected members was severely impaired, and brain activation was significantly reduced in the premotor, supplementary and primary motor cortices, as well as in the cerebellum and basal ganglia. We suggest that nonword repetition is the optimal endophenotype for *FOXP2* disruption in humans because this task recruits brain regions involved in the imitation and vocal learning of novel sequences of speech sounds.

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1. Introduction

Investigations of a multi-generational British family ("KE" family[1]) in whom half the members are affected by a speech-language disorder caused by a heterozygous mutation have led to the identification of *FOXP2*,[2,3] the first gene involved in speech acquisition. In addition to widespread language comprehension and production deficits,[4] the affected members have a speech disorder which is mainly characterized as an apraxia of speech, rendering their utterances highly unintelligible to the naïve listener. Although the affected members can pronounce most speech sounds (or phonemes) accurately in isolation, their words and sentences feature frequent and inconsistent phonemic omissions, substitutions, distortions and additions. Furthermore, affected members of the family present with mixed dysarthric features, although classified predominantly as spastic dysarthria with characteristic low pitch, reduced stress, and a breathy voice.[5] Disturbance of oral resonance has also been reported.[5]

Extensive behavioural assessments have revealed that the most sensitive task for discriminating between affected and unaffected status[4] involves the repetition of nonsense words (such as "foogal"), i.e., a "nonword repetition" task.[6] Unlike repetition and generation of real words, nonword repetition does not require semantic processing (access to meaning), and is therefore a powerful tool for the study of motor speech deficits,

Table 1 – Brain regions activated during nonword repetition (vs. listening to noise contrast) in the control and affected KE groups (see Methods). Results presented at a threshold of $p = 0.05$, corrected for whole-brain multiple comparisons. See Fig. 1 for an illustration of group activation patterns at a lower threshold. Coordinates indicate local maxima on the x (medial-lateral; negative left), y (anterior-posterior; negative, anterior) and z (ventral-dorsal; negative, ventral) axes.

Anatomical region	Brodmann's area	Controls		Affected KE	
		Coordinates (x, y, z)	T value	Coordinates (x, y, z)	T value
L STG	22	−66, −16, −5	7.32		
R cerebellum	Lobule IV (hem)/VIIa Crus I (hem)	36,−43, −41	7.28		
L dorsal precentral gyrus/postcentral gyrus	4/3	−60, −7, 37	6.88		
R STG	22	69, −19, −2	6.67		
R STG	22	66, −16, 10	6.27	69, −22, 4	5.58
R temporal pole	38	54, 17, −5	6.26		
R posterior STG	22	66, −40, 7	5.57		
L precentral gyrus	6	−36, −19, 67	5.52		
R posterior ITG	37	57, −49, −14	5.44		
L cerebellum	Lobule VIIIb/IX (hem)	−12, −61, −44	5.03		
R cerebellum	Lobule VIIIa (ver)	0, −64, −29	4.90		
L inferior parietal lobule	7	−51, −46, 52	4.81		
R thalamus (ld/lp)		18, −19, 16	4.8		
R cuneus	17	6, −79, 22	4.74		
L anterior STG/MTG/ITG	38/21/20			−45, 5, −23	11.34
L cerebellum	Lobule VIIa Crus II (hem)			−18, −82, −38	8.24
R postcentral gyrus	3/1			42, −37, 64	5.93
R supramarginal gyrus	40			63, −46, 31	5.92
R cerebellum	Lobule VIIa Crus II (hem)			15, −82, 44	5.79
L anterior insula				−27, 26, −5	5.28
Inferior occipital gyrus	17/18			−21, −94, −11	5.10
L dorsal precentral gyrus	4			−57, 2, 40	4.87

Abbreviations: BA, Brodmann's area. L, left; R, right. STG, superior temporal gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; ver, vermis; hem, hemisphere. See Fig. 1 for illustration.