Universidade do Minho
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Language and communication abnormalities in Williams Syndrome and Schizophrenia: Event-related potentials (ERP) evidence

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To all the special journeyers of this unknown

Land, named Life

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Not until the spring came, when the honeysuckle spray lengthened its growth, and achieved a wider swing, was it certain of a really solid grasp of the camellia.

Now I see a third part of the process.

Not only: The movement of the spray made it reach the camellia,

Or: The wind blew it so it could reach the camellia,

But: The further growth of the honeysuckle made it possible to reach the camellia.

But the element in which this process exists is – Time.

***Time is the whole point**. Timing.*

The surfer on the wave. The plant swinging in the wind. And it's just the same with – well, everything, and that's what I have to say, Doctor. Why can't you see that? [1]

I can see. *Time* is everything. Or: we are *time*. Or: *time* is the whole point.

Now that the honeysuckle spray lengthened its growth, now that a journey is coming to an end (or a beginning), I look back in time and remember the names of all the people who drove me during this journey, offering me their *time*, their experience, their support. And: my wish is to make their names resistant to the passage of *time*, as pieces of *time*-eternity.

To my mentors, Professor Óscar F. Gonçalves and Doctor Margaret Niznikiewicz, for their *time* of wisdom, scientific excitement, and models of *being*. For their (life and science) lessons, which will be stored as permanent synaptic changes in my brain. For always inspiring me.

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To my sisters (partners for life), and my family (in particular, Emília): your *time* has always been time for support, encouragement, and joy (*time* for feeling at *home*).

[1] Doris Lessing (1971). *Brief for a descent into hell*. New York: Vintage Books (p. 298).

To Marek, Magda, Mike and Aya, who have become very special journeyers of my life, for their unforgettable *time* of friendship that allowed me to live a non solitary journey, and for making me feel the sweet safety of being at *home*.

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To all the participants of these studies, because this work is also yours (*time* for giving time to science).

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To Luís, who lives in me. For there is no other place to go but love.

Language and communication abnormalities in Williams Syndrome and Schizophrenia: Event-Related Potentials (ERP) evidence

ABSTRACT

Language and communication abnormalities are a hallmark of both Williams Syndrome (WS) and Schizophrenia. Both disorders represent atypical developmental pathways, in which the complexity of the relationships between genes, brain, and behavior has been intriguing researchers for decades. On the one hand, WS represents a genetic disorder characterized by a submicroscopic deletion in chromosome 7. This syndrome was initially proposed as a paradigmatic example of cognitive dissociation and, in particular, of the independence of language from general cognition. On the other hand, Schizophrenia is characterized by a multiplicity of symptoms (e.g., hallucinations, delusions, thought disorder, flat affect), with genetic and environmental factors contributing to its onset. Dysfunction in language and emotional processing has been consistently reported in both disorders, contributing to deficits in social interactions.

The studies described in this dissertation aimed at analyzing the electrophysiological correlates of language processing in both WS and Schizophrenia, in particular semantics and prosody. The event-related potentials (ERP) technique was chosen due to its temporal resolution that is ideal for the investigation of language.

Study 1 explored the electrophysiological correlates of prosody processing in WS, comparing emotional intonations embedded in intelligible semantic information, and 'pure prosody' sentences. Abnormalities were found in N100, P200, and N300 components in WS individuals, when compared with typically developing controls. In particular, reduced N100 was observed for prosody sentences with semantic content but more negative N100 for pure prosody sentences, and more positive P200 for both pure prosody sentences and sentences with semantic content, in particular for happy intonations. These findings suggest abnormalities in early auditory processing, indicating a bottom-up contribution to the impairment in emotional prosody processing and comprehension. Also, the reduced N300 peak amplitude in individuals in WS at parietal electrodes and its enhancement at frontal electrodes may indicate abnormal electrophysiological response at the stage of evaluating the emotional significance of the auditory message.

Study 2 analyzed the ERP correlates of semantic processing in WS. A set of sentences was presented auditorily, with half ending with an expected word, and half ending with an unexpected and implausible word. Abnormalities were found in early sensorial components

(N100 and P200) in WS, although no differences between WS and a typically developing group were found for the N400 component (an index of semantic integration). Interestingly, more positive P600 amplitude was found for WS, suggesting difficulties in later integration processes.

Study 3 aimed at characterizing the electrophysiological correlates of prosody processing in Schizophrenia, using the same experimental paradigm described in Study 2. Results showed sensory abnormality in processing auditory signal for all prosody types (reduced N100), as well as failure to extract emotion-specific information from the auditory signal (P200). Importantly, both types of abnormalities were found in sentences with semantic content only, suggesting top-down modulation of sensory-level and automatic processing of prosodic information.

Study 4 aimed at investigating the effects of induced mood (neutral vs. positive vs. negative) on semantic processing in Schizophrenia. Data suggest differential access to semantic networks in this neuropsychiatric disorder, and abnormalities in the modulation of language processing by mood, as indexed by N400 amplitude to three types of sentence endings (expected words, unexpected words from the same semantic category as the expected exemplar, and unexpected words from a different semantic category of the expected exemplar), under neutral, positive, or negative mood. Differences were more pronounced under positive mood.

Together, these ERP studies provide, for the first time, electrophysiological evidence for atypical prosody processing in both WS and Schizophrenia, and for abnormal interactions of mood and cognition in Schizophrenia. Also, they extend few previous ERP studies with WS on semantic processing, including, for the first time, participants with European Portuguese as native language. These findings are expected to contribute to a better understanding of language atypicalities in both disorders.

Perturbação da linguagem e da comunicação na Síndrome de Williams e na Esquizofrenia: Evidência a partir de Potenciais Evocados

RESUMO

Alterações da linguagem e da comunicação são uma característica central da Síndrome de Williams (SW) e da Esquizofrenia. Ambas constituem trajectórias desenvolvimentais atípicas, em que a complexidade inerente às relações entre genes, cérebro e comportamento tem intrigado investigadores há várias décadas. Por um lado, a SW representa uma perturbação genética caracterizada por uma delecção submicroscópica no cromossoma 7. Esta síndrome foi, inicialmente, proposta como um exemplo paradigmático de dissociação cognitiva e, em particular, de independência da linguagem em relação à cognição geral. Por outro lado, a Esquizofrenia é caracterizada por uma multiplicidade de sintomas (e.g., alucinações, delírios, perturbação do pensamento, embotamento afectivo), sendo o seu início influenciado por factores genéticos e ambientais. Alterações ao nível do processamento da linguagem e emocional têm sido consistentemente reportadas em ambas as perturbações, contribuindo para os défices verificados ao nível das interacções sociais.

Os estudos descritos nesta Tese tiveram como objectivo a análise dos correlatos electrofisiológicos do processamento da linguagem na SW e na Esquizofrenia, em particular o processamento semântico e prosódico. A técnica de potenciais evocados (ERP) foi escolhida devido à sua resolução temporal, que é ideal para a investigação da linguagem.

No Estudo 1 exploraram-se os correlatos electrofisiológicos do processamento da prosódia na SW, comparando prosódia emocional em frases com conteúdo semântico perceptível, com prosódia em frases transformadas sem conteúdo semântico perceptível. Os resultados apontaram para anormalidades nos componentes de onda N100, P200 e N300 em indivíduos com SW, quando comparados com um grupo com desenvolvimento normal. Em particular, observou-se uma reduzida amplitude do componente N100 para frases com entoação prosódica e conteúdo semântico inteligível, e uma amplitude mais negativa do mesmo componente para frases de prosódia "pura". Ao mesmo tempo, a amplitude da P200 na SW foi mais positiva, em comparação com o grupo de desenvolvimento típico, quer para frases de prosódia "pura", quer para frases com entoação prosódica e conteúdo semântico inteligível, e em particular para prosódia alegre. Estes resultados sugerem anomalias em fases precoces do processamento auditivo, indicando uma contribuição *bottom-up* para as alterações evidenciadas no processamento e compreensão da prosódia emocional na SW. Finalmente, a observação de uma redução da amplitude do componente N300 em eléctrodos parietais e o seu aumento em

eléctrodos frontais poderá indicar anormalidades na resposta electrofisiológica associada à avaliação do significado emocional da mensagem acústica.

O Estudo 2 analisou os correlatos electrofisiológicos do processamento semântico na SW. Um conjunto de frases foi apresentado auditivamente, metade delas terminando com uma palavra esperada e metade terminando com uma palavra inesperada e implausível. Os resultados revelaram anomalias em componentes sensoriais precoces (N100 e P200), apesar de não terem sido observadas diferenças entre a SW e um grupo com desenvolvimento típico no componente de onda N400 (um indicador de processos de integração semântica). Interessantemente, a amplitude do componente P600 foi mais positiva na SW, o que sugere dificuldades em processos de integração tardios.

O Estudo 3 teve como objectivo a caracterização dos correlatos electrofisiológicos do processamento prosódico na Esquizofrenia, tendo como base o paradigma experimental descrito no Estudo 2. Os resultados sugerem anomalias sensoriais no processamento do sinal auditivo para todos os tipos de prosódia (redução da amplitude da N100), bem como dificuldades na extracção de informação emocional específica a partir do sinal auditivo (P200). Ambos os tipos de anomalias foram encontrados apenas para frases com conteúdo semântico, sugerindo uma modulação *top-down* do processamento sensorial e automático da informação prosódica.

O objectivo do Estudo 4 foi investigar os efeitos do humor induzido (neutro vs. positivo vs. negativo) no processamento semântico na Esquizofrenia. Os dados obtidos sugerem um acesso diferencial às redes semânticas nesta perturbação, bem como anomalias na modulação do processamento linguístico pelo estado de humor, tal como evidenciado pela amplitude do componente de onda N400 para três tipos de finais de frase (palavras esperadas, palavras não esperadas da mesma categoria semântica da palavra esperada, palavras não esperadas de uma categoria semântica diferente da da palavra esperada), em três tipo de humor (neutro vs. positivo vs. negativo). Estas diferenças foram mais pronunciadas na condição de humor positivo.

Em conjunto, estes estudos ERP apresentaram, pela primeira vez, evidência electrofisiológica para o processamento atípico da prosódia emocional quer na SW quer na Esquizofrenia, bem como para anormalidades nos processos de interacção entre humor e cognição na Esquizofrenia. Ao mesmo tempo, complementam estudos ERP prévios no âmbito do processamento semântico na SW, incluindo, pela primeira vez, participantes tendo como língua nativa o Português Europeu. Espera-se que estes resultados contribuam para uma melhor compreensão das alterações do processamento linguístico, observadas tanto na SW como na Esquizofrenia.

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LIST OF ABBREVIATIONS

ERP	Event-related potentials
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
MEG	Magnetoelectroencephalography
WS	Williams Syndrome
SZ	Schizophrenia
NC	Normal controls
TD	Typically developing group
DS	Down Syndrome
IQ	Intelligence quotient
FSIQ	Full Scale Intelligence Quotient
VIQ	Verbal intelligence quotient
PIQ	Performance intelligence quotient
WAIS-III	Weschsler Adult Intelligence Scale-III
PANSS	The Positive and Negative Syndrome Scale
PALPA	Psycholinguistic Assessment of Language Processing in Aphasia
PDP	Parallel Distributed Processing Model
ANOVA	Analysis of variance
LC	Low-constraint sentence contexts
HC	High-constraint sentence contexts
STG	Superior temporal gyrus
SES	Socioeconomic status
EE	Expected exemplar
WCV	Within-category violation
BCV	Between-category violation

OFC	Orbitofrontal cortex
ACC	Anterior cingulated cortex
IAPS	International Affective Picture System
POMS	Profile of Mood States
LH	Left hemisphere
RH	Right hemisphere

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CHAPTER IV: Global Discussion

Chapter I

INTRODUCTION AND THEORETICAL BACKGROUND

I. FROM GENES, TO BRAIN, TO LANGUAGE: THE IMPORTANCE OF STUDYING LANGUAGE AND COMMUNICATION ABNORMALITIES IN ATYPICAL DEVELOPMENTAL PATHWAYS

1. Some preliminary notes about the brain that "speaks"

Described by several authors as an exclusive ability of Homo Sapiens (e.g., Crow, 1997, 1998), language is one of the most fascinating cognitive functions and represents an evolutionary marker that separates modern Homo Sapiens from his ancestors (Crow, 2004).

First of all, language consists of the continuous process of coding and decoding symbols (e.g., Carruthers, 2002; Jackendoff, 1999; Kutas, Federmeier, & Sereno, 1999; Lieberman, 2000; Pinker, 1994). Representing a symbolic species (Deacon, 1997), Homo Sapiens is constantly manipulating and interchanging a universe of abstract representations (words, gestures, pictures, emotional expressions). Language is a tool that helps to process meaning. This contributes to social communication/interactions and also to the development of culture (Baumeister & Vohs, 2002). Also, the fact that language is so intrinsically associated with human experience explains why it is almost impossible to imagine life without this faculty (Pinker, 1994).

Second, language is a cognitive tool (Carruthers, 2002). This idea is supported by studies suggesting that language may serve a scaffolding role during cognitive development in children (e.g., Baddeley, Gathercole, & Papagno, 1998; Clark, 1998; Diaz & Berk, 1992). For example, language ability during toddlerhood has been found to be predictive of academic achievement in school years (Blachman, 1984; Evans & Bangs, 1972; Evans, Floyd, McGrew, & Leforgee, 2001; Magee & Newcomer, 1978; Semel & Wiig, 1975; Stedman & Adams, 1972; Storch & Whitehurst, 2002; Tramontana, Hooper, & Selzer, 1988; Walker, Greenhood, Hart, & Carta, 1994; Wiig & Semel, 1975). Also, the importance of language to cognitive development is supported by studies that suggest the co-development of linguistic and cognitive abilities (Astington, 1996; Peterson & Siegal, 1998).

Third, language depends on the development of inferences about the intentions of communicators and recipients. In other words, language is intimately related with theory of mind ability (Arbib, 2006; Harris, 1996; Peterson & Siegal, 1998). For example, when sending a communicative signal, the sender of the message needs to predict the intentions and possible reactions of the receiver, as well as his abilities to infer the intent of the sender (Noordzij et al., 2009; Willems et al., 2010). This is crucial for the effectiveness of communication. Interestingly, brain areas activated by language perception and production tasks include, besides posterior areas, regions associated with the processing of social cognition and self representation (e.g., Wible, Preus, & Hashimoto, 2009), overlapping in the posterior temporal, superior temporal sulcus, and inferior parietal regions.

Even though one of the most important functions of language is communication, it is worth noting that, ontogenetically and phylogenetically, language and communication have distinct origins. Long before language, gestures and sounds performed a communicative role (Levinson, 2006; Tomasello, Carpenter, Call, Behne, & Moll, 2005). This is supported by fMRI studies that show distinct brain mechanisms underlying communicative abilities and language (Willems et al., 2010).

Fourth, the development of language allowed the simultaneous evolution and complexification of the brain (Bickerton, 1990, 2007; Lieberman, 2000). An alternative hypothesis would be that the brain evolved to help people represent and make use of non-physical realities or symbols (Baumeister & Vohs, 2002). As stated by Brown and Hagoort (1999), language is seated in the brain. This means that many of the questions related with language may have their answers in this special organ. Following this argument, this means that researchers need techniques allowing the measurement of neurobiological activity related with the dynamics of language production and comprehension, as a combination of brain imaging techniques, namely positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoelectroencephalography (MEG), or event-related potentials (ERP).

Fifth, language is embodied in human experience (e.g., Glenberg, Havas, Becker, & Rinck, 2005; Glenberg & Kaschak, 2002; Larsen, Kasimatis, & Frey, 1992). In other words, symbols of language may become only meaningful when mapped to non-linguistic experiences, as emotions, actions or perceptions. For example, studies suggest that emotional language is better understood when the person who is trying to make sense of language is also experiencing the same emotional state described in words (e.g., Glenberg & Kaschak, 2002).

Together, the previous assumptions illustrate the complexity of language (see Brown & Hagoort, 1999). This faculty depends on spatio-temporal connections between multiple areas that make part of distributed cortico-cortical and cortico-subcortical networks (Duffau, 2008). The diversity of brain areas engaged in language processing doesn't preclude the idea of function specialization, as shown by reports of selective impairments in adult brain-damaged patients (e.g., Bellugi, Poizner, & Klima, 1983; Benton & Anderson, 1998; Berndt & Caramazza, 1980;

Caramazza, 1988; Caramazza & Berndt, 1978; Caramazza & Zuriff, 1976; Damasio, 1992; Dick et al., 2001). Aphasia syndromes suggest that different parts of the human brain are specialized, in adulthood, for different components of language, as semantic representations, phonology, prosody, or syntax (see Thomas & Karmiloff-Smith, 2005 for a review). Effective language production and comprehension require the activation, on-line coordination and integration of information at several (linguistic and non-linguistic) levels, which reaches the brain at millisecond speed (see Brown & Hagoort, 1999). The complexity of language requires the cooperation of both hemispheres during the processing and production of sounds/symbols (e.g., words, gestures, pictures), each one allowing specialized contributions. For example, while left hemisphere regions have a role in the access to verbal associates (in a word-to-word basis) and in the processing of the sequential logic of conversation, the right hemisphere is engaged in the integration of semantic information, as well as in the processing of non-literal meaning (e.g., Binder et al., 1997; Bottini et al., 1994; Bryan, 1989; Code, 1997; Gazzaniga & Hillyard, 1971; Geschwind, 2006; Martin, 2003; Robin, Tranel & Damasio, 1990; Ross, 1981; Ross & Mesulam, 1979; Schirmer & Kotz, 2006; St. George, Kutas, Martinez, & Sereno, 1999; Vigneau et al., 2006).

More recent studies indicating that brain regions far distal to the lesion site are affected in aphasic patients and that the same brain area may be recruited for different linguistic tasks increasingly suggest that the concept of "modules" (e.g., Baynes, Eliassen, Lutsep, & Gazzaniga, 1998; Gazzaniga, 1989; Ojemann, 1991; see Fodor, 1983) is not totally adequate to describe the organization of complex brain functions, as language (Bookheimer, 2002; Karmiloff-Smith, 1994). Functional studies suggest that the brain network that underlies language processing is based on the differentiation and interaction between several brain areas, so that the spatial and functional coupling of these areas can lead to a rapid and efficient processing of language (Bookheimer, 2002).

The complexity of language also led several researchers to question the relationship between genes and components of the language system (Bishop, 2002a, 2002b; Cavalli-Sforza, 1997; Enard et al., 2002; Fisher, Lai, & Monaco, 2003; Fisher & Marcus, 2006; Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Marcus & Fisher, 2003; Pinker, 2002; Searls, 2002; Thomas & Karmiloff-Smith, 2005), as stated in the following transcription:

"*In 1998 [researchers] linked the [KE] disorder to a small segment of chromosome 7, which they labelled SPCH1. Now...Lai et al. [Nature, October 2001] have narrowed the disorder down to a specific* *gene, FOXP2... . The discovery of the gene implicated in speech and language is amongst the first fruits of the Human Genome Project for the cognitive sciences. Just as the 1990s are remembered as the decade of the brain and the dawn of cognitive neuroscience, the first decade of the twenty-first century may well be thought of as the decade of the gene and the dawn of cognitive genetics*" (Pinker, 2001, p. 465).

The excitement caused by the discovery of a gene that was called the "gene for speech and language" – the FOXP2 gene – was associated with its promise of explaining the onset of language in human species and its impairment, as in neurodevelopmental disorders with genetic origin. These have been proposed as ideal targets for the study of genetic contributions to the specification of the different components of language and for a better understanding of the development of the language system. In fact, developmental disorders teach us that different aetiologies can have substantially different language outcomes. Dissociations between different components of language (e.g., phonology, semantics, morphosyntax, and pragmatics) have been found when comparing Down Syndrome, Williams Syndrome, Autism, and Fragile X Syndrome (Fowler, 1998; Tager-Flusberg & Sullivan, 1997).

However, genes can exert their effects in several ways, affecting: (a) brain size, (b) number of neurons or synapses, (c) neuronal migration, and (d) neurotransmission (Pennington, 2001). So, as noted by other researchers (e.g., Bishop, 2002a, 2002b; Newman, 2002; Phillips, 1998; Thomas & Karmiloff-Smith, 2005), it doesn't seem plausible that a single gene can explain the onset of this higher cortical function and it is more probable that genetic effects during brain development are diffuse across the entire brain. Also, there is additional evidence to conclude that the brain that is acquiring language can constrain processes of language acquisition and development (Fowler, 1998).

2. Some preliminary notes about the brain in which language is impaired

There are several ways in which language faculty can end up being impaired (Bates, 1997). Genetic mutations can lead to language impairment (e.g., Williams Syndrome, Down Syndrome). Also, environmental causes can affect language, as is the case of brain injury caused by lesions (e.g., aphasia). Social causes can also contribute for language impairment, as proved by reports of children who were deprived of social interactions during their early years (e.g., Curtiss, 1977; Fromkin, Krashen, Curtiss, Rigler, & Rigler, 1974).

On one hand, illustrating cognitive dissociations, aphasia syndromes in adulthood helped to specify the functional components of language, as lexicon, morphology, syntax, semantics, and pragmatics, teaching us that lesions in different brain areas can lead to very distinct functional outcomes and symptoms (Thomas & Karmiloff-Smith, 2005). On the other hand, neurodevelopmental disorders with a genetic origin (e.g., Williams Syndrome) illustrated the importance of development and the complex relationships between genes, brain, and cognition (Karmiloff-Smith, 1998, 2007; Karmiloff-Smith & Thomas, 2003; Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith, 1999; Thomas, 2003; Thomas & Karmiloff-Smith, 2003a, 2003b).

In the beginning of the nineties, several researchers believed that the study of neurodevelopmental disorders would give answers to some of the questions that have been intriguing scientists and philosophers for years (Thomas & Karmiloff-Smith, 2005): which are the relationships between genes, brain, and cognition?; do genes dictate a modular organization of cognition?; in which ways do genes powerfully influence the organization of human cognition?

During this time, genetic neurodevelopmental disorders were then claimed as representing prototypes of the modular organization of human cognition. So, for example, a relative proficiency in certain cognitive domain coexisting with severe impairments in other domains was seen as evidence for the coexistence of impaired and preserved "modules" (e.g., Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Bellugi, Bihrle, Neville, Doherty, & Jernigan, 1992; Bellugi, Marks, Bihrle, & Sabo, 1988; Thal, Bates, & Bellugi, 1989; Wang & Bellugi, 1994).

Specifically in what concerns language, different neurodevelopmental disorders seem to be associated with different language profiles, with specific patterns of impairments and relatively preserved abilities. For example, pragmatic deficits are present in autism, associated with impairments in theory-of-mind abilities (e.g., Baltaxe, 1977; Tager-Flusberg, 1996); phonological deficits characterize dyslexia (e.g., Bishop & Snowling, 2004; Joanisse, Manis, Keating, & Seidenberg, 2000; Wolf, 1967); lexical and sentence production deficits are present in Down Syndrome (e.g., Chapman, 1997; Chapman, Seung, Schwartz, & Bird, 1998; Chapman, Shwartz, & Bird, 1991). But can neurodevelopmental disorders "reveal the component parts of the human language faculty" (Thomas & Karmiloff-Smith, 2005, p. 65)?

3. From genes, to brain, to language: lessons from atypical developmental pathways

Two distinct disorders have been intriguing researchers, one in the neuropsychiatric domain (schizophrenia) and the other in the domain of neurodevelopmental disorders with genetic origin (Williams Syndrome).

First of all, both represent interesting examples of the complex relationships between genes, brain, and behavior.

It is well known that brain dysfunction may occur at multiple levels of neuronal organization, from genes, to cells, systems, and behavior (Andreasen, 1997, 1999; Brown & Hariri, 2006; Cicchetti & Tucker, 1994; Greenspan & Dierick, 2004; Guo, 2004; Herbert et al., 2005; Järvinen-Pasley et al., 2008; Minshew & Williams, 2007; Santangelo & Tsatsanis, 2005; Wahlsten, 1999). While we know which genes are affected in Williams Syndrome (see Figure 1), the same is not true of schizophrenia. Currently, the aetiology of neuropsychiatric disorders is still unknown, although we know that most have a strong genetic component (e.g., Comings et al., 1991; Craddock & Jones, 2001; Gingrich & Hen, 2001; Lachman et al., 1996; Meyer-Lindenberg & Zink, 2007; Todd, 2000; Uhl & Grow, 2004).

Phenotipic expressions of genetic alterations in both disorders include language abnormalities and social-emotional disturbances. For example, bizarre associations are a common theme in schizophrenic discourse (e.g., Harrow & Prosen, 1979; Lanin-Kettering & Harrow, 1985; Maher, 1972; Mathalon, Faustman, & Ford, 2002; Niznikiewicz et al., 1997; Nestor et al., 1997; Spitzer et al., 1994). In Williams Syndrome, a verborreic style of discourse is often coupled with the production of atypical lexical items (e.g., Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Bellugi, Wang, & Jernigan, 1994; Harris, Bellugi, Bates, Jones, & Rossen, 1997; Jones et al., 2000). The atypicalities found in several language components (semantics, pragmatics, prosody) are associated with deficits in social communication in both disorders (schizophrenia – Addington & Addington, 1999, 2000; Bellack, Morrison, Wixted, & Mueser, 1990; Lee, Farrow, Spence, & Woodruff, 2004; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997; Pinkham, Penn, Perkins, & Lieberman, 2003; Schenkel, Spaulding, & Silverstein, 2005; Williams Syndrome – Feinstein & Singh, 2007; Järvinen-Pasley et al., 2008; Laws & Bishop, 2004; Philofsky, Fidler, & Hepburn, 2007; Riby & Hancock, 2008; Stojanovik, 2006).

In addition, both disorders are characterized by emotional disturbances. For example, individuals with Williams Syndrome are anecdotally described as presenting a drive toward social interactions, although not discriminating their social partners (e.g., they go easily with strangers) (Bellugi, Adolphs, Cassady, & Chiles, 1999; Frigerio et al., 2006; Järvinen-Pasley et al., 2008; Jones et al., 2000). A fascination for human faces is shown early in development (Jones et al., 2000; Laing et al., 2002; Meyer-Lindenberg, Mervis, & Berman, 2006). Also, reduced amygdala activation for threatening faces characterizes this syndrome (Haas et al., 2009; Meyer-Lindenberg et al., 2005a).

On the other hand, schizophrenic patients typically show flat affect (e.g., Blanchard, Kring, & Neale, 1994; Gur et al., 2006). Deficits shown at the level of social skills give rise to problems in communication and social interactions (e.g., Bellack et al., 1990; Brunet-Gouet & Decety, 2006; Couture, Penn, & Roberts, 2006; Morrison & Bellack, 1987; Mueser, Bellack, Douglas, & Morrison, 1991).

However, even if genes may play a role in the origin of the behavioral phenotype of Williams Syndrome and schizophrenia, they do not represent diagnoses (e.g., McAdams & Arkin, 1997; Plomin & Rutter, 1998). Their role is in affecting the development and functioning of brain circuits underlying the processing of cognitive and emotional information (e.g., Guo, 2004).

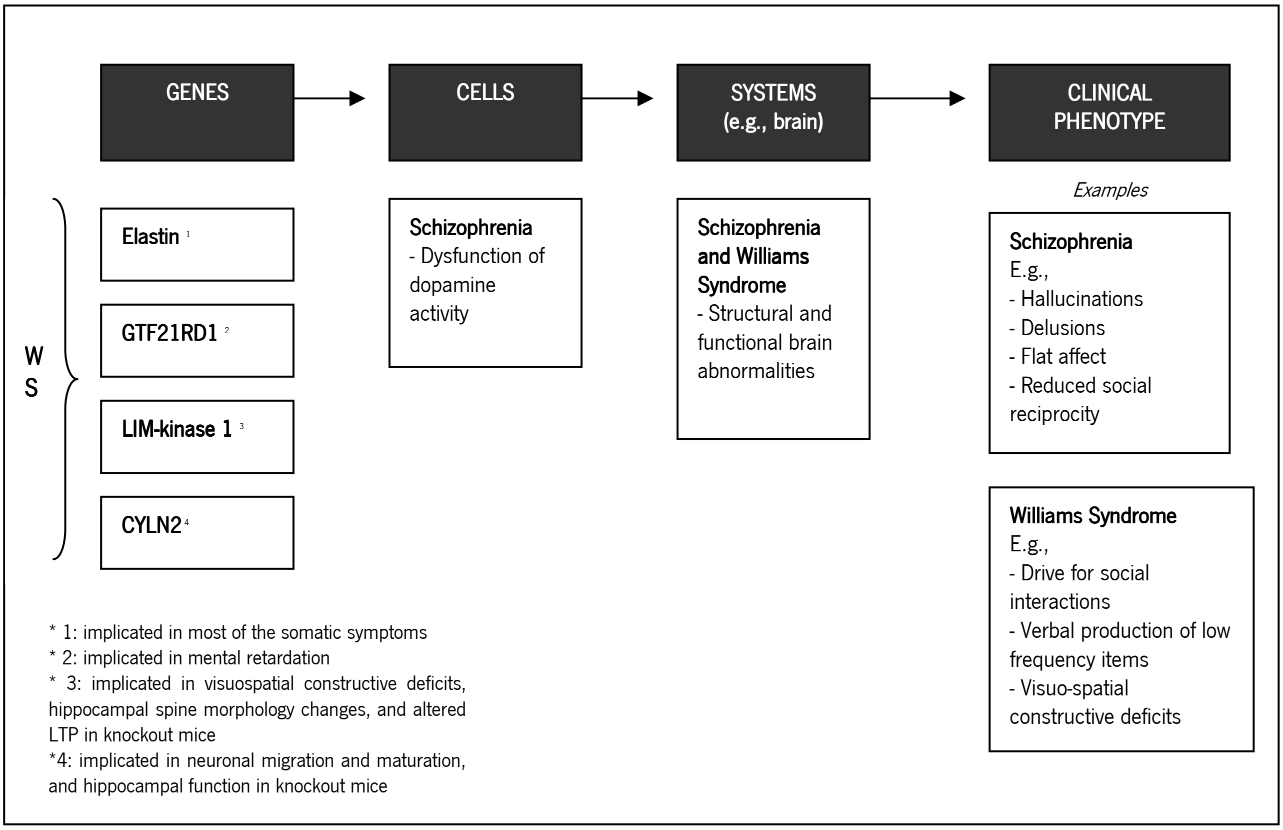


Figure 1. An illustration of the interaction between levels of neural organization in brain dysfunction (Williams Syndrome and schizophrenia).

Second, both disorders represent examples of altered developmental pathways. In both Williams Syndrome and schizophrenia, there is an abnormal cortical functional organization, namely abnormalities in the gyral and sulcal pattern (Williams Syndrome – Galaburda and Bellugi, 2000; Gaser et al., 2006; Kippenhan et al., 2005; Schmitt et al., 2002; Thompson et al., 2005; Van Essen et al., 2006; Schizophrenia – Kikinis et al., 1994; Kulynych, Luevano, Jones, & Weinberger, 1997; Kuperberg et al., 2003; Narr et al., 2004; White, Andreasen, Nopoulos, & Magnotta, 2003). It is worth noting that cortical folding occurs early during brain development (Chi, Dooling, & Gilles, 1977; Hansen, Balesteros, Soila, Garcia, & Howard, 1993; Garel et al., 2001), so this points to an atypical developmental pathway and, particularly in schizophrenia, to the fact that these structural abnormalities may be present before the appearance of functional symptoms. Also, both disorders are characterized by abnormalities in both structural and functional asymmetries (e.g., Williams Syndrome - Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Chiang et al., 2007; Reiss et al., 2000; Sampaio et al., 2008; schizophrenia – Crow, 1997a; Fallgatter & Strik, 2000; Gruzelier, 1999; Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001). Therefore, due to the specificities of the underlying neurocognitive and behavioral phenotype, both disorders have been used as paradigms for the specification of the role of gene expression in the determination of brain structure, cognition, and disease.

In the next section, Williams Syndrome and schizophrenia are briefly presented and the importance of language studies in these disorders is justified.

II. WILLIAMS SYNDROME: FROM GENES, TO BRAIN, TO COGNITION, TO BEHAVIOR

2.1. Introduction

> "*The genes of one group of children [children with specific language impairment] impair their grammar while sparing general intelligence; the genes of another group of children [children with Williams Syndrome] impair their intelligence while sparing their grammar*" (Pinker, 1999, p. 262).

> "*Williams Syndrome presents a rare decoupling of language from other cognitive capacities...: linguistic functioning is selectively preserved in the face of general cognitive deficits*" (Bellugi, Bihrle, Neville, Jernigan, & Doherty, 1992, p. 228).

Williams Syndrome, a genetic neurodevelopmental disorder resulting from a submicroscopic deletion of about 28 genes in the 7q11.23 region of chromosome 7, early intrigued researchers due to its curious cognitive phenotype. In particular, the language profile of these individuals motivated the first studies on this disorder, leading some authors to propose Williams Syndrome as a paradigmatic example of the modular preservation of language abilities and of the independence of language from general cognition (e.g., Bellugi et al., 1988, 1990, 1992; Pinker, 1994; Thal et al., 1989; Wang & Bellugi, 1994). For example, Bellugi and collaborators (1988, 1990, 1992, 1994) described several patients, highlighting their apparent proficiency in language production and their atypical vocabularies, suggestive of differential mechanisms of lexical access in this population.

But is language effectively an "intact" ability as proposed by these early studies? And, if so, what makes this cognitive function a special ability, in a background of mental retardation and severe cognitive deficits in other domains as well as of an atypical trajectory of brain development since the beginning?

In the next section, the physical, neuroanatomical, cognitive and behavioral profile of Williams Syndrome will be briefly described and the underlying language profile will be emphasized.

2.2. Williams Syndrome: assembling a jigsaw puzzle

2.2.1. Genotype

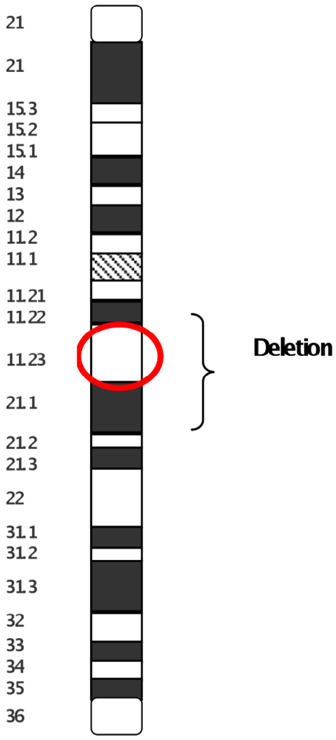


Figure 2. Schematic representation of the critical region involved in Williams Syndrome.

Williams Syndrome is a rare genetic disorder, occurring with a prevalence of 1/7500 live births (StrØmme, BjØrnstad, & Ramstad, 2002). In 1961, the cardiologist Williams and collaborators (Williams, Barratt-Boyes, & Lowe, 1961) described four unrelated cases of children who presented supravalvular aortic stenosis, mental retardation and similar facial features. An expanded medical phenotype was defined by Beuren (1972), as more individuals were identified. In the literature, descriptions of the syndrome include the following names: “idiopathic infantile hypercalcemia”, “supravalvular aortic stenosis syndrome”, “Williams elfin facies syndrome”, “Williams Syndrome”, or “Williams-Beuren syndrome” (see Morris, 2006a).

It starts from a hemizygous microdeletion of about 28 genes in chromosome 7q11.23 (Meyer-Lindenberg et al., 2006) (see Figure 2), involving approximately 1.6 Mb (Morris, 2006a). This deletion occurs with similar frequency in the maternally or paternally inherited chromosome (Pérez Jurado et al., 1998; Wang et al., 1999; Wu et al., 1998). Mental retardation is also a common problem, with a mean Full Scale IQ of 59 (Mervis, Morris, Bertrand, & Robinson, 1999).

The prevalence estimates of the syndrome suggest that Williams Syndrome (WS) can account for 6% of all cases of mental retardation with a genetic origin (Morris, 2006a). Variability also characterizes WS profile, which may be related with the fact that the expression of a genetic mutation in each individual may be affected by several different factors (Morris, 2006a).

In the following sections, a brief summary of WS phenotype will be presented. Adopting the definition of Morris (2006a), the concept *phenotype* is meant to represent all the observable and measurable traits that result from the interaction between genes (the *genotype*) and the environment.

2.2.2. Clinical phenotype

Associated with this genetic disorder is a distinctive physical phenotype, characterized by a particular facial appearance, often designed as "elfin facial profile", due to the following configuration of traits: flat nasal bridge, anteverted nares, wide mouth with fleshy lips, periorbital fullness, epicanthal folds, flat malar region, small mandible and prominent cheeks (Bellugi et al., 1990; Bellugi, Korenberg, & Klima, 2001; Donnai & Karmiloff-Smith, 2000; Morris, 2006a; Morris, Demsey, Leonard, Dilts, & Blackburn, 1988; Pagon, Bennett, LaVeck, Stewart, & Johnson, 1987). This condition is also associated with several medical problems, including cardiac and vascular problems, due to aortic narrowing, hypercalcemia (characterized by abnormally high concentrations of calcium in the blood), as well as hyperacusia (an abnormal reaction to certain sounds); other clinical conditions include renal tract abnormalities, vision problems, orthopaedic problems and gastrointestinal symptoms (Cherniske et al., 2004; Kaplan, 2006; Klein, Armstrong, Greer, & Brown, 1990; Lacro & Smoot, 2006; Morris, 2006a; Pober & Dykens, 1996). These are summarized in Figure 3.

Facial features
- Broad forehead
- Dolichocephalic cranium
- Narrowing at the temples
- Eyes: periorbital fullness, medial eyebrow flare, epicanthal folds, stellate iris pattern, strabismus
- Nose: low nasal root, broad nasal tip
- Malar flattening
- Long philtrum
- Full lips
- Wide mouth
- Full cheeks
- Prominent earlobes
- Small jaw
- Dental malocclusion

Cardiac problems:
- Supravalvular aortic stenosis

Connective tissue abnormalities:
- Soft, loose skin
- Umbilical hernia
- Inguinal hernia
- Bowl and/or bladder diverticula
- Joint laxity or contractures

Endocrine problems:
- Infantile hypercalcemia
- Hypothiroidism
- Diabetes

Neurologic problems:
- Microcephaly
- Hypotonia
- Hyperreflexia

Ophtalmologic problems:
- Hyperopia
- Strabismus
- Reduced stereo acuity

Auditory problems:
- Chronic otitis media
- Hyperacusia

Oral problems:
- Malformed or missing teeth
- Malocclusion
- Hoarse voice

Figure 3. Summary of medical problems in Williams Syndrome (based on Mervis, 2006a).

