Paloma García-Bellido[1,2], Ladan Baghai-Ravary[3], Sergio Grau[3] and Antonio Benítez-Burraco[1,4]
1. Modern Languages, Oxford, UK, 2. Linguistics, Oxford,UK, 3. Phonetics Laboratory, Oxford, UK, 4. Department of Spanish Philology, Huelva, Spain.

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UNIVERSITY OF OXFORD

Timing Language Disorders with a Chromosomal Translocation in 7q31

Introduction

Speaking and understanding must derive from performance limitations of both the auditory and motor-muscular pathways.[1] How auditory stimulation initiates comprehension remains a persistent puzzle. However, previous studies support a model in which short time intervals in the ~20–50 ms range might involve specific spontaneous endogenous oscillatory rhythms compared to longer ones[2,3]. Since language disorders provide a window for the search of the genetic basis of speaking and understanding[4], we focus on the speech and language performance of a subject, A, who has a translocation between chromosomes 7 and 11 (t[7;11] [p13;p13])[5] (Fig. 1), affecting 7q31, the **locus** of *FOXP2*. (Figs 2-3) In a previous measure of A's performance, it was found that articulatory overestimation of non-sensical aural subsequences (phonemes), in sequences ranging from 110ms to 2s, was statistically significant compared to a control[6]. We now measure if there is a correlation between failure to interpret an utterance and the presence of a relevant short interval (SI) subsequence (word), in the range of 20-200ms duration, whose integration is crucial for the understanding of the utterance. If there is one, then these two separate findings, would suggest that the right interaction of genes may be needed to support specific neuroanatomical and neurochemical substrates of interval timing[8] in order to respond to and execute short intervals. Ultimately these findings could be supporting that the same substrate[7], probably modulated by a dopaminergic circuit[8], determines both reception and transmission.

Fig. 1

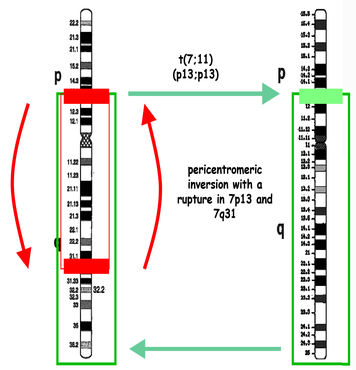


Fig. 2

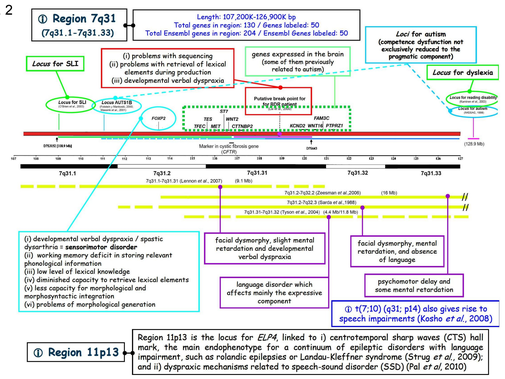


Fig. 3

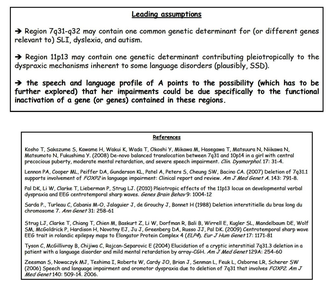
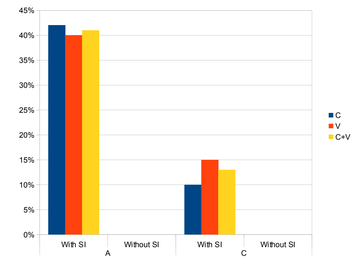


Fig. 12 Percentage of Errors in Utterances With and Without SI in Castilian and Valencian for A Compared to C



Both subjects made zero errors in all utterances without SI.

Design of Perception Experiment

A standard comprehension test of basic grammatical structures for a Spanish population between ages 4-11 was used[9]. The child had to point to one out of 4 images to match the communicative intention of the utterance (Fig 4). Utterances (n=80 Valencian and n=80 Castilian).

