Timing the integration of utterance duration and task shift in a case of genetic anomaly implicating 7q31 with language disorders.

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Presented at Sound Day, University of Oxford, March 5, 2011.

With a research grant from the John Fell OUP Research Fund

UNIVERSITY OF OXFORD

INTRODUCTION

The neural mechanisms of interval timing are not well understood but several lines of research suggest a role of midbrain dopamine. It has been proposed that the perception and production of durations in the seconds-to-minutes range can produce overestimation or underestimation when dopamine concentration levels fall or increase in the cortico-basal ganglia circuits (Malapani et al. 2002, Drew et al. 2003). It has also been proved that a humanized version of *FOXP2* affects dopamine concentration levels in these circuits (Enard et al. 2009). Consequently, since 7q31 is the *locus* for *FOXP2*, a gene involved in speech and language disorders (Fisher et al. 2009) (Figure 1,2), and this gene could have been disrupted by the translocation and the pericentromeric inversion in chromosome 7 in our subject with language disorders (García-Bellido et al. 2009) (Figure 3), we asked whether the estimation of time intervals in the 110 milliseconds-to-2 seconds range has been affected. We measured the subject's (A) deviation in the temporal reproduction time of two types of time intervals of the utterance: a longer utterance time interval clock (I) and a shorter articulatory time interval clock (II) of the sequence. The performance of the affected drug-free subject was compared with that of a non affected subject (C) matched for age and sex as well as languages, education and socioeconomic background.

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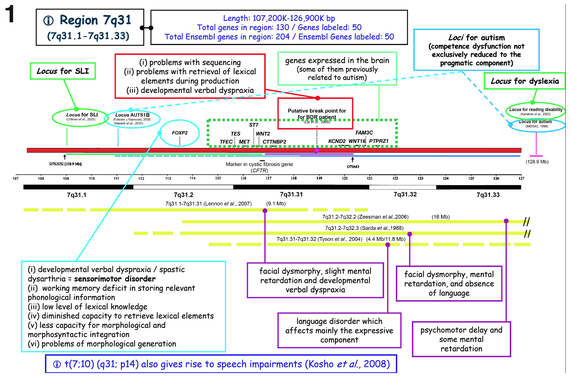

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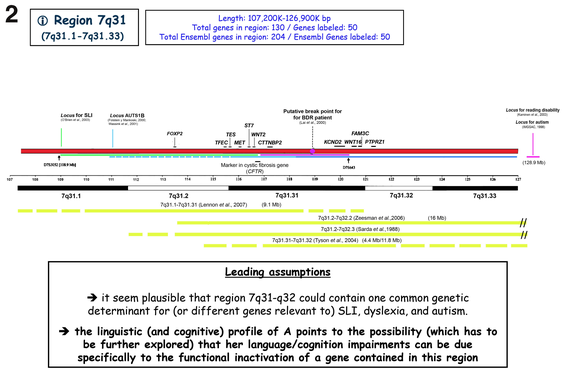

Leading assumptions

➔ it seem plausible that region 7q31-q32 could contain one common genetic determinant for (or different genes relevant to) SLI, dyslexia, and autism.

➔ the linguistic (and cognitive) profile of A points to the possibility (which has to be further explored) that her language/cognition impairments can be due specifically to the functional inactivation of a gene contained in this region

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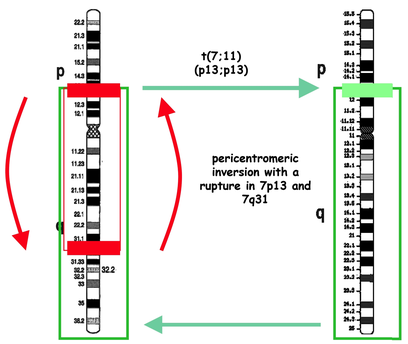

RESULTS

The percentage of clock II overestimation was significant p<.001 compared with the control (Figure 4), but the overestimation in the longer time interval (Clock I) was not significantly different in the two subjects (Figure 5). The experiment also showed that the affected subject differed significantly p<.0001 in the number of omissions, additions and conservations compared with the control(Figure 6).

