Avances en Lingüística Clínica

Selección de Comunicaciones del III Congreso Internacional de Lingüística Clínica

Coordinadores:

Ignacio Moreno-Torres Sánchez
Esther Moruno López
Sonia Madrid Cánovas

Universidad de Málaga

Ilustración de cubierta: Javier Fernández López
Diseño/maquetación: Paloma Murciano Herrera

ISBN: 978-84-9747-

Índice

Time interval integration with a chromosomal translocation affecting 7q31[1]

E. Paloma García-Bellido
University of Oxford (UK)
paloma.garcia-bellido@mod-langs.ox.ac.uk

Antonio Benítez-Burraco
University of Huelva (Spain)

Abstract: How exactly auditory stimulation initiates language comprehension is still unknown. Some lines of research point to the possible involvement of sub-cortical and cortical circuits, particularly through a functional network comprising the striatum-thalamus-cortex and cerebellum, in which FOXP2 is expressed. This network is thought to support the production and perception of time intervals. In order to evaluate if deficient perception and timing of short time interval words (SIW) in the range of 20 to 200 ms - crucial for timing correctly the integration of long time interval words (LIW) above 200ms - can increase the degree of difficulty in comprehension, we study here a 11 year old subject, A, with a break at some point in the 7q31 region, where FOXP2 is located. Using an audio-visual test with linguistically relevant SIWs contained in basic grammatical constructions and comparing A's difficulty score with that of a 4-11 year old normal population (NP) and that of a control matched in age, sex, schooling, language and socioeconomic background, it was found that A scored higher than a 6 year old but lower than a 7 year old. Subject A's anomalous degree of difficulty for specific constructions with SIWs is not consistent with these ages' performance, but rather suggests an anomalous impairment in perceiving and timing SIWs without which timing correctly the integration of LIWs might be disrupted.
Keywords: 7q31, FOXP2, genomic disorder, interval timing, language impairment, Spanish.

1. Introduction

Language disorders provide a window into the genetic bases of language (Newbury *et al.*, 2010). Audio-oral language emerges from hearing sequences of sounds, reproducing them orally and ultimately modulating these complex abilities to achieve successful communication with other organisms of the same species. However, which neural activity, genetically regulated to a great extent, supports the timing of auditory and articulatory intervals is unknown. Some lines of research point to the involvement of a specific circuit implicating the striatum (Coull *et al.*, 2011) in which dopamine selective receptors need to be responsive (Rammsayer, 1999). The striatum is part of a circuit which interconnects the cortex, the thalamus and the cerebellum, and which plausibly plays a relevant role in language processing (Lieberman, 2000). *FOXP2* is expressed in these four nuclei (Vargha-Khadem *et al.*, 2005).

1 This research has been supported by a John Fell Research Grant No 082/994. It obtained approval by the Social Sciences and Humanities Inter-Divisional Research Ethics Committee SSD/2/3/IDREC.

Moreover, how auditory stimulation initiates comprehension remains a persistent puzzle (Lau *et al.*, 2008). It is reasonable to expect that speaking and understanding must derive from performance limitations of both the auditory and oral articulatory pathways (Liberman & Whalen, 2000). Previous studies have searched for these biologically based limitations. Many of them support a model in which short time intervals (SIs) in the ~20–50 ms range might involve specific spontaneous endogenous oscillatory rhythms compared to longer ones (Boemio *et al.*, 2005; Giraud *et al.*, 2007). It has been suggested that synchronization changes in the oscillatory neuronal dynamics reflect the transient coupling and uncoupling of functional networks involved in different components of language processing (Bastiaansen *et al.*, 2009). Eventually, understanding how different neural oscillations can be produced, how they can be sustained and stopped, and how populations of neurons synchronise may rely on finding how gene interaction supports the production and timing of these changes. Understanding therefore this complex cascade of events could help to explain language disorders.