2.2.3. Neuroanatomical phenotype

The powerful influence of genes is shown in the specific profile of neuroanatomical organization in these individuals. MRI studies have shown reduced overall brain volume (e.g., Jernigan & Bellugi, 1990; Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993; Meyer-Lindenberg et al., 2006; Reiss et al., 2000); specific reductions in parietal areas (Boddaert et al., 2006; Eckert et al., 2006; Galaburda & Bellugi, 2000; Reiss et al., 2000; Schmitt et al., 2002), corpus callosum (Luders et al., 2007; Schmitt, Eliez, Bellugi, & Reiss, 2001; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001; Tomaiuolo et al., 2002; Wang, Doherty, Hesselink, & Bellugi, 1992a) and brainstem (Reiss et al., 2000, 2004); a relatively large auditory area (Bellugi, Mills, Jernigan, Hickok, & Galaburda, 1999; Galaburda & Bellugi, 2000; Holinger et al., 2005; Reiss et al., 2000) and cerebellum (Galaburda & Bellugi, 2000; Jernigan & Bellugi, 1990; Jones et al., 2002; Meyer-Lindenberg et al., 2006; Rae et al., 1998; Reiss et al., 2000; Schmitt et al., 2001c); increased cortical gyrification and complexity (Gaser et al., 2006; Schmitt et al., 2002); abnormal hippocampal shape (Meyer-Lindenberg et al., 2005b, 2006); and atypical neuron size and packing (Galaburda & Bellugi, 2000; Galaburda, Wang, Bellugi, & Rossen, 1994; see Meyer-Lindenberg et al., 2006 for a review) (see Table 1). Abnormalities of brain function have also been found (see Table 2).

In particular, studies on the superior temporal gyrus, a structure implicated in language, show increased (Boddaert et al., 2006) or preserved volume (Galaburda & Bellugi, 2000; Reiss et al., 2000), as well as atypical lateralisation (Sampaio et al., 2008).

Table 1

Summary of main findings from neuroanatomical studies in WS

(*Note*: references are presented in ascending chronological order)

AREA	FINDINGS	AUTHORS
I. BRAIN		
a) BRAIN SIZE	Reduced brain size	Jernigan & Bellugi (1990); Jernigan et al. (1993); Schmitt, Eliez, Bellugi, & Reiss (2001); Thompson et al. (2005); Sampaio et al. (2008); Cohen et al. (2010); Sampaio et al. (2010)
b) CORTICAL SHAPE	Reduction of the overall curvature of the brain (also, right and left cerebral hemispheres, as well as corpus callosum, bend to a lesser	Schmitt et al. (2001)

	degree in the sagittal plane)	
c) GYRI AND SULCI		
Central sulcus	Reduced length	Galaburda & Bellugi (2000)
	Less likelihood of reaching the interhemispheric fissure	Galaburda et al. (2001)
	Shortening of the dorsal end	Jackowski & Schultz (2005)
Central gyrus	Reduced length	Galaburda et al. (2001); Jackowski & Schultz (2005)
Superior temporal gyrus (STG)	Relative regional density increases	Boddaert et al. (2006)
	Preserved volume	Reiss et al. (2000)
	Reduced right and left STG Lack of normal left>right STG asymmetry	Sampaio et al. (2008)
Intraparietal sulcus	Reductions in symmetrical grey matter volume	Meyer-Lindenberg et al. (2004); Boddaert et al. (2006)
	Reductions in sulcal depth	Van Essen (2004); Kippenhan et al. (2005)
Occipitoparietal sulcus	Reduced sulcal depth	Kippenhan et al. (2005)
	Reduced grey matter	Meyer-Lindenberg et al. (2004)
Left collateral sulcus	Reduced sulcal depth	Kippenhan et al. (2005)
II. CORTICAL STRUCTURES		
a) FRONTAL LOBE		
Prefrontal cortex	Relative preservation of grey matter	Jernigan, Bellugi, Sowell, Doherty, & Hesselink (1993)
	Increased gyrification (left)	Schmitt et al. (2002)
	Relative regional density increases in the orbital and medial prefrontal cortices	Boddaert et al. (2006)
	Increased grey matter in frontal lobes	Campbell et al. (2009)
Orbitofrontal cortex	Reductions in symmetrical grey matter volume	Meyer-Lindenberg et al. (2004)
	Reduced sulcal depth	Kippenhan et al. (2005)
b) TEMPORAL LOBE		
Temporal lobe	Relative preservation of temporal limbic grey matter	Jernigan et al. (1993)
	Increased cortical thickness in the right perisylvian and inferior temporal zone	Thompson et al. (2005)
	Increased grey matter in left temporal lobe	Campbell et al. (2009)
Planum temporale	Larger right planum temporale (reduced leftward asymmetry)	Eckert et al. (2006)
	Lack of asymmetry	Galaburda & Bellugi (2000)
Primary auditory cortex	Larger neurons	Holinger et al. (2005)

Temporoparietal zone	Abnormally increased gyrification	Thompson et al. (2005)
c) INSULAR CORTEX		
Insular cortex	Relative regional density increases	Boddaert et al. (2006)
	Increased gyrification	Gaser et al. (2006)
	Total, anterior, and posterior volume reduction bilaterally	Cohen et al. (2010)
d) PARIETAL LOBE		
Parietal lobe	Abnormally increased gyrification (right)	Schmitt et al. (2002)
	Reduction of grey matter in the superior parietal area	Eckert et al. (2005)
	Significant decrease in grey matter	Boddaert et al. (2006); Campbell et al. (2009)
	Decreased volume of right parietal region	Campbell et al. (2009)
e) OCCIPITAL LOBE		
Occipital lobe	Abnormally increased gyrification	Schmitt et al. (2002) Gaser et al. (2006)
	Significant decrease in grey matter	Reiss et al. (2000); Boddaert et al. (2006); Campbell et al. (2009)
	Bilateral increase of gyrification	Gaser et al. (2006)
	Decreased volume of right occipital region	Campbell et al. (2009)
Primary visual cortex	Abnormal neuronal layering	Galaburda et al. (1994)
	Abnormal neuronal size	Galaburda & Bellugi (2000)
	Altered cell size and density (cells in some layers of left peripheral visual cortex are densely packed and significantly smaller)	Galaburda, Holinger, Bellugi, & Sherman (2002); Meyer-Lindenberg et al. (2004)
Cuneus	Increased gyrification bilaterally	Gaser et al. (2006)
III. SUBCORTICAL STRUCTURES		
LIMBIC SYSTEM		
Hippocampal formation (HF)	Preserved volume	Jernigan et al. (1993)
	Preserved hippocampal size, but subtle alterations in shape	Meyer-Lindenberg et al. (2005b)
	Preserved absolute volumes, but increase in left HF after normalization of volumes; lack of normal right > left HF asymmetry	Sampaio et al. (in press)
Amygdala	Preserved volume	Jernigan et al. (1993)
	Reduced volume	Galaburda & Bellugi (2000)
Anterior cingulate cortex	Relative regional density increases	Boddaert et al. (2006)
	Increased grey matter	Campbell et al. (2009)
	Increased white matter bilaterally	Campbell et al. (2009)

Posterior cingulate cortex	Increased gyrification	Gaser et al. (2006)
	Reduced white matter in right posterior cingulated gyrus	Campbell et al. (2009)
THALAMUS	Reduced grey matter	Campbell et al. (2009)
	Reduced volume of posterior forebrain	Galaburda et al. (2001)
BASAL GANGLIA		
Basal ganglia	Decreased volume	Campbell et al. (2009)
	Reduced white matter	Campbell et al. (2009)
Putamen / globus pallidus	Reduced grey matter in left putamen / globus pallidus	Campbell et al. (2009)
IV. INTER-HEMISPHERIC CONNECTION STRUCTURES		
Corpus callosum	Typical morphology	Wang et al. (1992a)
	Shape changes	Schmitt, Eliez, Warsofsky, Bellugi, & Reiss (2001); Tomaiuolo et al. (2002)
	Significant reduction of the splenium and isthmus	Schmitt et al. (2001)
	Smaller volume in the splenium and caudal sections; Less water content in the mid-section and caudal section	Tomaiuolo et al. (2002)
V. OTHER STRUCTURES		
Brainstem	Decreased volume	Reiss et al. (2000)
Cerebellum	Preserved cerebellar size	Jernigan & Bellugi (1990); Wang et al. (1992b); Reiss et al. (2000); Jones et al. (2002)
	Significantly increased size of neocerebellar lobules	Jernigan & Bellugi (1990)
	Preserved size of neocerebellar tonsils (but larger size in proportion to the cerebrum)	Wang et al. (1992)
	Significantly larger posterior vermis	Schmitt et al. (2001c)
	Abnormal enlargement (already observed in infants and toddlers with WS)	Jones et al. (2002)

Table 2

Summary of main findings from functional studies (fMRI) in WS

COGNITIVE DOMAIN	RESULTS	AUTHORS
1. AUDITORY PROCESSING		
Processing of music stimuli vs noise	Similarly to typically developing controls (matched for chronological age, handedness, gender, and musical experience), significant bilateral temporal lobe activation for music vs. noise and rest in WS; but reduced activation in the temporal lobes and greater activation in the right amygdala during music and noise processing (whole brain analysis) for WS participants; and widely distributed network of activation in cortical and subcortical structures (e.g., brain stem, right amygdala) during music processing	Levitin et al. (2003)
2. VISUAL PROCESSING		
Processing of spatial locations	Abnormal dorsal stream function: hypoactivation in the parietal portion of the dorsal stream	Meyer-Lindenberg et al. (2004)
Processing of visual objects	Abnormal functional connectivity between parahippocampal gyrus and parietal cortex, and between fusiform gyrus and brain regions such as the amygdala and portions of the prefrontal cortex, during passive house viewing	Sarpal et al. (2008)
2.1. FACE PROCESSING		
Passive viewing of face and house stimuli	Decreased activation in the parietal part of the dorsal stream in response to passively viewing face and house stimuli compared with viewing scrambled stimuli or baseline; bilateral lack of activation in the anterior portion of the hippocampal formation for the comparison of response to face and house stimuli	Meyer-Lindenberg et al. (2005b)
Face discrimination	Failure to recruite the amygdala in a face discrimination task (in spite of similar responses in ventral occipito-temporal cortex to developmental age controls)	Paul et al. (2009)
Processing face and eye-gaze direction	Increased activation in the right fusiform gyrus and several frontal and temporal regions; more extensive activation in the right inferior, superior, and medial frontal gyri, anterior cingulated, and several subcortical regions such as the anterior thalamus and caudate (in between-group analysis)	Mobbs et al. (2004)

Processing of emotional facial expressions (angry, fearful) and emotional scenes (threatening and fearful)	Decreased reactivity of the amygdala to threatening, socially relevant stimuli; increase of amygdala reactivity to socially irrelevant stimuli; absence of activation of regions in the dorsolateral prefrontal cortex, medial prefrontal cortex and OFC; absence of negative correlation between OFC and amygdala	Meyer-Lindenberg et al. (2005a)
	Increased amygdala reactivity to happy facial stimuli and absent or decreased amygdala reactivity to fearful facial stimuli	Haas et al. (2009)
Implicit emotion face processing	Abnormal (decreased) amygdala response to fearful face expressions that correlated with an increased tendency to approach strangers	Haas et al. (2010)
3. EXECUTIVE FUNCTIONING		
Response inhibition	Reduced activity in the striatum, dorsolateral prefrontal, and dorsal anterior cingulated cortices during a Go/No Go response inhibition task.	Mobbs et al. (2007)

2.2.4. Cognitive phenotype

The relationships between genes and brain also give rise to a distinctive pattern of cognitive organization. In a background of mental retardation, severe difficulties in spatial cognition and visual construction tasks, number reasoning and executive functions, coexist with a relative preservation of language and face processing, which give rises to a curious pattern of "peaks and valleys" of abilities (e.g., Bellugi et al., 1990, 1994, 1999, 2000, 2001; Meyer-Lindenberg et al., 2006; Pezzini, Vicari, Volterra, Milani, & Ossella, 1999).

The mean IQ described in several studies lies between 50 and 60, with a range of 40-100 (Bellugi et al., 1999; Lenhoff, Wang, Greenberg, & Bellugi, 1997; Levitin & Bellugi, 1998; Morris, 2006b; Reis, Schader, Milne, & Stephens, 2003).

2.2.4.1. Language processing

> "*You are looking at a professional bookwriter. My books will be filled with drama, action, and excitement. And everyone will want to read them… I am going to write books, page after page, stack after stack. I'm going to start on Monday*" (Bellugi et al., 1994, p. 8, citing an adolescent diagnosed with Williams Syndrome).

The initial studies with individuals diagnosed with WS proposed a dissociation between cognitive abilities, with a relative preservation of language and face processing coexisting with severe impairments in reasoning and visuospatial processing (e.g., Bellugi et al., 1988, 1990, 1992; Pinker, 1994; Thal et al., 1989; Wang & Bellugi, 1994). In fact, contrasting with severe deficits in tasks as block design (a task of the Wechsler Intelligence Scales), the linguistic production of these individuals gave the idea of a preserved language module. For example, they tend to produce sentences that are syntactically and grammatically appropriate (e.g., Bellugi et al., 1994, 2000; Mervis & Robinson, 2000; Mervis & Becerra, 2007), and longer than what is commonly observed in children with Down Syndrome (Harris et al., 1997; Rice, Warren, & Betz, 2005), as shown by the transcription above. Other studies described the use of grammatically complex forms, as passive sentences, conditional clauses and embedded relative clauses (Bellugi et al., 2000; Clahsen & Almazan, 1998, 2001; Karmiloff-Smith et al., 1997; Zukowski, 2004). Also, in narrative tasks, an extensive use of affective enrichment devices (e.g., affective prosody, interjections, exclamatory phrases, onomatopoeias) designed to attract audience's attention was reported (Gonçalves et al., 2004; Gonçalves et al. in press; Heinze, Prieto, Gonçalves, & Sampaio, 2007; Jones et al., 2000; Losh, Bellugi, Reilly, & Anderson, 2000; Reilly, Losh, Bellugi, & Wulfeck, 2004).

However, subsequent studies added evidence against a modular preservation of language in WS, in face of general cognitive impairment (see Thomas, 2000; Thomas et al., 2009; Thomas & Karmiloff-Smith, 2005) (see Figure 4 and Table 3). These studies suggest that language development is atypical (Grant et al., 1997; Karmiloff-Smith et al., 1997; Laing et al., 2002; Levy, 2004; Masataka, 2001; Mervis & Bertrand, 1997; Mervis et al., 1999) and that within-domain fractionations are observed in WS (e.g., Thomas & Karmiloff-Smith, 2005). For example, Jarrold, Baddeley, Hewes, and Philipps (2001) proposed that an apparent "strength" in language abilities in WS may be due to a diverging developmental pathway, where vocabulary levels progress at a faster rate than pattern construction abilities.

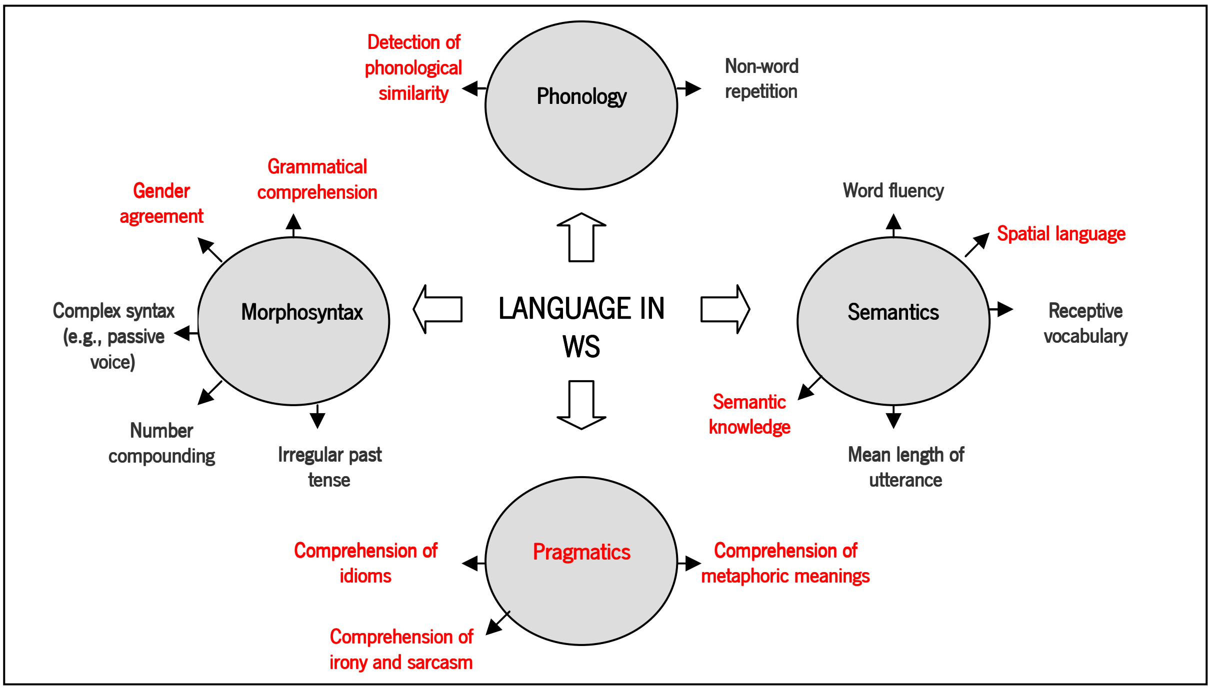


Figure 4: Summary of language abilities in WS: examples of relatively preserved (grey) and impaired (red) language subcomponents.

Caption: red= impairments; grey= relative preservation

It is worth noting the diversity in the results found across studies, which may be due to several factors, including the range of instruments to assess language abilities, the use of different control groups and small sample sizes (see Martens, Wilson, & Reutens, 2008 for a review).

Table 3

A summary of studies on language and communication in Williams Syndrome

(*Note*: references are presented in ascending chronological order)

Domain	Findings	References
LANGUAGE ACQUISITION		
Development of language production and comprehension abilities	- Delayed development (both expression and comprehension)	Capirci, Sabbadini, & Volterra (1996); Singer-Harris, Bellugi, Bates, Jones, & Rossen (1997); Paterson et al. (1999); Mervis & Klein-Tasman (2000); Mervis & Robinson (2000); Mervis et al. (2003)
	- Atypical profile *Examples:*	Grant et al. (1997); Mervis & Bertrand (1997); Mervis et al. (1999); Masataka

	(a) vocabulary spurt before engagement in spontaneous exhaustive sorting; (b) speech production before pointing; (c) impairments in triadic joint attention	(2001); Laing et al. (2002); Levy (2004); Mervis (2006)
	- Diverging developmental trajectories of verbal and non-verbal abilities	Jarrold et al. (2001)
PHONOLOGY		
Segmentation	- Impairments in syllable deletion and rhyme detection (but not in syllable segmentation)	Laing, Hulme, Grant, & Karmiloff-Smith (2001); Menghini, Verucci, & Vicari (2004)
	- Impairments in speech segmentation abilities	Nazzi et al. (2002)
	- Preservation of the ability to segment the words with strong-weak stress pattern - Delay in the onset of segmentation of weak-strong words	Nazzi, Patterson, & Karmiloff-Smith (2003)
Word repetition	- Normal similarity and length effects in word span tasks - Reduced frequency effects in repetition tasks	Vicari , Carlesimo, Brizzolara, & Pezzini (1996)
Non-word repetition	- Preserved repetition	Karmiloff-Smith et al. (1997); Grant et al. (1997)
Detection of phonological similarity	- Impaired rhyme detection	Majerus, Barisnikov, Vuillemin, Poncelet, & Van der Linden (2003)
Speech fluency	- Increased speech discontinuity and frequency of common hesitations and word repetition	Rossi, Souza, Moretti-Ferreira, & Giachetti (2009)
PROSODY		
Emotional prosody comprehension	- Impaired comprehension	Catterall, Howard, Stojanovik, Szczerbinski, & Wells (2006); Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg (2006)
	- Relatively spared ability to interpret affective prosody when no additional linguistic information is present in the acoustic stimulus	Plesa-Skwerer, Schofield, Verbalis, Faja, & Tager-Flusberg (2007)
Prosody production	- Impaired production (but not relative to the level of language comprehension)	Stojanovik, Setter, & van Ewijk (2007)
MORPHOSYNTAX		
Sentence structure	- Word-order and morphosyntactic errors in Italian	Volterra, Capirci, Pezzini, Sabbadini, & Vicari (1996)
	- Morphosyntactic abilities may be commensurate with non-verbal skills	Pezzini et al. (1999); Stojanovik, Perkins, & Howard (2001); Karmiloff-Smith, Brown, Grice, & Peterson (2003)
Gender inflection	- Impairments in grammatical gender assignment in French and Italian	Capirci et al. (1996); Karmiloff-Smith et al. (1998); Volterra et al., (1996)
	- Impairments in gender agreement in French	Boloh, Ibernon, Royer, Escudier, & Danillon (2009)
Compounding	- Preserved ability to produce novel noun-noun compounds	Zukowski (2005)

(number)	of the form of *X eater* with known nouns and nonsense nouns	
Compounding (verbs)	- No selective deficit in the production of irregular English past tense forms; deficits in generalising the "add-ed" past tense rule to novel forms	Thomas et al. (2001)
	- Impaired performance in existing irregular inflection; no differences on regular inflection	Clahsen & Almazan (1998); Pléh, Lukács, & Racsmány (2003)
	- Grammatical errors (e.g., deletion of tense markers or auxiliaries)	Mervis & Becerra (2007)
Relative clauses	- Impairments in left branching relative clause processing in English	Grant, Valian, & Karmiloff-Smith (2002)
Passivization; Syntactic binding	- Preservation of the ability to comprehend passive sentences	Bellugi, Lai, & Wang (1997); Clahsen & Almazan (1998); Stavrakaki (2003); Ring & Clahsen (2005)
	- Lower accuracy scores on reversible passives	Karmiloff-Smith et al. (1998)
Grammatical comprehension	- Difficulties in grammatical comprehension (in young children with WS)	Volterra et al. (1996)
LEXICAL ABILITIES AND SEMANTICS		
Expressive vocabulary	- Tendency to use words that are precocious, unexpected and sometimes inappropriate - Good expressive vocabulary (by adolescence)	Rossen et al. (1996); Udwin & Dennis (1995); Bellugi et al. (1997)
	- Performance at a relatively high level on standardized vocabulary tests, although still below chronological age	Grant et al. (1997); Jarrold, Baddeley, & Hewes (1998); Karmiloff-Smith et al. (1998)
Receptive vocabulary	- Higher levels of receptive vocabulary in comparison with mental age-matched controls (but when the child has to select from multiple distracters in the same semantic class, receptive vocabulary levels are significantly weaker than mental age controls)	Temple, Almazan, & Sherwood (2002)
	- More semantic errors, fewer circumlocutions than mental age controls	Ypsilanti, Grouios, Alevriadou, & Tsapkini (2005)
Naming	- Difficulties in word finding for irregularly (but not regularly) inflected forms	Bromberg, Ullman, Marcus, Kelly, & Coppola (1994)
	- Fewer errors on high than low frequency words	Lukács et al. (2001)
	- Larger proportion of atypical errors in naming errors	Temple et al. (2002)
	- Performance similar to DS and below MA expectations	Volterra, Caselli, Capirci, Tonucci, & Vicari (2003)
	- Naming is slower and less accurate than expected for receptive vocabulary, but the naming times are modulated in the same way by frequency and semantic category	Thomas et al. (2006)
	- Slower than controls in naming colours - Higher number of errors in naming pictures, but not in naming words	Ypsilanti, Grouios, Zikouli, & Hatzinikolaou (2006)

Semantic knowledge	- Deficits in semantic knowledge structures	Bellugi, et al. (1990); Neville, Mills, & Bellugi (1994); Rossen et al. (1996); Vicari et al. (1996a, 1996b); Volterra et al. (1996); Grant et al. (1997); Jarrold, Hartley Philips, & Baddeley (2000); Laing et al. (2001); Temple et al. (2002)
	- Impaired performance in word definition (impaired integration of distinctive features from perceptual input, which may have a grater impact in nonmanipulable objects than other knowledge categories)	Bellugi et al. (1990)
	- Poor understanding of deeper biological concepts (e.g., animal", "alive", "death"), in spite of relatively strong basic conceptual knowledge	Johnson & Carey (1998)
	- Impairment in the representation of semantic knowledge	Robinson & Temple (2009)
Semantic priming	- Normal priming effects	Tyler et al. (1997)
Semantic fluency	- More words produced than expected by mental age - Higher production of atypical category exemplars	Bellugi et al. (1988, 1990, 1992, 1994); Wang & Bellugi (1994); Rossen et al. (1996)
	- Production of items of equivalent frequency and representativeness to those generated by controls	Scott et al. (1995); Stevens (1996); Volterra et al. (1996); Tyler et al. (1997); Mervis et al. (1999); Jarrold et al. (2000); Levy & Bechar (2003)
	- Production of more infrequent words towards the end of each trial	Rossen et al. (1996)
	- Word fluency improves substantially after 10 years-old	Rossen et al. (1996); Bellugi et al. (2000)
	- More repetitions / perseverations	Jarrold et al. (2000)
	- No differences relative to controls with mental retardation with unknown etiology, matched on MA and CA, and TD controls	Levy & Bechar (2003)
	- Production of more items with 0 word frequency (e.g., not unusual but "pets" names for animals)	Lukács (2005)
Spatial language	- More errors for spatial prepositions	Bellugi et al. (2000); Lukács (2005)
	- Difficulties with path descriptors (omission)	Landau & Zukowski (2003); Landau, Hoffman, & Kurz, (2006)
	- WS spatial language performance is not uniformly poor (e.g., tendency for production of more path type errors on postpositions than on suffixes)	Lukács, Pléh, & Racsmány (2007)
	- Difficulty with relational language in general	Mervis & Morris (2007)
Categorization	- Difficulties in using verbal cues to form new object categories	Nazzi & Karmiloff-Smith (2002)
PRAGMATICS		

Social and communication abilities	- Pragmatic language impairment: excessive chatter; propensity for socially inappropriate statements and questions; propensity for talking with themselves	Davies et al. (1998); Stojanovik et al. (2001); Laws & Bishop (2004)
	- Poor referential communication skills (difficulties in understanding and verbalizing when verbal messages are not adequate)	John, Rowe, & Mervis (2009)
	- Deficits in attention-sharing communication	Asada, Tomiwa, Okada, & Itakura (2010)
Interpretation of non-literal meaning	- Difficulties (e.g., distinguishing lies from jokes)	Tager-Flusberg et al. (1997); Sullivan & Tager-Flusberg (1999); Tager-Flusberg & Sullivan (2000)
	- Comprehension of metonyms seems to be in line with receptive vocabulary	Annaz et al. (2009)
	- Difficulties in understanding metaphorical language comprehension (access to less abstract knowledge in figurative language comparisons)	Annaz et al. (2009) Thomas et al. (2010)
	- Difficulties in idioms understanding	Lacroix, Aguert, Dardier, Stojanovik, & Laval (2010)
NARRATIVE		
Structure	- Structure of narratives as sophisticated as expected by mental age	Reilly, Kima, & Bellugi (1991); Bellugi et al. (1997)
Process	- More advanced use of affective prosody and "evaluative" devices - Higher use of "audience engagement devices"	Reilly et al. (1991); Bellugi et al. (1997); Gonçalves et al. (2004, in press); Heinze et al. (2007); Lorusso et al. (2007)
	- Use of the same level of expressivity regardless of how many times the story was told and irrespective of audience	Bellugi et al. (1997)
Integration	- Difficulties in integrating single elements into coherent and meaningful structures	Gonçalves et al. (2004); Garayzábal, Prieto, Sampaio, & Gonçalves (2007); Lorusso et al. (2007)
READING		
Accuracy and speed	- Adequate reading abilities for the cognitive level of WS group, both for accuracy and speed of execution, except for nonword reading	Menghini et al. (2004)
	- Slower and less accurate reading	Heinze & Vega (2008)

2.2.4.2. Visuospatial and face processing skills

The relative preservation of language contrasts with the severe deficits exhibited in the visuospatial domain. Several studies show deficits in the processing of global aspects of visuospatial stimuli, indicating a bias in processing local features (Bihrle, Bellugi, Dellis, & Mark, 1989; Farran & Jarrold, 2003; Farran, Jarrold, & Gathercole, 2003).

Other studies suggest dissociation between the dorsal (responsible for processing information about the position of objects) and the ventral visual stream (related to face and object recognition) in WS, showing impairments in the dorsal stream that coexist with the relative preservation of the ventral stream (Atkinson et al., 1997; Wang, Doherty, Rourke, & Bellugi, 1995).

In terms of facial processing skills, individuals with WS seem to be equivalent to mental age-matched controls in face recognition and discrimination, although they are significantly below chronological age-matched controls (Deruelle, Mancini, Livet, Casse-Perrot, & de Schonen, 1999; Gagliardi et al., 2003). These studies suggest a relative preservation of skills related with the discrimination of facial expressions (Tager-Flusberg & Sullivan, 2000), or identification and labelling of emotional facial expressions (Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006a; Plesa-Skwerer, Verbalis, Schofield, Faja, & Tager-Flusberg, 2006b).

Together, these findings point to the fact that within a specific cognitive domain (as visual cognition), we can find an unusual pattern of "peaks and valleys" of abilities.

2.2.4.3. Executive functioning

Executive dysfunction has also been reported in individuals with WS, namely difficulties with abstract reasoning, flexibility, planning, self-monitoring, and behavior inhibition (Atkinson et al., 2003; Bellugi et al., 1994, 2001; Korenberg, Bellugi, Salandanan, Mills, & Reiss, 2003; Martin & McDonald, 2003; Meyer-Lindenberg et al., 2006; Mobbs et al., 2007; Tager-Flusberg, Sullivan, & Boshart, 1997). These deficits seem to be associated with frontal abnormalities (e.g., Mobbs et al., 2007).

2.2.4.4. Musical skills

Anecdotal descriptions suggest that individuals with WS share a keen interest for music and show preserved musical skills (Hopyan, Dennis, Weksberg, & Cytrynbaum, 2001; Levitin & Bellugi, 1998; Udwin, Yule, & Martin, 1987), which has been interpreted as evidence for the modularity of musical abilities (Levitin & Bellugi, 1998). However, a high heterogeneity exists regarding musical ability and achievement in WS (Levitin, & Bellugi, 2006).

Studies show similar performance on measures of rhythm production, rhythm perception, and timbral identification, when compared with typically-developing controls matched on chronological age (CA). Also, due to the unusual sensitiveness to sound in these individuals, auditory allodynia (aversion to specific types of normal-volume sounds), adynacusis (perception of sounds that are not too loud for others as painfully loud), and fascination for certain types of sounds are typically present (Levitin & Bellugi, 2006). We should also mention the fact that ERP tests of auditory recovery cycle showed normal auditory brainstem-evoked potentials (Neville et al., 1994).

2.2.5. Behavioral phenotype

A striking characteristic of WS behavioral phenotype is what has been described as hypersociability (Bellugi et al., 1999; Doyle, Bellugi, Korenberg, & Graham, 2004; Jones et al., 2000; Porter, Coltheart, & Langdon, 2007).

Behaviourally, these individuals seem to be overly friendly with strangers and show an intense desire to be engaged in social interactions. For example, toddlers show a preferential focusing on human faces during social interactions, and less interest in objects, which is related with difficulties in joint attention (Laing et al., 2002; Mervis et al., 2003).

The strong interest in human faces coexists with diminished fear of strangers (Bellugi et al., 2007; Jarvinen-Pasley et al., 2008; Meyer-Lindenberg et al., 2005a; Porter et al., 2007; Skwerer et al., 2009), contrasting with the increased levels of anxiousness (inclusively phobias) towards non-social targets, as objects or noises (e.g., Davies, Udwin, & Howlin, 1998; Dykens, 2003; Dykens, Rosner, Ly, & Sagun, 2005; Udwin & Yule, 1991).

It is also worth noting the impulsiveness and hyperactivity, characteristics of this behavioral profile, as well as the extreme anxiousness often revealed in new situations where unexpected things may happen (Dykens, 2003; Klein-Tasman & Mervis, 2003; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Semel & Rosner, 2003).

Together, these characteristics make this syndrome “an experiment of nature” (Reiss et al., 2004) or, in other words, a curious scenario for the study of the complex interactions between genes, brain and cognition.

III. SCHIZOPHRENIA: A DISORDER OF THE CONDITION THAT DEFINES *HOMO SAPIENS*?

> "*Schizophrenia, a condition which apparently occurs in all societies with approximately the same incidence, may best be understood as an anomaly of the function which is most characteristically human – language*" (Crow, 1997a, p. 343).

> "*It is a disease (perhaps* the *disease) of humanity*" (Crow, 2008, p. 33).

3.1. Introduction

Schizophrenia is a puzzling disorder, characterized by a diversity of symptoms that reflect abnormalities in several areas of cognition, emotion and behaviour (see Wible et al., 2009 for a review). The complexity of this pathology was first noted by Kraepelin (1919), who defined it as *dementia praecox*. Later, Jackson (1931) proposed two major categories to describe schizophrenia symptoms: positive (e.g., hallucinations and delusions) and negative (e.g., anhedonia, flat affect) symptoms. While the first were seen as representing an exaggeration of normal function, the later were assumed to represent a loss of function.

The evolving concept of schizophrenia is related with its complexity. Auditory hallucinations represent a nuclear symptom of the disorder, occurring in more than 74% of patients (Crow, 2004; Silbersweig & Stern, 1996). The incidence of schizophrenia is similar in all human populations, which suggests the relative independence of this disorder from the environment (Crow, 1997a, 1997b).

Impairments in verbal learning and memory have also been reported (Heinrichs & Zakzanis, 1998; Saykin et al., 1994). Other features include executive dysfunction (Goldman-Rakic, 1991), in particular abnormalities in attention, inhibitory control, action monitoring or initiation of desired actions (Carter et al., 1998; Cohen & Servan-Schreiber, 1992; Frith et al., 1995; Goldman-Rakic, 1991; Heinks-Maldonado et al., 2007; Honey & Fletcher, 2006) (see Table 4).

Table 4

Description of key elements of nuclear symptoms (Wing, Cooper, & Sartorius, 1974), according to the glossary of the Present State Examination (adapted from Crow, 1998)

Symptom	Description
Thought echo or commentary	The subject experiences his own thought as repeated or echoed with very little interval between the original and the echo
Voices commenting	A voice or voices heard by the subject speaking about him and therefore referring to him in the third person.
Passivity (delusions of control)	The subject experiences his will as replaced by that of some other force or agency.
Thought insertion	The essence of the symptom is that the subject experiences thoughts which are not his own intruding into his mind.
Thought withdrawal	The subject says that his thoughts have been removed from his head so that he has no thoughts.
Thought broadcast	The subject experiences his thoughts actually being shared with others.
Primary delusions	The patient suddenly becomes convinced that a particular set of events has a special meaning, based upon sensory experiences.

Underlying the behavioral manifestations of the disorder, several brain structure and function abnormalities have been found (e.g., Chua & McKenna, 1995; Goldstein et al., 1999; Lawrie, Whalley, Job, & Johnstone, 2003; McCarley et al., 1999; Niznikiewicz, Kubicki, & Shenton, 2003; Shenton, Dickey, Frumin, & McCarley, 2001). The proposal of schizophrenia as a brain disorder is not a recent assumption. In fact, Kraepelin (1899) was the first to suggest that *dementia praecox* was characterized by damage of cells of the cerebral cortex, tentatively proposing that dysfunction of the frontal lobe was associated with deficits of reason and volition, while dysfunction in the temporal lobe would cause hallucinations and delusions.

Since language disturbance symptoms seem to be at the core of this disorder (Bleuler, 1911/1950; Kraepelin, 1919/1971), schizophrenia is viewed by several authors as a disorder of language (Crow, 1997a, 1997b, 1998, 2004, 2008). The centrality of language in the symptomatic characterization of schizophrenia has led some to propose this disorder as a uniquely human condition (e.g., Crow, 1997a, 1997b, 1998, 2004, 2008) (see Figure 5).

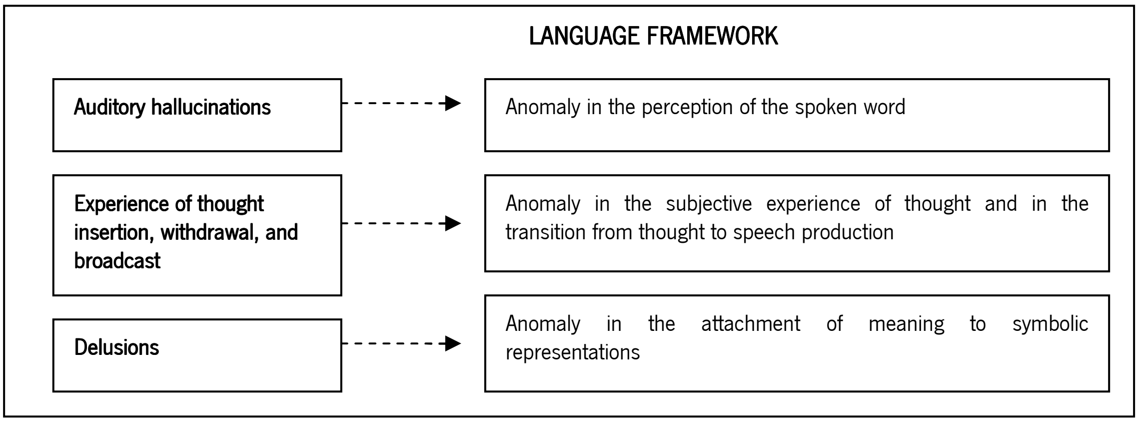


Figure 5. Examples of schizophrenia symptoms and its conceptualization under a linguistic framework (adapted from Crow, 2004).

3.2.1. Onset

Although it is still not well understood, the onset of schizophrenia occurs from late adolescence (corresponding to the end of frontal lobe maturation) through middle adulthood, being slightly earlier (two to three years) in males than in females (Crow, 1997a).