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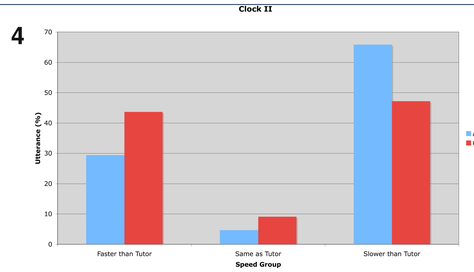

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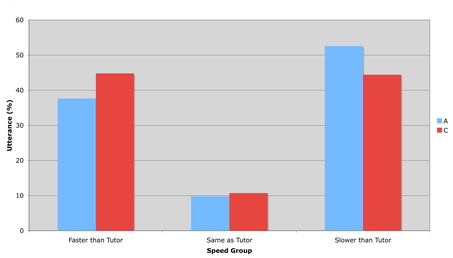

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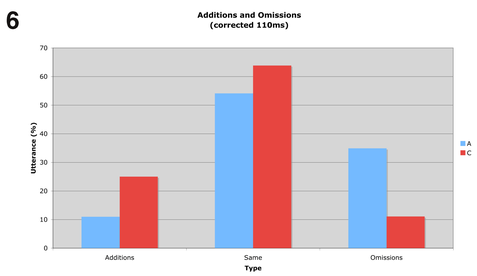

DESIGN OF PERCEPTION and PRODUCTION EXPERIMENT

Subjects (n=2). Age at the time of the test (A:10;4/C:10). Utterances (n=255 (A)) (n=252(C)). Subjects were sitting 2m in front of tutor unable to see the tutor's face in order to preclude lip reading interference with auditory stimulus. Subjects were asked to repeat one utterance at a time. Six types of nonsensical sequences were produced by the tutor whereby the utterance could not have more than a sub-sequence of two C or V (FIGURE 7). Temporal Production Time from Tutor: Max: 2s. Min 110ms

7

CN X	VOICED								VOICELESS
CN X								NASAL	
					Fricative	Flap	Trill		Fricative
Tongue up FRONT CN XII	v			i	e	ɜ	ɾ	r	n	s
Tongue up BACK CN XII	u	o	b	ɛ						
Uvular								ʁ		
Lips CN VII	ROUNDED			UNROUNDED						
Sequences	V	V¹C¹V²	V²C²							
	C	C¹V¹C²	C²V²							

CN= Cranial nerve. IPA symbols. V=v i e u o ɛ. C= b ɜ ɾ r ʁ n s

METHODS OF ANALYSIS

Praat Sound Analyser and a camcorder were used. The 1014 utterances were transcribed by three experimenters. Temporal production and reproduction time was measured by two experimenters.

ANALYSIS OF RESULTS

Nine types of two-clock integration were obtained (Figure 8). A correction of 110ms was allowed for each addition or omission (Figure 8 & 9) to isolate relevant speed deviations (Figure 10 shows the types without correction).

Since A produced more omissions than C we asked

Q1. Do omissions increase as a function of the number of attempts to reproduce the tutor's target suggesting increasing tiredness?

Yes. However, there is a statistically relevant tendency for C ($p<0.0006$) to produce less additions as a function of the number of attempts to reproduce the tutor's target (Figure 11). There is a tendency, though not statistically relevant, for A ($p<0.5256$) to produce more omissions as a function of the number of attempts to reproduce the tutor's target (Figure 12).

Q2: Do omissions correlate with increase on number of task shifts?

Yes. There was a tendency for both subjects to produce more omissions the more task shifts (transitions) the target had. However this correlation was only significant ($p<.0003$) for A (Figure 13), not for C ($p<0.4886$) (Figure 14).

8

Frequency of A's divergence from the tutor's TPT and TPTA, compared to C (N trials: =255 (A)/=252 (C)) with 110ms correction per Articulation for Ads. and Oms.

Additions 25.00% C (63) 10.98% A (28) T S	I II 9 II 16.27% C (41) II 5.49% A (14)	I0 II 3 II 0.79% C (2) II 0.78 % A (2)	I' II' 4 II' 7.94% C (20) II' 4.71 % A (12)
Neither Ads. Nor Oms. 63.89% C (161) 54.12% A (138) T S	I II 6 II 26.59% C (67) II 23.14% A (59)	I0 II0 1 II0 9.13% C (23) II0 4.70% A (12)	I' II' 7 II'28.17% C (71) II'26.27% A (67)
Omissions 34.90% A (89) 11.11% C (28) T S	I II' 5 II' 9.02% A (23) II' 1.98% C (5)	I0 II' 2 II' 4.31% A (11) II' 0.79% C (2)	I' II' 8 II' 21.57% A (55) II' 8.33% C (21)
	I Underestimation 44.84% C (113) 37.65% A (96)	I0 Neither Ov. nor Un. 10.71% C (27) 9.80% A (25)	I' Overestimation 52.54% A (134) 44.44% C (112)
T S			

A=Subject with chromosomal rearrangement. C= Control Subject.I-9=Types of two-clock integration. TPT=Temporal Production Time. TPTA= Temporal Production Time of Articulation. TRTA= Temporal Reproduction Time of Articulation (Clock II). TRT=Temporal Reproduction Time of Utterance (Clock I). I= TRT (Clock I). II= TRTA (Clock II). 0=Neither slower nor faster TRT, (accurate stopping, i.e isosentiation). I'= Slower TRT (later stopping, i.e. overestimation). I= Faster TRT (earlier stopping, i.e. underestimation). II' = Slower TRTA (later stopping, i.e. overestimation). II= Faster TRTA (earlier stopping, i.e. underestimation).T= tutor. S=Subject.