Taking into consideration these two main lines of research in neurogenetics which may shade some light on the bases of language disorders, we focused on the speech and language performance of a subject, A, who has a translocation between chromosomes 7 and 11 (t[7;11][p13;p13]), affecting 7q31, the locus of *FOXP2* (García-Bellido *et al.*, 2009). In a measure of A's performance, it was found that articulatory overestimation in the reproduction of aural subsequences (phonemes), using non-sensical oral sequences ranging from 110ms to 2s, was statistically significant compared to a control (García-Bellido *et al.*, 2011). It was subsequently found that there is a correlation between failure to interpret correctly an utterance and the presence of a relevant SIW in the range of 20-200 ms whose perception and timing is crucial for timing the semantic integration of LIWs, a basic ability for the understanding of the utterance (García-Bellido *et al.*, 2012). Since A scored as a 5 year old with respect to her good answers compared to a large NP and a control, C. (García-Bellido *et al.*, 2012), it is here investigated if A deviates with respect to the degree of difficulty (DD) of particular structures- all containing crucial SIWs – from this NP and control. If this the case, it is plausible that A's genetic anomaly causes a neural disruption that prevents to correctly perceive and time SIWs which are crucial for timing the integration of LIWs. We speculate that the right interaction of genes is needed to support specific neuroanatomical and neurochemical substrates of interval timing (see Lieberman, 2000) in order to respond to and execute short-intervals. Ultimately these findings could be supporting that the same substrate, probably modulated by a dopaminergic circuit (Coull *et al.*, 2011, Wong *et al.*, 2012), determines both reception and emission (see also Lieberman, 2000).

2. Research questions

Q1: What is A's age, using a DD measure for 20 different linguistic constructions, compared to a 4-11 NP of 1,404 subjects who speak the same language (Spanish) in the same geographical country (Spain) and to a control, C, matched in sex, age, schooling and socioeconomic background but crucially sharing the same local linguistic background since their birth?

Q2: Since four specific linguistic structures with relevant SIWs were particularly difficult for A, is A's performance in these and their family structures consistent with the DD age she scored?

3. Method

3.1. Subjects

Subject A

CLINICAL HISTORY OF A

We only report what is relevant for the experiment we discuss here. A more complete clinical description is presented in García-Bellido *et al.* (2009). Subject A is a female born 13/01/1999. She was unable to produce comprehensible speech from the outset. She has been under close paediatric, school and speech-therapy monitoring, receiving one hour individual speech and language therapy classes per week and one hour special reading and writing throughout most of her schooling. Despite this support, she still had acute difficulties using language for communication when the test was administered. She was following the normal curriculum with difficulty. She wore glasses to deal with her astigmatism. An audiometry gave normal, although one of her ears was slightly worse. According to experts, (J. Shnupp, Department of Physiology Anatomy and Genetics, University of Oxford, personal communication) this could only affect the perception of sounds produced beyond a fairly long distance. By the time of the present experiment she was not taking any medication. No member of her family in three generations has suffered any language problems and they all speak Spanish.

CYTOGENETIC ANALYSIS

Subject A is characterised by the presence of a translocation between chromosomes 7 and 11. In chromosome 7 a pericentromeric inversion also exists. The whole rearrangement has been described as (t[7;11] [p13; p13]) (García-Bellido *et al.*, 2009). The most interesting breakpoint for our study is the one in 7q31. Although the breakpoints in 7p and 11p could have affected some relevant gene(s), both the location of the breakpoint at 7q31 and her clinical phenotype are consistent with what is known so far of the involvement of *FOXP2* in linguistic disabilities as suggested in the discussion below.

Subject C

Subject C was born 13/04/1999. She was selected as a control because she is female, has no language or other medical dysfunctional history, is not taking any medication, has, for her age, normal locomotion, hand movements, hearing and vision. She has followed the same school curriculum as A in the same village school since both were 2 years old. She is not receiving any special support at school. She has been brought up in the same socioeconomic level as A and has shared with A the same linguistic background since both were born. No member of her family has any language problems and all speak Spanish.

1,404 normal subjects

(Mendoza *et al.*, 2005:41-42). These were selected from a NP of children between 4 and 11, who neither received speech therapy nor special school support, were not suffering from any developmental delay in their education and whose parents spoke Spanish.

3.2. Procedures

Design of audio-visual comprehension experiment

A standard comprehension test of basic grammatical structures for a Spanish population between ages 4-11 was used (Mendoza *et al.*, 2005).