The existing studies suggest that several factors may play a role in the onset of schizophrenia, namely genes and environmental factors (e.g., prenatal exposure to viral infections). For example, it is well established that heredity plays a crucial role in the pathophysiology of schizophrenia (e.g., Bertolino & Blasi, 2009; Bray & Owen, 2001; Craddock, O'Donovan, & Owen, 2005; Jones & Murray, 1991; Kendler & Diehl, 1993; Owen & McGuffin, 1992; Weinberger et al., 2001). For the last decades, we have learned that genes have the power to modify neurobiological mechanisms (e.g., Greenspan & Dierick, 2004; Siebner, Callicott, Sommer, & Mattay, 2009), with recent studies suggesting a reliable effect of *DRD2* polymorphism risk (Glatt, Faraone, & Tsuang, 2003).

Also, the course of development of schizophrenia symptoms, its common age of onset, and its prodromal symptoms suggest an atypical developmental pathway. For example, across studies, a common finding is that individuals diagnosed with schizophrenia may be distinguished from individuals not predisposed to the disorder during childhood and adolescence, 10 or 15 years before the onset of psychosis (Crow, Done, & Sacker, 1995; Marenco & Weinberger, 2000; Rapoport, Addington, Frangou, & Psych, 2005; Rapoport et al., 1999). This suggests that schizophrenia is characterized by an altered developmental pathway. Therefore, due to an increase in the number of studies and to advancements in technologies for brain research, schizophrenia is increasingly viewed as a neurodevelopmental disorder, characterized by atypical brain development during the critical periods of the second and third decades of life (Lewis & Levitt, 2002). For example, regarding the rare childhood-onset schizophrenia (onset by age 12 years), we know that there is a posterior-to-anterior tissue loss, in that parietal gray matter loss is followed by frontal and temporal gray matter loss during adolescence (Thompson et al., 2001).

The neurodevelopmental hypothesis (Weinberger, 1987; Murray & Lewis, 1987; Rapoport, Addington, Frangou, & Psych, 2005) suggests that an atypical development of synaptic pathways that involve structures as the hippocampus and the prefrontal cortex may end up in dysregulated dopamine signalling and the clinical symptoms that characterize this disorder. Also, it is commonly accepted that genetic risk in schizophrenia dynamically interacts with risk factors belonging to the psychosocial environment where the high-risk subjects live, resulting in increased vulnerability (Keshavan, Diwadkar, Montrose, Rajarethinam, & Sweeney, 2005). This is consistent with the theory that biological mechanisms or risks factors may predispose to disorganized neuronal firing and brain function in severe psychiatric disorders (Bertolino & Blasi, 2009).

Although we still don't know exactly the susceptibility genes for schizophrenia, the common assumption is that this disorder has a strong genetic component (Baron, 2001; Craddock et al., 2005; Jones & Murray, 1991; Kendler & Diehl, 1993; O'Donovan, Williams, & Owen, 2003; Owen, Craddock, & O'Donovan, 2005; Owen & McGuffin, 1992; Owen, O'Donovan, & Harrison, 2005; Weinberger et al., 2001). This idea is supported by studies showing a strong relationship between schizotypal personality disorder and schizophrenia. For example, schizotypal personality features are found among relatives of schizophrenic patients and relatives of schizotypal individuals present a higher risk for developing schizophrenia (Asarnow et al., 2001; Kendler & Gruenberg, 1984; Kendler, Masterson, Ungaro, & Davis, 1984; Siever et al., 1990; Torgersen, 1985). Also, there is a stronger relationship between schizophrenia and schizotypal personality disorder than between other types of personality disorders (Kendler et al., 1993). In addition, individuals with schizotypal personality disorder share with schizophrenic patients some biological markers for schizophrenia, as impaired startle prepulse inhibition (Cadenhead, Geyer, & Braff, 1993; Cadenhead, Light, Geyer, McDowell, & Braff, 2002) (see Figure 6).

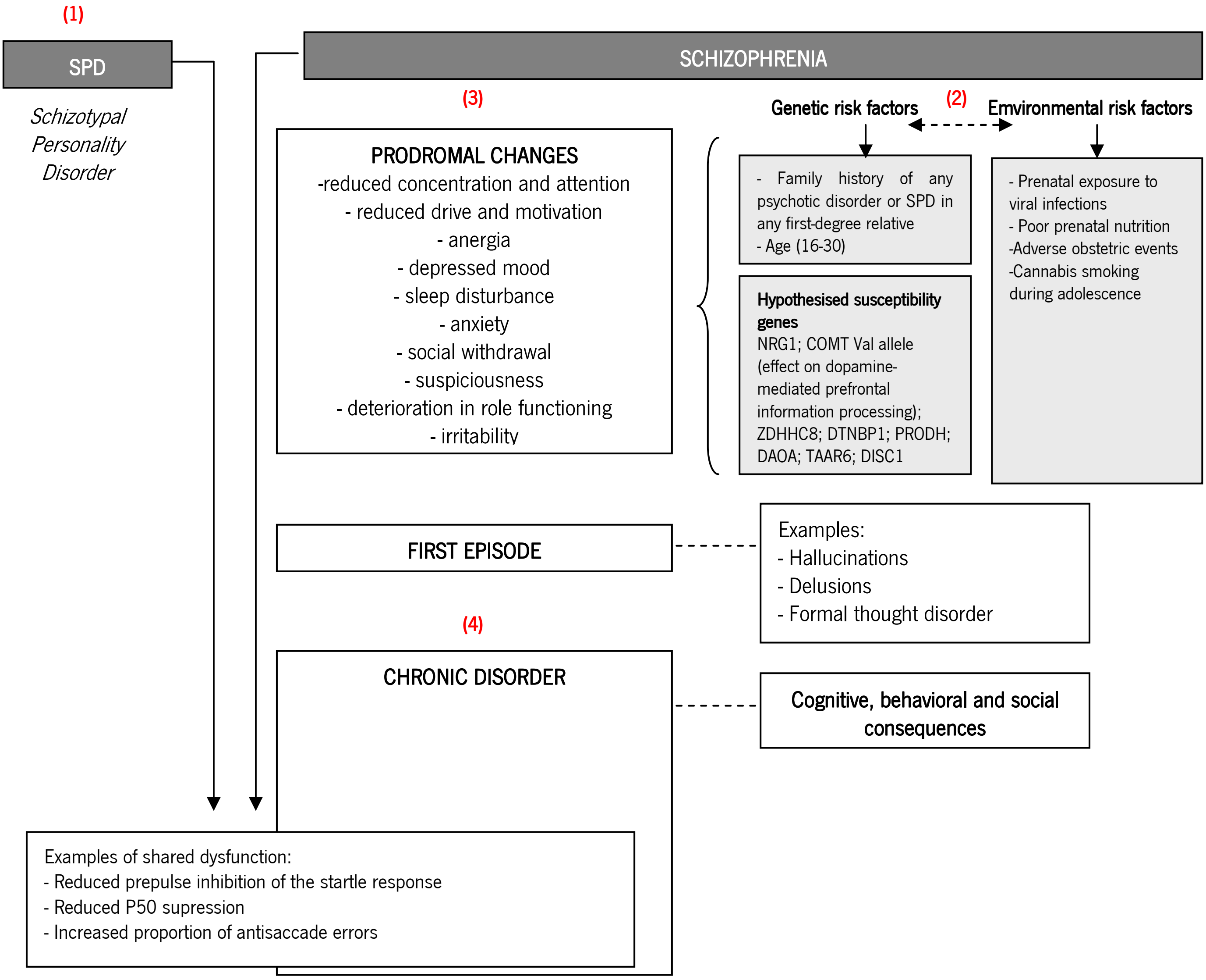


Figure 6. Risk factors, symptoms, and neurobiological markers of schizophrenia (a summary of different studies).

(1) SPD has a strong genetic relationship to schizophrenia (e.g., Kendler, Gruenberg, & Strauss, 1981). For example, it has been shown that there is a higher risk of schizophrenia among the relatives of SPD individuals (e.g., Torgersen, 1985). Both disorders share some brain abnormalities (e.g., cortical abnormalities, as cortical sulcal enlargement – e.g., Cannon et al., 1994; STG volume reduction – Dickey et al., 1999). Cognitive dysfunction is also observed in both disorders (e.g., impairments in working memory, verbal learning, and attention – e.g., Cadenhead, Perry, Shafer, & Braff, 1999), in particular, similar language abnormalities (e.g., more negative N400 in both congruent and incongruent sentence completions - e.g., Niznikiewicz et al., 1999). (2) Both genetic and environmental factors play a role in the etiology of schizophrenia. Even though several susceptibility genes have been identified in schizophrenia (Craddock, O'Donovan, & Owen, 2005), more work has still to be done. Schizophrenia is clearly a complex disorder, and understanding its etiology has been a considerable challenge. (3) Schizophrenia is generally characterized by prodromal changes and the identification of these longitudinal precursors has great importance for the understanding of the disorder. Its clinical manifestations include

hallucinations, delusions, and thought disorder. The cognitive and behavioral abnormalities are also associated with deficits in social interactions (e.g., Addington & Addington, 1999; Green, 1996). (4) The progression of disease is associated with symptoms early in its course, as more negative symptoms may reflect a process leading to higher functional disability in the long-term (e.g., Fenton & McGlashan, 1991). However, stability of brain structural changes over time has been shown.

3.2.2. Neuroanatomy of schizophrenia

Due to the implications of structural abnormalities to cognitive performance and electrophysiological findings, we present the major findings of structural studies with schizophrenia patients. Considering the high number of MRI studies during the last two decades, we present only the major significant results presented in two comprehensive review papers from the last ten years. One of these meta-analyses was carried out by Shenton, Dickey, Frumin, and McCarley (2001) and another one was published by Antonova, Sharma, Morris, and Kumari (2004).

Table 5

Brain structural and functional abnormalities in schizophrenia: a selective review

(*Note*: references are presented in ascending chronological order)

Brain area	Findings in schizophrenia	References
I. BRAIN		
Whole Brain Volume (WBV)	Reduced	Ward, Friedman, Wise, & Schulz (1996)
	WBV reduction in deficit but not non-deficit patients	Kareken et al. (1995)
	Reduced whole brain grey matter volume	Zipursky, Lambe, Kapur, & Mikulis (1998); Gur, Turetsky, Bilker, & Gur (1999)
II. VENTRICULAR SYSTEM		
Lateral ventricles (LV)	Enlarged (left-side prominence)	Johnstone et al. (1989); Becker et al. (1990); Bogerts et al. (1990); Degreef, Bogerts, Ashtari, & Lieberman (1990); DeLisi et al. (1991); Shenton et al. (1992); Kawasaki et al. (1993); Roy et al. (1998); Niemann, Hammers, Coenen, Thron, & Klosterkotter (2000)
	Increased volume of the temporal horn	Kovelman & Scheibel (1984); Bogerts et al. (1985); Brown et al. (1986); Falkai & Bogerts (1986); Colter et al. (1987); Falkai et al. (1988); Crow et al. (1989); Jakob & Beckmann (1989);

		Jeste & Lohr (1989)
Third and fourth ventricles	Enlarged; increased fluid in the third ventricle	Staal et al. (2000); Baaré et al. (2001)
Cavum septi pellucidum	Larger	Degreef, Lantos, Bogerts, Ashtari, & Lieberman (1992); DeLisi , Hoff, Kushner, & Degreef (1993); Jurjus, Nasrallah, Olson, & Schwarzkopf (1993); Kwon et al. (1998)
	Also found in first episode patients	Degreef et al. (1992); DeLisi et al. (1993); Kwon et al. (1998)
III. GYRY AND SULCI		
Superior temporal gyrus (STG)	Volume reduction of left STG	Barta et al. (1990); Shenton et al. (1992); Hirayasu et al. (1998); Velakoulis et al. (1999)
Lateral sulcus	Females lack normal left > right asymmetry	Hoff et al. (1992)
Supramarginal gyrus	Reduced volume	Goldstein et al. (1999)
Angular gyrus	Reversal of the normal left > than right asymmetry	Niznikiewicz et al. (2000)
II. CORTICAL STRUCTURES		
a) FRONTAL LOBE		
Prefrontal cortex	Reduced volume	Raine et al. (1992)
	Volume reductions in prefrontal white matter; Volume reductions of right and left inferior gyri	Buchanan, Vladar, Barta, & Pearlson (1998)
	Decreased anisotropic diffusion in the right inferior prefrontal region	Buchsbaum et al. (1998)
Prefrontal cortex (PFC) regions		
Dorsolateral PFC	Reduced volume (only grey matter) in both male and female patients	Gur et al. (2000)
Dorsomedial PFC	Greater volume reduction (only grey matter) in males than females	Gur et al. (2000)
Orbitofrontal cortex	Volume reduction in the middle frontal, middle, medial and right sided fronto-orbital subregions	Goldstein et al. (1999)
	Reduced (only grey matter) only in females	Gur et al. (2000)
b) TEMPORAL LOBE		
Medial temporal lobe	Tissue loss, with a corresponding volume increase in the temporal horn of the surrounding lateral ventricles	Bogerts (1984); Bogerts, Meertz, & Schonfeldt-Bausch (1985); Brown et al. (1986); Falkai & Bogerts (1986); Colter et al. (1987); Falkai, Bogerts, & Rozumek (1988); Crow et al. (1989); Jeste & Lohr (1989); Benes et al. (1991)
Planum temporale	Reversal of left > right asymmetry	Rossi et al. (1992); Petty et al. (1995); Barta et al. (1997); Kwon et al. (1999); Hirayasu et al. (2000)
	Less asymmetry anteriorly and more asymmetry posteriorly	DeLisi, Hoff, Neale, & Kushner (1994)
	Volume reduction in the left hemisphere	Barta et al. (1997); Kwon et al. (1999); Hirayasu

		et al. (2000)
	Reduced left asymmetry	Kwon et al. (1999); Hirayasu et al. (2000)
c) PARIETAL LOBE		
Inferior parietal lobule	Reversal of the normal left > than right asymmetry	Frederikse et al. (2000)
d) OCCIPITAL LOBE		
Occipital cortex	Reduced left-right asymmetry	Falkai, Schneider, Greve, Klieser, & Bogerts (1995)
III. SUBCORTICAL STRUCTURES		
a) LIMBIC LOBE		
Amygdala-hippocampal complex	Reduced volume	Kovelman & Scheibel (1984); Bogerts et al. (1985); Brown et al. (1986); Falkai & Bogerts (1986); Colter et al. (1987); Falkai et al. (1988); Crow et al. (1989); Jakob & Beckmann (1989); Jeste & Lohr (1989)
	Bilateral hippocampal volume reduction	Suddath et al. (1989); Velakoulis et al. (1999)
	Volume reductions in the amygdala-hippocampal complex and the parahippocampal gyrus in chronic and first-episode schizophrenia, especially in the left hemisphere	Bogerts et al. (1990); Hirayasu et al. (1998); Lawrie et al. (1999); Stefanis et al. (1999); Velakoulis et al. (1999); Copolov et al. (2000)
Anterior Cingulate Cortex (ACC)	Reduced number and altered interconnectivity of neurons	Benes, McSparren, Bird, SanGiovanni, & Vincent (1991)
	Absence of the typical leftward ACC sulcal asymmetry (reduced folding in the left ACC)	Pantelis & Maruff (2002)
b) BASAL GANGLIA	Increased volume	Hokama et al. (1995); Gur et al. (1998)
	Exceptions: -Decreased volume in the caudate in patients with tardive dyskinesia	Mion, Andreasen, Arndt, Swayze II, & Cohen (1991)
	Exceptions: -Trend for decrease in the caudate and lenticular nuclei	DeLisi et al. (1991)
	Exceptions: - Trend for decrease in striatum and lenticular nuclei	Rossi et al. (1994)
	Bilateral reduction of caudate volume (not putamen volume) in newly diagnosed psychotic patients	Keshavan, Rosenberg, Sweeney, & Pettegrew (1998); Shihabuddin et al. (1998); Corson et al. (1999)
c) THALAMUS	Correlation between early onset and smaller thalamus	Corey-Bloom, Jernigan, Archibald, Harris, & Jeste (1995)
	Decreased volume	Gur et al. (1998)
	Correlation between smaller thalamic volumes	Portas et al. (1998)

	and smaller prefrontal white matter in patients	
	Absence of the adhesion interthalamica and third ventricle enlargement in first episode patients	Snyder et al. (1998)
IV. INTER-HEMISPHERIC CONNECTION STRUCTURES		
Corpus callosum	Volume reduction	Rosenthal & Bigelow (1972)
	Decreased anisotropy in the splenium	Foong et al. (2000)
V. OTHER STRUCTURES		
Cerebellum	Cerebellar atrophy	Shelton & Weinberger (1986)
	Decrease in vermal-to-brain ratio in male patients compared to female patients	Rossi, Stratta, Mancini, de Cataldo, & Casacchia (1993)
	No alteration of total cerebellar volume in male patients	Levitt et al. (1999); Nopoulos, Ceilley, Gailis, & Andreasen (1999)
	Volume reduction in the anterior lobe of the vermis	Nopoulos et al. (1999)
	Increase in vermis volume in chronic male patients	Levitt et al. (1999)
	Greater left-than-right cerebellar asymmetry of grey matter	Levitt et al. (1999)
	Increased cerebellar white matter	Seidman et al. (2000)
Olfactory bulb	Bilateral volume reduction	Turetsky et al. (2000)

3.2.3. Language profile in schizophrenia

Language dysfunction in schizophrenia is a hallmark of the disorder. The existing studies show widespread abnormalities in production, comprehension and cerebral lateralization of language (DeLisi, 2001). For example, there is increasing evidence to suggest that auditory hallucinations may arise from abnormal activity in brain areas traditionally associated with language and adjacent regions (see Wible et al., 2009 for a review).

The centrality of these symptoms in the symptomatic configuration of schizophrenia led some authors to suggest that this disorder represents the price that Homo Sapiens pay for language (e.g., Crow, 1997b) and, for example, to propose that symptoms as hallucinations represent major dysfunctions of language processes, as syntax (Crow, 2004).

Clinically, language disorder is evidenced in loose associations that underlie thought disorder. Other symptoms include derailment, loose associations, tangentiality, poverty of speech, and difficulties maintaining a topic (see Wible et al., 2009 for a review).

Abnormalities have been found in several language components, namely syntax (e.g., receptive syntax – Condray, Steinhauer, van Kammen, & Kasparek, 2002; DeLisi, 2001; production and comprehension of complex syntax – Lelekov, Franck, Dominey, & Georgieff, 2000; Morice & McNicol, 1985; concatenation – Lehmann et al., 2005; production of grammatically complex sentences – Kircher, Oh, Brammer, & McGuire, 2005), phonology (e.g., auditory sensory memory – Li, Chen, Yang, Chen, & Tsay, 2002; Kawakubo et al., 2006; Kayser et al., 2001; Michie, 2001; Näätänen & Kähkönen, 2009), semantics (e.g., semantic fluency – Rossell, Rabe-Hesketh, Shapleske, & David, 1999; semantic network – Paulsen et al., 1996; spread of activation in the semantic network – Moritz, Woodward, Küppers, Lausen, & Schickel, 2003; semantic priming – Minzenberg, Ober, & Vinogradov, 2002; word recall – Nestor et al., 1998); prosody (expression - Alpert, Rosenberg, Pouget, & Shaw, 2000; perception and recognition - Borod et al., 1989, 1990; Bozikas et al., 2006; Edwards, Pattison, Jackson, & Wales, 2001; Haskins, Shutty, & Kellogg, 1995; Hooker & Park, 2002; Kerr & Neale, 1993; Kucharska-Pietura, David, Masiak, & Phillips, 2005; Leentjens, Wielaert, van Harskamp, & Wilmink, 1998; Leitman et al., 2005, 2007; Murphy & Cutting, 1990; Pijnenborg, Withaar, Bosch, & Brouwer, 2007; Ross et al., 2001; Rossell & Boundy, 2005; Shaw et al., 1999; Shea et al., 2007); or pragmatics (e.g., understanding of second-order meanings – Brüne & Bodenstein , 2005; Kiang et al., 2007; pragmatic abilities – Champagne-Lavau, Stip, & Joanette, 2006; Langdon, Coltheart, Ward, & Catts, 2002; Meilijson, Kasher, & Elizur, 2004).

Other variables may exert a moderator role in the explanation of these findings, namely working memory impairments (Condray, Steinhauer, van Kammen, & Kasparek, 1996).

Electrophysiological studies suggest abnormalities in the N400 event-related potential (ERP) component, an index of semantic integration. For long stimulus onset asynchrony (SOA), more negative N400 amplitudes have been found for both congruent and incongruent sentence endings (Nestor et al., 1997; Niznikiewicz et al., 1997; Salisbury, Shenton, Nestor, & McCarley, 2002; Sitnikova, Salisbury, Kuperberg, & Holcomb, 2002), with the increased N400 to congruent sentences suggesting a decreased use of semantic context provided by precedent words to narrow the search of most plausible endings (McCarley et al., 1999).

Two hypotheses have been proposed to explain language abnormalities in schizophrenia: (a) language abnormalities are due to dysfunctional early processes of activation (overactivation) (e.g, Frith, 1979; Maher, Manschreck, Redmond, & Beaudette, 1996; Manschreck et al., 1988; Spitzer, Braun, Hermle, & Maier, 1993; Henik, Nissimov, Priel, & Umansky, 1995; Kwapil, Hegley, Chapman, & Chapman, 1990; Moritz et al., 2003; Maher, Manschreck, Linnet, & Candela, 2005; Peled, Netzer, & Modai, 2005; Quelen, Grainger, & Raymondet, 2005); (b) language abnormalities are due to dysfunctional late processes of context utilization (e.g., Adams et al., 1993; Barch et al., 1996; Blum & Freides, 1995; Chapin, Vann, Lycaki, Josef, & Meyendorff, 1989; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Grillon, Ameli, & Glazer, 1991; Hokama, Hiramatsu, Wang, O'Donnell, & Ogura, 2003; Iakimova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kiang, Kutas, Light, & Braff, 2008; Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003; Koyama et al., 1991; Nestor et al., 1997; Niznikiewicz et al., 1997; Passerieux et al., 1997; Salisbury et al., 2002; Sitnikova et al., 2002; Titone, Levy, & Holzman, 2000; Vinogradov, Ober, & Shenaut, 1992).

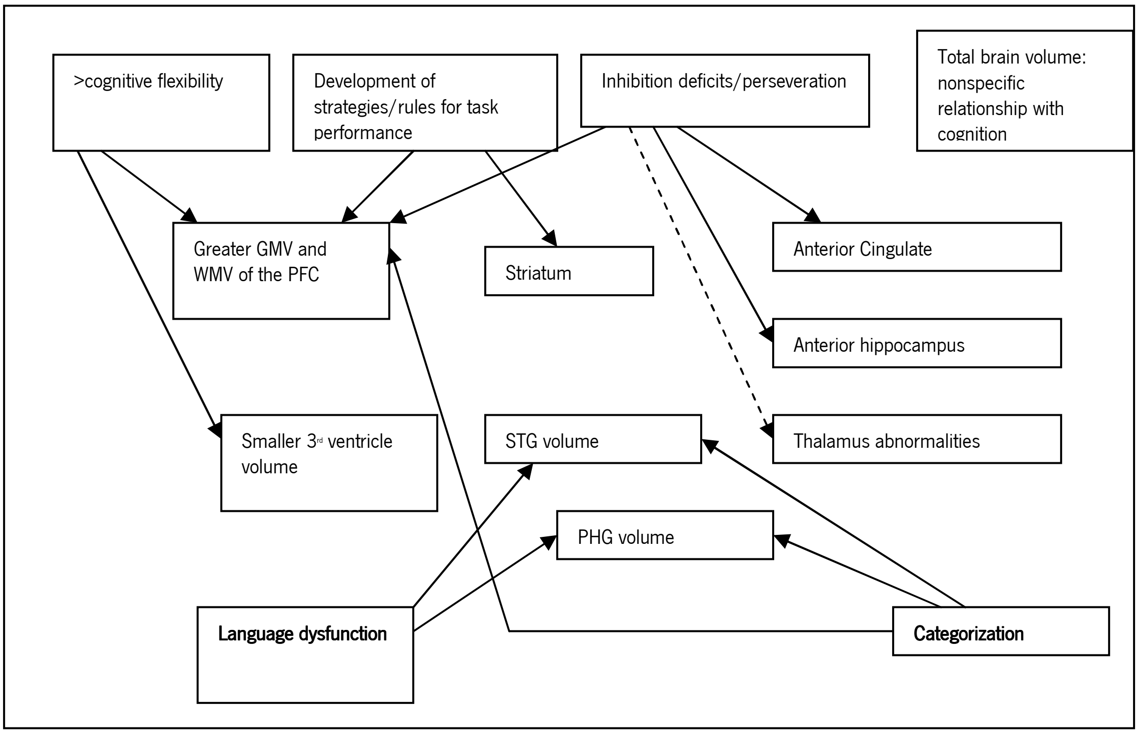


Figure 7. An illustration of the interactions between brain abnormalities and language dysfunction.

> = higher; GMV = grey matter volume; WMV = white matter volume; STG = Superior Temporal Gyrus; PHG = Parahippocampal Gyrus.

The existing evidence increasingly suggests that both early and late stages of semantic processing are impaired (Niznikiewicz, Mittal, Nestor, & McCarley, 2009) and that schizophrenia is a disorder of language and semantic memory processes. Failure in suppressing associations, at the behavioral level, may be associated with inhibitory abnormalities at the cellular and molecular levels, as failure of recurrent inhibition associated with abnormal excitatory-aminoacid neurotransmission, and with abnormalities in structures functionally related with language processes, as temporal lobe structures (McCarley et al., 1999) (see Figure 7). Abnormalities have also been observed in the neurobiological processes that underlie language processing, as evinced by altered event-related potentials (ERP).

The next section will briefly describe the basic principles underlying this technique for the study of brain function.

IV. THE EVENT-RELATED POTENTIALS TECHNIQUE (ERP): LANGUAGE IN MICROVOLTS[1]

One of the fundamental questions in neuroscience is how the human brain analyzes and produces language (Duffau, 2008).

Language consists of the interchange of electrochemical signals from neurons in communication. So how can we study language and, in particular, the brain that processes language?

The study of language, a complex function dynamically happening with a milliseconds speed, is not an easy task. Language is more than processing words in isolation: it is also the computation of semantic, syntactic and thematic relationships among words (e.g., Kutas & Besson, 1999; Kutas & Schmitt, 2003).

Therefore, especially due to the speed that characterizes language expression and comprehension, not all methods are equally suitable for its study. For example, behavioral measures provide limited information about language processing, since they only allow us to understand the product (e.g., comprehension of a given sentence) but not the dynamic processes that lead to those results. The event-related potentials technique (ERP), due to its temporal resolution, can overcome some of the limitations of functional methods that can only answer to localization questions, as functional magnetic resonance imaging (fMRI).

The event-related potentials technique allows the study of brain function and different cognitive processes (e.g., language, memory, attention) in typical and atypical populations. It depends on the averaged electrical activity (extracted from the raw EEG) associated with a particular cognitive task. In this sense, it is assumed that components are correlated with a particular cognitive process (Kutas & Schmitt, 2003; Luck, 2005).

Several components indexing language processes have been found, proving the special nature of language (see Table 6 and Figure 8).

[1] The title is adapated from Kutas and Schmitt (2003).

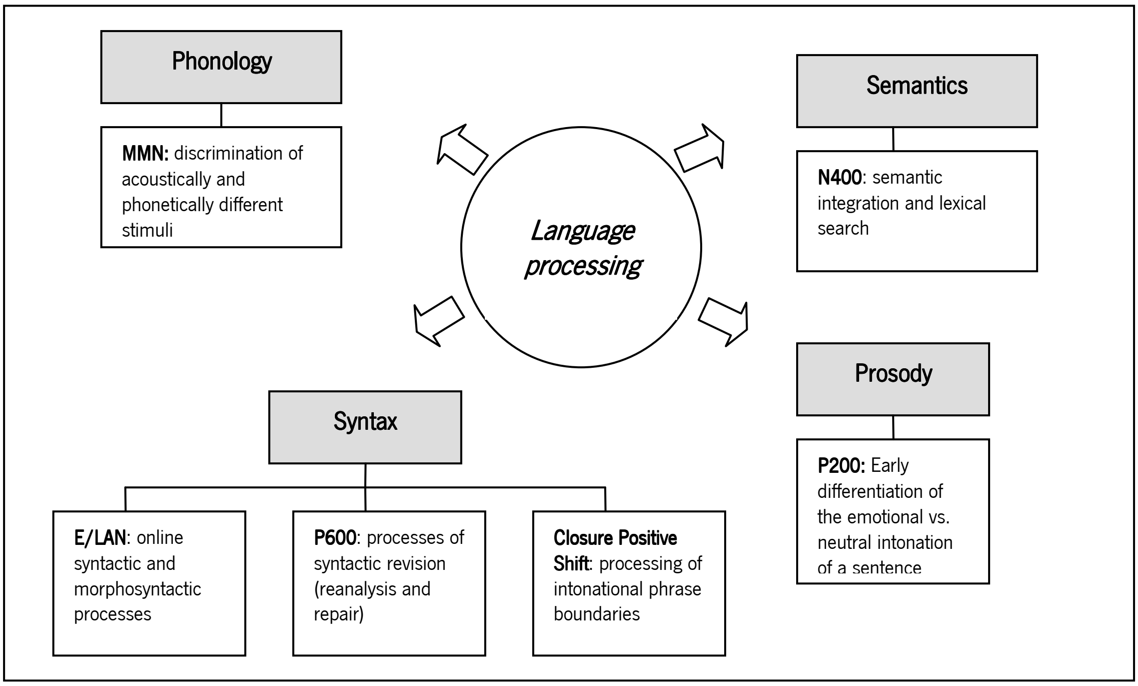


Figure 8. An illustration of ERP components associated with different language components (e.g., syntax, semantics, phonology, and prosody).

Different parameters of brain activity occurring in response to a particular stimulus or event can be analyzed to elucidate the underlying cognitive processes: polarity (negative and positive), latency, amplitude and scalp distribution. In this way, changes within these dimensions can reflect alterations in the timing of a particular cognitive process (latency), alterations in terms of processing demands or efficiency (amplitude), as well as changes in the cortical tissue supporting a particular process (topography) (Friederici, 2005).

When we hear a word or when we read a sentence, a flow of neural activity happens in the brain. The electrical activity synchronized in time to the stimulus' appearance (e.g., a word) is the evoked potential to that event, and that constitutes the aim of the electrophysiologist. So, for example, it has been suggested that the N400 can be used to ask questions about the organization of semantic memory (Kutas & Iragui, 1998)

Table 6

ERP components related with language processes

Notes. LH = left hemisphere; RH = right hemisphere

COMPONENT	POLARITY	PEAK LATENCY (MSEC)	LOCATION OF MAXIMAL EFFECT	LARGER AMPLITUDES	MEANING
Mismatch Negativity	-	100-250	Frontal-central sites	Deviant stimuli (stimuli representing change in the ongoing repetitive stimulation)	Detection of change in some repetitive aspect of the ongoing auditory stimulation (irrespective of subject's attention or task); Measure of auditory discrimination accuracy (e.g., discrimination of linguistic material)
Left Anterior Negativity	-	200-700	Frontal-central sites of the LH	Greater working memory load	Reflects the capacity of the working memory system for linguistic material
Lexical Processing Negativity	-	250-350	Anterior sites of the LH	Larger for closed-class /lower frequency words	As a function of the frequency of occurrence of a word in the language
N400	-	200-500	Posterior sites of the RH	Amplitude is inversely related to the cloze probability of a word in a sentence	Integration of a word into its precedent context
P600	+	300-800	Overly distributed, especially over bilateral posterior sites	Morphosyntactic violations	Detection of morphosyntactic violations (gender agreement, reflexive-antecedent case agreement, phrase-structure violations, constraints on the movement of sentence constituents, verb subcategorization)

V. ELECTROPHYSIOLOGICAL CORRELATES OF LANGUAGE AND COMMUNICATION ABNORMALITIES IN WILLIAMS SYNDROME AND SCHIZOPHRENIA: STRUCTURE AND AIMS OF THE DISSERTATION

Given language and communication abnormalities found both in Williams Syndrome and in schizophrenia, the studies presented in this dissertation aimed at characterizing the electrophysiological correlates of language processing in both disorders. Two language subcomponents were chosen – semantics and prosody. Studies on prosody processing were expected to provide more evidence on the processing of supra-segmental cues in both atypical developmental pathways, while studies on semantic processing aimed at investigating a segmental aspect of communication.

Four main questions were addressed:

(1) Electrophysiologically, do individuals with Williams Syndrome process prosody in a different way from typically developing individuals? (Study 1)

(2) Are the electrophysiological signatures of semantic processing in Williams Syndrome and schizophrenia distinct from what is observed in typically developing individuals? (Study 2)

(3) Electrophysiologically, do individuals with schizophrenia process prosody in a different way from healthy controls with no history of neurologic or psychiatric disorder? (Study 3)

(4) In which ways does transient mood (negative *vs.* positive *vs.* neutral) affect semantic processing and access to semantic memory in schizophrenia, relative to normal controls? (Study 4)

This dissertation was organized in two major sections. Chapter 2 describes studies on Williams Syndrome, in particular prosody processing (Study 1) and semantic processing (Study 2), which has been carried out in the Neuropsychophysiology Lab of the School of Psychology, at the University of Minho. Chapter 3 presents studies on schizophrenia, describing the electrophysiological correlates of prosody processing (Study 3) in the same disorder, and the effects of induced mood on semantic processing (Study 4). Both studies were carried out in the Cognitive Neurosciences Lab of Harvard Medical School (Boston, USA).

A preliminary study (*Sentence final word completion norms for European Portuguese children and adolescents: effects of age and sentence context*) is presented in Appendix 1, which allowed the construction and validation of experimental sentences used in the study of semantic processing in Williams Syndrome (Study 2). In particular, it aimed at computing cloze probabilities for 73 sentence contexts, varying in constraint (35 low- and 38 high-constraint sentence stems). These sentence contexts were presented to 90 children and 102 adolescents, and they were asked to complete the sentence contexts with the first word that came to their mind. Besides cloze probability, the proportion of idiosyncratic and inappropriate responses for each group was computed. This study allowed the construction and validation of experimental sentences used in the study of semantic processing in Williams Syndrome (Study 2).

In the first study of Chapter 2, the electrophysiological correlates of prosody processing in WS are described. Behavioral studies suggest an extensive use of emotional prosody by individuals with WS during social conversations, as a social engagement device. Other studies suggest that these patients have difficulties understanding distinct emotional prosody intonations. However, no study was conducted with the aim of exploring the electrophysiological correlates of emotional prosody processing. This study tried to fill the gap in this research domain, and aimed at characterizing the electrophysiological response to three emotional intonation patterns in WS, and also at examining if this response was dependent on the semantic content of the utterance. A group of twelve participants (5 female and 7 male), diagnosed with WS, with age range between 9 and 31 years, was compared with a group of typically developing subjects, individually matched in chronological age, gender and laterality. Participants were presented with three types of sentences (neutral, positive, and negative prosody), in two conditions: (1) with intelligible semantic and syntactic information (prosodic sentences with semantic content); (2) with unintelligible semantic and syntactic information ('pure prosody' condition). They were asked to decide which emotion was underlying the auditory sentence. While participants listened to the sentences, the electroencephalogram (EEG) was recorded using QuickAmp EEG recording system (Brain Products, 2003) with 22 Ag-AgCl electrodes mounted in an elastic cap (Easy Cap), according to the 10-20 System. After inspection of grand averages, three major peaks were selected for analysis: N100, P200, and N300. Results are presented and discussed.

In Study 2, the electrophysiological correlates of semantic processing in WS are described. In spite of early claims proposing the independence of language from general cognition in WS, a detailed investigation of language subcomponents has demonstrated several abnormalities in lexical-semantic processing. However, the neurobiological processes underlying language processing in WS remain to be clarified. The aim of this study was to examine the electrophysiological correlates of semantic processing in WS, using the event-related potentials (ERP) technique, and taking typical development as a reference. A group of twelve individuals diagnosed with WS, with age range between 9 and 31 years, was compared with a group of typically developing subjects, individually matched in chronological age, gender and handedness. Subjects were presented with sentences that ended with words incongruent (50%) with the previous sentence context or with words judged to be its best completion (50%), and they were asked to decide if the sentence made sense or not. While participants listened to the sentences, the EEG was recorded using QuickAmp EEG recording system (Brain Products, 2003) with 22 Ag-AgCl electrodes mounted in an elastic cap (Easy Cap), according to the 10-20 System. Early auditory ERP components (N100 and P200) were measured, as well as N400 (an index of semantic integration), and P600. Results are presented and discussed.

Studies 3 and 4 (Chapter 3) describe the electrophysiological correlates of prosody and semantic processing in a neuropsychiatry disorder: schizophrenia.

Study 3 aimed at characterizing the electrophysiological correlates of prosody processing in schizophrenia. Given that this disorder is characterized by social deficits and difficulties in social interactions, including deficits in the perception and understanding of emotional cues (e.g., auditory cues - prosody), the relevance of studies on emotional prosody understanding is justified. Notably, no ERP studies of prosody processing have been conducted in the same disorder. Also, it is not clear if a prosody processing impairment exists both for sentences with semantic content and also for "pure prosody" when semantic content has been filtered out. In this study, seventeen participants with schizophrenia were compared with seventeen normal controls. Stimuli were 228 auditory sentences. One hundred and fourteen sentences with neutral semantic content were generated by a female speaker with training on theatre techniques (38 with happy intonation, 38 with angry intonation, and 38 with neutral intonation). The same 114 sentences were used in the pure prosody condition where semantic content was removed from sentences, using Praat software. Subjects were instructed to make judgements about the emotional tone of sentences, while the EEG was recorded with 64 electrodes mounted on a custom-made cap (Electro-cap International), according to the modified expanded 10-20 system

(American Electroencephalographic Society, 1991). Amplitude and latency of the N100 and P200 components were measured. Results are presented and discussed.