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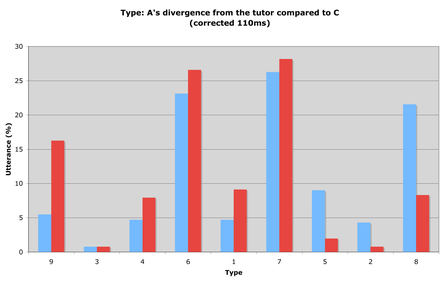

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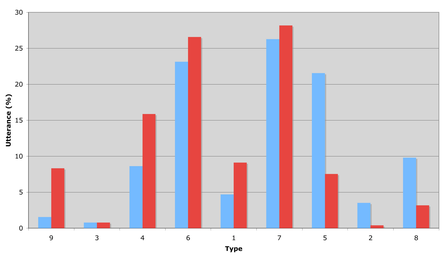

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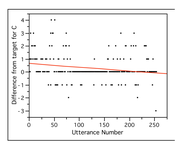

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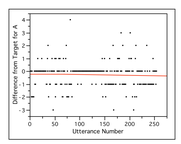

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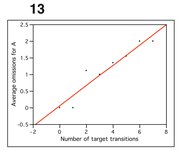

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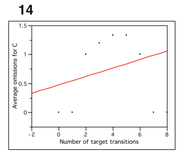

DISCUSSION

These results indicate that A has more difficulties in estimating the temporal reproduction time of short intervals compared with C when attempting to imitate speech.

This may suggest that more dopamine depletion states in A than in C may be correlated with more overestimation and this may cause a general slowdown in speech and language perception and production. This would be in agreement with both Malapani et al. (2002) and Drew et al. (2003) where it is found that a state of depletion of dopamine may affect the estimation of interval timing with the consequent effect of slowing it down. However, Malapani et al. (2002) suggest that "When time intervals are stored in memory while the subjects are dopamine depleted, the process is slowed leading to overestimation of two different time intervals. Conversely when retrieval occurs in a dopamine depleted state, interference or coupling occurs between two remembered time intervals producing overestimation of the shorter and underestimation of the longer one". This retrieval effect, termed "migration", is not found in mice when D2 receptors are blockaded with the antogonist haloperidol (Drew et al.2003). However while the migration retrieval effect is found in type 5 (Figure 8) producing more omissions in A than in C, the storage effect is found in types 8, 7, and 4 producing additions, omissions and conservations (Figure 8). Therefore, our findings that A produces omissions more frequently than C cannot follow from overestimating shorter intervals alone.

However, while Malapani et al. (2002) and Drew et al. (2003) used each type of interval as a separate stimulus, this experiment analyses time intervals as the result of an integration of both. Therefore a different underlying mechanism may be responsible for the high percentage of omissions in A compared with C (Figure 6).

REFERENCES

Drew, Michael R. Fiarhurst, Stephen, Malapani Chara, Horvitz Jon C. and Balsam Peter D. (2003) Effects of dopamine antagonists on the timing of two intervals. *Pharmacology, Biochemistry and Behavior 75*, 9-15.

Enard, W et al (2009) A humanized version of *FOXP2* affects Cortico-Basal Ganglia Circuits in Mice. Cell 137, 961-971.

Fisher S E and C Scharff (2009) *FOXP2* as a molecular window into speech and language. *Trends in Genetics 25:4*, 166-177.

García-Bellido E P, A Benítez-Burraco, M Roselló, S Monfort, F Martínez, S Oltra, R Quiroga, C Orellana (2009) A case of Spanish language disorders with a rare genetic cause. In Marrero V & I Pineda. Linguistics: the challenge of clinical application. Proceedings of the II Internatinal Conference on Clinical Linguistics. UNED. Madrid. Pp 365-370.

Malapani, C. Deweer B. and Gibbon J. (2002) Separating Storage from Retrieval Dysfunction of Temporal Memory in Parkinson's Desease. *Journal of Cognitive Neuroscience 14:2*, pp 311-322.

ACKNOWLEDGE-MENTS

We thank Greg Kochanski, Silvia Xicola-Tugas, Amir Nettler, and the subjects for their collaboration and help at different stages in this research.