Subject A was 11;8 and Subject C was 11;5 when the test was administered. The child was sitting next to the experimenter at a distance of 60 cm. Before the test, the child had to match an auditory stimulus for words which will be used in the test associated with actions or shapes and, a sequence of two words associated with shapes and dimensions or colours. Since colours were recognized, it was assumed that neither of our two subjects had audio-visual synaesthesia for language-sounds with colours. The native Spanish speaker experimenter read aloud an utterance at a normal pace and volume in a noise-free room. The child had to select with her finger one visual image out of four different ones. The child is expected to make a decision based on the assumption that she had matched the selected picture because she had worked out its meaning and the other three ones. Once the child would have selected one, then the examiner would produce a new page. There were N= 80 auditory stimuli (arranged in 20 blocks of 4, each of a different grammatical construction) (minimal utterance reading interval = 870 ms; maximun = 5.55 s). Each utterance contained subsequences (words) ranging from minimum 20 ms duration interval to a maximum of 960 ms. Words, automatically timed -aligned (García-Bellido *et al.*, 2012), with more than 200 ms were classified as long time intervals (LIs), while those below, as SIs. We identified a correct semantic integration when two aural words, produced at different times in the utterance, were properties of the same entity (see Fig. 5 in García-Bellido *et al.*, 2012 for details).

Scoring

Since producing more errors is assumed to be a symptom of more difficulty, and the test was only administered once to A and C, while the degree of difficulty (DD) for NP (Mendoza *et al.*,2005) was obtained as the mean score of errors of many subjects, grouped by age, we plotted the number of potential errors (1-4 Errors) in a block with a specific grammatical construction to the DD (4 -1 DD) obtained for the NP (Fig. 1). If a child points the wrong image, this is counting as one error. DD3 was the cutting point separating blocks that are difficult (1-3 DD) from those that are easy (3.01-4 DD).

4. Results

Answering research questions:

1. Subject A is classified between a 6 year-old child and a 7 year-old child of our NP (Fig 2) compared to C who is classified not significantly above a 11 year-old of this NP.

Considering that A took the test at 11;8, she presents a 4.5 year deviation with respect to 11 year-old subjects of the NP. Since subject C took the test at 11;05 her score is consistent with a 11 year- old NP, giving a slightly higher score (less percentage of difficult blocks) than a 11 year-old NP.

2. We found that four constructions with relevant SIWs were in the Non Easy band (1-3DD) in A: Cleft, Relative clause, Clitic and Negative. We identified constructions that can be related (*families*) and constitute a prototype of task. The DD of these families can be plotted across ages showing a DD for every structure compared to its family members at a particular age. We expect that this DD value or its order relation within its family is preserved in A and/or C answers, to be consistent with the DD age we have found for each of them. Consequently, both, the DD value of each construction and its order in its family are to be considered here the markers to assess if they correlate with the DD age they have scored.

We have identified and evaluated four different families of grammatical constructions.