N=80 sequences (utterances) (min 870ms-max. 5.55s) were used as auditory stimuli for each variety. Each utterance contained subsequences (words) ranging from minimum 20ms duration to a maximum of 960ms. Words with more than 200ms were considered Long Intervals (LI) and those below Short Intervals (SI). We identified two types of Sustained Attention[8]: a Short Sustained Attention Interval and a Long Sustained Attention Interval between two LIs, a SI and LI, and two SIs. (Fig 5).

The duration of the vocoid system is the same. Speakers of both varieties use the same grammatical structures with only lexical differences. Valencian does not have an interdental voiceless fricative [θ] but has three additional articulations: a post alveolar fricative with two variants: voiceless [ʃ] and voiced [ʒ] and a voiced alveolar fricative [z].

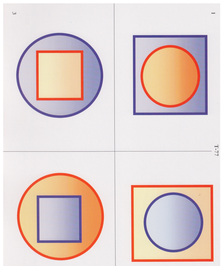


Fig 4. Sample of visual stimulation for a type 3 Relative clause construction.

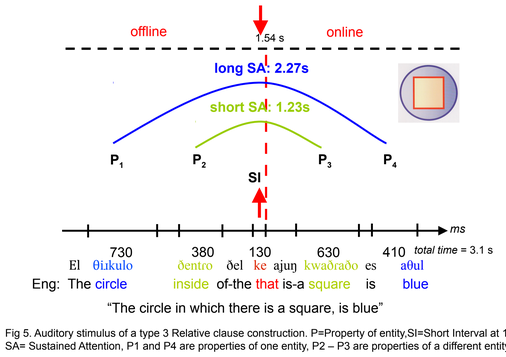


Fig 5. Auditory stimulus of a type 3 Relative clause construction. P=Property of entity,SI=Short Interval at 1.54s, SA= Sustained Attention, P1 and P4 are properties of one entity, P2 – P3 are properties of a different entity.

Subjects

Subject (n=2). Age at the time of the test: A=11y8m, C=11y5m. Subject A was matched with C by age (11y), sex (Female), school level, socioeconomic level and speech varieties (Valencian and Castilian). Both were drug free. Neither had an auditory nor visual nor hand motor dysfunction, nor auditory-visual synaesthesia of colours.

Research questions

Q1. Is there a significant difference between the performance of A compared to C?
Q2. Is there a significant difference between the performance of each subject in their two languages?
Q3. Is there a significant difference in errors between A and C in both languages for utterances with a relevant SI?

Method

Both Spanish and Valencian utterances were automatically time-aligned with transcripts to find word (and phone) boundaries.

CMU Sphinx-II speech recognition software[10] in forced aligned mode was used to force align recordings of the Castilian and Valencian utterances with their corresponding words. Due to the phonetic similarities of Castilian and Valencian languages we only use Castilian acoustic models and pronunciation dictionary to perform the forced alignment for both languages. The acoustic models used for the forced alignment were trained using read sentences by male and female speakers in Castilian. The pronunciation dictionary was generated automatically using the ort2fon tool as explained in[11].

The average duration of each utterance as well as the individual words were then calculated for each language.

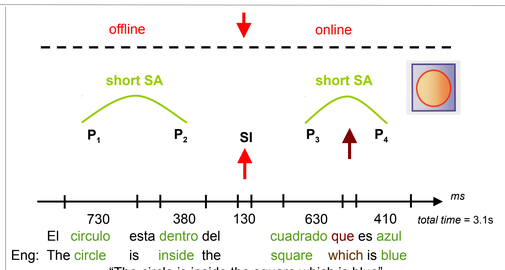


Fig 9. Hypothesis of integration of Properties in which P3 and P4 synchronise for the same entity, possibly with the Relative Pronoun particle (Brown arrow) facilitating it.

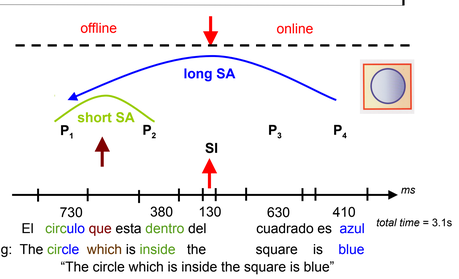
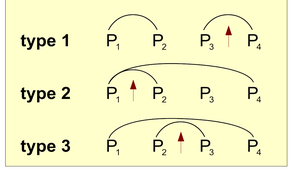


Fig 10. Hypothesis of integration of Properties in which P1 and P4 synchronise for the same entity, possibly with the Relative Pronoun particle (Brown arrow) facilitating it.