Study 4 discusses the effects of induced mood states on semantic processing in schizophrenia. Schizophrenia is characterized by language and emotional processing abnormalities. However, few studies have examined the influence of affect on semantic processing. This study used ERP to examine affective modulation of semantic information processing in schizophrenia, extending previous studies on N400 in schizophrenia by manipulating mood. Fifteen male chronic schizophrenia and fifteen normal control subjects read 324 pairs of sentences: 108 under neutral mood, 108 under positive, and 108 under negative mood. Before a task of sentence understanding, mood was induced using pictures of positive, negative, or neutral valence from the International Affective Picture System (IAPS). Sentences ended with three word types: expected words (EE); within-category violations (WCV) - unexpected words from the same semantic category as EE; and between-category violations (BCV) - unexpected words from a different semantic category. Participants were asked to read the sentences and instructed to answer, via key presses, if they made sense or not. The EEG was recorded with 64 electrodes mounted on a custom-made cap (Electro-cap International), according to the modified expanded 10-20 system (American Electroencephalographic Society, 1991). N400 amplitude and latency was measured to the three word types. Results and their implications are discussed.

Chapter II

ELECTROPHYSIOLOGICAL CORRELATES OF LANGUAGE PROCESSING IN WILLIAMS SYNDROME

Study 1

Electrophysiological correlates of abnormal prosody processing in Williams Syndrome

1. Introduction

Williams Syndrome (WS), a genetic neurodevelopmental disorder due to microdeletion in chromosome 7, has been described as syndrome with an intriguing socio-cognitive phenotype (Bellugi, Bihrle, Neville, Jernigan, & Doherty, 1992; Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Bellugi, Marks, Bihrle, & Sabo, 1998; see Martens, Wilson, & Reutens, 2008 for a review). Cognitively, in spite of a relative preservation of language and face processing abilities, individuals with WS experience severe difficulties in visual-spatial tasks, as well as in tasks involving abstract reasoning (e.g., arithmetic) (e.g., Bellugi et al., 2000; Crisco, Dobbs, & Mulhern, 1988; Eckert et al., 2005; Gray, Karmiloff-Smith, Funnel, & Tassabehji, 2005; Korenberg et al., 2000; Meyer-Lindenberg et al., 2004; Vicari, Belluci, & Carlesimo, 2005).

The initial descriptions of individuals with WS made reference to their apparently preserved abilities of linguistic expression, as exemplified by complex and elaborated narratives along with an intense interest in being engaged in social communication (e.g., Bellugi et al., 1992, 1998; Pinker, 1994). However, this keen interest in engaging in social interactions (coupled with an overfriendly personality and empathic behavior) seems to coexist with severe pragmatic impairments (Laws & Bishop, 2004), such as the difficulty to adjust the amount of speech production to the listener's interests and attitudes. For example, some narrative studies suggest that participants with WS use significantly more affective expressive prosody than individuals with Down's syndrome and typically developing children (Jones et al., 2000; Reilly, Klima, & Bellugi, 1991; Reilly, Losh, Bellugi, & Wulfeck, 2004), and that this pattern seems to be independent of the audience and on how many times they tell the story. In other words, the frequent use of dramatic devices and social hookers, used to capture the attention of the audience, may have been masking WS individuals' deficits in understanding social cues (Skwerer, Schofield, Verbalis, Faja, & Tager-Flusberg, 2007).

Thus, the hypersociable phenotype of individuals with WS (e.g., Bellugi, Adolphs, Cassady, & Chiles, 1999; Jones et al., 2000; Klein-Tasman & Mervis, 2003) may be co-existing with difficulties in effective deployment and interpretation of paralinguistic devices as illustrated by difficulties in theory-of-mind tasks (e.g., Sullivan & Tager-Flusberg, 1999; Tager-Flusberg & Sullivan, 2000), judgements of faces as more approachable/trustworthy than controls (e.g., Bellugi et al., 1999), and identifying and discriminating emotions (e.g., Tager-Flusberg & Sullivan, 2000; Catterall, Howard, Stojanovik, Szczerbinski, & Wells, 2006; Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006), particularly negative emotions (Plesa-Skwerer et al., 2006).

One of the powerful paralinguistic cues routinely employed in verbal communication is prosody. Emotional prosody has been referred to as a paralinguistic device that allows human beings to represent and convey affect (Scherer, 1986). It relies on language suprasegmental features such as fundamental frequency (F0), and sound intensity and duration (Hesling, Clément, Bordessoules, & Allard, 2004). Thus, the study of prosody processing may provide us with information on how individuals recognize and interpret sensory input (e.g., voice inflection), an ability that is crucial to social interactions and, in particular, to social reciprocity.

Behavioral studies on prosody processing in WS have found deficits in prosody comprehension (Catterall et al., 2006; Plesa-Skwerer et al., 2006; Skwerer et al., 2007), suggesting that, in spite of an easy sociability, these individuals may be impaired in their ability to use vocal cues to interpret emotional states particularly in the presence of a semantic conflict such as sarcasm or irony (Skwerer et al., 2007; Sullivan, Winner, & Tager-Flusberg, 2003).

However, in spite of their difficulties in using linguistic prosody for semantic processing, individuals with WS still seem to perform better than participants with learning or intellectual disabilities on the recognition of emotional tone of voice in filtered speech (Plesa-Skwerer et al., 2006), suggesting that sensitivity for non-linguistic affective information may be relatively spared in WS.

Studies focusing on prosody production suggest that individuals with WS tend to use emotional prosody abundantly (Gonçalves et al., 2004, in press; Jones et al., 2000; Reilly et al., 1991, 2004; Catterall et al., 2006). This apparent affective prosody strength was explained as related to WS individuals' use of longer vowels and higher pitch levels, which may lead them to be perceived as more emotionally involved than individuals matched for receptive language and chronological age (Setter, Stojanovik, Ewijk, & Moreland, 2007). However, in different tasks such as repeating sentences with exactly the same prosodic pattern individuals with WS seem to perform below their chronological age, but still at the same level as children matched for receptive language abilities (Stojanovik, Setter, Ewijk, 2007). In addition, contrary to what happens in typical development, no significant correlations were found between WS general linguistic abilities and intonation abilities, suggesting that prosodic competence doesn't develop in line with other aspects of receptive and expressive language (Stojanovik et al., 2007).

Together, these studies suggest that some aspects of prosodic processing in WS may be more impaired than other linguistic abilities, such as for example receptive vocabulary or the comprehension of syntactic structures (e.g., passives or binding) on which WS individuals tend to score higher than predicted by their overall or nonverbal mental age (see Brock, 2007, for a review).

In spite of the few studies devoted to prosody processing in WS reviewed above, there is a dearth of data on this issue, in contrast to the number of studies focusing on the morphosyntactic and semantic aspects of language processing in WS individuals.

Importantly, electrophysiological studies of prosody processing in WS are, to the best of our knowledge, nonexistent. Due to their temporal resolution, Event Related Potentials (ERPs) (Coles & Rugg, 1995; Münte, Urbach, Düzel, & Kutas, 2000) provide valuable information on the order of msec about cognitive processes under consideration. As such, they afford a window of enquiry into the neural underpinnings of sensory and cognitive processes associated with prosody processing in WS.

ERP studies in normal individuals show that prosody comprehension has distinct electrophysiological signatures. For example, expectancy violations of integrative emotional prosodic and semantic information elicited a negativity in the time window between 500-650 msec, while expectancy violations of emotional prosodic information were linked to a positivity in the time window between 450-600 msec, in a task using the cross splicing technique (Paulmann & Kotz, 2008a). The differentiation of basic vocal emotional expressions from prosodically neutral sentences seems to occur around 200 msec, with emotional sentences eliciting less positive P200 amplitudes, irrespective of valence (positive vs. negative) (Paulmann & Kotz, 2008b). These authors suggested that there is an automatic and early detection of emotional salience, which is probably followed by the differentiation of specific emotional prosodic intonations at later stages (Paulmann & Kotz, 2008b), around 600 msec.

The aim of the current study was to provide initial evidence regarding the electrophysiological correlates of prosody processing in a group of individuals with WS, taking advantage of the ERP methodology, and especially of its temporal resolution. More specifically, we aimed at: (1) characterizing the electrophysiological responses (ERP) elicited by three emotional intonation patterns; and (2) examining whether the ERP response was modulated by the semantic content of the utterance. Given the relative paucity of ERP studies on prosody processing, the research questions fell into two categories: those related to ERP correlates of prosody processing irrespective of group membership and those focused on electrophysiological differences in prosody processing between the two groups (WS and normal individuals). The specific *a priori* hypotheses were:

(1) Our central hypothesis concerned group differences between WS and typically developing (TD) individuals. Adopting the hypothesis of preserved sensitivity to "pure" affective prosody (Plesa-Skwerer et al., 2006) we predicted that group differences will be found for sentences with semantic content but not for sentences without it ('pure prosody' sentences).

In addition, we formulated two hypotheses regarding processing prosodic sentences:

(2) Based on previously published studies Paulmann and Kotz (2008b), we predicted that neutral and emotional prosodic sentences will be differentiated in the early (N100 and P200) components.

(3) Based on previously published studies (Kotz et al., 2003; Kotz & Paulmann, 2007; Paulmann & Kotz, 2008b), we predicted that there will be differences in processing sentences as a function of their semantic content. That is we predicted that comparable emotional prosody sentences will be processed in different ways depending on whether they carry both semantic and prosodic information or prosodic information only.

In order to address these hypotheses, 12 participants with WS and 12 typically developing individuals were presented with three types of sentences (neutral, positive and negative prosody), in two conditions: (1) with intelligible semantic and syntactic information; (2) with unintelligible semantic and syntactic information.

2. Methods

2.1. Participants

A group of twelve participants (5 female and 7 male), diagnosed with Williams Syndrome, with age range between 9 and 34 years, (M = 17.3, SD = 6.50) was compared with a typically developing group (12 participants), individually matched for chronological age (M = 17.3, SD = 6.50), gender, and handedness (see Table 1).

Participants with WS were recruited at a large Genetic Medical Institute in Oporto, Portugal, and also in collaboration with the Portuguese Williams Syndrome Association. WS diagnoses were made by fluorescent in situ hybridization (FISH) confirmation of elastin gene deletion (Korenberg et al., 2000). Exclusion criteria included: (a) the presence of severe sensory (e.g., hearing problems) or speech disorder; (b) comorbidity with severe psychopathology not associated with the syndrome; (c) use of any medication that might affect cognitive function or electroencephalogram (EEG) recordings, such as steroids and barbiturates; (d) and use of any psychoactive medication. Controls were typically developing individuals without evidence of psychiatric, neurological disorder or cognitive impairment. All subjects were right-handed, according to the Edinburgh handedness inventory (Oldfield, 1971), and spoke European Portuguese as their first language. Each participant and their guardians (in the case of minor participants) gave written informed consent for their participation in the study, after a detailed description of the study. The Ethics Committee of the University of Minho approved this study.

The mean socioeconomic status, as measured by an adapted version of Graffar Scale (Graffar, 1956), with 5 being the highest and 1 being the lowest score, was 3.00 (SD = 1.28) for the Williams Syndrome group and 2.92 (SD = 1.44) for the typically developing control group (TD). Groups didn't differ in socioeconomic status ($F(1, 22) = 0.02$, $p > .05$), but did differ in years of education ($F(1, 22) = 7.64$, $p = .011$).

Table 1

Demographic characteristics of the participants – Mean (SD)

	WS Group	TD Group
Age (years)	17.30 (6.49)	17.30 (6.49)
Parental SES	3.00 (1.28)	2.92 (1.44)
Years of education	7.58 (1.78)	10.83 (3.66)

To assess general cognitive functioning (Full Scale IQ), participants with chronological age between 9-16 years were administered the Wechsler Intelligence Scale for Children – Third Edition (WISC–III) (Wechsler, 1991), while participants over 16 years old were administered the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997). Since the experimental task in this study was auditory, the following measures of auditory (phonological) processing were used, from the Portuguese version of Psycholinguistic Assessment of Language Processing in Aphasia – PALPA (Castro et al., 2007): Discrimination of Minimal Pairs in Pseudowords; Auditory Lexical Decision and Morphology, Repetition of Pseudowords. Neurocognitive tests were in the native language of the participants and were administered and scored accordingly. Results of general cognitive assessment are presented in Table 2.

Table 2

Results of the neurocognitive assessment of Williams Syndrome (WS) and Typically Developing (TD) groups

	WS Group *N* = 12 Mean (SD)	TD Group *N* = 12 Mean (SD)	Significance test *F* (*p*)
1. Global intellectual functioning			
Verbal IQ	58.55 (9.18)	116.45 (14.75)	122.17 (.000**)
Performance IQ	52.18 (5.96)	111.73 (16.32)	129.15 (.000**)
Full Scale IQ	51.55 (7.10)	114.00 (13.71)	182.87 (.000**)
2. Language (Phonological processing)			
a) Discrimination of Minimal Pairs in Pseudowords			
Similar pairs	31.44 (0.73)	31.92 (0.29)	4.24 (.053)
Different pairs	29.44 (3.71)	31.67 (0.49)	4.27 (.053)
b) Auditory Lexical Decision and Morphology			
Regular words	12.38 (2.45)	14.67 (0.89)	8.98 (.008*)
Derivated words	12.25 (3.24)	13.92 (1.31)	2.60 (.124)
Pseudowords	21.63 (7.98)	28.00 (4.20)	5.49 (.031*)
c) Repetition of Pseudowords			
1 syllable	8.88 (1.13)	9.75 (0.45)	5.95 (.025*)
2 syllables	8.63 (2.07)	10.00 (0.00)	5.47 (.031*)
3 syllables	8.38 (0.92)	10.00 (0.00)	38.83 (.000**)

* $p < .05$; ** $p < .005$

Mean distribution of Full Scale Intelligence Quotient (FSIQ) in WS was found to be within the moderate mental retardation interval, with verbal intelligence quotient (IQ) slightly higher than performance IQ.

In order to test for group differences on neurocognitive and language measures, one-way analyses of variance (ANOVAs) were computed. As seen in Table 2, groups were different on all measures, with the exception of auditory lexical decision and morphology, for derivated words. Also, it is worth noting that groups were only marginally different during discrimination of minimal pairs in pseudowords, for similar and different pairs.

2.2. Stimuli

A set of 216 semantically neutral sentences, presented binaurally with angry, happy or neutral intonation, was used as stimuli in this experiment.

The sentences were developed using a validation study where a set of 157 actions (e.g., "to read a magazine", "to hurt the eye", "to hug a child") were presented to a sample of children and adolescents (*N* = 190) from different age groups (from 2nd grade to high school). Participants were asked to judge if these sentences were associated with an unpleasant, pleasant or neutral feeling. From this set, 60 actions rated by at least 95% of the subjects as "neutral" in semantic content were selected and forty eight sentences were developed. Following the procedure used by Kotz et al. (2003), all sentences had the same syntactic structure (noun + verb + direct object) and length (4 words) and began with a personal pronoun (e.g., "She stirred the soup", "She fried an egg", "He opened the closet", "He peeled the banana"). Subsequently, they were recorded by a female native speaker of Portuguese with training in theatre techniques, each with a positive (happy), negative (angry and sad), or neutral intonation. The recordings were made in a sound proof room with an Edirol R-09 recorder and a CS-15 cardioid-type stereo microphone, using a sampling rate of 22 kHz and 16-bit quantization. Sentences were then digitized, downsampled at a 16 bit/16 kHz sampling rate and normalized in amplitude.

Sentences with sad intonation were included as fillers, in order to provide a broader range of options for the participants rating the sentences. The raters were children and adolescents (*N* = 125), from 4th to 9th grades, who judged the emotional intonation of the sentences. Thirty six sentences of neutral, happy, and angry prosody with inter-rater agreement of at least 90% were then selected (31 for the experimental session and 5 for the training session). Sentences were pseudo randomly distributed into three experimental lists to be presented as stimuli in the first part of the experiment (see Table 3). These sentences were intelligible, so that the participants could understand their semantic and syntactic content.

Table 3

Acoustical analyses of the sentences presented in the experiment

	Neutral	Happy	Angry
Mean duration	1.88 (0.18)	2.00 (0.16)	1.79 (0.13)
Fundamental Frequency (F0)	203.97 (5.11)	448.01 (33.16)	293.44 (32.51)
Intensity	80.00 (2.32)	77.00 (1.67)	77.00 (1.83)

Notes: F0 is measured in Hz; duration is measured in milliseconds. Numbers in parentheses show standard deviations.

The same stimuli were delexicalized and served as stimuli in the second part of the experiment. All the phonological and lexical information was suppressed but the prosodic modulations were kept (see Figures 2 and 3). The phonemes of each sentence were manually segmented in Praat (Boersma & Weenink, 2006). The fundamental frequency (F0) was automatically extracted in Praat at four points of each segment (20%, 40%, 60% and 80%). Occasional F0 error measurements were manually corrected. Based on the procedures of Ramus and Mehler (1999), duration and F0 values were then transferred to MBROLA (Dutoit, Pagel, Pierret, Bataille, & Van Der Vreken, 1996) for concatenative synthesis by using the European Portuguese (female) diphone database. In order to omit linguistic information and test the perception of different emotions by means of prosodic information, all fricatives were replaced with the phoneme /s/, all stop consonants with /t/, all glides with /j/, all stressed vowels with /æ/ and all unstressed vowels with /ə/. Thus, as in Ramus and Mehler (1999), the synthesis of the new sentences preserved "global intonation, syllabic rhythm, and broad phonotactics"(p. 514).

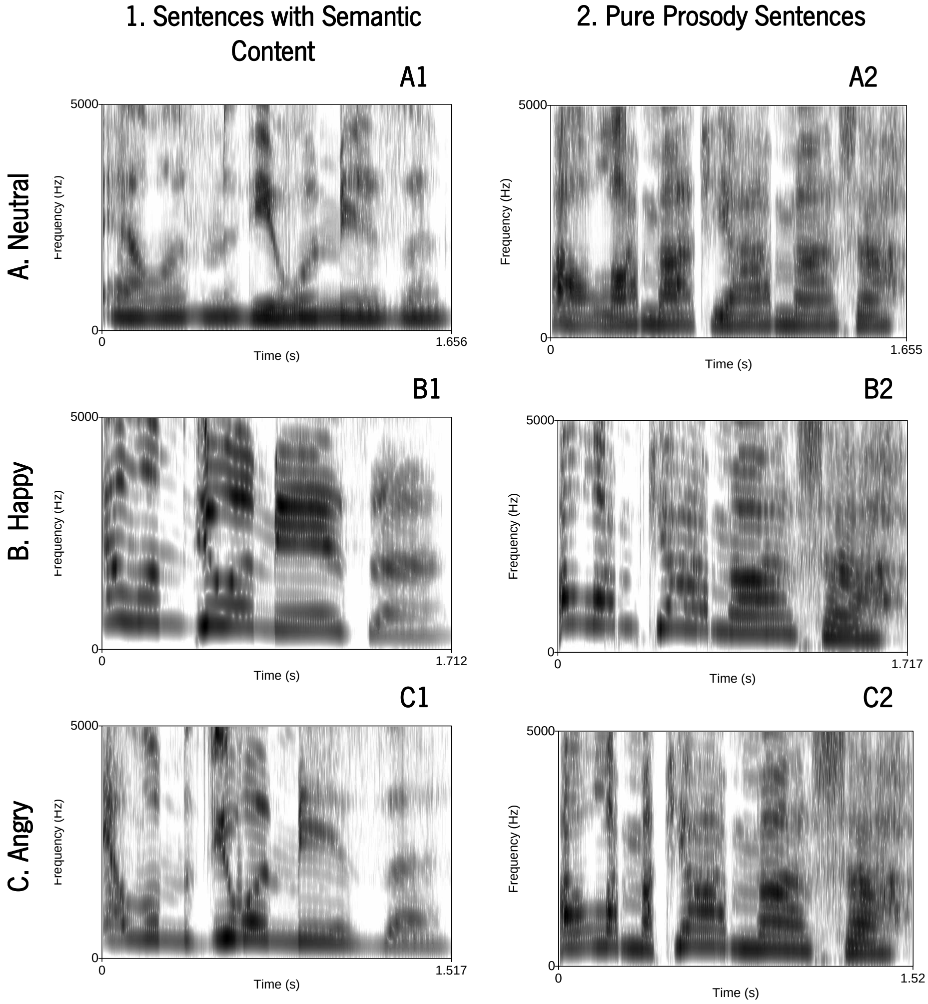


Figure 1. Examples of sentences' spectograms. This figure shows spectograms for a neutral (A), happy (B), and angry (C) sentence, in the condition of prosody with semantic content (A1, B1, C1), and 'pure prosody' (A2, B2, C2).

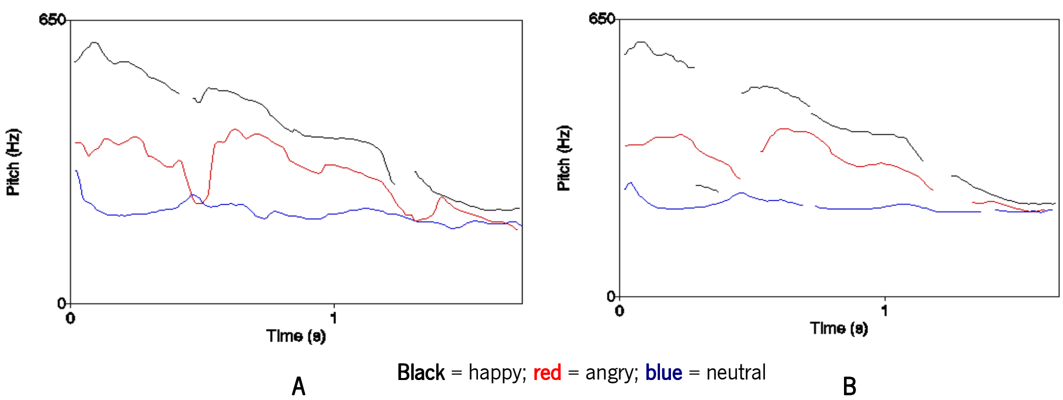


Figure 2. Shifts in fundamental frequency (F0) for each emotion (happy, angry, and neutral) in both sentence conditions (prosodic sentences with semantic content = A; 'pure prosody' sentences = B). This

figure illustrates that sentences' F0 was preserved after transformation aimed at extraction of intelligible semantic content.

2.3. Procedure

Each participant was seated comfortably at a distance of 115 cm from a computer monitor in a sound-attenuating chamber, with a button box in front of them. Sentences were presented binaurally through headphones. Since the second task could be more complex (the sentences were not natural and different from what the participants are used to hear) and because participants could have more difficulties in understanding the task instructions, the semantically meaningful sentences were presented first for all participants. Thus, participants listened to ninety three intelligible sentences presented in three separate lists, in order to provide a short break during sentences' presentation, minimize participants' fatigue and movements, and maximize their focus on the task. In a second block, they listened to ninety three unintelligible sentences, also presented as three separate lists (see figure 3). No sentences were repeated.

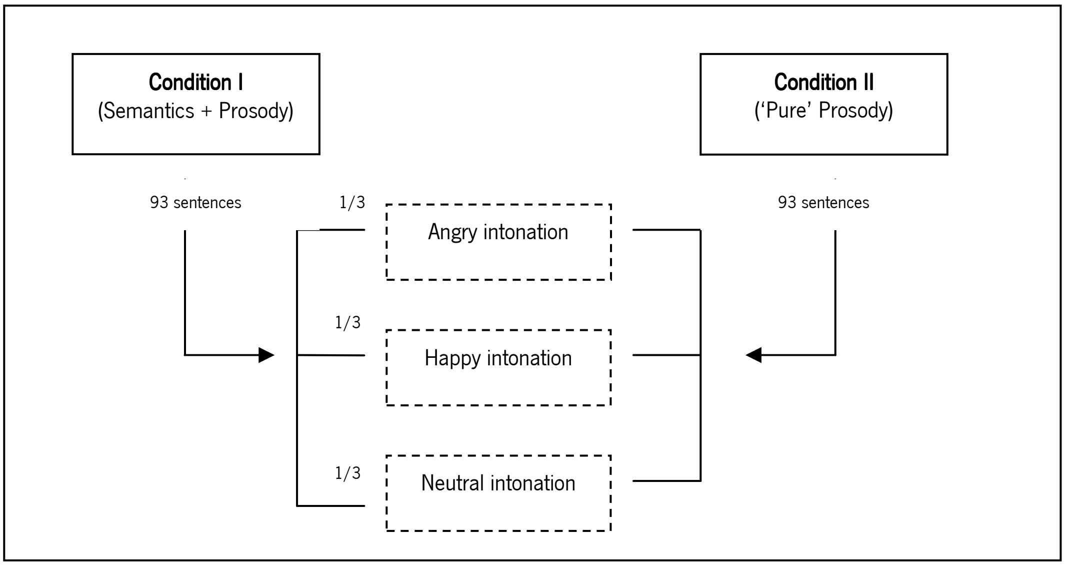


Figure 3. Illustration of the experimental paradigm. Experimental conditions (Condition I – Prosody with intelligible semantic content; Condition II – 'Pure' Prosody sentences) and types of stimuli (angry, happy, and neutral sentences) are presented.

Before the experimental session, participants were given a brief training with feedback using 15 sentences (5 neutral, 5 happy and 5 angry), in order to insure that they were properly differentiating emotional intonations. Participants were instructed to decide whether each sentence was spoken in a neutral, positive or negative intonation, pressing a response key (after the presentation of a visual clue – a question mark) with a picture of a cartoon of emotion in order to minimise working memory demands. The order of buttons for each response was counterbalanced across subjects.

The average sentence length was 1.890 msec. Each trial started with a cue (2000 msec) consisting of a visual icon that warned participants that the sentence was about to begin. After a sentence's presentation, an inter-stimulus interval of 3000 msec followed in order to avoid contamination of ERP response from any motor response. After that, participants saw a question mark (1000 msec) and then a cartoon reminding them to press a response button presented for a maximum of 4000 msec. As soon as participants gave a response, the next trial started.

2.4. Data acquisition and analysis

2.4.1. EEG data recording

While the participants listened to the sentences, the electroencephalogram (EEG) was recorded using QuickAmp EEG recording system (Brain Products, 2003) with 22 Ag-AgCl electrodes mounted in an elastic cap (Easy Cap), according to the 10-20 System, using an average reference. Electrodes were placed at Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T7, T8, Pz, P3, P4, P7, P8, Oz, O1, O2. Electrode impedance was kept below 5 kΩs. The electrooculogram (EOG) was recorded from electrodes placed at the outer canthus of each eye and from sites below and above the right eye. A ground electrode was placed at Fpz. The EEG signal was recorded continuously and digitized at 250 Hz. Participants were asked to avoid eye and head movements during sentences presentation.

2.4.2. Data analysis

The number of correct responses to the experimental task was analyzed with repeated measures analyses of variance, with sentence condition (prosodic sentences with semantic content vs. pure prosody sentences) and emotionality (neutral, angry, happy) as within-subjects factors, and group (individuals with WS vs. typically developing controls – TD) as between-subjects factor. Reaction time data were not analyzed, because a delay was introduced between the end of the auditory sentence and the response, as described in the previous section.

The EEG data were analysed using the software package Brain Analyzer (Brain Products, Inc, 2000). EEG epochs containing eye blinks or movement artefacts exceeding +/- 100 microvolts were removed from individual ERP averages. After artifact rejection, at least 75% of trials per condition per subject entered the analyses. Following Paulmann and Kotz (2008b), individual averages were constructed to the onset of the sentence. Averages were computed using a 200-msec prestimulus baseline and 1500 msec after the onset of the sentence.

Due to excessive artifacts, data from two typically developing controls and three WS individuals were not included in statistical analyses or grand averages.

After the inspection of grand averages, three peaks were selected for analysis: N100, P200 and N300. Since peaks were occurring at different times for prosodic sentences with and without semantic content, different latency windows were selected for peak measurement in each sentence condition.

N100 was measured as the most negative data point between 100-200 msec post-stimulus, for sentences with semantic content; and between 100-160 msec post-stimulus for pure prosody sentences. P200 was measured as the most positive data point between 200 and 320 msec post-stimulus for sentences with semantic content; and between 160 and 260 msec for pure prosody sentences. N300 was measured as the most negative data point between 320 and 450 msec post-stimulus for sentences with semantic content; and between 280 and 380 for pure prosody sentences.

Electrodes were grouped into three different regions – frontal (Fz, F3, F4), central (Cz, C3, C4), and parietal (Pz, P3, P4) in order to get more refined analyses of possible topographical differences across groups and conditions.

Peak amplitude analyses were conducted for each of the selected peaks: N100, P200, and N300. To address the hypotheses of differential processing of emotional and neutral prosody, and of differences in processing prosody with and without semantic content, as indexed by ERP components, repeated measures analyses of variance (ANOVAs) were calculated with group as between-subjects factor and emotionality (neutral, happy, angry), sentences' condition (intelligible vs. unintelligible), region (frontal, central, and parietal), and electrodes as within-subjects factors.

To address the hypothesis of group differences in the processing of sentences with semantic content but not in the sentences with 'pure prosody', separate ANOVAs were conducted for the sentences with and without semantic content with within factors of emotionality, region and electrodes and a between factor of group.

To directly address the hypothesis of differential processing of emotional relative to neutral prosody as reflected by P200 amplitude, we conducted separate analyses for each emotion with group as a between factor, and sentence condition, region and electrode as within factors.

Peak latency was analyzed for the three components of interest: N100, P200 and N300 with repeated-measures analyses of variance, with group as a between subject factor, and condition, region, and electrode as within subject factors, similar to amplitude analyses. The Geisser-Greenhouse correction (Geisser & Greenhouse, 1959) was applied to all repeated-measures with greater than one degree of freedom in the numerator.

Significant interactions were followed by pairwise comparisons. In addition, when appropriate, post-hoc tests included additional ANOVAs to find the source of significant interactions.

Given that the majority of participants included in our sample were adolescents and young adults, but that two participants from each group did not fit this age cohort (a 9-years-old and a 34-years-old participant and their respective controls), amplitude and latency analyses were repeated, eliminating these four subjects from the analyses, in order to test if the inclusion of these four participants influenced the results. In general, very similar but not identical pattern of statistical effects emerged. Only these main effects and their interactions which were found significant in both analyses are reported in the Results Section (i.e., they are reported for 9 WS participants and 10 TD controls)

3. Results

3.1. Behavioral Results

A significant effect of sentence condition ($F(1, 22) = 19.88$, $p = .000$) was observed: more correct responses were found for sentences with semantic content relative to pure prosody sentences. Also, a main effect of emotion ($F(2, 44) = 12.58$, $p = .000$) was observed, with angry sentences being associated with more errors relative to happy and neutral sentences. In addition, results showed a significant sentence condition x emotion interaction ($F(2, 44) = 7.33$, $p = .003$). A difference between sentence conditions was observed only for happy and angry prosody, with more errors found in the pure prosody condition.

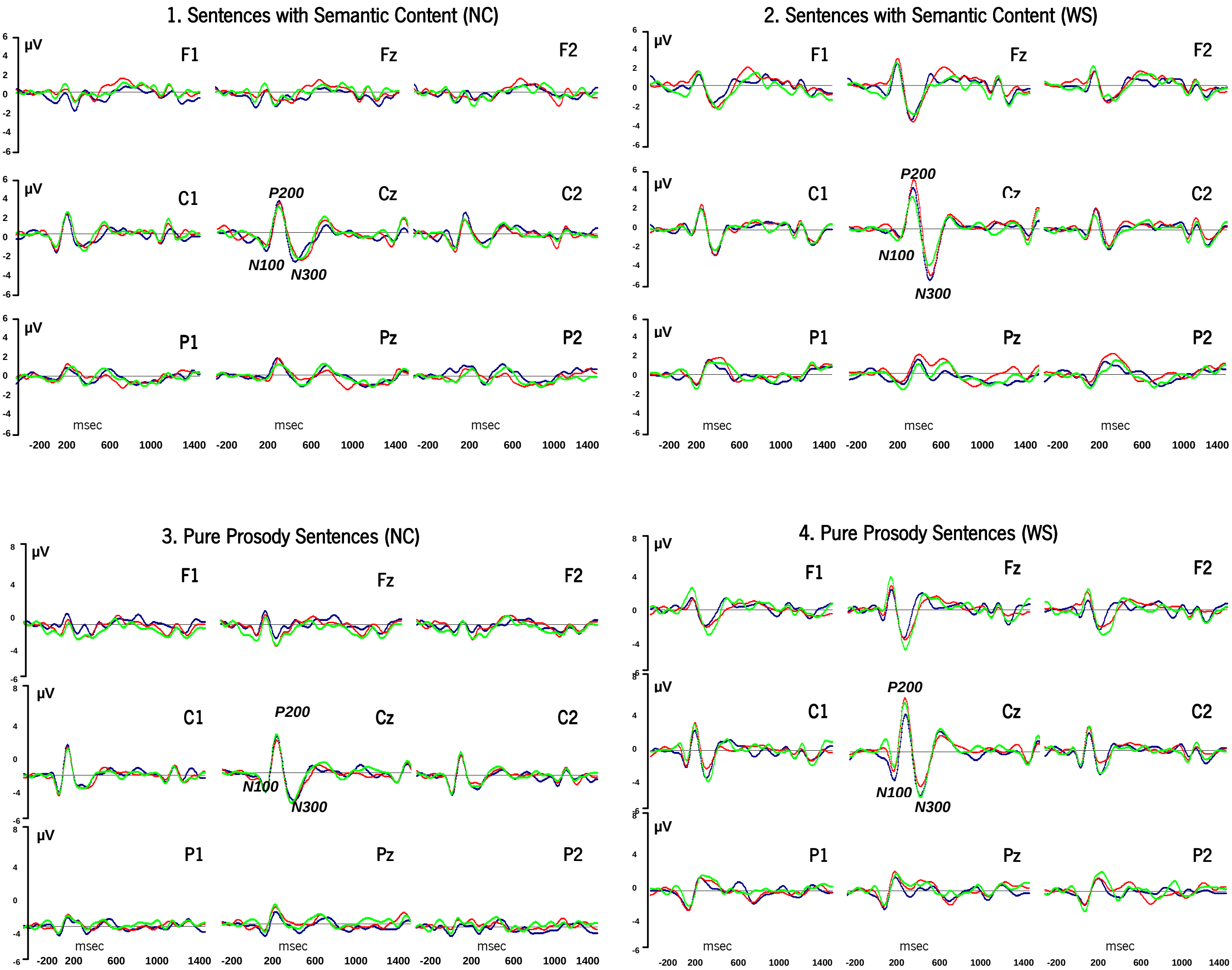
There were no significant differences between groups in the accuracy of emotional prosody discrimination ($p > .05$), although the TD group showed somewhat higher number of correct responses (see Table 4). A significant group x emotion type interaction was observed ($F(2, 44) = 3.42$, $p = .044$): participants with WS showed more errors than TD controls for angry sentences.

Table 4

Mean number of correct responses in WS and TD Groups

Sentence Condition	Emotion	Group	Mean (SD)
Prosodic Sentences with Semantic Content	*Neutral*	WS	24.13 (10.71)
		TD	26.75 (7.09)
	Happy	WS	26.88 (7.04)
		TD	27.38 (7.15)
	Angry	WS	20.88 (7.61)
		TD	27.25 (6.09)
Pure Prosody Sentences	*Neutral*	WS	21.50 (9.27)
		TD	26.75 (5.26)
	Happy	WS	21.71 (10.03)
		TD	22.00 (7.47)
	Angry	WS	14.17 (8.95)
		TD	19.78 (6.78)

3.2. ERP Results



Caption: Blue = Neutral; Red = Happy; Green = Angry

Figure 4. ERP Grand Averages for Sentences with Semantic Content and Pure Prosody Sentences in TD (1 and 3) and WS (2 and 4) groups. Frontal, central, and parietal electrodes are shown. The maximal effects were observed for central and frontal electrodes. Three main peaks (N100, P200, N300) were modulated by the emotional content of auditory sentences and by the presence or absence of intelligible semantic information.

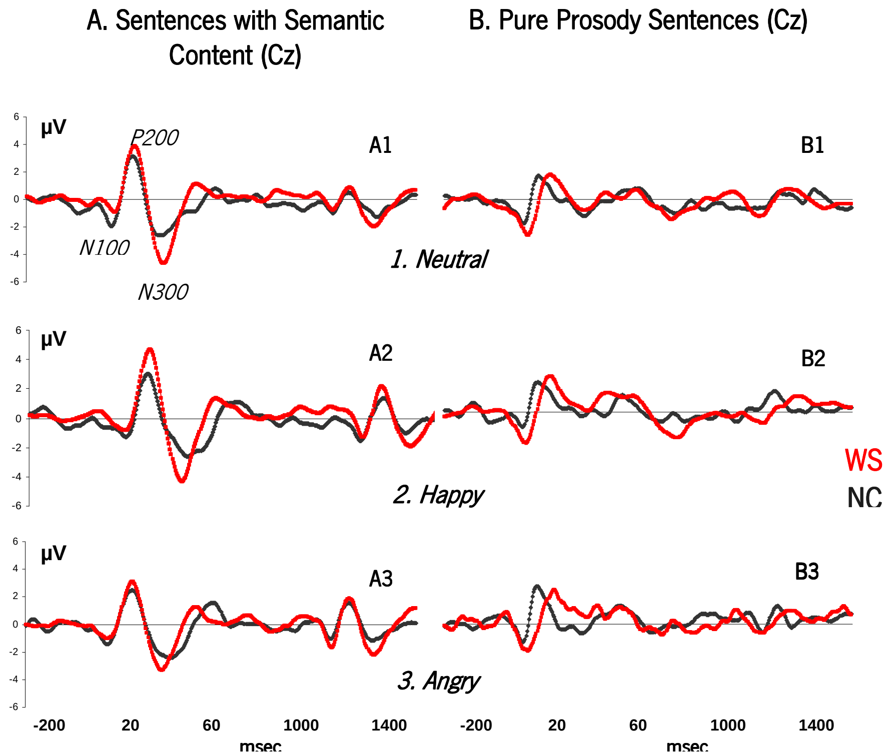


Figure 5. ERP Grand Averages at Cz. Group contrasts are shown for each prosody type (1 - neutral, 2 - happy, and 3 - angry) in each sentence condition - prosodic sentences with semantic content (A), and pure prosody sentences (B).

Figures 4 and 5 illustrate Grand Average waveforms for WS and TD groups, showing a negativity around 100 msec post-stimulus onset (N100), followed by P200 and N300.

Below, we discuss the significant main effects and interactions for each component for each electrode region of interest. We have divided the description of the results into those that were observed in both groups (General prosody effects) and those that pointed to group differences – WS group vs. TD group – in the processing of prosody (Group prosody effects).