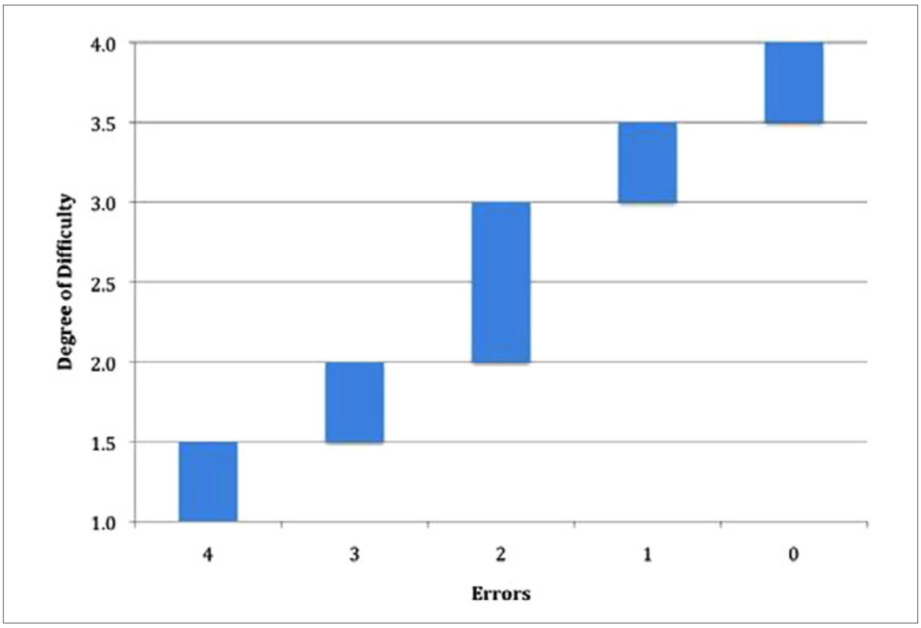

Figure 1. Relation of degree of difficulty and number of errors. DD3 is the cutting point that divides the difficult-easy axis into difficult (1-3 DD) and easy (3.1-4DD).Structures whose DD is between 1-1.5DD are classified as Very Difficult, 1.5-2DD Medium Difficult, 2-3DD Slightly Difficult, 3-3.5 Easy and 3.5-4 Very Easy

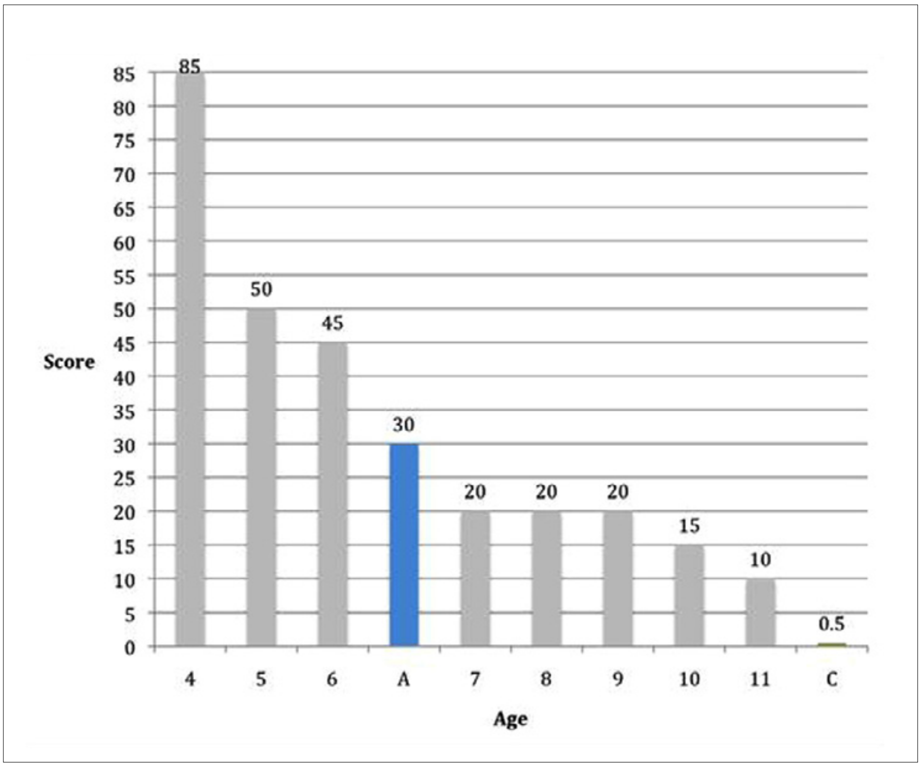

Figure 2. Percentage of blocks (Max. 100% for Total N=20 blocks) scoring between 3-1 DD for A (blue) compared to a 4-11 year-old Normal Population (grey) and a control subject C (green)

Family I: Relative particles

It encompasses three different types: type 1, type 2 and type 3 [see García-Bellido *et al.*, 2012 and example 1].

Example 1

T1: El cuadrado (LIW) está dentro (LIW) del círculo (LIW) que (SIW) es azul (LIW)
'The square is inside of the circle that is blue'
T2: El cuadrado (LIW) que (SIW) está dentro (LIW) del círculo(LIW) es azul (LIW)
'The square that is inside of the circle is blue'
T3: El cuadrado (LIW) dentro (LIW) del que (SIW) está el círculo (LIW) es azul (LIW)
'The square inside of which is the circle is blue'

If A were behaving like a 6-7 year -old we would expect Type 3 to be the most difficult as Fig. 3 shows.

As Fig.3 shows, C correlates with a 11 year-old NP. Compared A to a 6-7 year- old NP, T2 = Medium Difficulty vs Slightly Difficulty and T1, T3 = Easy vs Slightly Difficult respectively.