Fig 11. Relative Clause Construction types arranged by level of difficulty in ascending order during development. The brown arrow indicates relative pronoun particle.



Results

Answering research questions:

1. Subject A's performance reached a 5 year level compared to the control who was normal for her age (Fig 6). The differences between A and C with respect to the utterances were significant to a confidence level more than 99% (Fig 8).
2. The differences between two languages (Valencian and Castilian) with respect to the utterances or blocks were not significant (Figs 7 and 8) for each subject.
3. Comparing the errors between A and C for utterances in which SI is crucial for the interpretation in both languages, we found a statistical significance of $p=1.042\times10^{-7}$ (Fig 12).

It was also found, but not quantified, that whether a crucial SI stimulus was not perceived (Passive auxiliary, Accusative Cleft, Accusative topicalization) or perceived (Relative Pronoun constructions (Figs 5, 9,10), non-reflexive clitic constructions, and negative constructions), the integration of LIs was generally achieved nevertheless but producing a wrong meaning. Subject A performed in Relative Clause construction of type 3 (Figs 5, 11) providing the Short Sustained Attention integration given in Fig 9, corresponding to type 1 (Fig 11), which is developmentally at an earlier stage than type 2[9], produced instead by C (Fig 10 and 11). Subject A produced 14 utterances out of 80, with the same error in both languages, while C produced only 4 for both languages.

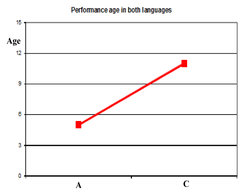


Fig. 6

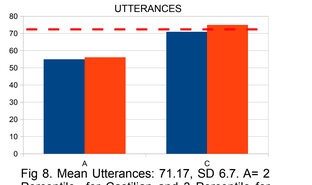


Fig 8. Mean Utterances: 71.17, SD 6.7. A= 2 Percentile for Castilian and 3 Percentile for Valencian.

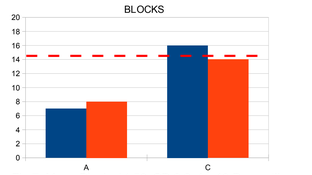


Fig 7. Mean Block: 14.56, SD 3.2. A= 10 Percentile for both languages. C= 40 Percentile for Valencian and 60 for Castilian.

Discussion

The neural mechanisms for sustaining the perception or execution of one interval or for sustaining the attention of two intervals is not well understood but it has been suggested that dopaminergic modulation of timing is mediated through an action on the dopaminergic receptors, rather than through Dopamine synthesis.[8] Haloperidol, a D2 receptor antagonist, reduced temporal sensitivity in both the milliseconds and seconds range, whereas pergolide, a D1/D2 receptor agonist, improved temporal sensitivity in the milliseconds range[12]. This modulation of timing may be supported by a functionally integrated network involving the striatum, thalamus, cortex and cerebellum[8]. Since *FOXP2* is known to be expressed in these nuclei[13] (Fig 11), our findings, which suggest that timing short intervals in the syntax is compromised in this subject compared to a control matched for age, schooling and linguistic background, are coherent with the role that *FOXP2* may play, together with other genes, in supporting the anatomy and physiology of this network.

Fig 11. Proposed circuit for *FOXP2*-dependent speech and language (taken from [13]). 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.

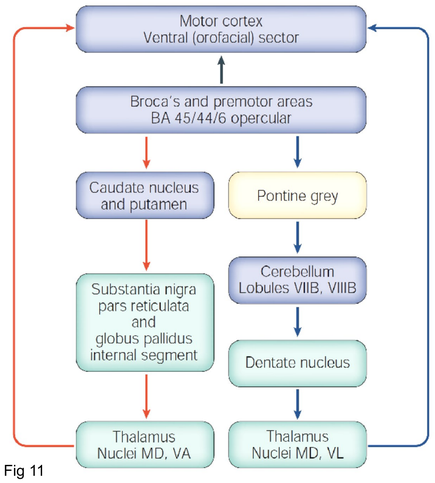


Fig 11

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Acknowledgements

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