3.2.1. Amplitude

3.2.1.1. N100

General prosody effects

A significant effect of sentence condition ($F(1, 17) = 14.52$, $p = .001$), and region ($F(2, 34) = 4.29$, $p = .040$), as well as a sentence condition x region interaction ($F(2, 34) = 4.80$, $p = .018$), were observed. N100 amplitudes were more negative for pure prosody sentences relative to sentences with semantic content, and this was observed only at central electrodes relative to frontal and parietal electrodes.

Group prosody effects

No main effect of group was observed when computing an omnibus ANOVA with sentence condition, emotion, region and electrodes as within-subjects factors. Given our *a priori* hypothesis of differential group effects for sentences with and without semantic content, we conducted separate ANOVAs for each of the conditions.

A main effect of group was found for sentences with semantic content ($F(1, 17) = 4.51$, $p = .049$): N100 amplitudes were more negative in the typically developing group relative to WS.

In addition, given the main effect of region, we further focused our analyses performing separate analyses for sentences with and without semantic content for each region separately.

The results were a function of semantic status and region. For sentences with semantic content, a main effect of group was observed ($F(1, 17) = 4.51$, $p = .049$) at central electrodes, with controls showing more negative N100 amplitude relative to WS individuals. In contrast, for pure prosody sentences, a main effect of group was observed ($F(1, 17) = 4.99$, $p = .039$) at parietal electrodes with more negative N100 in the WS group relative to the control group.

3.2.1.2. P200

General prosody effects

Significant effects of sentence condition ($F(1, 17) = 14.70$, $p = .001$), and region ($F(2, 34) = 18.34$, $p = .000$) were observed. P200 amplitude was more positive for pure prosody sentences relative to sentences with semantic content. More positive amplitudes were observed at central electrodes, relative to frontal and parietal electrode sites, suggesting the central distribution of the P200 effect.

Group prosody effects

For the omnibus ANOVA with sentence condition, emotion, region and electrodes as within-subjects factors, a main effect of group ($F(1, 17) = 3.70$, $p = .071$) approached significance, suggesting a trend for more positive amplitudes in the WS group across sentence conditions and emotional prosody types.

Given our a priori hypothesis of group differences in the sentences with but not without semantic content, we did separate analyses for each condition as described above. A main effect of group was observed for sentences with semantic content only ($F(1, 17) = 4.40$, $p = .051$), with more positive P200 in the WS group relative to controls.

To focus these analyses further we also conducted ANOVAS for each region separately. At frontal electrodes, there was a main effect of group for both sentences with semantic content ($F(1, 17) = 7.66$, $p = .013$) and pure prosody sentences ($F(1, 17) = 5.84$, $p = .027$), with more positive P200 in the WS group than in the control group. In addition, in pure prosody sentences there was a significant group x emotion interaction ($F(2, 34) = 4.26$, $p = .028$) with more positive P200 found in WS relative to TD individuals to angry sentences.

Given the significance of P200 during the early discrimination of neutral and emotional prosody (Paulmann & Kotz, 2008b) and our hypothesis that neutral and emotional prosodic sentences would be differentiated in this early component, we conducted separate ANOVAs for each prosody type (neutral, happy, and angry), with sentence condition, region and electrodes as within-subjects factors. We found a main effect of group for happy sentences ($F(1, 17) = 5.84$, $p = .027$), with more positive amplitudes observed in the WS relative to the control group, consistent with reports of greater sensitivity of WS to happy intonations.

3.2.1.3. N300

General prosody effects

A significant effect of sentence condition ($F(1, 17) = 20.23$, $p = .000$), and region ($F(2, 34) = 52.35$, $p = .000$) was found. More negative N300 was found for pure prosody relative to semantic prosody sentences. Also, more negative N300 was found for angry sentences relative to neutral sentences only. N300 was larger at central and frontal electrodes relative to parietal electrodes.

Group prosody effects

A significant region x group interaction ($F(2, 34) = 6.89$, $p = .005$) was found. More negative N300 amplitudes were found for TDs relative to WS individuals at parietal electrodes.

As for N100 and P200, we conducted separate analyses for each sentence condition. No main effect of group was observed.

Given the region effect observed in the omnibus ANOVA, we also conducted separate analysis for each region. A main effect of group was observed for semantic prosody: at frontal electrodes (F(1, 17) = 4.85, p = .042), where N300 amplitude was more negative in the WS group relative to TD controls; at parietal electrodes (F(1, 17) = 9.31, p = .007), where N300 amplitude was more negative in the TD group relative to the WS group.

Summary

Consistent with our initial hypothesis based on existing literature, sentences with and without intelligible semantic content were processed differently, as indexed by N100, P200, and N300. The processing of pure prosody sentences was associated with more negative N100, more positive P200, and more negative N300, when compared to sentences with semantic content. For all of the components, the effect was predominantly central. The results also suggest group differences in the processing of both sentence conditions and emotional prosodic intonations. Typically developing controls showed more negative N100 amplitude for sentences with intelligible semantic content, at central electrodes; and more negative N300 amplitude, at parietal electrodes relative to WS. The WS group showed more negative N100 amplitude to pure prosody sentences at parietal electrodes; more positive P200 amplitude at frontal electrodes, for both types of sentence conditions, and, in particular, for happy sentences; and less negative N300 at parietal electrodes.

3.2.2. Latency

3.2.2.1. N100

General prosody effects

A significant effect of sentence condition (F(1, 17) = 29.14, p = .000), emotion (F(2, 34) = 3.25, p = .052), and region (F(2, 34) = 3.87, p = .037) was observed.

N100 latency peaked earlier to pure prosody sentences (M = 136.94 msec; SD = 2.46) relative to prosodic sentences with semantic content (M = 157.94 msec; SD = 4.38). Although pairwise comparisons did not reveal significant differences between emotional prosody types, a trend was observed for earlier N100 peak latencies for angry sentences (M = 141.39 msec; SD = 4.33) relative to neutral (M = 148.51 msec; SD = 3.74) and happy sentences (M = 152.47 msec; SD = 3.62). Also, N100 peaked earlier at frontal electrodes.

Group prosody effects

Results showed a significant region x group interaction ($F(2, 34) = 13.33$, $p = .000$). Groups differed at frontal and parietal regions: at frontal regions, N100 peaked earlier in the WS group; while at parietal electrodes, N100 peaked earlier in TD group (see Table 5).

3.2.2.2. P200

General prosody effects

A significant effect of sentence condition was observed ($F(1, 17) = 339.86$, $p = .000$): P200 peaked earlier to pure prosody sentences relative to sentences with semantic content.

Additionally, an effect of region ($F(2, 34) = 9.18$, $p = .003$) was found. At frontal and central electrodes, P200 peak latency was earlier relative to parietal electrodes.

Group prosody effects

The group x region interaction ($F(2, 34) = 9.13$, $p = .003$) was significant. At frontal electrodes, P200 latency peaked earlier in the WS group, while at parietal electrodes, the reverse was found, with controls showing an earlier P200 latency relative to WS individuals.

3.2.2.3. N300

Global prosody effects

A main effect of sentence condition was observed ($F(1, 17) = 58.03$, $p = .000$), as well as an effect of region ($F(2, 34) = 7.02$, $p = .009$). An earlier N300 peak latency was again observed for pure prosody sentences. Also, peak onset occurred later at parietal electrodes relative to frontal and central electrodes.

Group prosody effects

No main effect of group or interactions with group factor were observed (see Table 5).

Table 5

Peak latency values (N100, P200, N300), at Cz, for sentences with semantic content and pure prosody sentences

		Sentence condition					
Peak	**Groups**	**Sentences with Semantic Content** Mean (SD)[1]			**Pure Prosody Sentences** Mean (SD)[1]		
		Neutral	*Happy*	*Angry*	*Neutral*	*Happy*	*Angry*
N100	**WS**	148.00 (38.21)	167.56 (26.72)	147.11 (43.99)	120.44 (32.95)	127.56 (8.82)	127.56 (9.68)
	TD	168.00 (22.07)	149.60 (51.02)	152.80 (20.38)	131.60 (8.10)	130.00 (14.88)	128.40 (10.57)
P200	**WS**	269.78 (17.10)	277.33 (15.10)	262.67 (19.60)	210.22 (12.98)	209.33 (10.77)	206.67 (12.96)
	TD	267.20 (13.17)	266.80 (15.44)	262.00 (23.34)	213.20 (25.16)	213.60 (25.03)	210.80 (11.93)
N300	**WS**	395.11 (9.55)	405.33 (21.07)	378.22 (30.40)	320.44 (18.60)	328.89 (31.99)	318.67 (21.35)
	TD	378.80 (27.72)	422.00 (67.84)	396.40 (45.19)	331.20 (39.72)	330.00 (28.86)	325.60 (32.51)

[1] Msec

Summary

Earlier peak latencies were observed for pure prosody sentences relative to prosodic sentences with semantic content, for all ERP components (N100, P200, and N300).

Group differences were observed for peak latency measures for N100 and P200. The WS group showed an earlier N100 and P200 peak latency at frontal electrodes, for sentences with semantic content. In contrast, at parietal electrodes, TD had earlier peak latencies. No group differences in peak latency values were observed for the N300 peak.

4. Discussion

The current study explored the following questions: (a) Do WS individuals process prosody differently relative to typically developing individuals at both behavioral and electrophysiological levels? (b) Does the presence of semantic and lexical information influence the processing of prosodic information at both behavioral and electrophysiological levels?

Previous studies have suggested an extensive use of prosodic devices by individuals with WS, as well as a relative sensitivity to emotional prosody (Plesa-Skwerer et al., 2006), but few studies have investigated WS individuals' ability to identify different prosody patterns and none has investigated the electrophysiological correlates of prosody processing.

Based on the existing evidence that suggests deficits in the understanding of emotional cues in voice (e.g., Catterall et al., 2006; Skwerer et al., 2007), we hypothesised that participants with WS would show abnormal ERP patterns while processing emotional prosody in intelligible semantic sentences but will show normal ERP patterns while processing 'pure prosody' sentences (Plesa-Skwerer et al., 2006). In addition, we formulated two hypotheses regarding processing emotional prosody and expected differences in the processing of prosodic features as a function of semantic status of sentences.

These hypotheses were addressed by presenting subjects with meaningful, semantically neutral sentences spoken with different emotional intonations, and with the same sentences after they were transformed to eliminate semantic and lexical information. We hypothesised that stimuli with no lexical content should, as in previous studies, elicit prosodic effects that are not dependent of semantic information (Paulmann & Kotz, 2008a).

Both behavioral and ERP data were collected. Behavioral data suggested differences between groups in the recognition of negative (angry) prosody, with more errors found in WS. In both groups, emotion recognition was better for sentences that contained semantic information than for pure prosody sentences devoid of it (77.29% vs. 61.71% correct for the WS group; 87.52% vs. 73.68% for the TD group), confirming the findings of previous studies (Paulmann, Seifert, & Kotz, 2009) that interpreting prosody in the absence of meaningful semantic content is more difficult (Kotz & Paulmann, 2007).

ERP data pointed to important group differences and similarities. In both groups, N100, P200 and N300 amplitudes were larger and their latencies peaked earlier in pure prosody sentences than in sentences with semantic content. This result suggests that, in the absence of intelligible semantic information, the subject has fewer linguistic channels to process, so that the processing of suprasegmental features can be faster. At the same time, the amplitude data support behavioral results in terms of greater difficulty in processing pure prosody in the absence of semantics as documented by larger peak amplitudes of the components related to different stages of prosody processing.

The WS group showed a similar morphology and sequence of ERP components to typically developing controls. At the same time, group differences were observed in the N100, P200 and N300 components. Relative to controls, individuals with WS showed more negative N100 amplitude for pure prosody sentences; more positive P200 amplitude for both pure prosody and semantic prosody, specifically for happy intonation; and less negative N300. Also, differences in latency were observed for N100 and P200, with peaks occurring earlier at frontal electrodes and later at parietal electrodes in the WS group.

In the following section, an integrative approach for abnormal electrophysiological correlates of prosody processing in WS is presented, based on Schirmer and Kotz (2006).

Understanding the emotional meaning of a vocal message relies on the analysis and integration of several acoustic cues such as amplitude, timing or fundamental frequency, which is a multi-stage process (Hoekert, Bais, Kahn, & Aleman, 2008; Schirmer & Kotz, 2006; Wildgruber, Ackermann, Kreifelts, & Ethofer, 2006). In terms of emotional prosody processing, the existing evidence suggests that the first stage occurs around 100 msec, when the sensory processing of acoustic cues takes place (Schirmer & Kotz, 2006). The auditory N100 amplitude has been proposed to reflect cortical responsiveness to natural speech sounds (Ford & Mathalon, 2004; Ford, Roach, Faustman, & Mathalon, 2007), being modulated by the physical characteristics of stimuli such as intensity (Keidel & Spreng, 1965) and sound complexity (Wunderlich & Cone-Wesson, 2001). In the current study, N100 in WS was found reduced to sentences with semantic content but not to pure prosody sentences suggesting that early stages of prosody processing are adversely influenced by the processes related to extracting semantic information: WS individuals can process prosodic information effectively only if they are unimpeded by additional demands of processing a semantic channel. Thus, for N100, the results are in keeping with the notion that difficulty in prosody processing is conferred by the simultaneous need to process semantic content (Plesa-Skwerer et al., 2006). However, since N100 amplitude is modulated by a long list of variables such as attention, arousal, motivation, fatigue, and hearing thresholds, we cannot rule out a possibility that they may have additionally contributed to the observed results.

The second stage of emotional prosody processing, occurring around 200 msec, corresponds to the integration of emotionally significant acoustic cues that allow subjects to derive emotional significance from the stimuli (Schirmer & Kotz, 2006). This is consistent with the functional significance of the auditory P200 component believed to index some aspects of the stimulus classification process (Garcia-Larréa, Lukaszewicz, & Mauguière, 1992), and sensitive to the acoustic properties of stimuli such as intensity (e.g., Picton, Goodman, & Bryce, 1970), duration (e.g., Roth, Ford, Lewis, & Kopell, 1976), and pitch (e.g., Alain, Woods, & Covarrubias, 1997; Jacobson et al., 1992). Variations in these acoustic features (e.g., pitch, intensity) define emotional prosody (see Schirmer & Kotz, 2006). Our findings point to more positive P200 amplitude to both sentences with semantic content and pure prosody sentences, in particular to happy intonation sentences in WS. The finding of larger P200 to both sentences with and without semantic content suggests an impairment that is present regardless of the semantic status of a sentence; here pure prosody sentences are not easier to process than semantic content sentences. This result suggests a greater sensitivity of WS individuals to prosodic cues that transcends the semantic status of sentences and thus argues against a selective role of semantic content as a *sine-qua non* mediating factor in prosodic abnormalities in WS.

In addition, the finding of enhanced P200 specifically to happy intonation corroborates the findings of an emotional facial expressions processing study (Haas et al., 2009) where a heightened reactivity/attention was observed to positive facial expressions in WS (larger P300-500 difference to happy minus neutral facial expressions), as well as a decreased activity to fearful vs. neutral expressions (indexed by a reduced N200 mean amplitude for fearful expressions). It is possible that the higher spectral complexity of happy voice stimuli, as pointed out in other studies (Spreckelmeyer, Kutas, Altenmuller, & Munte, 2009), could be a factor contributing to the larger P200 amplitude observed to happy relative to angry and neutral stimuli in WS individuals. However, that was not observed in the TD group, or in the study of Paulmann and Kotz with normal individuals (2008b).

In spite of a larger P200 observed in grand averages to neutral relative to emotional prosody, an emotion effect was not found to be statistically significant. This may have been due to a large variability in the P200 response related to age variability in our sample.

In the N300 component peaking around 360 msec, more negative amplitudes were found to pure prosody sentences. The N300 has been associated with the cognitive evaluation of emotional significance of the acoustic signal (around 400 msec) related to integrating information provided by the physical properties of the stimuli (as intensity, pitch, duration) and meaning conveyed by linguistic (e.g., semantic) information so that cognitive judgments can be made (e.g., what type of emotion is being presented?) (Schirmer & Kotz, 2006; see also Kotz & Paulmann, 2007; Paulmann & Kotz, 2008b; Wambacq & Jerger, 2004).

The reduced N300 peak amplitude in individuals in WS at parietal electrodes and its enhancement at frontal electrodes suggests abnormal electrophysiological response at the stage of evaluating emotional significance of the message. It may suggest that the simultaneous processing of segmental and suprasegmental information may pose difficulties to these individuals. Difficulties in accessing semantic system and in semantic integration have been previously identified in WS in behavioral studies (Bromberg, Ullman, Marcus, Kelly, & Levine, 1994; Temple, Almazan, & Sherwood, 2002; Temple, Almazan, & Sherwood, 2002; Ypsilanti, Grouios, Zikouli, & Hatzinikolaou, 2006; Neville, Mills, & Bellugi, 1994; Tyler et al., 1997).

Together, these results are different from previously published behavioral results (Plesa-Skwerer et al., 2006; Skwerer et al., 2007). First, group differences in behavioral responses were limited only to angry sentences. This finding is different from Plesa-Skwerer et al. (2006), who found better recognition for angry intonation than for other emotions in WS, but is consistent with anecdotal reports of WS abnormalities in processing negative social information (Bellugi et al., 1999; Jones et al., 2000; Klein-Tasman & Mervis, 2003). Second, ERP results paint a more nuanced picture of abnormalities in processing prosody in WS due to the ERP sensitivity to processes that are not accessible to behavioral measures

At the level of sensory signal processing, indexed by N100, its reduced amplitude to sentences with semantic content suggests an impairment that is likely mediated by the impact of semantic channel on the efficient processing of prosodic cues. At the level of the integration of specific emotional cues, as indexed by P200, its amplitude enhancement to both sentences with and without semantic content suggests that heightened sensitivity to prosodic cues is present regardless of whether WS individuals need to process semantic information or not. Finally, abnormal N300 in WS suggests abnormal processes of cognitive evaluation of emotional significance of acoustic signal and its potential integration with semantic information.

We do not believe that these abnormalities stem from WS individuals' inability to retain pitch variations over longer prosodic segments in short-term memory since a relative preservation of phonological short-term memory in WS has been reported (Grant et al., 1997;

Majerus, Barisnikov, Vuillemin, Poncelet, & Van der Linden, 2003; Robinson, Mervis, & Robinson, 2003). Instead, we believe that these results suggest specific impairments in prosody processing that span the three stages: 1. Sensory processing of acoustic signal; 2. Integration of emotionally specific acoustic cues; and 3. Cognitive evaluation of the emotional significance of acoustic cues and its integration with semantic information.

It is worth noting that the less negative N100 and more positive P200 in WS individuals has already been described in previous studies using normal speech (St. George, Mills, & Bellugi, 2000; Mills et al., 2003), a finding that was interpreted as indexing the hyperexcitability of the auditory system in WS, and can be related to structural abnormalities in brain areas thought to be the generators of N100, i.e., the superior temporal gyrus (STG). For example, Reiss et al. (2000) reported a relative increase of STG volume relative to decreased overall brain and cerebral volumes, and the absence of a normal left>right asymmetry was reported by Sampaio et al. (2008).

The different sensitivity to happy prosody in WS is consistent with the behavioral phenotype of this syndrome, namely the hypersociable profile (e.g., Bellugi et al., 1999; Jones et al., 2000; Klein-Tasman & Mervis, 2003). The suggestion, from behavioral studies, that individuals with WS use or interpret intonation in a different way from what would be expected for their chronological age is corroborated by ERP findings.

The major contribution of this study is providing, for the first time, electrophysiological evidence for the abnormalities in prosody processing in WS. However, some limitations should be highlighted. Due to the small sample that participated in this study, the current results should be treated with caution. In addition, the intra-group variability and heterogeneity of Williams Syndrome (e.g., Plesa-Skwerer et al., 2006) that could lead to observing different patterns of prosodic deficit in WS across different samples (Catterall et al., 2006) should be kept in mind. Future studies should include larger samples to provide a more comprehensive view of prosody processing in WS.

Conclusion

Overall, the findings of the current study suggest that prosody in WS is processed in a different way from typically developing controls, both in terms of different types of emotionality (positive vs. negative vs. neutral) and in terms of the presence or absence of semantic content of a sentence.

Abnormalities indexed by N100, P200 and N300 likely represent deficits in early sensory stages of prosody processing and suggest that dysfunction in the processing of suprasegmental features in WS may not be entirely mediated by higher order cortical deficits such as for example executive functioning (e.g., Greer, Brown, Pai, Choudry, & Klein, 1997; Lincoln, Lai, & Jones, 2002; Morris & Mervis, 2000; see Martens, 2008 for a review); instead, they indicate a bottom-up contribution to the impairment in emotional prosody processing and comprehension.

The current study showed, for the first time, that abnormalities in ERP measures of early auditory processing in WS are also present during the processing of emotional vocal information. This may represent a physiological signature of underlying impaired on-line language processing, as proposed for other neurodevelopmental disorders such as schizophrenia (e.g., Rosburg, Boutros, & Ford, 2008). ERP abnormalities indexing deficits in prosody understanding (Catterall et al., 2006; Plesa-Skwerer et al., 2006; Skwerer et al., 2007) may be related to the often reported difficulties in social interaction, especially in the understanding of subtle changes in acoustic information such as irony or sarcasm (Laws & Bishop, 2004; Sullivan et al., 2003), and giving rise to less satisfactory relationships (Deutsch, Ross, & Schwartz, 2007; Klein-Tasman, Mervis, Lord, & Philips, 2007; Laws & Bishop, 2004). Given that during speech perception, both segmental and suprasegmental information closely interact (e.g., Dietrich, Ackermann, Szameitat, & Alter, 2006; Schirmer & Kotz, 2006), deficits in understanding the "emotional melody" of discourse will compromise the ability to understand the intentions and affective states of the speaker in WS. This suggests that clinical interventions with WS individuals should include strategies for training the ability to differentiate different emotional prosodic intonations.

Study 2

Electrophysiological correlates of semantic processing in Williams Syndrome

1. Introduction

Williams Syndrome (WS), a rare neurodevelopmental disorder characterized by a deletion on chromosome 7 q11.22-23, has called the attention of researchers due to its intriguing phenotype in which an apparent preservation of language and face processing seems to coexist with severe intellectual deficits in other cognitive domains such as visual-spatial processing and executive functioning (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; see Martens, Wilson, & Reutens, 2008 for a review). This syndrome was initially proposed as a paradigmatic example of cognitive dissociation and of a modular organization of the brain and, more specifically, an example of the independence of language from general cognition (Bellugi, Marks, Bihrle, & Sabo, 1988; Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Bellugi, Bihrle, Neville, Jernigan, & Doherty, 1992; Pinker, 1994).

In fact, when compared with other developmental disorders such as Down Syndrome (DS) there is evidence for an increased verbal production in WS (e.g., Mervis & Robinson, 2000). Other aspects of language production, such as affective prosody and the use of audience hookers, seem to be not very different from typically developing chronological age matched controls (Jones et al., 2000; Reilly, Klima, & Bellugi, 1991; Gonçalves et al., 2004, in press). Additionally, WS verbal abilities seem to develop at a faster rate than their nonverbal abilities (Jarrold, Baddeley, & Hewes, 1998).

However, contrary to initial claims of modular language preservation, recent studies show that language abilities are below age-appropriate levels (Grant, Valian, & Karmiloff-Smith, 2002; Lukács, Pléh, & Racsmány, 2004; Landau & Zulowski, 2003; Laws & Bishop, 2004; Phillips, Jarrold, Baddeley, Grant, & Karmiloff-Smith, 2004; Pléh, Lukács, & Racsmány, 2003; Sullivan, Winner, & Tager-Flusberg, 2003; Vicari et al., 2004) and follow an atypical developmental pathway (e.g., Laing et al., 2002; Mervis & Bertrand, 1997; Mervis et al., 2003). It appears that some subcomponents (receptive vocabulary, phonological short-term memory, regular morphology, production of affective prosody) are relatively more preserved than others (e.g., repetition of syntactically complex sentences, production of grammatical gender, irregular morphology, comprehension of spatial terms, comprehension of figurative language, pragmatics) (see Brock, 2007, for a review).

There is less agreement in the literature when it comes to semantic fluency. While some studies suggest a higher production of words in semantic fluency tasks in WS individuals than would be expected for their average mental age along with an increased production of atypical category exemplars (e.g., Bellugi et al., 1988, 1990, 1992, 1994; Rossen, Klima, Bellugi, Bihrle, & Jones, 1996; Wang & Bellugi, 1993), others suggest that this is not the case (Jarrold, Hartley, Philipps, & Baddeley, 2000; Johnson & Carey, 1998; Scott et al., 1995; Stevens & Karmiloff-Smith, 1997; Volterra, Capirci, Pezzini, Sabbadini, & Vicari, 1996).

There is a similar lack of consensus in relation to semantic priming. Some studies found the same effects of priming on reaction times of individuals with WS and controls (e.g., Tyler et al., 1997), which may suggest a normal organization of semantic system in WS. However, other studies suggested abnormal lexical knowledge in WS (e.g., Bellugi et al., 1988, 1990; Jarrold et al., 2000; Johnson & Carey, 1998; Rossen et al., 1996; Volterra et al., 1996; Ypsilanti, Grouios, Alevriadou, & Tsapkini, 2005), as well as deficits in lexical access (e.g., Bromberg, Ullman, Marcus, Kelly, & Levine, 1994; Temple, Almazan, & Sherwood, 2002; Ypsilanti et al., 2006). This finding led some authors to propose a dissociation between preserved structure of semantic memory and impairment in the integration of word meanings into on-line developing sentential representations (Tyler et al., 1997).

The impairments found in semantic memory may be explained by a lack of maturity in conceptual organisation of semantic categories (e.g., Jarrold et al., 2000; Johnson & Carey, 1998) in the sense that individuals with WS can put information in semantic networks but might have difficulties in conceptually reorganising this information. This hypothesis seem to be corroborated by studies showing a decreased sensitivity to word frequency in WS and a nearly equal preference for primary and secondary meaning of homonyms (Rossen et al., 1996), a trend for the production of infrequent words towards the end of a trial in semantic fluency tasks (Rossen et al., 1996), or an atypical semantic development in the sense that older individuals with WS do not present a more sophisticated conceptual structure than younger individuals (Jarrold et al., 2000).

Together, these findings question the claim for a modular preservation of language in WS. It is possible that the idea of the intact language may have arisen from the comparisons with DS where more severe language impairment is observed (e.g., Mervis, 2003). Another contributing factor may have been the techniques used to study this genetic disorder. Most studies used behavioral measures to probe language function in Williams Syndrome. While these are valuable studies, they preclude observation of neural processes that underlie language performance. Both reaction times and error rates are, by definition, aggregate measures of all processes that went into making a response. As such they do not provide information about possible abnormalities at different stages of information processing prior to the response. Thus, a more comprehensive approach to the study of language in both normal and clinical population is the concurrent use of behavioral and event related potential techniques (e.g., Hsu, Karmiloff-Smith, Tzeng, Chin, & Wang, 2007).

Event related potential (ERP) techniques are one of the few methodologies that document real time changes in neuro-cognitive processes. As such they are a valuable supplement to the study of language (Kutas & Federmeier, 2000). One of the components that has been associated with language processing in numerous studies is the N400, a negative going potential that peaks around 400 msec after the presentation of visual stimuli, and around 300-350 msec to auditorily delivered stimuli (see Lau, Philipps, & Poeppel, 2008, for a review). The N400 has been found sensitive to processing semantic information regardless of the physical nature of the stimulus, i.e., it has been found to both visual and auditory language stimuli (e.g., Anderson & Holcomb, 1995; Besson & Macar, 1986; Kutas & Iragui, 1998; Niznikiewicz et al., 1997) as well as to pictures (e.g., Coch, Maron, Wolf, & Holcomb, 2002; Federmeier & Kutas, 2002; West & Holcomb, 2002; Willems, Özyürek, & Hagoort, 2008). It seems to reflect the ease with which two concepts can be linked together and as such it has been used as an index of priming and context use (e.g., Brown & Hagoort, 1993; Federmeier & Kutas, 1999a, 1999b; Halgren, 1990; Kutas & Hillyard, 1980, 1984; Rugg, Doyle, & Holdstock, 1994; van Petten, 1993). The N400 has been found to peak maximally at centro-parietal electrodes and is more negative going to words or pictures that do not fit well the proceeding context relative to these semantic items that fit the previous context well. In addition, its amplitude can be influenced by word frequency, word type (e.g., closed vs. open class), word lexical status, or the semantic or associative relationship between words, but it is insensitive to decision-related and response-selection mechanisms (Heinze, Muente, & Kutas, 1998). Therefore, the N400 component may be a good probe to study language processes in WS.

In addition to N400, other components have been studied in language paradigms. Specifically, the N100, P200, and N250 have been proposed as correlates of initial, more sensory based processes (Barnea & Breznitz, 1998; Hagoort, & Brown, 2000; Niznikiewicz & Squires, 1996; Liu, Perfetti, & Hart, 2003; van den Brink, Brown, & Hagoort, 2001; van Petten, Coulson, Rubin, Plante, & Parks, 1999) and a later component, P600, was also extensively studied as a correlate of late integration processes (e.g., Friedman, Simson, Ritter, & Rapin, 1975; Kramer & Donchin, 1987; Osterhout & Holcomb, 1992).

Developmentally, studies using connected speech found that an N400 with an adult-like pattern, in terms of amplitude, is observed by age 7 (Cummings, Ceponiene, Dick, Saygin, & Townsend, 2008; Hahne, Eckstein, & Friederici, 2004), although there is a decrease in latency as a function of age, with 10-year-old children showing N400 latency similar to adults (Hahne et al., 2004). Other studies found marked reductions in latency and amplitude from 5 until 15 to 16 years of age, with the largest N400 effects being observed for 5-6 year-old children (Holcomb, Coffey, & Neville, 1992).

Language studies in WS using auditory sentences suggested ERP abnormalities in early components within N1 and P2 latency. More positive P200 amplitude during auditory sentences processing was reported by Neville, Mills, and Bellugi (1994). In the same study, a larger positivity to congruous words in auditory sentences was observed in WS adults and children relative to normal age matched controls, over the left hemisphere. The amplitude of the N400 response (i.e., difference between congruent and incongruent sentence endings) was larger in WS adults than in normal comparison subjects, over both hemispheres. This finding was interpreted as reflecting atypical semantic activation (enhanced connections between related lexical items) which, at the behavioral level, was associated with the unusual performance in semantic fluency tasks, commonly described in this population such as, for instance, the retrieval of atypical members of a given semantic category (Neville et al., 1994).

A second ERP study in WS (St. George, Mills, & Bellugi, 2000) also showed differences in the N400 response, with this being larger in WS relative to normal controls and with a bilateral distribution. In addition, the WS group did not show a greater early left anterior negativity to function words and later posterior negativity (N400) to content words (relative to function words) found in normal comparison subjects. Abnormalities in the earlier ERP components were also found by Mills et al. (2003) to auditorily presented sentences. These authors reported an atypical "W" pattern (small N1, large P1/P2) linked to the processing of auditory linguistic information, in the WS group (8 year-olds and older participants), but not in any normal control age groups. These findings were interpreted as suggestive of hyper-activation within the auditory system.

In spite of the contributions of the studies described above, the neural and cognitive mechanism(s) that lead to language difficulties in WS have yet to be elucidated. One hypothesis suggests that atypical performance in some language tasks may reflect too broad spread of activation in the semantic networks which could account for the activation of weakly associated items. A second hypothesis suggests that these abnormalities reflect a failure to use verbal context in order to modulate the initial semantic activation appropriately, suggesting deficits in later executive functions.

Unfortunately, the few studies on N400 in WS do not provide enough details about experimental procedures and results analysis to be able to understand the source of discrepancy between the studies. In addition, no ERP study was conducted with Portuguese participants and, therefore, we don't know if language abnormalities found in the previous studies are observed regardless of the language used in the study.

The aim of the present study was to investigate the electrophysiological correlates of semantic processing in WS using auditory sentences. More specifically, we aimed at characterizing the temporal course of processing congruent and incongruent sentence endings, examining early auditory ERP responses (N100 and P200), ERP responses related to semantic integration (N400), and ERP responses related to semantic and syntactic integration or reanalysis processes (P600).

Based on previous studies (Neville et al., 1994; Mills et al., 2003; St. George et al., 2000), we predicted that processes of semantic integration would be preceded by abnormalities in early ERP components: reduced N100 and enhanced P200 amplitude. Also if, as suggested in the literature, individuals with WS have difficulties integrating context efficiently, more negative N400 amplitude to congruent and incongruent endings will be expected. Difficulties with semantic integration and comprehension would be indexed by more positive P600 amplitude in WS for both types of sentence endings.

In order to address these hypotheses, 12 participants with WS and 12 typically developing individuals were presented with auditory sentences in two conditions: (1) sentences ending with an expected and valid word; and (2) sentences ending with an invalid word given its previous semantic context.

2. Methods

2.1. Participants

A group of twelve participants (5 female and 7 male), diagnosed with WS, with age range between 9 and 34 years, (*M* = 17.3; *SD* = 6.50) was compared with a typically developing group, individually matched for chronological age (*M* = 17.3; *SD* = 6.50), gender and handedness. Participants were matched for chronological age rather than mental age for several reasons. First, our major aim was to compare a group of individuals with WS to a group of typically developing individuals and to understand which differences exist in the ERP responses to auditory language stimuli in WS and, in particular, what is deviating from typical development. Second, studies suggest differences in amplitude and latency in language ERP components throughout development. For example, N400 seems to be well established around age 9 (Cummings et al., 2008; Hahne, Eckstein, & Friederici, 2004). Matching participants with WS and controls on MA would result in comparing these participants with younger age groups, so that potential differences could be due to the age of participants and not to the cognitive processes underlying the ERP responses. Third, control participants who are matched on IQ (e.g., Down Syndrome or nonspecific mental retardation) generally have language abilities that are inferior to those of individuals with WS.

Participants with WS were recruited at a large Genetic Medical Institute in Oporto, Portugal, and also by the Portuguese Williams Syndrome Association. WS diagnoses were made by fluorescent in situ hybridization (FISH) confirmation of elastin gene deletion (Korenberg et al., 2000). Exclusion criteria were: (a) the presence of severe sensory (e.g., hearing problems) or speech disorder; (b) comorbidity with severe psychopathology not associated with the syndrome; (c) use of any medication that might affect cognitive function or electroencephalogram (EEG) recordings, such as steroids and barbiturates; (d) and use of any psychoactive medication. Controls were typically developing individuals without evidence of sensory, psychiatric, neurological disorder or cognitive impairment. All subjects were right-handed, according to the Edinburgh handedness inventory (Oldfield, 1971) and had European Portuguese as their first language. Each participant and their guardians (in the case of minor subjects and patients) gave written informed consent for their participation in the study via consent forms, after a detailed description of the study. The Ethics Committee of the University of Minho approved this study.

The mean socioeconomic status, as measured by an adapted version of Graffar Scale (Graffar, 1956) was 3.00 (SD = 1.28) for the Williams Syndrome group and 2.92 (SD = 1.44) for the typically developing (TD) control group. The two groups didn't differ in socioeconomic status ($F(1, 22) = 0.02$, $p > .05$). However, as expected, groups differed in mean years of education ($F(1, 22) = 7.64$, $p = .011$), with more years of education in the TD group (M = 10.83; SD = 3.66) than in WS (M = 7.58; SD = 1.78).

To assess general cognitive functioning (Full Scale IQ), participants with chronological age between 9-16 years were administered the Wechsler Intelligence Scale for Children-Third Edition (WISC–III) (Wechsler, 1991), while participants over 16 years old were administered the

Wechsler Adult Intelligence Scale- Third Edition (WAIS-III) (Wechsler, 1997). Since the experimental task in this study was auditory, the following measures of auditory (phonological) processing were used, selected from the Portuguese version of Psycholinguistic Assessment of Language Processing in Aphasia – PALPA (Castro et al., 2007): Discrimination of Minimal Pairs in Pseudowords; Auditory Lexical Decision and Morphology, Repetition of Pseudowords. Neurocognitive tests were in the native language of the patients and were administered and scored accordingly. Results of general cognitive assessment are presented in Table 1.

Table 1

Results of the neurocognitive assessment of Williams Syndrome (WS) and Typically Developing (TD) groups

	WS Group (*N* = 12)	**TD Group** (*N* = 12)	**Significance test**
	Mean (SD)	Mean (SD)	*F* (*p*)
1. Global intellectual functioning			
Verbal IQ	58.55 (9.18)	116.45 (14.75)	122.17 (.000**)
Performance IQ	52.18 (5.96)	111.73 (16.32)	129.15 (.000**)
Full Scale IQ	51.55 (7.10)	114.00 (13.71)	182.87 (.000**)
2. Language (Phonological processing)			
a) Discrimination of Minimal Pairs in Pseudowords			
Similar pairs	31.44 (0.73)	31.92 (0.29)	4.24 (.053)
Different pairs	29.44 (3.71)	31.67 (0.49)	4.27 (.053)
b) Auditory Lexical Decision and Morphology			
Regular words	12.38 (2.45)	14.67 (0.89)	8.98 (.008*)
Derivated words	12.25 (3.24)	13.92 (1.31)	2.60 (.124)
Pseudowords	21.63 (7.98)	28.00 (4.20)	5.49 (.031*)
c) Repetition of Pseudowords			
1 syllable	8.88 (1.13)	9.75 (0.45)	5.95 (.025*)
2 syllables	8.63 (2.07)	10.00 (0.00)	5.47 (.031*)
3 syllables	8.38 (0.92)	10.00 (0.00)	38.83 (.000**)

* $p < .05$; ** $p < .005$

Mean distribution of Full Scale Intelligence Quotient (FSIQ) in WS was found to be within the moderate mental retardation interval, with verbal intelligence quotient (IQ) slightly higher than performance IQ.

In order to test for group differences on neurocognitive and language measures, one-way analyses of variance (ANOVA) were computed. As seen in Table 1, groups were different on all measures, with the exception of auditory lexical decision and morphology, for derivated words. Also, it is worth noting that groups were only marginally different during discrimination of minimal pairs in pseudowords, for similar and different pairs.

2.2. Stimuli

Eighty eight sentences, each one composed by five words, were developed and presented auditorily.

The choice of the simplest syntactic structure and reduced number of words was due to the difficulties shown by individuals with WS in interpreting more complex sentences (e.g., Grant et al., 2002; Landau & Zulowski, 2003; Lukács, Pléh, & Racsmány, 2004; Vicari et al., 2004) and as a way of minimising working memory demands (see Tyler et al., 1997).