Family II: preposition particles and non-logical LIs preceding event

It encompasses three different types: cleft , passive, and topicalisation constructions [see example 2].

Example 2

Topicalisation: A (SIW) la mujer (LIW) la (SIW) pinta (LIW) el hombre (LIW)
'To the woman her paints the man'
Passive: La mujer (LIW) es pintada (LIW) por (SIW) el hombre (LIW)
'The woman is painted by the man'
Cleft sentence: Es (SIW) a (SIW) la mujer (LIW) a (SIW) la que (SIW) pinta (LIW) el hombre (LIW)
'Is to the woman to the which paints the man'

As Fig. 4. shows, C correlates with a 11 year-old NP, A shows anomalous DD scores and ordering for passive & topicalisation compared to a 6-7 year-old NP. If A were behaving like a 6-7 year-old we would expect passive and topicalisation to

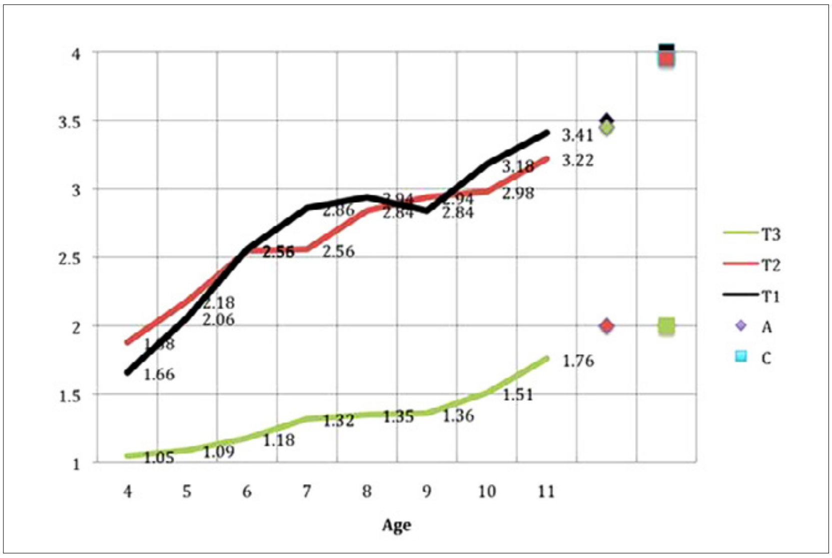

Figure 3. DD values for three types of relative clause construction

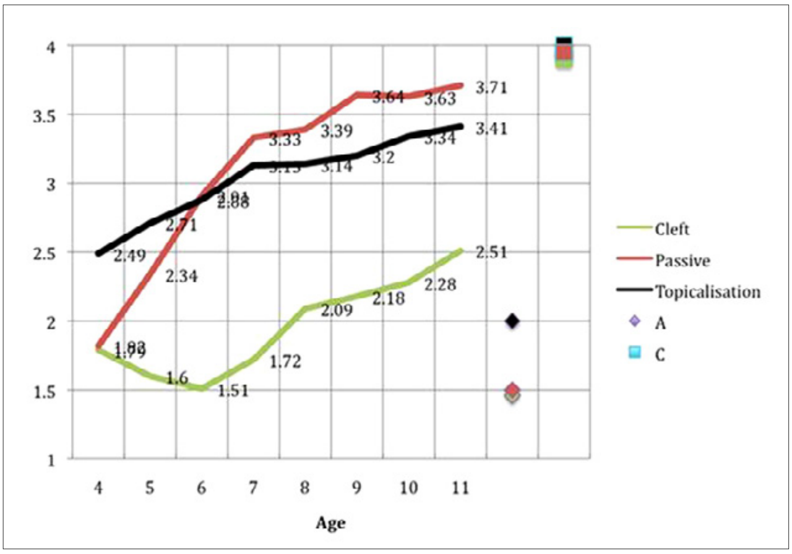

Figure 4. DD values for three constructions with preposition particle and a non-logical LI preceding the event

score Slightly Difficult-Easy (between 2-1 Errors). However passive in A clusters with cleft construction at Very Difficult. Moreover, the order of the DD in the family changes at 7, suggesting that A is deviating also from that order giving instead the order of a 4 to 5 year-old NP.

Family III: clitic particles

It encompasses three different types: possessive, transitive gender, and transitive gender number [see example 3].

Example 3

Possessive: La niña (LIW) le (SIW) pinta (LIW) la cara (LIW)
'The girl him paints the face'
Transitive gender : Las niñas (LIW) lo/la (SIW) miran (LIW)
'The girls him/her watch'
Transitive gender number: La mujer (LIW) los/las/lo/la (SIW) lleva (LIW)
'The woman them (fem.)/them (masc.)/him/her carries'

As Fig.5 shows, C correlates with a 11 year-old NP. Compared A to a 6-7 year-old NP, possessive is in a Difficult vs Very Easy band respectively.

Family IV: negative particles. It encompasses four different types: N1 [negatives per se], N2 [pseudonegatives], N3 [adversative negatives]and N4 [coordination negatives] [see example 4].

Example 4

N1: El perro no (SIW) es negro
'The dog not is black'
N2: No (SIW) solo el perro es negro, sino (SIW) también el gato
'Not only the dog is black, yesno (but) also the cat'
N3: El perro es negro, pero el gato no (SIW)
'The dog is black, but the cat not'
N4: Ni (SIW) el perro ni (SIW)el gato son negros
'Nor the dog nor the cat are black'

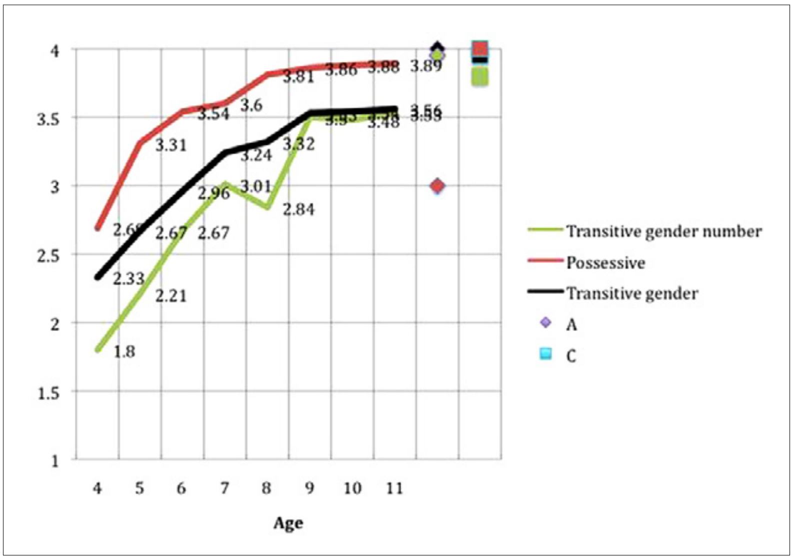

Figure 5. DD values for three clitic constructions with a Logical subject preceding the event

As Fig.6 shows, compared C to a 11 NP, N3 is slightly deviating: Easy-Very Easy respectively. Compared A to 6-7 NP, N3 is slightly deviating: Difficult- Easy respectively.

In conclusion, A's DD age and her anomalous DD score in specific grammatical structures encompassing SIWS which are crucial for timing the integration of LIWS, both deviate from the NP and C.

5. Discussion

The low DD score in relative clause type 2, which A resolves as a Type 1 or Type 3, is consistent with an inability to time the SI relative particle which, if perceived, is timed too late in the sequence. This probably makes LWIs to integrate, as a Type 1 or Type 3. (See García-Bellido *et al.,* 2012).

The low DD value scored by A for passive also suggests that not only the preposition particle but also the morphological information of the event (past participle subsequence), may not be perceived and consequently cannot block the integration of the preceding LIW non-logical subject with the LIW event.

The low DD of the possessive LIW clitic ([*le*]) which A incorrectly integrates with the following LIW event (example 3), makes the clitic to be the logical subject while the LIW preceding the event is integrated as the non-logical subject. This finding, either challenges the view that there is a tendency to integrate a LIW as the logical subject when it precedes the event, since we would expect this principle to have been used if the clitic is not perceived, or else this anomalous clitic integration is consistent with A's dysfunction which miss-times sequences ([*le*] for [*el*]). Alternatively, this error could suggest that A has difficulty in sustaining the clitic long enough to semantically integrate it with the last LIW in the utterance.