The set of experimental sentences was developed after an earlier study that established cloze probability for the sentence final words (see Appendix 1). The cloze probability study was conducted using eleven groups of children and adolescents (N = 192), from second to twelveth grades (Early Middle School, Middle School, Late Middle School, and High School), with ages ranging between 6 and 18 years old. These participants were asked to complete a set of 73 sentence contexts with the first word that came to their mind. Cloze probability of the words selected by the majority of subjects was then computed. For the incongruent condition, a set of words was selected, after controlling for psycholinguistic variables (age of acquisition, familiarity, frequency, length, number of syllables, concreteness, imageability), in order to complete the same sentence contexts but now in a semantically anomalous way. All sentences (congruent and incongruent) were presented to a different group of children and adolescents, from second to twelveth grades (190 participants), who were asked to judge if the sentences made sense or not. After the analysis of their plausibility ratings, 49 congruent and incongruent sentences endings were selected (44 for the experimental list and 5 for the training session). The sentence was selected if at least 95% of the participants rated the sentence as correct or incorrect.

The sentences were then recorded by a female native speaker of European Portuguese, with emotionally neutral intonation, in a sound proof room with an Edirol R-09 recorder and a CS-15 cardioid-type stereo microphone, with a sampling rate of 22 kHz and 16-bit quantization. Sentences were then digitized, downsampled at a 16 bit/16 kHz sampling rate and normalized in amplitude.

The stimuli were divided into four blocks (22 sentences each). The sentences were pseudo-randomized across blocks, in order to avoid presenting the same sentence twice within the same block. Following Kutas and Hillyard's (1980) paradigm, half of the sentences ended with words incongruent with the previous sentence context (e.g., *The girl curls her biscuit*) and half ended with a word judged to be the best completion (e.g., *The girl curls her hair*). The final words had a mean length of 5.53 letters across conditions (congruent and incongruent sentence endings) and had low age of acquisition (Marques, Fonseca, Morais, & Pinto, 2007) (see Table 2). No critical word was repeated within and between blocks.

Table 2

Psycholinguistic characterization (duration, length, age of acquisition, familiarity, concreteness, and imageability) of congruent and incongruent targets

Variable	Sentence ending	
	Congruent Mean (SD)	Incongruent Mean (SD)
Duration	2.45 (0.39)	2.33 (0.31)
Length (letters)	5.51 (1.63)	5.55 (1.96)
Age of acquisition	2.02 (0.60)	2.25 (0.61)
Familiarity	1.55 (0.38)	1.70 (0.39)
Concreteness	5.96 (1.27)	5.93 (1.13)
Imageability	6.00 (1.16)	5.77 (1.29)

Data were collected from European Portuguese lexical databases (Marques et al., 2007; Nascimento, Casteleiro, Marques, Barreto, & Amaro, no date)

No differences were found between critical words of both conditions in any of the measured psycholinguistic variables.

2.3. Procedure

Each participant was seated comfortably in a reclining chair in a sound-attenuating chamber. All sentences were presented binaurally through headphones using Presentation software (www.neurobs.com) at a sound level that was rated as comfortable for each participant (60 dB SL), with a mean duration of 2390 msec, one word about every 598 msec. Sentences were presented in four blocks with short breaks offered between them (about 5 minutes). A monitor with a resolution of 1,024 3 768 and a refresh rate of 60 Hz was used to display a fixation cross. The distance between the participants and the computer screen was about 100 cm. Subjects were instructed to decide if the last word was a good completion for a given sentence by pressing one response button for "yes" and another one for "no". The mapping between response and right or left hand was counterbalanced across subjects. Half of the subjects pressed a button with their right hand for congruent sentences and with their left hand for incongruent sentences, and the other half pressed a button with their left hand for congruent sentences and with their right hand for incongruent sentences.

A visual cue presented in the middle of the computer screen for 2000 msec and a warning signal preceded the presentation of each sentence. A fixation cross remained on the screen while participants were listening to the sentences, to minimize eye movements. Each sentence was followed with a visual cue lasting for 5000 msec to remind subjects to press a response button. The next trial started 100 msec after the response was made. As soon as the subject pressed a button, and after an inter-stimulus interval of 100 msec, the next trial started. The time between the offset of one sentence and the onset of the following sentence was 5100 msec.

Prior to the experimental procedure, participants were exposed to a short practice (five sentences) designed to reiterate the instructions and to acclimate participants to the task.

Accuracy data (number of hits) were recorded. Hits were defined as the number of correct responses made after the appearance of the prompt to make a response.

2.4. Data acquisition and analysis

2.4.1. EEG data acquisition and analysis

While participants were listening to sentences, the EEG was recorded using a 32-channel QuickAmp amplifier (www.brainproducts.com) with 20 Ag-AgCl electrodes mounted in an elastic cap (Easy Cap), according to the 10-20 System (Jasper, 1958). The set of 20 electrodes included: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T7, T8, Pz, P3, P4, P7, P8, Oz, O1, and O2. Additional bipolar electrodes placed at the external canthi of both eyes were used to record horizontal eye movements. Vertical eye movements were monitored with electrodes placed at left supra- and infraorbital sites. Average reference was used during EEG acquisition, with forehead as ground electrode. Impedance levels were kept at or below 5 KΩ at all electrode locations. The EEG was digitized on-line at a sampling rate of 250 Hz and stored on a computer disk for off-line processing. EEG data were analyzed using Brain Analyzer software (www.brainproducts.com). Separate individual average waveforms were constructed to congruent and incongruent sentence endings, with 100 msec baseline and 900 msec epoch, post-stimulus onset. The Gratton, Coles, and Donchin (1983) algorithm was used to remove contamination from eye movements. Single sweeps were rejected if the amplitude at any electrode site exceeded ±75 mV. Data from three subjects (one from WS group and two typically developing controls) were discarded due to excessive artifacts. On average, 43 (*SD* = 3.91) epochs out of 44 possible trials were retained after artifact rejection.

2.4.2. Statistical analysis

Statistical analyses were conducted separately for behavioral and ERP data. Accuracy rates were calculated for each participant as the number of correctly performed trials within each condition (congruent vs. incongruent) relatively to all trials in that condition. Only data from participants who judged sentence appropriateness in each experimental condition above chance level were included in ERP analyses.

Behavioral data were analyzed according to repeated-measures analyses of variance, with condition (congruent vs. incongruent) as within-subjects factor, and group (WS vs. typically developing controls – TD) as between-subjects factor.

After the inspection of the individual and grand average waveforms, three peaks were selected for analysis in order to provide a comprehensive description of processes associated with sentence analysis at a neuronal level: N100, P200, N400, and P600. Based on the inspection of individual averages and grand averages, the N100 was measured as the most negative voltage within the latency of 80 and 160 msec, the P200 was measured as the most positive voltage within the latency of 160 and 260 msec, and the N400 was measured as the most negative deflection within the latency window of 300 and 450 msec. The latency of the N400 measuring window is in agreement with previous studies reporting an earlier onset of the

N400 effect for auditorily presented language stimuli (e.g., Holcomb & Neville, 1990). Finally, P600 was measured as mean amplitude in two latency windows: 500 to 600 msec, and 600 to 700 msec. Peak and mean amplitudes respect to baseline were measured at all selected electrode locations.

In order to provide a comprehensive analysis of the ERP differences between the two groups under study, a region analysis was conducted, using repeated-measures analyses of variance (ANOVA) separately for amplitude and latency, with sentence condition (congruent vs. incongruent), region (frontal vs. central vs. parietal), and electrodes (Fz, F3, F4; Cz, C3, C4; Pz, P3, P4) as within-subjects factors, and group (WS vs. TD) as between-subjects factor. Also, in order to test for hemispheric differences, an additional analysis was conducted, using sentence condition (congruent vs. incongruent), hemisphere (left vs. right) and electrodes (F3, C3, P3; F4, C4, P4) as with-subjects factors, and group as between-subjects factor.

The p-values in analyses of variance (ANOVA) with within-subject factors are reported before Greenhouse-Geisser Epsilon correction (Geisser & Greenhouse, 1995). Post-hoc tests were conducted for significant main effects and interactions, using pairwise comparisons, with Bonferroni correction.

3. Results

3.1. Behavioral Results

Mean number of correct responses for individuals with WS and controls for the two target conditions (congruent vs. incongruent) is presented in Table 3. Data from one participant from the WS group (the youngest subject) was excluded, because he didn't discriminate between the response buttons. The results indicate a high rate of correct responses for both groups, showing that participants were paying attention to the stimuli and were able to make a congruency judgment.

There was a significant effect of condition on the number of correct responses ($F(1, 21) = 6.45$, $p = .019$), with correct response rate significantly higher for congruent than for incongruent sentence endings. A trend for a main group effect was observed ($F(1, 21) = 4.22$, $p = .053$), indicating more correct responses in the TD group relative to WS.

Table 3

Mean number of correct responses, by group and sentence condition

	Group					
	Williams Syndrome (*n* = 11)			Typically developing controls (*n* = 12)		
Target	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*
Congruent	40.27	4.54	29-43	42.92	1.12	41-44
Incongruent	41.82	3.13	33-44	43.58	0.67	42-44

3.2. ERP Results

Figure 1 shows Grand Average waveforms at Cz in both groups, for congruent and incongruent conditions. ERP group contrasts are shown separately for congruent and incongruent sentence endings in Figures 2 and 3.

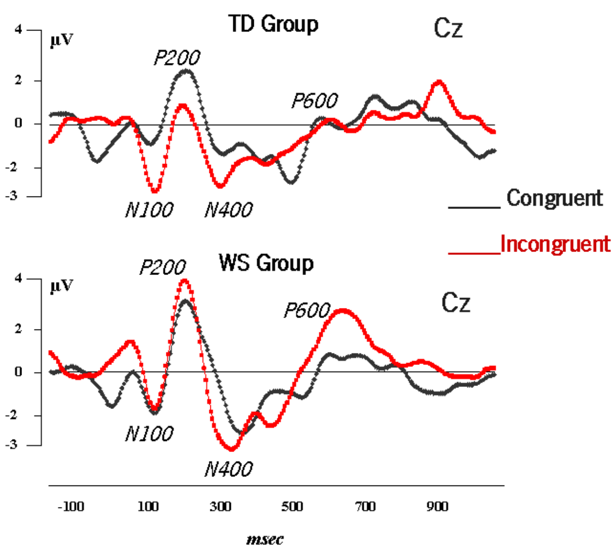


Figure 1. Grand Averages waveforms for congruent and incongruent sentence endings in WS and TD groups (selected electrode: Cz).

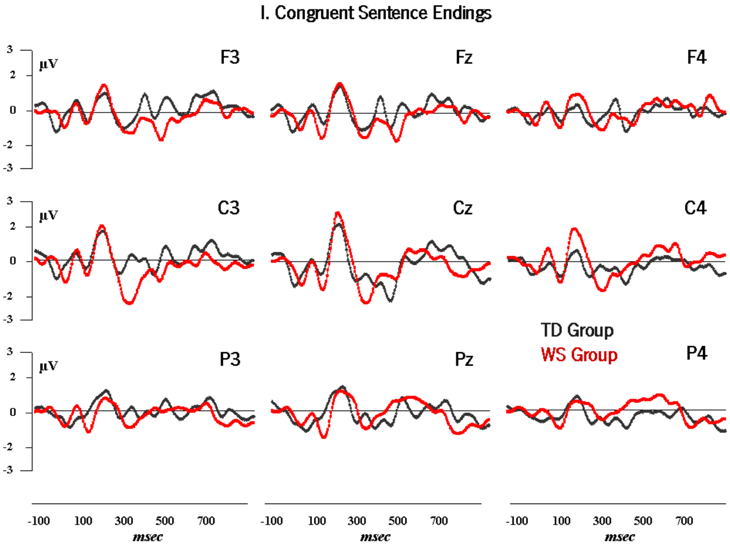


Figure 2. Grand average waveforms of TD controls and WS participants recorded to final congruent sentence completions, at frontal, central, and parietal electrode sites.

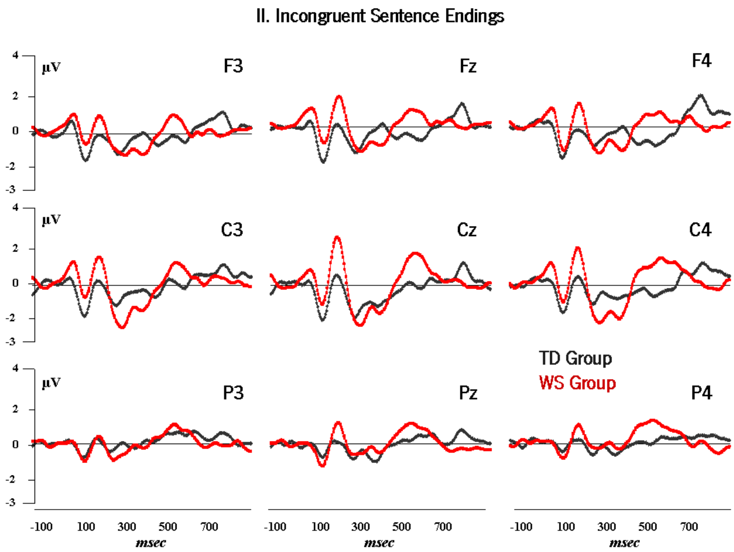


Figure 3. Grand average waveforms of TD controls and WS participants recorded to final incongruent sentence completions, at frontal, central, and parietal electrode sites.

In the following sections, amplitude and latency results will be described separately for each ERP component. Only significant main effects and interactions are reported.

In order to control for chronological age and IQ effects, a multivariate general linear model was used, adding chronological age and IQ as covariates. No significant effects of age and IQ were found.

3.2.1. N100

A repeated measures ANOVA showed a significant interaction of sentence condition x region x group ($F(2, 38) = 3.85$, $p = .051$). A difference between sentence conditions was found only in the TD group, with more negative N100 for incongruent relative to congruent sentence endings, at frontal and central electrodes. In addition, repeated measures ANOVA testing for hemispheric differences in N100 amplitude showed a significant interaction of sentence condition x hemisphere x group ($F(1, 19) = 5.08$, $p = .036$): N100 was more negative for incongruent relative to congruent sentence endings, at left electrode sites, only for the TD group.

N100 peak latency analyses showed a significant effect of region ($F(2, 38) = 4.73$, p = .026). Subsequent pairwise comparisons showed a trend for earlier peak latency at parietal relative to frontal electrode sites (p = .065).

3.2.2. P200

A significant effect of region was observed for P200 peak amplitude ($F(2, 38) = 3.92$, p = .034): more positive P200 amplitudes were found at central relative to parietal electrodes. In addition, a significant sentence condition x region interaction ($F(2, 38) = 3.58$, p = .038) was found: P200 differed between sentence conditions at frontal electrodes only, being more positive for congruent sentence endings. A repeated measures ANOVA testing for hemispheric differences showed a significant sentence condition x region x hemisphere x group interaction ($F(2, 38)$ = 3.36, p = .053): a trend for group differences (more positive P200 for WS relative to the TD group) was found at central electrodes of the right hemisphere (C4) for incongruent sentence endings (p = .098).

No significant main effects of group or group interactions were found for P200 latency.

3.2.3. N400

As expected, N400 amplitude was more negative for incongruent relative to congruent sentence endings, as evinced by the significant main effect of sentence condition ($F(1, 19)$ = 6.75, p = .018). The N400 effect had a central distribution, as evinced by a main effect of region ($F(2, 38) = 11.64$, p = .001): amplitudes were significantly more negative at central relative to parietal electrodes. No effects of hemisphere or group were observed.

Analysis of N400 peak latency showed a significant effect of sentence condition ($F(1, 19)$ = 15.01, p = .001): N400 peaked earlier for incongruent sentence endings.

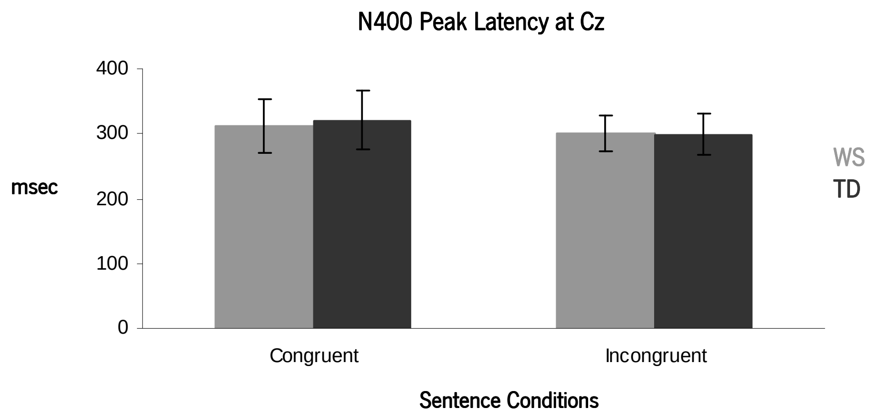


Figure 4. Mean N400 peak latency for congruent and incongruent final endings in WS and TD groups.

Mean N400 peak latency across groups for both sentences' conditions was 308.17 msec, consistent with previous studies showing an earlier onset of N400 in the auditory relative to the visual modality (e.g., Holcomb & Neville, 1990). In both groups N400 peaked earlier to incongruent sentence endings (see Figure 5).

3.2.4. P600

There was a significant main effect of group ($F(1, 19) = 5.63$, $p = .028$) for the 500-600 msec latency window: more positive mean amplitudes were found in WS relative to the TD group. In addition, a significant sentence condition x region x group ($F(2, 38) = 3.89$, $p = .033$) interaction was observed: differences between groups were found for incongruent sentence endings at frontal and central electrodes, with more positive amplitudes in WS. Repeated measures ANOVA indicated a marginally significant sentence condition x hemisphere interaction ($F(1, 19) = 4.03$, $p = .059$): amplitudes tended to be more positive for incongruent than for congruent sentence endings at electrodes of the left hemisphere.

No significant effects were observed for the 600-700 msec latency window. However, a significant hemisphere x group interaction ($F(1, 19) = 11.34$, $p = .003$) was found: in WS group only a larger positivity was found in the right relative to the left hemisphere.

Summary

Overall, results indicate a difference in amplitude for congruent and incongruent sentence endings with an N400 effect showing a frontal-central and left-hemisphere distribution.

ERP waveforms revealed group differences in early components, as indexed by N100 and P200. No group differences were observed for the N400 component. Groups differed significantly in the P600 latency window, with participants with WS showing more positive amplitudes relative to controls. No differences between groups were found in terms of peak latencies.

In addition, the TD group tended to be more accurate than WS individuals in classifying the sentences as congruent or incongruent.

4. Discussion

In this study, the ERP method was used to assess the functional organization of semantic memory and online integration of words into their preceding context in WS. A major aim was to analyze the morphology of ERP waveforms elicited by congruent and incongruent sentence endings in participants with WS, in comparison with typically developing controls, in order to best understand potential deviations from typical development.

Groups tended to differ in the number of correct responses for both congruent and incongruent sentence endings, with more errors found in the WS group.

For ERP analyses purposes, four components were selected: N100, P200, N400, and P600 analysed in two latency windows: 500-600 msec, and 600-700 msec. No main effect of group was found for the N100, P200, and N400 components. However, only for the TD group, a significant difference between sentence conditions was found for N100 peak amplitudes, with more negative N100 amplitudes to incongruent sentence endings. A trend for more positive P200 amplitude to congruent sentence endings was found in the WS group, consistent with previous studies (e.g., Neville et al., 1994).

These early components (N100 and P200) have been proposed to be sensitive to phonological processing (Barnea & Breznitz, 1998; Liu et al., 2003; Niznikiewicz & Squires, 1996). In particular, more positive P200 amplitudes for related than to unrelated word pairs have been described in previous studies in normal individuals (Holcomb et al., 1992; Landi & Perfetti, 2007), but the opposite was observed in WS. It has been suggested that early semantic effects on the P200 may be due to the onset of the N400 (Coulson, Federmeier, Van Petten, & Kutas, 2005). Since our study didn't aim to assess this relationship, future studies should explore the clear relationship between these two components. The current finding may suggest dysfunctional early sensory processes in WS, as previously noted by studies on auditory processing (Bellugi et al., 1994, 1999; Mills et al., 2003; Neville et al., 1994).

Interestingly, no group differences were found for the N400, although grand averages showed a trend for a smaller difference between congruent and incongruent sentence endings in the WS group.

Overall, the mean latency for the N400 component was earlier for both groups than what has been commonly reported for the visual modality. These findings are in line with previous studies showing differences in N400 effects dependent on modality of stimuli presentation (visual vs. auditory), with respect to onset latency, duration and scalp distribution (Hagoort & Brown, 2000). In the auditory modality, the N400 effect seems to have an earlier onset (e.g., Holcomb & Neville, 1990) and a longer duration (e.g., Holcomb & Neville, 1990). The N400 effect was more pronounced at central and frontal electrode sites, a finding that is consistent with some studies revealing a more sustained negativity over anterior than posterior sites (Holcomb & Neville, 1990; McCallum, Farmer, & Pocock, 1984).

As several studies on N400 in typical and atypical groups suggest, this component reflects processes of lexical access and search, as well as of semantic integration (e.g., Brown & Hagoort, 1993; Federmeier & Kutas, 1999a, 1999b; Hagoort & Brown, 2000; Kutas & Hillyard, 1980, 1984; Rugg et al., 1994). The findings of the current study suggest that these processes occur in a similar way in both groups. The lack of N400 amplitude differences suggests similar semantic integration processes in WS and in typical development. A similar finding was observed also in developmental dyslexia (Sabisch, Hahne, Glass, von Suchodoletz, & Friederici, 2006), although it doesn't support previous studies on WS (Neville et al., 1994).

Abnormalities in the N400 morphology have been reported for other neurodevelopmental disorders, in particular an attenuated N400 effect in children at-risk for dyslexia (Torkildsen, Syversen, Simonsen, Moen, & Lindgren, 2007) and with specific language impairment (Sabisch et al., 2006) or learning disability (Miles & Stelmack, 1994), and also in adults with learning disability (Plante, van Petten, & Senkfor, 2000). Larger N400 effects have also been found for children with learning impairment (Neville, Coffey, Holcomb, & Tallal, 1993). Since most of the literature related to N400 effect in developmental disorders has reported group amplitude differences, it is somewhat unexpected that this difference was not observed in our study. The likely reason for this discrepancy may lie in the differences between experimental designs. For example, some studies used pictures and words that could be congruous or incongruous with the picture content (Plante et al., 2000; Sabisch et al., 2006; Torkildsen et al., 2007), word pairs (Landi & Perfetti, 2007) or pairs of words and pictures that were related or unrelated (Landi & Perfetti, 2007). Other studies required that participants read single words or sentences (e.g., Neville et al., 1993).

Given that reading problems are often found in individuals with developmental disorders the experimental task could have introduced an important confound. At the same time, the linguistic complexity of the stimulus material may also explain differences in results. In the current study, short sentences with low complexity were used. Furthermore, they were delivered auditorily. Taking into account the present results, it seems that in simple and short semantic contexts, there is a similar neural response to semantically anomalous linguistic stimuli in the WS and TD groups, in the N400 latency window. This is consistent with studies on semantic priming showing the same effects of priming on reaction times of WS individuals (e.g., Tyler et al., 1997) and with the claims of a relative preservation of language processing in WS (see Brock, 2007 for a review). However, when the task becomes more complex and linguistically demanding, differences in semantic processing may be observed.

In addition, in both groups, semantic violations elicited a late positive component. Although no significant differences were found for N400 amplitude, a main effect of group was observed in the 500-600 msec latency window. In normal controls, the P600 component (a positivity that starts around 500 msec and can continue for more 500 msec) was proposed as an index of processes of sentential judgment (Kolk, Chwilla, van Herten, & Oor, 2003; see Hagoort, Brown, & Osterhout, 1999 for a review). Previous studies with normal population, in which the task was to judge the congruency of a word taking into account its preceding context (e.g., Holcomb et al., 1992), also found a late positivity that seems to be related to post-lexical wrap-up processes (e.g., Juottonen, Revonsuo, & Lang, 1996). P600 has been considered an index of the integration of syntactic and semantic information into a coherent representation (Friederici, Hahne, & Mecklinger, 1996; Friederici, Pfeifer, & Hahne, 1993; Hoeks, Stowe, & Doedens, 2004; Kim & Osterhout, 2005; Kolk et al., 2003; Kuperberg, Kreher, Sitnikova, Caplan, & Holcomb, 2007; Niewland & van Berkum, 2005; van Herten, Kolk, & Chwilla, 2005; van Herten, Chwilla, & Kolk, 2006). Therefore, the more positive-going waveform, observed around 600 msec for the WS group relative to typically developing controls, for both types of sentence endings, may suggest high semantic integration demands, probably reflecting additional difficulties in processes of semantic integration and reanalysis, or an increased effort in performing the judgment task, consistent with the higher error rates observed in the behavioral task.

This finding seems to be consistent with the suggestion of Tyler et al. (1997) that a preserved access to semantic information may coexist with deficits in the integration of semantic information in sentence comprehension in WS, as indexed by abnormalities in later integrative ERP components and by behavioral measures such as narrative integration (Reilly, Losh, Bellugi, & Wulfeck; Stojanovik, Perkins, & Howard, 2004).

Together, the current findings showed atypicalities in both early (N100 and P200) and late (P600) ERP components, supporting the hypothesis that abnormalities in early sensory (auditory) processing have an influence on language relevant systems (e.g., semantic processing), as suggested by a previous study (Neville et al., 1994).

The current findings also confirm the importance of combining methodologies for a better understanding of semantic processing. In fact, behavioral studies only provide a limited source of information on language and communication difficulties in WS. Functional measures can overcome the limitation of reaction time or accuracy measures, allowing the study of brain processes before the response is made or even in its absence (Niznikiewicz, 1997). The present results can offer a new perspective on language processing difficulties in individuals with WS. More studies are needed for a better understanding of the neural processes that underlie semantic processing in this disorder. Future studies should also include larger samples and additional control groups (e.g., other neurodevelopmental disorders), for a better understanding of the specificities of semantic processing difficulties in WS.

CHAPTER III

Electrophysiological correlates of language processing in schizophrenia

Study 3

Electrophysiological correlates of prosody processing in schizophrenia

1. Introduction

Schizophrenia is a psychiatric disorder associated with several abnormalities at the cognitive, behavioral and brain levels (Antonova, Sharma, Morris, & Kumari, 2004; Calhoun, Eichele, & Pearlson, 2009; Chua, & McKenna, 1995; Frith, 1996; Hoff & Kremen, 2003; Kubicki et al., 2007; Lakhan & Vieira, 2009; Ribolsi et al., 2009; Shenton, Dickey, Frumin, & McCarley, 2001; Tamminga & Holcomb, 2005; Tan, 2009; van Os & Kapur, 2009; Wible, Preus, & Hashimoto, 2009).

Behaviorally, these patients are described as having severe difficulties in social interactions, lacking friends and showing several impairments in social-cognitive abilities, such as social reciprocity. Several studies confirm processing deficits of socially relevant stimuli (Bigelow et al., 2006; Heimberg, Gur, Erwin, Shtasel, & Gur, 1992; Salem, Kring, & Kerr, 1996; Schneider, Gur, Gur, & Shtasel, 1995). The symptomatic profile associated with schizophrenia also includes impairments in the ability to decode emotional cues based on facial expression or voice intonation (Bozikas et al., 2006; Edwards, Pattison, Jackson, & Wales, 2001; Gur et al., 2002; Huang et al., 2009; Kerr & Neale, 1993; Kohler et al., 2003; Kucharska-Pietura, David, Masiak, & Phillips, 2005; Leentjens, Wielaert, van Harskamp, & Wilmink, 1998; Leitman et al., 2007; Matsumoto et al., 2006; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2004; Murphy & Cutting, 1990; Phillips et al., 1999; Scholten, Aleman, & Kahn, 2008; Seiferth et al., 2009; Shea et al., 2007; Silver, Bilker, & Goodman, 2009), as well as abnormalities in global emotional processing (e.g., Bigelow et al., 2006; Kerr & Neale, 1993; Schneider et al., 1995; Taylor, Liberzon, Decker, & Koeppe, 2002).

In particular, deficits in the perception of emotional prosody have been consistently found, both in behavioral and fMRI investigations in schizophrenia (Borod et al., 1989, 1990; Bozikas et al., 2006; Edwards et al., 2001; Haskins, Shutty, & Kellogg, 1995; Hooker & Park, 2002; Kerr & Neale, 1993; Kucharska-Pietura et al., 2005; Leentjens et al., 1998; Leitman et al., 2005, 2007; Murphy & Cutting, 1990; Pijnenborg, Withaar, Bosch, & Brouwer, 2007; Ross et al., 2001; Rossell & Boundy, 2005; Shaw et al., 1999; Shea et al., 2007; see Hoekert, Kahn, Pijnenborg, & Aleman, 2007 for a review). For example, behavioral studies are consistent in suggesting that these deficits are stable over time, being detected in the early years of the disease (Edwards et al., 2001; Kucharska-Pietura et al., 2005), and seem to be restricted to the extraction of emotional information from voice, since no difficulties in understanding non-emotional prosody have been reported (Murphy & Cutting, 1990; Pijnenborg et al., 2007). This suggests that deficits in prosody comprehension are a major feature of the disorder and not merely an artifact of duration of illness or institutionalisation (see Hoekert et al., 2007). A possible association between auditory hallucinations and inefficient prosody processing in schizophrenia has also been noted (Shea et al., 2007). Also, fMRI abnormalities were observed in the involvement of the right vs. left side of the brain in processing emotional prosody (Bach et al., 2009; Mitchell et al., 2004), as well as in more extensive activation of inferior parietal lobule (IPL) and insula in schizophrenia.

Beyond semantics, syntax or pragmatics, prosody is also an integral part of spoken language and, thus, of human communication. For example, in the sentence “Tom will visit on Monday”, the intonation shift may let the listener know if the speaker is happy, sad, angry, or neutral about the fact that Tom will visit on Monday. Emotional prosody represents the non-verbal vocal expression of emotion. At the perceptual and physical levels, emotional prosody is instantiated by loudness (acoustic correlate: sound intensity), pitch (fundamental frequency – F0), speech rhythm (duration of syllables and pauses), and voice quality/timbre (distribution of spectral energy) (Kotz & Paulmann, 2007; Wildegruber, Ackermann, Kreifelts, & Ethofer, 2006). The perception of emotional process is a multi-stage process that consists of the analysis of acoustic features of spoken words, deriving emotional significance from acoustic cues, applying it in higher cognition operations, and integrating emotional prosody in language processing (Hoekert, Bais, Kahn, & Aleman, 2008; Schirmer & Kotz, 2006; Wildgruber et al., 2006). Not surprisingly, studies for the last decades have demonstrated that a fast decoding of emotions is crucial for survival and for social interactions (LaBar & Cabeza, 2006; LeDoux, 1996, 1999; LeDoux & Phelps, 2008).

Several event-related potential (ERP) studies explored prosody processing (e.g., Eckstein & Friederici, 2006; Kotz & Paulmann, 2007; Paulmann & Kotz, 2008a, 2008b). Studies that used a ‘prosody violation’ approach reported late occurring negativities and positivities that indexed processing incongruities between the prosody in the initial and the final part of the sentence (e.g., initial happy prosody ending with sad prosody) or between semantics and prosody. Studies that focused on processing prosody in naturalistic designs reported early effects within 200 msec after stimulus onset, with reduced P200 amplitude recorded to emotional relative to neutral stimuli (Paulmann & Kotz, 2008b).

Notably, no ERP studies of prosody processing have been conducted in schizophrenia. While there is an agreement that there is an abnormality in prosody processing in schizophrenia, several questions remain unresolved. In addition to the absence of ERP studies of prosody processing noted above, it is not clear if a prosody processing impairment exists both for sentences with semantic content and also for 'pure prosody' sentences, when semantic content has been filtered out.

The current experiment aimed at characterizing the electrophysiological correlates of prosody processing in schizophrenia and at investigating whether the presence of intelligible semantic information interferes in prosody processing.

In particular, the current study was designed to answer the following questions:

(1) Is schizophrenia characterized by different ERP responses to different types of emotional prosodic information (positive vs. negative vs. neutral) relative to normal controls?

Taking into account the existing evidence (Paulmann & Kotz, 2008b), we hypothesised that normal controls would display larger positive amplitudes for neutral intonations, around 200 msec, than for emotional vocalizations. Given that previous studies reported difficulties in prosody discrimination in schizophrenia, we hypothesized abnormal ERP responses to prosodic sentences in this disorder. In particular, we expected a lack of ERP response differentiation between different prosody types, as indexed by similar P200 amplitudes for the three types of emotional prosody.

(2) Is the extraction of emotional information from the acoustic signal influenced by the presence of semantic content at both behavioral and electro-physiological levels? We expected that, at behavioral level, it may be more difficult to distinguish between different prosody types in the absence of semantic information (Kotz & Paulmann, 2007). Since there are no published electrophysiological studies in normal population on processing prosodic information in naturalistic designs (i.e., not using a splicing technique), we reasoned that there may be different patterns of ERP responses to sentences with semantic prosody and to 'pure prosody' sentences given that different streams of information would be processed for these two types of stimuli. Even though semantic information is evaluated later in the processing stream (around 300-400 msec), there is evidence that it is processed much earlier and that these processes can impact N100 and P200 ERP responses (e.g., Coulson et al., 2005; Hagoort & Brown, 2000; Holcomb, Coffey, & Neville, 1992; Landi & Perfetti, 2007; Liu, Perfetti, & Hart, 2003; van den Brink, Brown, & Hagoort, 2001). In addition, different attentional demands were expected to be associated with processing prosodic information with and without semantic content. Furthermore, we reasoned that normal control individuals would be affected less by the absence

of semantic information in prosodic sentences given both language related (e.g., Chapman & Chapman, 1973; Kiang, Kutas, Light, & Braff, 2007; Nestor et al., 1997, 1998; Niznikiewicz et al., 1997, 2004; Salisbury, 2008) and attentional (e.g., Basar-Eroglu, Schmiedt-Fehr, Mathes, Zimmermann, & Brand, 2010; Granholm, Fish, & Verney, 2009; Le Pelley, Schmidt-Hansen, Harris, Lunter, & Morris, 2010; Luck & Gold, 2008; Nestor et al., 2001; Nestor, Klein, Pomplun, Niznikiewicz, & McCarley, 2010; Yee et al., 2010) abnormalities in schizophrenia.

In order to address these hypotheses, 17 participants with schizophrenia and 17 normal controls were presented with three types of sentences (neutral, positive and negative prosody), in two conditions: (1) with intelligible semantic and syntactic information; (2) with unintelligible semantic and syntactic information.

2. Methods

2.1. Participants

A total of 17 right-handed men with diagnosis of chronic schizophrenia, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition (American Psychiatric Association - APA, 1994), with ages ranging between 31 and 57, and 17 male normal controls matched for age, handedness and parental socioeconomic status (SES) participated in the experiment (see Table 1). Comparison subjects were recruited from internet advertisements and matched to the patients on the basis of age, gender and handedness (see Tables 1 and 2).

The inclusion criteria included: (a) be a native speaker of English; (b) no history of electroconvulsive treatment; (c) no history of neurological illness; (d) no history of DSM-IV diagnosis of drug or alcohol abuse; (e) no present medication for medical disorders that would have deleterious effects in electroencephalogram (EEG) morphology, as well as neurological, and/or cognitive functioning consequences; (f) verbal intelligence quotient (IQ) above 75 (see Table 2). For normal controls, an additional exclusion criterion was history of psychiatric disorder in oneself or in first-degree relatives.

Before participating in the study, all participants had the procedures fully explained to them and read and signed an informed consent form to confirm their willingness to participate in the study (following Harvard Medical School and Veterans Affairs Boston Healthcare System guidelines). The consent form has been approved by the local Institutional Review Board committee for the protection of human subjects.

Table 1

Social-demographic characterization of schizophrenia participants (SZ) and normal controls (NC)

VARIABLE	PARTICIPANTS		GROUP COMPARISONS
	SZ (*N* = 17)	NC (*N* = 17)	Significance test
	Mean (SD)	Mean (SD)	*F, p*
Age	47.71 (8.59)	44.29 (8.70)	1.33, NS[a]
Years of education	14.06 (1.85)	14.79 (1.71)	1.45, NS[a]
Parents' social-economic status	2.38 (1.31)	2.29 (1.05)	0.04, NS[a]

[a]NS = non-significant

For patients, the average duration of illness was 17.06 ± 10.33 years. One patient was receiving conventional neuroleptics, fourteen patients were receiving atypical antipsychotics, and one was receiving both types. Mean equivalent chlorpromazine dosage was 347.86 ± 178.29 mg. Mean score of Hallucinations was 4.24 (*SD* = 2.28) and mean score of Dellusions was 4.41 (*SD* = 1.94). Both were derived from the Positive and Negative Syndrome Scale – PANSS (Kay, Fizbein, & Opler, 1987).

The two groups did not differ in age, IQ, or parental socio-economic status (see Table 1), There were also no differences between schizophrenia patients (SZ) and normal controls (NC) in neurocognitive variables (see Table 2).

Table 2

Cognitive characterization of participants

VARIABLE	PARTICIPANTS		GROUP COMPARISONS
	SZ (*N* = 17)	NC (*N* = 17)	Significance test
	Mean (SD)	Mean (SD)	*F, p*
Verbal IQ[b]	90.00 (35.04)	96.08 (31.83)	0.218, NS[a]
Performance IQ[b]	82.73 (32.27)	93.42 (32.50)	0.73, NS[a]
Full-Scale IQ[b]	88.27 (35.86)	90.50 (40.02)	0.02, NS[a]
Digit span[b,c]	9.43 (2.82)	11.36 (3.32)	1.12, NS[a]

[a] NS: non-significant; [b] WAIS-III: Weschler Adult Intelligence Scale – III (Weschler, 1997); [c] scaled score.

2.2. Stimuli

Stimuli were 228 sentences presented in the auditory modality, in a pseudo-randomized order. One hundred and fourteen sentences were spoken by a female speaker of American English with training in theatre techniques, in a sound proof room at a 16 bit/44.1 kHz sampling rate. The recordings were made in a quiet room with an Edirol R-09 recorder and a CS-15 cardioid-type stereo microphone, with a sampling rate of 22 kHz and 16-bit quantization. Sentences were subsequently digitized, down sampled at a 16 bit/16 kHz sampling rate and normalized in amplitude.