Finally, the fact that A, for N3, sometimes does not perceive the negative particle or miss-times it suggests that, as with the other particles in this test, they are a risk factor for comprehension.

Given that the two markers we have applied to assess if A deviates from a 6-7 year- old NP in-

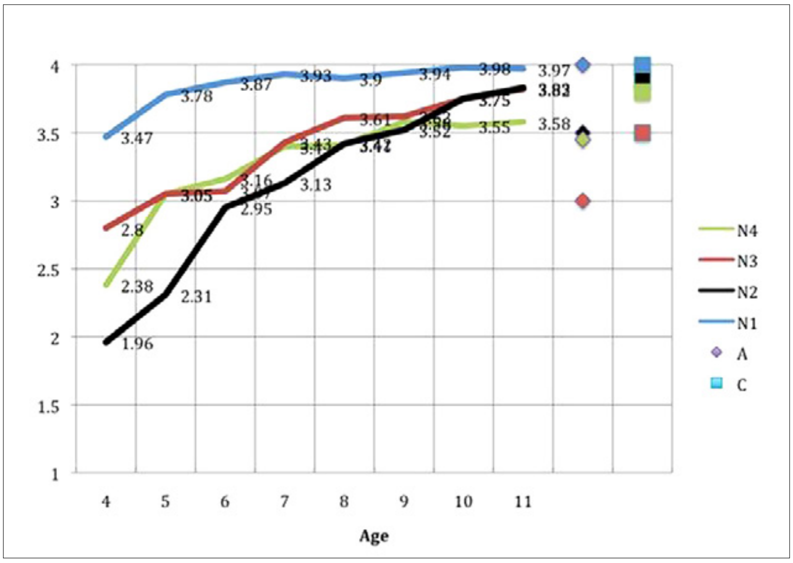

Figure 6. DD values for negative particles in four constructions

dicate that she does, this suggests that these findings are consistent with a dysfunction in timing short intervals.

Although it is possible that some functional gene could have been affected by the ruptures in 7p and 11p, both the fact that one rupture point corresponds to the *locus* of *FOXP2* and that the observed oromotor (García-Bellido *et al.*, 2010), linguistic (García-Bellido *et al.*, 2012) and even cognitive (García-Bellido *et al.*, 2009) dysfunctions of A are similar to the ones observed in other cases in which the codifying region of this is mutated, suggest that A' disordered profile can be specifically caused by the interruption of *FOXP2*. In fact, A's symptoms are also similar to the observed symptoms in people bearing deletions of different extension encompassing *FOXP2* (Zeesman *et al.*, 2006; Lennon *et al.*, 2007). We furthermore hypothesise that the functional inactivation of this gene gives specifically rise to A's abnormal timing phenotype. The precise clinical profile linked to *FOXP2* mutations is controversial (Vargha-Khadem *et al.*, 1995; Watkins *et al.*, 2002). Nonetheless, it is plausibly that the underlying deficit not only affects perceiving and articulating short intervals, but more importantly it may affect their timing, suggesting that sequencing capacities are at risk, thus potentially disturbing different domains. In fact, deficits in timing control have also been observed in people bearing a mutation of *FOXP2*, particularly, in the KE family. According to Alcock *et al.* (2000), nine affected members showed lower rhythm skills during a music perception and song production task. As pointed out by Alcock *et al.* (2000: 34), "neither their linguistic nor oral praxic deficits can be at the root of their impairment in timing; rather, the *reverse* may be true".

We suggest therefore that interval timing has a specific neurogenetic basis that deserves to be characterised if we are to understand how the brain processes language.

References

Alcock, K.J., Passingham, R.E., Watkins, K. & Vargha-Khadem, F. (2000). Pitch and timing abilities in inherited speech and language impairment. *Brain and Language*, *75*, 34–46.

Bastiaansen, M., Magyari, L. & Hagoort, P. (2009). Syntactic unification operations are reflected in oscillatory dynamics during on-line sentence comprehension. *Journal of Cognitive Neuroscience*, 22, 1333–1347.