All sentences had a similar syntactic structure (subject + verb + object) and length (4 words), and all started with a proper noun (50% a male noun, and 50% a female noun). Their semantic content was always neutral (e.g., *Benny opened the cupboard*). Last words (nouns) were controlled for word frequency (*M* = 10.38; *SD* = 11.05), familiarity (*M* = 582.37; *SD* = 25.88), age of acquisition (*M* = 232.54; *SD* = 55.15), concreteness (*M* = 594.60; *SD* = 43.79), and number of letters (*M* = 5.14; *SD* = 1.81).

A third of the sentences (38) were spoken with a positive intonation (a happy voice), a third with negative intonation (an angry voice), and finally a third with neutral intonation. Only two emotional intonations were included because of the working memory difficulties shown by individuals with schizophrenia (e.g., Fleming, Goldberg, Gold, & Weinberger, 1995; Goldman-Rakic, 1994; Lee & Park, 2005; Manoach, 2003) and because there is evidence suggesting that the inclusion of a high number of emotions in the differentiation process increases task difficulty and cognitive demands, potentially masking impairments in emotion perception (see Hoekert et al., 2007).

Auditory stimuli were acoustically analyzed using Praat (Boersma & Weenink, 2006) (see Table 3). Mean pitch, intensity and duration were compared across conditions (angry, happy, and neutral). Results revealed significant differences across emotional categories for each of these acoustical measurements: mean pitch ($F(2, 41) = 357.47$, $p = .000$), mean intensity ($F(2, 41) = 32.16$, $p = .000$), and mean duration ($F(2, 41) = 61.89$, $p = .000$).

Table 3

Acoustic characteristics (pitch, duration, and intensity) of the original (non-transformed) sentences

	Angry Mean (SD)	**Happy** Mean (SD)	**Neutral** Mean (SD)
Pitch (F0)	261.51 (42.88)	336.47 (33.01)	182.93 (30.35)
Duration (sec)	1.41 (0.21)	1.52 (0.17)	1.71 (0.20)
Intensity	72.08 (2.82)	73.19 (2.37)	75.69 (2.10)

Note. Transformed sentences kept these features.

In order to assess the emotional valence of the sentences, a previous rating study was conducted. Eighteen participants (11 female) who weren't included as subjects in the ERP experiment rated all sentences as "happy", "angry" or "neutral". Angry sentences were rated as "angry" by 94.08% (*SD* = 7.72) of participants, happy sentences were rated as "happy" by 91.44% (*SD* = 7.54) of participants, and 99.87% (*SD* = 0.85) of participants rated neutral sentences as "neutral".

Thirty-eight of these sentences, from each emotional condition, were then used as experimental stimuli. For the prosodic speech condition, and in order to assure that the sentences would sound as natural as possible, the phones of each sentence (from the list of 114 sentences) were manually segmented in Praat (Boersma & Weenink, 2006). The fundamental frequency (F0) was automatically extracted in Praat at four points of each segment (20%, 40%, 60% and 80%). Occasional F0 error measurements were manually corrected. Based on the procedures of Ramus and Mehler (1999), duration and F0 values were then transferred to MBROLA (Dutoit, Pagel, Pierret, Bataille, & Van Der Vreken, 1996) for concatenative synthesis by using the American English (female) diphone database. In order to omit linguistic information and test the perception of different emotions by means of prosodic information, all fricatives were replaced with the phoneme /s/, all stop consonants with /t/, all glides with /j/, all stressed vowels with /æ/ and all unstressed vowels with /ə/ (see Figures 1 and 2), assuring that the synthesis of new sentences preserved characteristics as global intonation, syllabic rhythm and broad phonotactics (Ramus & Mehler, 1999).

The inclusion of stimuli with non-semantic content, as proposed by other authors (e.g., Paulmann & Kotz, 2008a), should allow investigating clear prosodic effects independent of lexical-semantic information. The advantage of this technique is that, in comparison with filtered speech, it creates more natural sentences by eliminating intelligible lexical content while preserving emotional prosody.

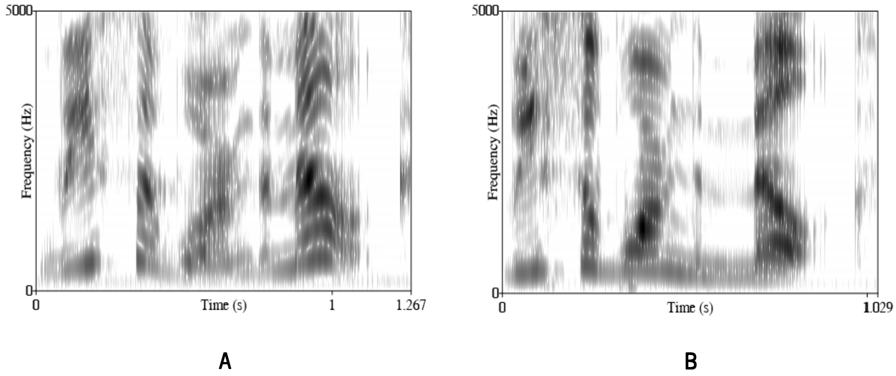
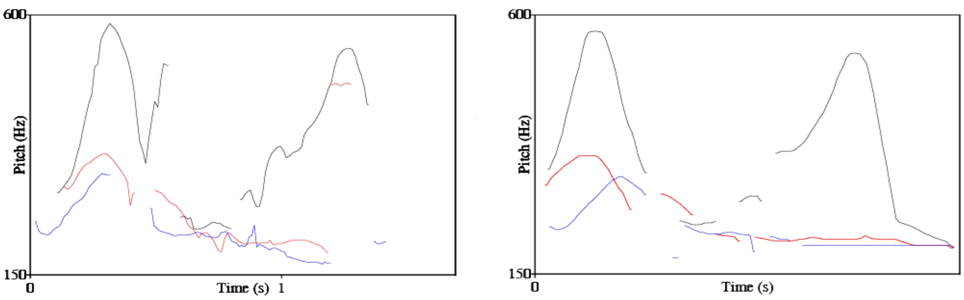


Figure 1. Wide band spectrogram of speech signals for a happy sentence ("Lisa warmed the milk"), before (A) and after (B) resynthesis in Praat software. The left spectrogram (A) illustrates the frequency spectrum (0-5 kHz) of a normal sentence with semantic content. The right spectrogram (B) illustrates the frequency spectrum of a transformed sentence, for the 'pure prosody' condition. The spectral information was similar across conditions, so that sentences could sound as natural as possible, although no intelligible semantic information was present in 'pure prosody' sentences.



Black: happy; Red: angry; Blue: neutral

Figure 2. Pitch contour of speech signals before (A) and (B) after resynthesis in Praat software, for each of the prosody types (happy, angry, and neutral).

2.3. Procedure

Each participant was seated comfortably at a distance of 100 cm from a computer monitor in a sound-attenuating chamber, with a button box in front of them.

The experimental session was divided in two major blocks. In the first block ("prosodic sentences with semantic content" condition), 114 sentences with emotional prosody and intelligible semantic information were presented, 38 of each type of emotional intonation (happy, angry, and neutral). The second block was composed by 114 synthesized sentences (38 of each type of emotional prosody), in the "pure prosody" condition. In this part of the experiment, the listener could only perceive modulations of emotional prosody but could not understand any semantic information. Sentences were not repeated during the experiment.

Stimuli presentation, timing of events and recording of subjects' responses were controlled by Superlab Pro software package (2008).

Before each experimental block, participants were given a brief training with feedback, to make sure they understood the instructions and to get them familiarized with the task and with the response box. First, subjects were provided with an example of each type of emotional intonation (angry, neutral and happy). Then, they started a practice block, consisting of five examples of each emotional intonation, presented in a pseudo-randomized way, where the task was to identify the type of intonation. If the subject made more than three errors, the practice session was repeated until the subject got the desired number of hits (i.e., no more than two errors). When the training phase was completed, the experimental session began.

Before each sentence, a fixation cross was presented centrally on the screen for 1000 msec. Participants were asked not to blink or move during the sentence presentation. After one second, the auditory sentence started. While the subjects were listening to the sentence, the fixation cross was kept on the screen. At the end of the sentence, a blank screen was shown and, 1500 msec later, a question mark was presented for 2 seconds. Participants responded after they saw the question mark, making a decision if the sentence was spoken in a neutral, positive or negative intonation. The order of the keys, on a seven-button response panel, was counterbalanced across subjects. Each response button had a visually presented cartoon of emotion in order to minimise working memory demands.

A short pause was provided after 57 sentences. Sentences had a mean duration of 1410 ± 160 msec (see Table 3). No feedback was provided during the experiment.

The second part of the experiment, the "pure prosody" condition, was similar to the first one, the only exception being the absence of intelligible semantic information.

Before the beginning of the second part of the experiment, an example of each type of sentence was given to the subjects and a practice block was completed, in order to insure that they could differentiate between the intonations.

The experimental session lasted about 45 minutes.

2.4. Data acquisition and analysis

2.4.1. EEG recording procedure

While participants listened to the sentences, the electroencephalogram was recorded with 64 electrodes mounted on a custom-made cap (Electro-cap International), according to the modified expanded 10-20 system (American Electroencephalographic Society, 1991). Sixty-four channel EEG was collected using custom designed electrode caps from Biosemi system (Active 2) that furnished amplification. EEG signal was acquired in continuous mode at a digitization rate of 500 Hz, with a bandpass of 0.01 to 100 Hz. Data were re-referenced offline to the mathematical average of the mastoid channels. Horizontal and vertical EOGs were recorded for eye movement and blink detection and rejection, via electrodes placed on the left and right temples and one below the left eye. Electrode impedances were kept below 5 KΩ.

2.4.2. EEG data analysis

The EEG data were processed using the software package Brain Analyzer (Brain Products, Inc, 2000). EEG epochs containing eye blinks or movement artefacts exceeding +/- 100 microvolts were rejected and not included in individual ERP averages. After artifact rejection, at least 75% of trials per condition per subject entered the analyses. Separate ERPs for each condition were averaged for each participant. Averages were computed using a 200-msec prestimulus baseline and 1500 msec after the onset of the sentence, following previous studies (Paulmann & Kotz, 2008).

After the inspection of grand average waveforms, two peaks were selected for analysis: the N100 and P200. The analysis of P200 was of particular interest, given the existing literature on emotional prosody processing that suggests an early differentiation of emotional and neutral intonations around 200 msec (P200 component – Paulmann & Kotz, 2008b).

For hypothesis testing, N100 was measured as the most negative data point between 100-200 msec post-stimulus, and P200 was measured as the most positive data point between 200 and 300 msec.

Since maximal effects were observed at fronto-central electrode sites, consistent with the effects found by Paulmann and Kotz (2008b), N100 and P200 were measured at frontal (Fz, F1/2, F3/4) and central electrodes (Cz, C1/2, C3/4).

2.4.3. Statistical analysis

(a) Behavioral data

Accuracy data were subjected to repeated-measures analyses of variance, with sentence condition (prosodic sentences with semantic content vs. pure prosody sentences) and emotion (happy vs. angry vs. neutral) as within-subjects factors, and group (schizophrenia patients vs. normal controls) as between-subjects factor. Pairwise comparisons were run for significant main effects and interactions, with Bonferroni correction.

(b) ERP data

Repeated measures analyses of variance (ANOVAs) were computed for the between-group comparisons of N100 and P200 peak amplitudes, and of peak latency, with group (schizophrenia patients vs. normal controls) as between-subjects factor and sentence condition (with semantic content vs. without semantic content), emotion (neutral vs. happy vs. angry), region (frontal vs. central), and electrodes (Fz, F1/2, F3/4; Cz, C1/2, C3/4) as within-subjects factors.

If a significant interaction involving group was found, separate follow-up ANOVAs for that factor were conducted.

In addition, in order to best understand the effects of sentence condition and prosody type, separate ANOVAs were conducted for each group separately. For testing sentence condition effects, separate ANOVAs were conducted for angry, happy, and neutral intonations (within-subjects factors: sentence condition, region, and electrodes).

For testing emotion effects, separate ANOVAs were conducted for each sentence condition in order to understand how the different types of emotional prosody were processed in sentences with semantic content and with semantic content removed (within-subjects factors: emotion, region, and electrodes).

The Geisser-Greenhouse correction (Geisser & Greenhouse, 1959) was applied to all repeated-measures with greater than one degree of freedom in the numerator. Main effects or interactions were followed with pairwise comparisons.

(c) Correlational analyses

Given the suggested relationship between prosody dysfunction and auditory hallucinations (Cutting, 1990; Shea et al., 2007), Spearman's Rho correlations were performed in the exploratory analysis of the relationships between N100 and P200 amplitudes in both semantic content condition and in pure prosody condition at what electrodes and hallucination and delusion scores for patients. These correlations were performed without Bonferroni correction given the exploratory nature of the work.

3. Results

3.1. Behavioral results (accuracy)

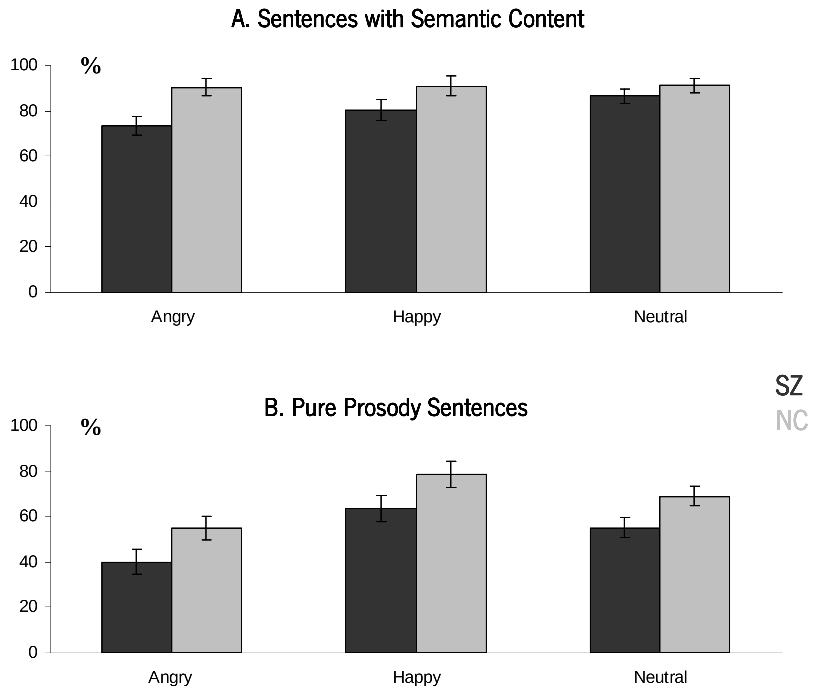


Figure 3. Percent of correct responses in normal controls (NC) and schizophrenia patients (SZ), for each type of prosody (angry, happy, and neutral) in each sentence condition (sentences with semantic content – A; and 'pure prosody' sentences – B).

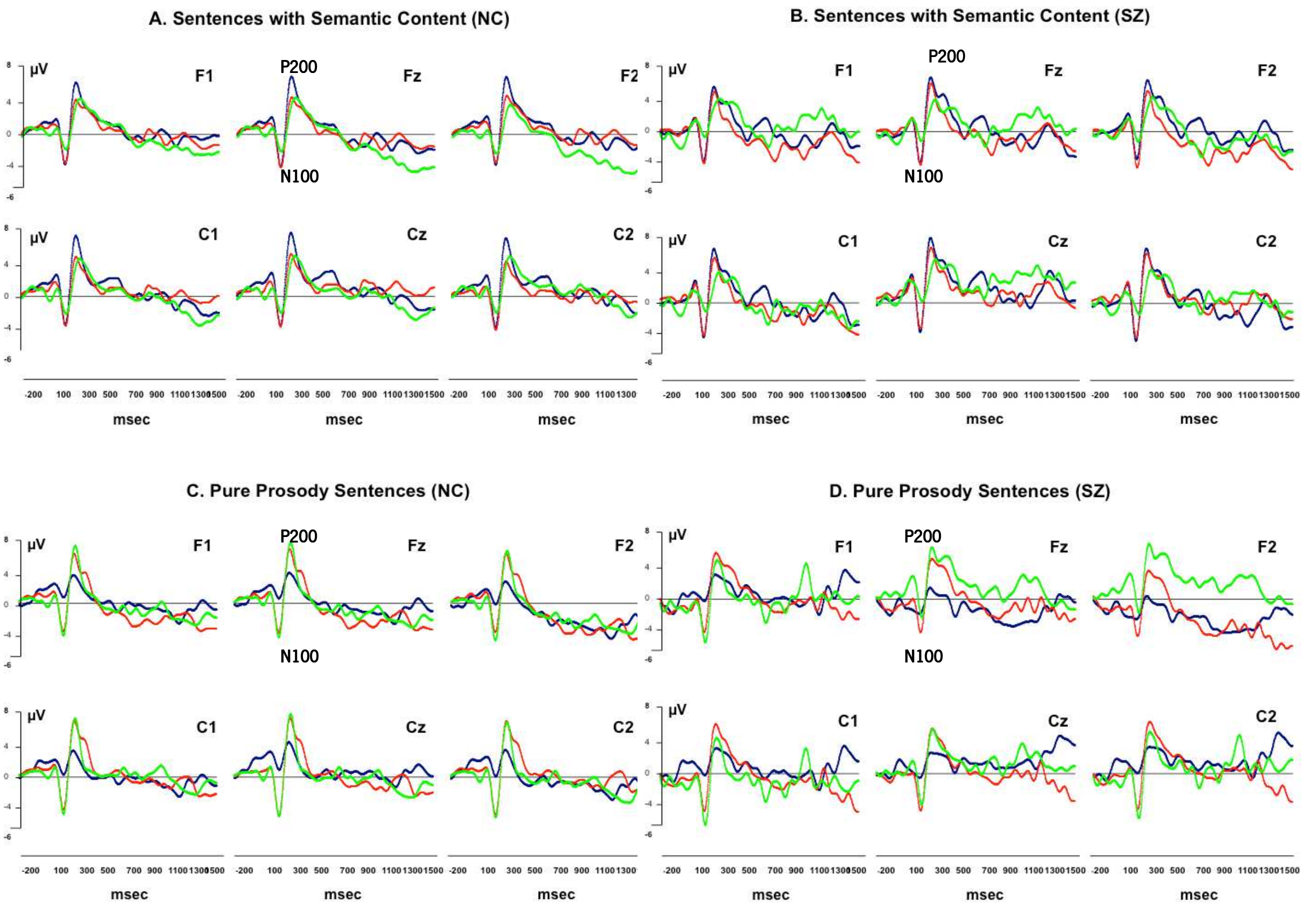
General prosody effects

A main effect of sentence condition (F(1, 32) = 174.23, p = .000) and emotion (F(2, 64) = 13.16, p = .000) was observed. In addition, a significant sentence condition x emotion interaction (F(2, 64) = 9.43, p = .000) was found. More correct responses were found for sentences with semantic content (M = 85.55%; SD = 2.49) relative to pure prosody sentences (M = 60.20%; SD = 2.49), and less correct responses for angry (M = 64.73%; SD = 2.61) relative to happy (M = 78.37%; SD = 3.49) and neutral (M = 75.53%; SD = 2.15) intonations (see figure 3).

Group prosody effects

Groups differed in the percent of correct responses (F(1, 32) = 7.64, p = .009). More correct responses were found in the control group (M = 79.22%; SD = 3.25) relative to the schizophrenia (M = 66.53%; SD = 3.25) group (see figure 3).

3.2. ERP Results



Caption: **Blue** = Neutral; **Red** = Happy; **Green** = Angry

Figure 4. Grand Averages waveforms for angry, happy, and neutral intonations, in the condition of prosody with semantic content and 'pure prosody', in normal controls (A and C) and schizophrenia patients (B and D), at frontal and central electrode sites.

Grand average waveforms for schizophrenia patients and normal controls are shown in Figure 4.

In the following sections, general prosody effects and group prosody effects will be presented separately for N100 and P200 components. In particular, for within-group analyses, the effects of sentence condition and emotionality are described.

3.2.1. Amplitude

3.2.1.1. N100

1. General prosody effects

A main effect of emotion ($F(2, 60) = 4.77$, $p = .022$) and region ($F(1, 30) = 9.52$, $p = .004$) was observed. Amplitudes were significantly more negative for happy relative to neutral sentences ($p = .004$). Also, more negative amplitudes were found at central relative to frontal electrodes ($p = .004$).

In addition, a significant sentence condition x emotion ($F(2, 60) = 20.06$, $p = .000$) was found: for angry sentences, peak amplitude was more negative for pure prosody sentences relative to sentences with semantic content ($p = .006$); for neutral sentences, amplitude was more negative for sentences with semantic content relative to pure prosody sentences ($p = .000$).

2. Group prosody effects

(a) Emotion effects

In normal controls, the emotion effect was observed for both sentence conditions: sentences with semantic content ($F(2, 30) = 3.85$, $p = .034$) and pure prosody sentences ($F(2, 32) = 15.21$, $p = .000$). More negative N100 amplitudes were observed for neutral relative to angry sentences in the semantic sentence condition. In the pure prosody condition, more negative N100 amplitudes were observed for happy and angry sentences relative neutral intonations.

In schizophrenia patients, a main effect of emotion was found for pure prosody sentences only ($F(2, 30) = 6.03$, $p = .009$): more negative amplitudes were observed for happy relative to neutral sentences ($p = .008$).

(b) Sentence condition effects

In normal controls, a main effect of sentence condition was found for neutral sentences only ($F(1, 15) = 29.10$, $p = .000$): N100 amplitudes were more negative for sentences with semantic content relative to pure prosody sentences.

In schizophrenia patients, a significant effect of sentence condition was observed for angry sentences ($F(1, 15) = 7.40$, $p = .016$): amplitudes were more negative for pure prosody sentences relative to sentences with semantic content. No differences between sentence conditions were found for happy or neutral sentences.

3.2.1.2. P200

1. General prosody effects

Significant effects of sentence condition ($F(1, 30) = 4.15$, $p = .051$) and emotion ($F(2, 60) = 3.92$, $p = .026$) were observed. P200 amplitudes were more positive for sentences with semantic content relative to pure prosody sentences, and happy sentences ($M = 5.02$; $SD = 0.63$) were associated with more positive amplitudes relative to neutral sentences ($M = 4.96$; $SD = 0.71$).

In addition, the significant sentence condition x emotion ($F(2, 60) = 12.97$, $p = .000$) interaction suggested that, only for neutral sentences, significant differences were observed between the two sentence conditions, with semantic sentence condition associated with a more positive P200 relative to the pure prosody condition.

2. Group prosody effects

(a) Emotion effects

In the control group, an emotion effect was observed for both sentences with semantic content ($F(2, 30) = 6.62$, $p = .005$) and pure prosody sentences ($F(2, 32) = 12.78$, $p = .000$). For sentences with semantic content, more positive P200 amplitudes were found for neutral relative to angry sentences. The reverse pattern was observed for pure prosody sentences, where P200 amplitudes were significantly less negative for neutral relative to angry and happy intonations.

In the schizophrenia patients, no main effect of emotion was found for sentences with semantic content ($F(2, 32) = 1.14$, $p = .317$). However, it was observed for pure prosody sentences (F(2, 30) = 4.17, p = .035), where P200 amplitudes were significantly larger for angry relative to neutral sentences.

(b) Sentence condition effects

Groups processed differently sentences with and without semantic content. In normal controls, the sentence condition effect was observed for all emotion types: angry (F(1, 15) = 8.05, p = .012), happy (F(1, 15) = 4.32, p = .055), and neutral (F(1, 15) = 19.41, p = .001). For angry and happy sentences, more positive P200 amplitudes were found in the pure prosody condition; for neutral sentences, sentences with semantic content showed more positive P200 amplitudes. In schizophrenia patients, a significant effect of sentence condition was found only for neutral sentences (F(1, 15) = 9.58, p = .007): P200 amplitudes were more positive for sentences with semantic content relative to pure prosody sentences.

3.2.2. Latency

3.2.2.1. N100

1. General prosody effects

Peak latency differed between regions (F(1, 32) = 5.08, p = .031): N100 peaked earlier at frontal relative to central electrodes. A significant interaction between region and emotion was also observed (F(2, 64) = 4.80, p = .012): at frontal electrodes, earlier latencies were found for happy relative to angry sentences.

2. Group prosody effects

(a) Emotion effects

Between-group comparisons showed a trend for group differences in the processing of neutral sentences, in the pure prosody condition (F(1, 32) = 3.88, p = .057), with N100 peaking earlier in the schizophrenia group.

For within-group comparisons, in normal controls, the significant emotion effect was observed only for sentences with semantic content (F(2, 15) = 3.96, p = .042). Pairwise comparisons showed a trend for later N100 peak for happy relative to neutral sentences. In the schizophrenia group, a significant effect of emotion was observed only for pure prosody sentences (F(2, 32) = 5.86, p = .009): the N100 effect occurred earlier for neutral relative to angry sentences.

(b) Sentence condition effects

A significant sentence condition effect was found only for neutral sentences in the control group ($F(1, 16) = 4.27$, $p = .055$). N100 peaked earlier for sentences with semantic content relative to pure prosody sentences.

3.2.2.2. P200

1. General prosody effects

As for N100, a significant effect of emotion was observed ($F(2, 64) = 16.46$, $p = .000$): P200 peaked later for angry relative to happy and neutral sentences. This effect interacted with sentence condition ($F(2, 64) = 8.84$, $p = .001$): peak latencies were earlier for angry sentences in the pure prosody condition, and for neutral sentences in the condition of sentences with semantic content.

2. Group prosody effects

(a) Emotion effects

A main effect of group was found for happy ($F(1, 32) = 5.04$, $p = .032$) and neutral ($F(1, 32) = 4.79$, $p = .036$) sentences in the pure prosody sentence condition. For neutral sentences, P200 latencies occurred earlier for normal controls than for schizophrenia patients. The reverse situation was observed for happy sentences, with earlier P200 latencies being observed for patients relative to normal controls.

In within group comparisons, in normal controls, a main effect of emotion was found both for sentences with semantic content ($F(2, 32) = 7.30$, $p = .010$) and for pure prosody sentences ($F(2, 32) = 5.46$, $p = .013$). In both conditions, P200 peaked earlier for neutral relative to angry intonations. In the schizophrenia group, a significant main effect of emotion was observed for sentences with semantic content ($F(2, 32) = 13.59$, $p = .000$): P200 peaked later for angry relatively to happy and neutral sentences.

(b) Sentence condition effects

No significant sentence condition differences were observed in the control group.

In the schizophrenia group, differences between sentence conditions were observed for angry ($F(1, 16) = 4.60$, $p = .048$) and neutral ($F(1, 16) = 11.67$, $p = .004$) sentences. P200 peaked earlier for angry sentences in the pure prosody condition and for neutral sentences with semantic content.

3.3. Clinical – electrophysiological correlations

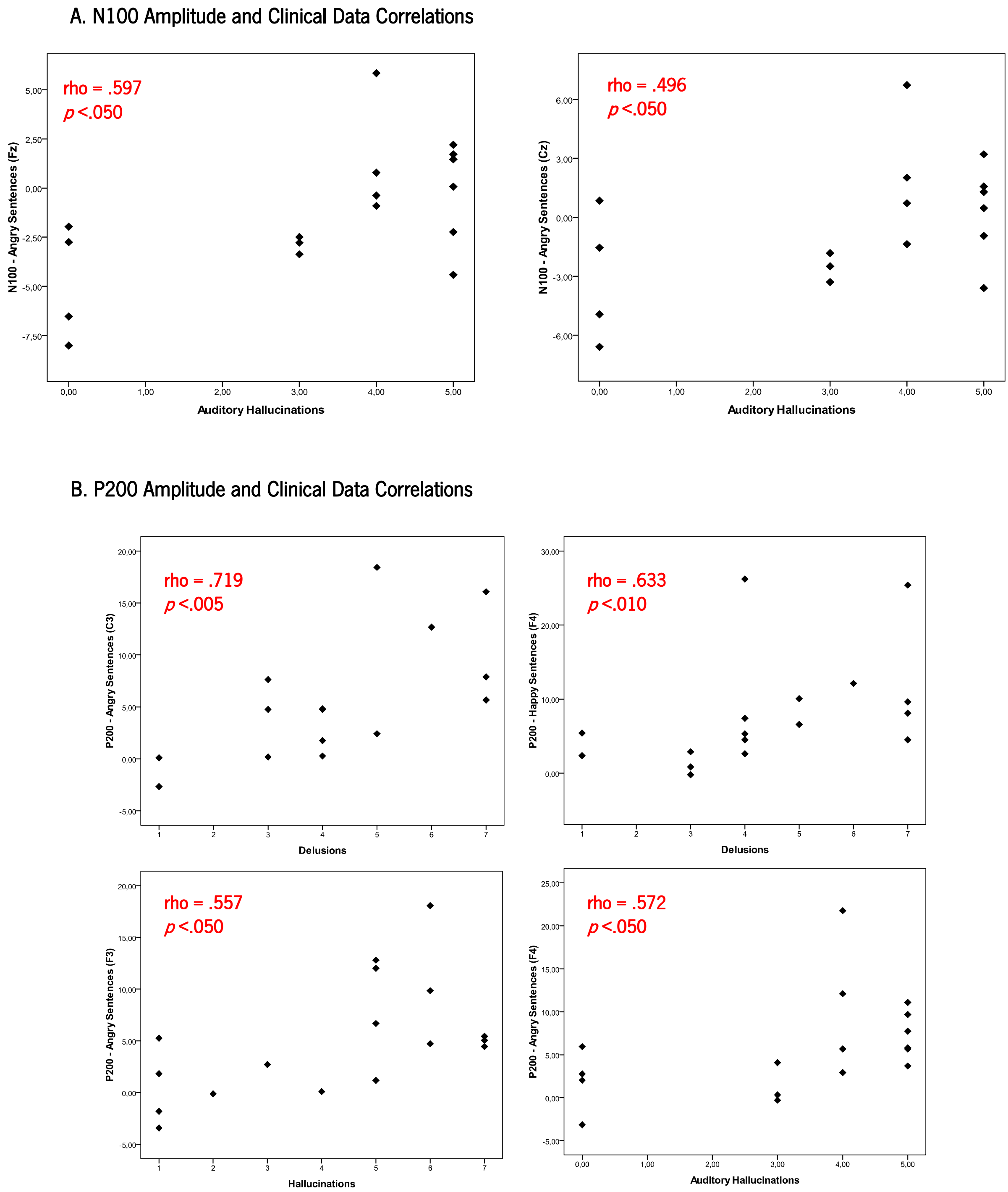


Figure 5. Scatterplots of correlations between clinical measures and N100 (A) and P200 (B) amplitudes.

Correlational analyses suggested stronger correlations between emotional prosody and delusions/hallucinations, than neutral prosody. Less negative N100 amplitude was related with higher scores on auditory hallucinations (see Figure 5 and Table 4). Also, stronger correlations were found between P200 and delusions/hallucinations, i.e., higher scores on hallucination and delusion scales were related with more positive P200.

Table 4

Clinical / ERP (N100 and P200) correlations

Clinical Measure	ERP Component	Emotional Prosody	Electrode	ROH	*p*
Delusions	*N100*	Happy	F1	.582	.014
	P200	Neutral	F1	.699	.002
		Happy	F3	.722	.001
		Angry	F2	.714	.001
		Happy (Pure Prosody condition)	C2	.553	.026
Hallucinations	*N100*	Angry	F2	.526	.030
Auditory hallucinations	*N100*	Angry	Fz	.597	.011

Correlations between N100 and P200 amplitude values and clinical criteria (delusions, and hallucinations) are given. Only correlations with the highest statistical significance are shown.

Summary

1. Emotional prosody effects

N100 and P200 amplitudes for pure prosody sentences were larger for emotional (angry and happy) relative to neutral prosody. For sentences with semantic content, amplitudes were larger for neutral prosody. Latencies of N100 and P200 peaked earlier to emotional prosody in the pure prosody condition, and for neutral prosody in the semantic content condition.

Grand average waveforms showed a similar pattern for both normal controls and schizophrenia patients, in particular less negative N100 for angry sentences and more positive

P200 for neutral sentences in the condition of prosody with semantic content; and less negative N100 and less positive P200 for neutral sentences in the pure prosody condition.

In normal controls, a significant emotion effect was found for both types of sentences: sentences with semantic content (N100: neutral > angry; P200: neutral > angry) and pure prosody sentences (N100: neutral < angry and happy; P200: neutral < angry and happy). In schizophrenia patients, a significant emotion effect existed only for pure prosody sentences, both for N100 (happy > neutral) and P200 (angry > neutral) components.

In terms of latency, there was a significant main effect of group for the P200 in the pure prosody sentences condition: P200 peaked earlier in the schizophrenia group to happy prosody, while in normal controls P200 peaked earlier to neutral prosody sentences.

In addition, significant correlations were found between N100 / P200 amplitude for emotional prosody (in particular, angry) and clinical data, i.e., hallucinations and delusions.

2. Normal speech vs. prosodic speech

In normal controls, a sentence condition was found only for neutral sentences in N100 (more negative N100 for sentences with semantic content), and for all types of prosody in P200 (more positive P200 for angry and happy pure prosody sentences and for neutral sentences with semantic content). In schizophrenia patients, a main effect of sentence condition was found only for angry sentences in N100 (more negative N100 for pure prosody sentences), and for neutral intonation in P200 (more positive P200 for sentences with semantic content).

4. Discussion

The aims of this study were to explore: (1) whether schizophrenia patients process neutral and emotional prosody in a similar way to normal comparison individuals at the electrophysiological and behavioral levels; and (2) if the recognition and differentiation of emotional prosody in schizophrenia is affected by the semantic status of a sentence. Sentences with neutral, happy or angry intonations were presented, in two conditions: with and without intelligible semantic content.

Due to its high temporal resolution, the ERP technique was chosen to investigate the temporal unfolding of vocal emotional processing with and without semantic content (Kotz & Paulmann, 2007; Paulmann & Kotz, 2008a, 2008b; Schirmer & Kotz, 2003).

In both groups, a higher percent of correct responses was found for prosodic sentences with semantic content, in agreement with previous studies (Paulmann, Seifert, & Kotz, 2009). The absence of a memory representation for the pure prosody sentences may have increased task demands and contributed to these findings (Kotz et al., 2003). Normal comparison individuals were more accurate than patients.

ERP results uncovered noteworthy differences both in the processing of sentences with and without semantic content, and in the processing of emotional prosody in the two groups, as well as in the interactions between these two factors. In the following discussion, the effects of sentence condition (speech with and without semantic content) and emotional valence (happy vs. angry vs. neutral) will be discussed according to a multi-stage approach to prosody processing proposed by Schirmer and Kotz (2006).

1. Early analysis of perceptual features of the acoustic signal (N100)

N100 amplitude recorded in simple auditory paradigms was found reduced in several studies in schizophrenia (e.g., Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Brown, Gonsalvez, Harris, Williams, & Gordon, 2002; Bruder et al., 1999; Kogoj, Pirtosek, Tomori, & Vodusek, 2005; Oades, Zerbin, Dittmann-Balcar, & Eggers, 1996; O'Donnell et al., 1993, 1994; O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004; Potts, Hirayasu, O'Donnell, Shenton, & McCarley, 1998; Stefansson & Jonsdottir, 1996), and it was proposed as to be a potential trait marker of schizophrenia (Ahveninen et al., 2006; see Rosburg, Boutros, & Ford, 2008 for a review). In this study, in patients with schizophrenia, N100 was found reduced in sentences with semantic content but enhanced (more negative) for pure prosody sentences.

The auditory N100 component has been proposed to reflect cortical responsiveness to natural speech sounds (Ford & Mathalon, 2004; Ford, Roach, Faustman, & Mathalon, 2007) and to be modulated by the physical characteristics of the stimuli such as intensity (Davis & Zerlin, 1966; Keidel & Spreng, 1965), presentation rate (Davis, Mast, Yoshie, & Zerlin, 1966), or sound complexity (Wunderlich & Cone-Wesson, 2001), as well as attention (e.g., Lijffijt et al., 2009; Thornton, Harmer, & Lavoie, 2007).

The reduced N100 amplitude in sentences with semantic content is consistent with previous studies (Boutros et al., 2004; Brown et al., 2000; Force et al., 2008; Laurent et al., 1999; Williams, Gordon, Wright, & Bahramali, 2000; Young et al., 2001), suggesting abnormalities in the sensory registration of the auditory stimuli.

However, the increased N100 amplitude to pure prosody sentences may suggest that schizophrenia patients can benefit from the absence of an additional linguistic channel (semantics), during the processing of pitch and pitch changes. In addition, in the patient group, the significant effect of emotion was found only in the pure prosody condition, where more negative N100 amplitudes were observed for happy relative to neutral sentences suggesting that, in the absence of semantic demands, patients are able to differentiate the acoustic signal in terms of emotional meaning.

2. Deriving emotional significance from acoustic cues (P200)

In normal controls, P200 was significantly more positive to neutral relative to emotional intonations. This finding is consistent with the study by Paulmann and Kotz (2008b), confirming that, for normal subjects, the early extraction of meaning from auditory emotional stimuli occurs around 200 msec (see Schirmer and Kotz, 2006 for a review).

In patients, the P200 was not modulated by emotion type for sentences with semantic content, suggesting that patients were not discriminating between neutral and emotional prosody when listening to sentences whose semantic content was intelligible. However, a similar trend for both groups was observed: P200 amplitudes were larger for pure prosody sentences with emotional valence (angry or happy), while in the sentence condition with semantic content, P200 was larger to neutral sentences. This finding suggests that there is a higher responsivity to emotional intonations (positive and negative) in the prosodic speech condition, which may be related to the enhancement of the relative importance of prosodic parameters (e.g., fundamental frequency, intensity, duration) in the absence of intelligible semantic information (see Kotz et al., 2003).

Functionally, P200 is related with early stimulus encoding (Picton & Hillyard, 1974), in particular encoding of emotional significance of vocalizations (Schirmer & Kotz, 2006), reflecting attentional mechanisms and stimulus detection or classification (Picton & Hillyard, 1974). These findings point to a failure to extract emotion specific information from the auditory signal in schizophrenia, at least for normal speech.

Similarly to the pattern found for N100, P200 findings for 'pure prosody' sentences suggest that patients benefit from the absence of semantic information in order to process emotional information, and that attentional and semantic abnormalities may mediate the early sensorial abnormalities often reported in schizophrenia (e.g., Han et al., 2007; McKay et al., 1996; Nestor et al., 1997, 1998, 2006; Niznikiewicz et al., 1997; Paulsen et al., 1996; Rossell & David, 2006).