Boemio, A., Fromm, S., Braun, A. & Poeppel, D. (2005). Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nature Neuroscience*, 8, 389-395.

Coull J.T., Cheng, R.-K. & Meck, W.H. (2011) Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology Reviews*, *36*, 3-25.

García-Bellido, P., Benítez-Burraco, A., Roselló, M., Monfort, S., Martínez, F., Oltra, S. & Orellana, C. (2009) A case of Spanish language disorders with a rare genetic cause. In V. Marrero & I. Pineda (Eds.), *Linguistics: The Challenge of Clinical Application* (pp. 365-370). Madrid: UNED-Euphonia Ediciones.

García-Bellido, P., Benítez-Burraco, A., Park, K. & Molineaux, B. (2011). Timing the integration of utterance duration and task shift in a case of genetic anomaly implicating 7q31 with language disorders. Poster session presented at the Oxford Sound Day, Oxford, UK. Oxford Research Archive, http://ora.ox.ac.uk/objects/uuid:1cd8d130-564a-4ee6-bdbd-a3abd8fdd97c.

García-Bellido, P., Baghai-Ravary, L., Grau, S. & Benítez-Burraco, A. (2012) Timing language disorders with a chromosomal translocation in 7q31. Poster session presented at The 3rd Annual Oxford Neuroscience Symposium, Oxford, UK. Oxford Research Archive, http://ora.ox.ac.uk/objects/uuid:c45fd03e-c5c7-4f06-b504-5ba58755d5a6.

Giraud, A.L., Kleinschmidt, A., Poeppel, D., Lund, T.E., Frackowiak, R.S.J. & Laufs, H. (2007) Endogenous cortical rhythms determine cerebral specialization for speech perception and production. *Neuron, 56*, 1127-1134.

Lau, E.F., Phillips, C. & Poeppel, D. (2008) A cortical network for semantics: (de)constructing de N400. *Nature Reviews. Neuroscience*, *9,* 920-933.

Lennon, P.A., Cooper, M.L., Peiffer, D.A., Gunderson, K.L., Patel, A., Peters, S., Cheung, S.W. & Bacino, C.A. (2007) Deletion of 7q31.1 supports involvement of *FOXP2* in language impairment: Clinical report and review. *American Journal of Medical Genetics A, 143*, 791-798.

Liberman, A.M. & Whalen, D.H. (2000) On the relation of speech to language. *Trends in Cognitive Science*, *4,* 187-196.

Lieberman, P. (2000) *Human Language and Our Reptilian Brain. The Subcortical Bases of Speech, Syntax and Thought*. Cambridge: Harvard University Press.

Mendoza, E., Carballo, G., Muñoz, J. & Fresnada, M. D. (2005). *Test de comprensión de estructuras gramaticales*. Madrid: TEA.

Newbury, D. F., Fisher, S. E. & Monaco, A. P. (2010) Recent advances in the genetics of language impairment. *Genome Medicine, 6*, 1-8.

Rammsayer, T.H. (1999). Neuropharmacological evidence for different timing mechanisms in humans. *The Quarterly journal of experimental psychology. B, Comparative and physiological psychology*, 52, 273-286.

Vargha-Khadem, F., Watkins, K., Alcock, K., Fletcher, P. & Passingham, R. (1995) Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proceedings of the National Academy of Sciences of the United States of America, 92,* 930-933.

Vargha-Khadem, F., Gadian, D.G., Copp, A. & Mishkin, M. (2005). FOXP2 and the neuroanatomy of speech and language. *Nature Reviews. Neuroscience, 6*, 131-138.

Watkins, K.E., Dronkers, N.F. & Vargha-Khadem, F. (2002). Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain, 125*, 452-64.

Wong, P.C.M., Morgan-Short, K., Ettlinger, M. & Zheng, J. (2012) Linking neurogenetics and individual differences in language learning: the dopamine hypothesis. *Cortex, 48*, 1091-102

Zeesman, S., Nowaczyk, M.J., Teshima, I., Roberts, W., Cardy, J.O., Brian, J., Senman, L., Feuk, L., Osborne, L.R. & Scherer, S.W. (2006), Speech and language impairment and oromotor dyspraxia due to deletion of 7q31 that involves *FOXP2*. *American Journal of Medical Genetics A, 140*, 509-514.