Also, results from correlational analyses are consistent with the hypothesis of a relationship between prosodic deficit and clinical data, in particular hallucinations (Cutting, 1990; Rossell & Boundy, 2005; Shea et al., 2007). It is worth noting that all correlations were stronger for emotional than for neutral prosody. Contrary to the study of Shea et al. (2006) suggesting a nonspecific deficit of emotional prosody processing in schizophrenia, our findings suggest a stronger relationship between ERP abnormalities and negative (i.e., angry) prosody. In addition, these findings suggest that emotional prosody deficits are associated also with the presence of delusions, and not exclusively with the presence of auditory hallucinations, contrary to a previous study (Shea et al., 2007). These differences may have been due to the type of emotional intonations presented to participants (in our study, angry, happy, and neutral prosody were presented, in contrast to the neutral, happy and sad intonations presented in the study of Shea et al., 2006) or to the number of stimuli (114 in our study and 45 in the cited study).

Conclusions

Together, the results of our study point to a dysfunction of language processes at early stages of auditory processing, confirming previous studies on auditory processing, and extending these findings to the domain of emotional prosody. Importantly, these results underscore the interplay between bottom-up and top-down processes in bringing about the dysfunction.

On one hand, early ERP abnormalities, as indexed by N100 and P200 amplitudes, suggest that higher cortical processes (such as an executive processes dysfunction – e.g., Eisenberg & Berman, 2009; Kantrowitz, Revheim, Pasternak, Silipo, & Javitt, 2009; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Raffard et al., 2009; Royer et al., 2009; Thoma et al., 2009) cannot exclusively explain difficulties in prosody understanding in schizophrenia and that bottom-up processes have a contributory role. This is consistent with previous studies on schizophrenia showing deficits in pitch (Javitt, Shelley, & Ritter, 2000; Matsumoto et al., 2006) and duration (Todd, Michie, & Jablensky, 2003) discrimination, or impairments in the perception of auditory looming or dynamic intensity (Bach, Buxtorf, Strik, Neuhoff, & Seifritz, 2009). Other abnormalities in auditory processing have already been reported: mismatch negativity (Fisher, Labelle, & Knott, 2008; Javitt, Grochowski, Shelley, & Ritter, 1998; Kircher et al., 2004; Magno et al., 2008; Näätänen, & Kähkönen, 2009; Niznikiewicz et al., 2009; Rasser et al., 2009;

Shelley et al., 1991; Turetsky, Bilker, Siegel, Kohler, & Gur, 2009), stimulus classification indexed by N200 (Force, Venables, & Sponheim, 2008), sensory gating (Boutros et al., 2009; Brenner et al., 2009; de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Magnée, Oranje, van Engeland, Kahn, Kemner, 2009), prepulse inhibition (Geyer & Braff, 1982; Maier, Mössner, Quednow, Wagner, & Hurlemann, 2008; Moriwaki et al., 2009; Woznica, Sacco, & George, 2009), and echoic memory for speech (Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; Oades et al., 2006; Rabinowicz, Silipo, Goldman, & Javitt, 2000; Strous, Cowan, Ritter, & Javitt, 1995).

On the other hand, our findings also point to top-down modulation of sensory-level processes in schizophrenia, since the availability of semantic information impacted N100 and P200 amplitudes, contributing to difficulties in the extraction of emotional meaning from the acoustic signal. Interestingly, previous studies have reported a more reduced mismatch negativity (MMN) amplitude in response to speech sounds than in response to pure tones, consistent with language dysfunction in schizophrenia (Kasai et al., 2002). Our study follows this line, suggesting that abnormalities in the processing of emotional prosody are more pronounced when prosody is embedded in semantic information, than when it is presented in isolation.

These results provide, for the first time, electrophysiological evidence for prosody processing abnormalities in schizophrenia, suggesting ERP abnormalities that are consistent with the often reported difficulties in prosody comprehension, at the behavioral level (see Hoekert et al., 2007 for a review).

These findings have important implications in the domain of social interactions, since difficulties in decoding emotions based on tone of voice may contribute to difficulties in social reciprocity (Brekke et al., 2005) and to poor outcome in schizophrenia (Green, Kern, Braff, & Mintz, 2000).

In spite of the significance of the current results, they should be interpreted with caution. All the patients recruited are chronic and medicated patients, and studies suggest that deficits in emotional prosody perception tend to be dependent on schizophrenia subtype (Edwards et al., 2002; Shea et al., 2007). Future studies should also include different schizophrenia subtypes and compare the electrophysiological signatures of prosody processing in these different subgroups.

The second limitation is related to participants' gender. Some studies suggest that emotional perception deficits are worse in male than in female patients (Bozikas et al., 2006;

Sholten et al., 2008). Therefore, future studies should include women participants, in order to explore potential gender differences in ERP correlates of prosody processing.

In spite of these limitations, this study provides, for the first time, evidence for electrophysiological abnormalities in schizophrenia related to prosody processing. These results strengthen the importance of including clinical strategies for training schizophrenic patients in the differentiation of emotional prosodic intonations, suggesting that the training should start at a more basic level aimed at the discrimination of acoustic features of auditory stimuli, such as pitch, duration and intensity.

Study 4

The effects of transient mood on semantic processing in schizophrenia: electrophysiological (ERP) evidence

1. Introduction

Schizophrenia has been described as a disorder of language, a cognitive function proposed by several authors as uniquely human (Crow, 1997a, 1997b, 1998, 2004, 2008; Dean, 2009). In fact, language abnormalities are key features of its nuclear symptoms, as incoherent and disorganized discourse, bizarre associations, tangentiality, auditory verbal hallucinations, or delusions (APA, 2000). In addition, emotional abnormalities are also a hallmark of this disorder, as pointed out by several studies (e.g., Kuperberg, Kreher, Swain, Goff, & Holt, 2009; Li, Chan, McAlonan, & Gong, in press; Namiki et al., 2007; Phillips & Seidman, 2008; Rasetti et al., 2009; Strauss, Jetha, Ross, Guke, & Allen, 2010; Yee et al., 2010).

However, few studies have examined the links between affect and cognition in schizophrenia. Studies with normal population suggest an intricate relationship between both domains (e.g., Adolphs, 2001; Ashby, Isen, & Turken, 1999; Dolan, 2002; Gray, Braver, & Raichle, 2002; Isen, Daubman, & Nowicki, 1987; Isen, Johnson, Mertz, & Robinson, 1985; LeDoux, 1989; Leventhal & Scherer, 1987). From these studies, it has become apparent that a full understanding of cognitive states in normal populations and cognitive and social abnormalities in clinical populations may be difficult without taking into account the relationship between affective states and cognition (Barch, 2008). In fact, reaction to appetitive (positive) and aversive (negative) environmental stimuli and the ability to modulate these reactions impacts memory and attentional processes and has profound influence on an individual's ability to engage in successful social interactions (Adolphs, 2001; Ashby et al., 1999; Frith & Frith, 2010; Kim & Hamann, 2007; Lang & Bradley, 2009; Peyk, Schupp, Elbert, & Junghofer, 2008).

On one hand, studies on semantic processing in schizophrenia show overactivation of more dominant associations and an underactivation of weaker associations in the schizophrenic lexicon (e.g., Chapman & Chapman, 1973; Nestor et al., 1998), also suggesting that the incoherent disorganized and bizarre speech is the result of dysfunction in semantic memory operations (e.g., Niznikiewicz et al., 2004). Results from studies with event-related potentials (ERP) also confirm semantic dysfunction at the brain level. Electrophysiologically, semantic abnormalities in schizophrenia are associated with a prolonged N400 after anomalous sentence endings and an enhanced N400 negativity, independent of the sense of the sentence ending (e.g., Kiang, Kutas, Light, & Braff, 2007; Nestor et al., 1997; Niznikiewicz et al., 1997), reflecting difficulties in context use. It is worth noting that N400, a negativity around 400 msec, has been proposed as an index of semantic integration (e.g., Brown & Hagoort, 1993;

Federmeier & Kutas, 1999a, 1999b; Halgren, 1990; Kutas & Hillyard, 1984; Rugg, Doyle, & Holdstock, 1994; van Petten, 1993). Evidence for small N400 to related and unrelated items at short stimulus onset asynchronies (SOA), and large N400 to related and unrelated items at long SOAs (e.g., Kiang et al., 2007), may thus suggest an initial semantic hyperpriming followed by a failure of maintaining information in verbal working memory (Salisbury, 2008).

On the other hand, emotional perception and comprehension are also disrupted in schizophrenia. In particular, abnormalities have been found in the perception of emotional faces (Alfimova et al., 2009; Marwick & Hall, 2008; Morris, Weickert, & Loughland, 2009; Norton, McBain, Holt, Ongur, & Chen, 2009; Pomarol-Clotet et al., 2009; Tsoi et al., 2008; Vernet, Baudouin, & Franck, 2008) and intonations (e.g., Borod et al., 1989, 1990; Bozikas et al., 2006; Edwards, Pattison, Jackson, & Wales, 2001; Haskins, Shutty, & Kellogg, 1995; Hooker & Park, 2002; Kerr & Neale, 1993; Kucharska-Pietura, David, Masiak, & Phillips, 2005; Leentjens, Wielaert, van Harskamp, & Wilmink, 1998; Leitman et al., 2005, 2007; Murphy & Cutting, 1990; Pijnenborg, Withaar, Bosch, & Brower, 2007; Ross et al., 2001; Rossell & Boundy, 2005; Shaw et al., 1999; Shea et al., 2007), or expression of emotions (Falkenberg, Bartels, & Wild, 2008; Kohler et al., 2008; Kring & Moran, 2008), although emotional experience in these patients seem to be preserved (Kohler et al., 2008; Kring & Earnst, 1999). These abnormalities are related with abnormalities in several of the regions implicated in emotional processing. Functional MRI (fMRI) studies implicate medial and lateral orbitofrontal cortex (OFC), insula, amygdala, and anterior cingulated cortex (ACC) in the processing of emotions and in interfacing these processes with memory and semantic systems (Craig, 2009; Dolcos, LaBar, & Cabeza, 2004; Kensinger & Schacter, 2006; Kim & Hamann, 2007; Krueger, Barbey, & Grafman, 2009). Studies focusing explicitly on brain regions and emotional processing in schizophrenia point to abnormalities in anterior cingulate (Fujiwara et al., 2007; Reske et al., 2007), frontal lobe and amygdala (Yamada et al., 2009), orbitofrontal cortex, temporal areas and hippocampus (Reske et al., 2007), and insular cortex (Nagai, Kishi, & Kato, 2007). Studies of peripheral physiological responsivity to emotional pictures in schizophrenia are less clear cut. Some suggest greater impairments in reaction to positive emotions (Hempel et al., 2005), while others suggest greater impairment in reacting to negative emotions (An et al., 2006; Lee et al., 2006), inability to process effectively all emotions (Silver, Bilker, & Goodman, 2009) or 'normal' responses to emotional stimuli but abnormal integration with goal-setting and motivational and memory systems (Herbener, Song, Khine, & Sweeney, 2008).

Mood and semantic memory

Consistent with more recent studies suggesting an intricate relationship between emotion and cognition, there is evidence from studies with healthy population to suggest that transient moods have an effect on the way semantic memory is used on-line (e.g., Federmeier, Kirson, Moreno, & Kutas, 2001). Some studies showed that transient positive mood states are associated with increased flexibility of thinking and creative problem solving (e.g., Bolte, Goschke, & Kuhl, 2003; Isen et al., 1985, 1987; Isen & Means, 1983), increased scope of visuospatial attention but decreased visual selective attention (e.g., Rowe, Hirsh, & Anderson, 2007) as well as an enhanced access to remote associates in semantic memory (e.g., Kirson, 1990; Rowe et al., 2007), a finding corroborated by ERP studies that show small N400 amplitudes for expected items and for unexpected items from an expected semantic category under positive mood (Federmeier et al., 2001). These more recent studies point thus to the fact that the N400 component is not only an index of semantic processing and lexical access, but it also reflects semantic integration within a larger context, originated by subjects' expectations or other contextual constraints, namely transient mood states (e.g., Federmeier et al., 2001). So, in this sense, N400 can represent an appropriate ERP component for the assessment of emotion effects (Kissler, Assadollahi, & Herbert, 2006).

To our knowledge, until now, no other study has systematically studied the effect of transient moods on semantic memory processes in schizophrenia. In this study, sentence pairs with three different types of endings (an expected exemplar - EE; an unexpected word from the same semantic category of the expected word – within-category violation: WCV; an unexpected word from a different semantic category of the expected word – between-category violation: BCV) were presented. In addition, before sentences' presentation, a positive, negative, or neutral mood was elicited. We used the ERP technique since it constitutes an ideal functional imaging modality due to its temporal resolution, providing more sensitive evidence for altered processing of linguistic stimuli in "real time" (McCarley et al., 1999).

Two major questions were addressed in this study:

1. Does the organization of semantic memory play a role in how a sentence context affects word processing in schizophrenia? For normal controls, we predicted both a congruency (see Kutas & Hillyard, 1984), and a category effect, so that changes in the organization and access to semantic memory would be reflected in changes of N400 amplitude. This would be consistent

with Federmeier and Kutas (1999a, 1999b) who showed differences in the N400, an ERP component indexing semantic operations, as a function of semantic category membership.

For schizophrenia, based on data suggesting difficulties in semantic integration (as indexed by larger N400 amplitudes for both congruent and incongruent sentence endings), and abnormalities in semantic networks, we predicted a differential use of context to actively predict semantic features of upcoming words, as well as a differential effect of semantic memory structure in sentences' processing. Therefore, we expected similar amplitudes for the three types of sentence endings (EE, WCV, and BCV), under neutral mood.

2. Do transient mood states affect the way schizophrenic patients access semantic information? As shown previously, the existing literature suggests that positive mood may, in fact, broaden the scope of activation during lexical access (Federmeier et al., 2001). Therefore, for controls, we expected smaller N400 amplitudes for both expected items and within-category violations, relative to between-category violations, during positive transient states. In other words, we predicted that, under positive mood, the processing of distantly related items would be facilitated, such that they would be treated like correct sentence endings.

In line with the concept of investigating the effects of neutral, positive and negative affective states, we extended affect manipulation to negative mood. Considering behavioral studies that suggest a restrictive effect of negative mood states on spreading activation (Bolte, Goshke, & Kuhl, 2003; Fiedler, 1988), we hypothesised that controls would show larger N400 amplitudes for both types of unexpected endings (both within- and between-category violations), relative to expected targets.

For schizophrenia patients, due to abnormalities in emotional processing in schizophrenia, we predicted abnormal modulation of semantic processing by mood. In particular, we expected that, in comparison with normal controls, schizophrenia data would show a different impact of mood (positive: broadening semantic network activation; negative: narrowing semantic network activation) on access to semantic nodes that are more distantly related, sharing (WCV) or not (BCV) features with the expected item (EE).

2. Methods

2.1. Participants

Fifteen male subjects diagnosed with schizophrenia and fifteen male controls participated in the study (see Table 1). Inclusion criteria for participation in this study included: (1) age between 18 and 50 years; (2) right handedness; (c) no history of neurological illness; (d) no history of alcohol or drug abuse/dependence; (e) no current medication for medical disorders that would have effects on electroencephalogram (EEG) morphology or consequences at the level of neurological and/or cognitive functioning; (f) verbal intelligence quotient (IQ) above 75; (g) no alcohol use in the 24 hr before testing; (h) an ability and desire to cooperate with the experimental procedures, as demonstrated by given informed consent, following Harvard Medical School and Veterans Affairs Boston Healthcare System guidelines.

Comparison subjects were recruited from internet advertisements, and matched to the patients on the basis of age, gender and handedness. For normal controls, an additional exclusion criterion was history of psychiatric disorder in oneself or in first-degree relatives.

For patients, the average duration of illness was 16.47 years (*SD* = 9.40). Most of the patients were receiving atypical antipsychotics (13), one patient was receiving conventional neuroleptics, and one was receiving both types. Mean equivalent chlorpromazine dosage was 415.57 mg (*SD* = 309.49).

Table 1

Between-groups (schizophrenia patients vs. normal controls) comparison of demographic and cognitive data

	SCHIZOPHRENIA GROUP Mean (SD)	CONTROL GROUP Mean (SD)	Significance test *F, p*
Age	48.31 (8.77)	45.06 (8.93)	1.079, NS[a]
Years of education	13.94 (1.91)	14.72 (1.73)	1.466, NS[a]
Parents' social-economic status	2.82 (1.24)	2.19 (1.05)	2.527, NS [a]
Verbal IQ[b]	100.57 (12.73)	104.86 (18.07)	0.526, NS[a]
Performance IQ[b]	96.50 (8.47)	96.77 (17.56)	0.003, NS[a]
Full-Scale IQ[b]	100.29 (14.66)	103.58 (15.80)	0.305, NS[a]
Vocabulary[b, c]	10.36 (2.62)	10.69 (3.28)	0.087, NS[a]

[a] NS = non-significant; [b]WAIS-III: Weschler Adult Intelligence Scale – III (Weschler, 1997); [c] scaled score.

Groups were compared for socio-demograpic and neurocognitive data using one-way ANOVA. As seen by inspection of Table 1, groups didn't differ in any of the variables reported.

2.2. Materials

Three hundred and twenty-four pairs of sentences, distributed by three main lists, were used as stimuli. Additionally, thirty pictures of positive, negative or neutral valence were used for the emotional elicitation procedure.

Following the procedure of Federmeier and Kutas (1999a, 1999b), the sentences ended with three possible types of target words: (1) expected words (items with the highest cloze probability - EE); (2) within-category violations (WCV - items that were unexpected given the semantic context and that were derived from the same semantic category as the expected items); (3) between-category violations (BCV - items that were unexpected given the semantic context and that were derived from a different semantic category of the expected exemplars, but were not lexically associated). Thus, the first sentence of the pair established the context and the second sentence completed the first one, with an expected (and appropriate) or an unexpected (and inappropriate) ending. All these target final words were concrete nouns. Criteria for the selection of categories were the same as used by Federmeier and Kutas (1999a, 1999b): categories were chosen to be those at the lowest level of inclusion.

Experimental sentences followed the additional criteria:

(a) Considered separately, the second sentence could be completed appropriately by any of the critical words – EE, WCV, or BCV (e.g., *The little girl was fascinated by the aquarium where big bug-like animals with huge claws, strong tails and long antennae crawled around. Her Mom told her that they were called lobsters* (EE) / *shrimp* (WCV) / *shark* (BCV)).

(b) For the sentence containing the critical target, no word with a lexical association with the target was introduced.

(c) The sentences were distributed by three main blocks (block 1 – sentences 1-108; block 2 – sentences 109-216; block 3 – sentences 217-324). Each sentence context could end with a plausible (EE) or implausible ending (WCV; BCV).

(d) Each target word appeared three times, once in each type of ending – EE, WCV, or BCV (e.g., EE - *Paul loved to watch all TV shows that were set in hospitals. He has always wanted to be a doctor*, WCV - *Louise was suffering from a toothache for several days, but she still refused to do anything about it. She has always been afraid of going to the* doctor; BCV - *Michaela loved to read and she couldn't wait to check out a new set of books. She knew they were set aside for her by the friendly doctor*), and once per set. The sentences were rotated across blocks and lists, so that no sentence context or critical word was repeated for a particular participant within a given block (see Figure 1).

(e) Across participants, each target word appeared in one of the three possible conditions (EE, WCV, and BCV).

(f) The three target conditions were matched for length (*mean number of letters* = 5.76; *SD* = 1.73), frequency (*M* = 50.21; *SD* = 79.37), imageability (*M* = 585.93; *SD* = 39.67), concreteness (*M* = 582.63; *SD* = 44.09), and age of acquisition (*M* = 282.55; *SD* = 81.86). Francis and Kucera (1982) norms were used to get frequency information.

The expected exemplars were obtained from a previous study that aimed to calculate cloze probabilities for the final words of each of the sentence contexts (324) presented in the experiment. Twenty-six volunteers were asked to complete each sentence context with the first word that came to mind and that they thought would complete appropriately the precedent semantic context. Cloze probability was calculated as the proportion of individuals who chose a particular word to complete a given sentence context. Mean cloze probability for the expected exemplars was 0.75.

Final words in the WCV condition were derived from the same semantic category of the expected exemplar. In the BCV condition, words belonged to a semantic category that, in spite of being different from the EE, shared some key features of the category used for the expected items (e.g., EE = rose; WCV = carnation; BCV= palm). In order to check if WCVs were, in fact, assessed as more plausible than BCVs, a different group of individuals was asked to rate the plausibility of all sentence endings within their contexts. Each pair of sentences was presented to a set of twenty volunteers who did not participate in the study but judge the appropriateness of each ending. These sentences were divided into three lists of 108 sentences each (so that no sentence context or critical word was repeated within each list), corresponding to the three experimental blocks, and each one was presented to a different subset of subjects. They were asked to rate the appropriateness of the sentences ("How well do these sentences make sense together?") in a percent scale (0% = "the two sentences together make no sense – it is not at all what I expected"; 100% = "the two sentences together make perfect sense – the last word is the one and only word I expected"). Mean plausibility was calculated as the average of the ratings for all items of each of the three conditions (EE, WCV, and BCV). Mean rated plausibility for EEs was 86.44%, for WCVs was 24.22%, and for BCVs was 12.54%.

These plausibility ratings were subjected to a repeated-measures analysis of variance, with ending type (EE vs. WCV vs. BCV) as a factor. Results showed a significant effect of ending type ($F(2, 40) = 123.12$, $p = .000$), with EE being rated as significantly more plausible than WCV and BCV, and WCV being rated as more plausible than BCV.

After cloze probability and plausibility ratings were obtained, the experimental sentences were divided into nine main lists of 108 sentences each. Each participant viewed one different list in each mood. Sentence contexts and items were used only once per list and each list consisted of thirty-six of each type of target (see Figure 1).

	MOOD					
	NEUTRAL		**POSITIVE**		**NEGATIVE**	
SENTENCE CONTEXTS	**Block 1 (1-108)**	EE (36)	**Block 1**	EE (36)	**Block 1**	EE (36)
		WCV (36)		WCV (36)		WCV (36)
		BCV (36)		BCV (36)		BCV (36)
	Block 2 (109-216)	EE (36)	**Block 2**	EE (36)	**Block 2**	EE (36)
		WCV (36)		WCV (36)		WCV (36)
		BCV (36)		BCV (36)		BCV (36)
	Block 3 (217-324)	EE (36)	**Block 3**	EE (36)	**Block 3**	EE (36)
		WCV (36)		WCV (36)		WCV (36)
		BCV (36)		BCV (36)		BCV (36)

Figure 1. Illustration of the counterbalancing procedure. Colours (black, dark grey, and light grey) show different orders for the presentation of blocks in each mood, so that no critical word or sentence context was repeated in a given experimental session.

Caption: EE = expected exemplar; WCV = within-category violation; BCV = between-category violation.

In order to balance the umber of plausible and implausible sentences read by each participant, thirty-six plausible filler sentences were added to each list (see Federmeier & Kutas, 1999a, 1999b). In the end, all the lists ended up with the same number of expected and unexpected sentence endings (72 sentences of each type).

For emotional elicitation purposes, thirty pictures with positive, negative and neutral valence, with moderate levels of arousal, were selected from the International Affective Picture System database (IAPS; Lang, Bradley, & Cuthbert, 1997). In previous studies, IAPS pictures have been shown to have enough salience to elicit mild changes in affect (e.g., Federmeier et al., 2001; Patrick & Lavoro, 1997; Simon-Thomas & Knight, 2005).

Pictures for the positive condition (e.g., babies, people smiling, animals) were selected according to the following criteria: having valence ratings between 7.5-9 and mean arousal ratings of 4.5, with a standard deviation of 0.6. Negative pictures (e.g., people crying, mutilation, people in fearful situations) were selected if they had valence ratings between 2 and 3.5 and the same arousal ratings as positive pictures. Neutral pictures (e.g., household objects, vegetables) were selected if they had valence ratings between 4.5 and 5.0 and mean arousal ratings of 2.5, with a standard deviation of 0.4 (see Table 2).

Table 2

Mean (SD) scores for pictures' valence and activation, in each mood condition.

Condition	**Valence**	**Activation**
	Mean (SD)	Mean (SD)
Positive	7.85 (0.25)	4.48 (0.38)
Negative	2.74 (0.35)	4.78 (0.28)
Neutral	5.05 (0.19)	2.65 (0.36)

2.3. Procedure

Participants were tested in three experimental sessions (one session for each mood induction: neutral, positive, and negative), conducted in a soundproof, electrically-shielded chamber. They were seated in a comfortable chair 40 inches in front of a monitor.

Before the experiment, participants were asked to complete the *Profile of Mood States* (McNair, Lorr, & Droppleman, 1971/1981), a questionnaire with 65 adjectives rated on a 5-point scale that covers different mood states (tension-anxiety; depression-dejection; anger-hostility; fatigue-inertia; vigor-activity; confusion-bewilderment). In order to have a more comprehensive description of the current mood states of participants, the following positive items were added and coded separately: "happy", "clear headed", "relaxed", "content", "satisfied", "hopeful". Following, Norcross, Guadagnoli, and Prochaska (1984) we have subsequently grouped the answers into seven factors that described positive and negative affect states. The same questionnaire was administered after the subject finished the sentences' processing session. The questionnaire was administered for each subject in each affect induction session.

In the first phase of the experiment, participants were presented with thirty pictures from the IAPS database, corresponding to the set of pictures selected for the induction of a particular mood (positive, negative, or neutral). The order of mood induction was counterbalanced across participants. They were not informed about the true purpose of the pictures but, as in the study of Federmeier et al. (2001), they were instructed to pay attention to the stimuli and informed that later they would be asked to judge if the pictures were appropriate for being used in another experiment.

After that, a short practice run of 12 sentences began. The aim was to get the participants familiarized with the task and assure that they understood the instructions. All sentences and pictures were presented via Superlab software 4.0.6.b (Cedrus Corporation, 2008).

Before each pair of sentences, a picture from the set of selected IAPS pictures for a specific mood induction was presented briefly, for 350 msec, to keep mood constant across the experiment. After the picture, a fixation cross appeared on the screen, for 1500 msec, alerting the subject that a sentence would be seen (see Figure 2). The first sentence of the pair appeared fully on the screen. Participants read this sentence at their own pace and pushed a button to view the second sentence. The second sentence was presented one word at a time, horizontally, each word for about 600 msec. Final words were presented in the centre of the screen, for 1000 msec. Participants were asked not to blink or move their eyes during the second sentence. The final word was followed by a question mark (for 3000 msec), warning the participants to press a button, after which the next sentence appeared automatically. They were instructed to read the sentences for comprehension and press a button in the end of the second sentence (in a RB-x30 series response pad), answering if the sentence made sense or not. The order of response buttons (for "yes" and "no" responses) was counterbalanced across subjects. Participants had three seconds to press a button. After that time, the next trial would be automatically presented. A short break was given after every 20 pairs of sentences.

In the end of the experiment, in order to assess the effectiveness of the mood state induction, participants were asked again to fill out the *Profile of Mood States* (McNair et al., 1971/1981). In addition, they were asked to answer a written questionnaire, designed by the authors, asking them to report: (a) how much did they like the set of pictures, (b) how much did seeing the pictures influence the way they felt, and (c) how much did the pictures influence their decision whether the sentences made sense or not.

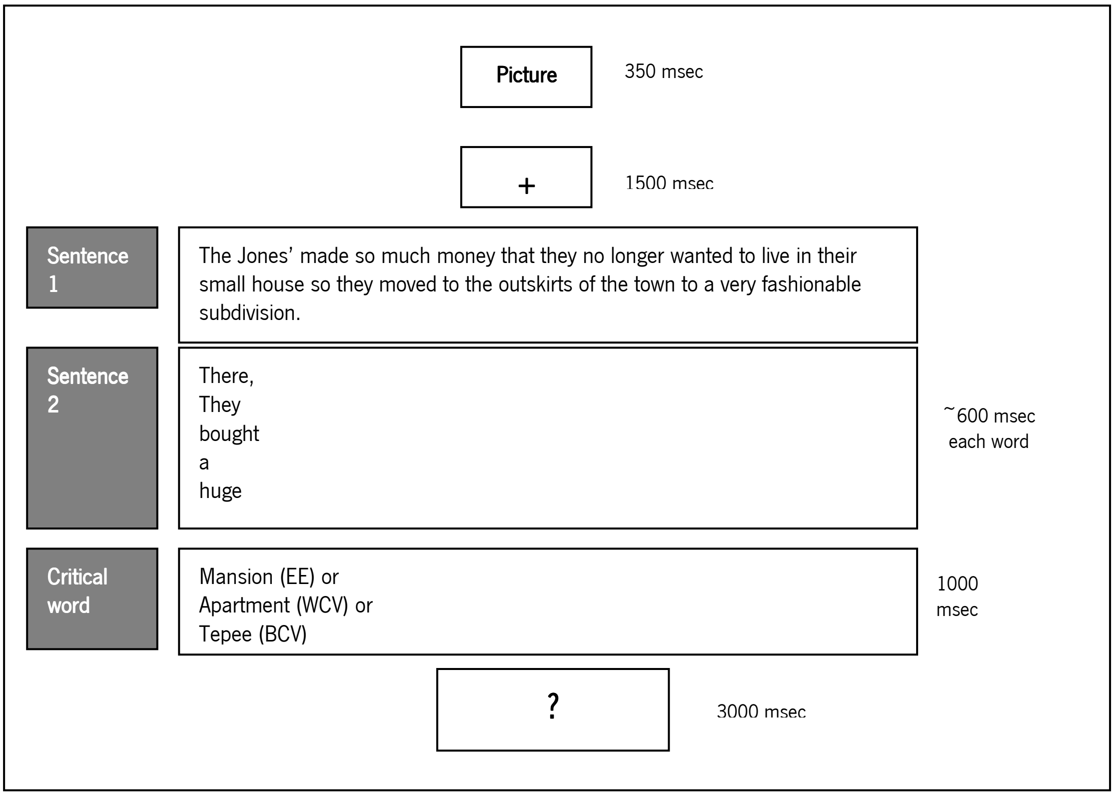


Figure 2. Schematic illustration of the experimental paradigm.

2.4. Data acquisition and analysis

2.4.1. EEG recording parameters

Sixty-four channel EEG was collected using custom designed electrode caps from Biosemi system (Active 2). EEG was acquired in continuous mode at a digitization rate of 500 Hz, with a bandpass of 0.01 to 100 Hz, and stored on hard disk for later analysis.

Blinks and eye movements were monitored via electrodes placed on left and right temples and one above the left eye. Electrode impedances were kept below 5 Kohms.

2.4.2. ERP Data analysis

Analysis of raw EEG data was conducted with Analyzer software package (Brain Products, Inc, 2000). Data were re-referenced off-line to the algebraic sum of the left and right mastoids. Trials containing excessive eye movements, blinks, muscle activity or amplifier blocking were rejected off-line before averaging. Eye blink and movement artifacts were corrected by the method of Gratton, Coles, and Donchin (1983, BrainVision Analyzer package).

For sentences, ERPs were computed for epochs ranging from 150 msec before stimulus onset to 1000 msec after stimulus onset. Separate averages were calculated for each type of target word, after subtraction of the 150 msec pre-stimulus baseline. N400 was measured as a peak amplitude between the latency of 300-500 msec, post-stimulus onset to each sentence ending type, in each mood, at frontal (Fz, F1/2, F3/4), central (Cz, C1/2, C3/4), and parietal (Pz, P1/2, P3/4) regions.

2.4.3. Statistical Data Analyses

In order to explore the effectiveness of mood elicitation procedure, paired sample t-tests were computed for each group separately. In addition, to test for group differences, one-way ANOVAs were computed for each factor, before and after mood elicitation.

Behavioral data (accuracy) were subjected to repeated-measures analyses of variance, with mood (neutral, positive, and negative), and sentence condition (EE, WCV, and BCV) as within-subjects factors and group as between-subjects factors.

For the ERP analyses we used both the between group comparison approach for each mood separately, as well as within group analyses given that we were interested in capturing both the group differences for a given mood as well as the patterns of N400 amplitude for each mood and each group. Therefore, repeated measures analyses of variance (ANOVA) were computed for the between-group comparison of N400 peak amplitude for each type of mood separately (neutral, positive, and negative), with group (normal controls – NC vs. schizophrenia patients – SZ) as between-subjects factor, and sentence condition (EE, WCV, and BCV), region (frontal, central, and parietal), and electrodes (Fz, F1, F2; Cz, C1, C2; Pz, P1, P2) as within-subjects factors. In addition, within group comparisons were conducted using ANOVAs with the same factors as listed above.

The Geisser-Greenhouse correction (Geisser & Greenhouse, 1959) was applied to all repeated-measures with greater than one degree of freedom in the numerator. Main effects or interactions were followed with pairwise comparisons with Bonferroni correction.

3. Results

3.1. Mood induction

Paired t-tests examining mood before and after mood elicitation procedure, showed the effects of mood manipulations in both groups. However, one should mention here that, given the design of the study, the assessment of the effectiveness of the mood manipulation took place after the participants finished the entire experiment, i.e., viewing pictures and rating the sentences. In controls, paired t-tests showed a reduction in tension-anxiety after neutral mood elicitation ($t(15) = 2.15$, $p = .048$), a reduction in depression-dejection after positive mood elicitation ($t(14) = 2.13$, $p = .051$), as well as a trend for reduced happiness ($t(14) = 2.09$, $p = .055$), reduced vigor-activity ($t(14) = 1.94$, $p = .073$), and increased depression-dejection ($t(14) = -1.90$, $p = .078$) following negative mood elicitation.

In schizophrenia individuals, paired t-tests showed a reduction in depression-dejection after neutral mood elicitation ($t(14) = 2.18$, $p = .047$); a trend for reduced depression-dejection after positive mood elicitation ($t(12) = 2.05$, $p = .063$); a decrease in friendliness ($t(16) = 2.15$, $p = .047$), and a trend towards increased confusion-bewilderment after negative mood elicitation ($t(16) = -1.85$, $p = .083$).

In between group comparisons before mood induction showed differences between normal controls and schizophrenia patients. Before neutral mood induction, patients reported higher fatigue-inertia ($F(1, 30) = 4.56$, $p = .041$), higher confusion-bewilderment ($F(1, 30) = 8.32$, $p = .007$), and lower happiness ($F(1, 30) = 4.42$, $p = .044$) relative to normal controls. Before positive mood induction, patients showed higher depression-dejection ($F(1, 27) = 4.03$, $p = .055$), higher fatigue-inertia ($F(1, 27) = 8.52$, $p = .007$), lower vigor-activity ($F(1, 26) = 10.09$, $p = .004$), lower friendliness ($F(1, 27) = 6.34$, $p = .018$), higher confusion-bewilderment ($F(1, 27) = 7.32$, $p = .012$), and lower happiness ($F(1, 27) = 9.45$, $p = .005$). Before negative mood induction, patients reported higher depression-dejection ($F(1, 30) = 4.07$, $p = .053$), lower vigor-activity ($F(1, 30) = 9.95$, $p = .004$), lower friendliness ($F(1, 30) = 12.57$, $p = .001$), higher confusion-bewilderment ($F(1, 30) = 4.60$, $p = .040$), and lower happiness ($F(1, 30) = 10.66$, $p = .003$), relative to controls.

In between group comparisons of the effect of individuals with schizophrenia showed higher confusion-bewilderment after neutral mood elicitation ($F(1, 30) = 4.56$, $p = .041$), while normal controls reported higher happiness ($F(1, 30) = 4.56$, $p = .041$), after the elicitation of the same mood. After positive mood elicitation, normal controls reported lower depression-dejection than patients ($F(1, 28) = 7.46$, $p = .011$), lower fatigue-inertia ($F(1, 28) = 8.07$, $p = .008$), higher vigor-activity ($F(1, 28) = 10.95$, $p = .003$), higher friendliness ($F(1, 28) = 12.25$, $p = .002$), lower confusion-bewilderment ($F(1, 28) = 6.77$, $p = .015$), and higher happiness ($F(1, 28) = 21.26$, $p = .000$). After negative mood induction, normal controls reported higher friendliness ($F(1, 30) =

7.93, *p* = .009), lower confusion-bewilderment (*F*(1, 30) = 5.69, *p* = .024), and higher happiness (*F*(1, 30) = 5.71, *p* = .023) than schizophrenia patients.

Interestingly, differences between groups were also observed in the questionnaire filled out by participants about the subjective experience of seeing the pictures. Normal controls reported they liked more the pictures presented for neutral (*F*(1, 29) = 20.07, *p* = .000) and positive (*F*(1, 29) = 4.39, *p* = .047) mood induction relative to patients. Also, patients reported more difficulties in deciding whether the sentences made sense or not after seeing neutral (*F*(1, 29) = 4.31, *p* = .047) and negative (*F*(1, 28) = 6.67, *p* = .016) pictures, when compared with normal controls, but not after seeing positive pictures.

3.2. Behavioral data (Accuracy)

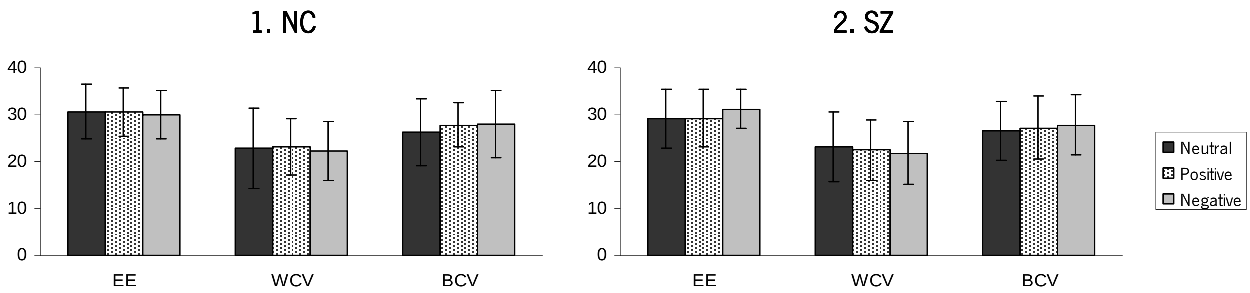


Figure 3. Means (SD) for correct responses in NC (1) and SZ (2), for each sentence condition (EE, WCV, and BCV), in each induced mood (neutral, positive, and negative).

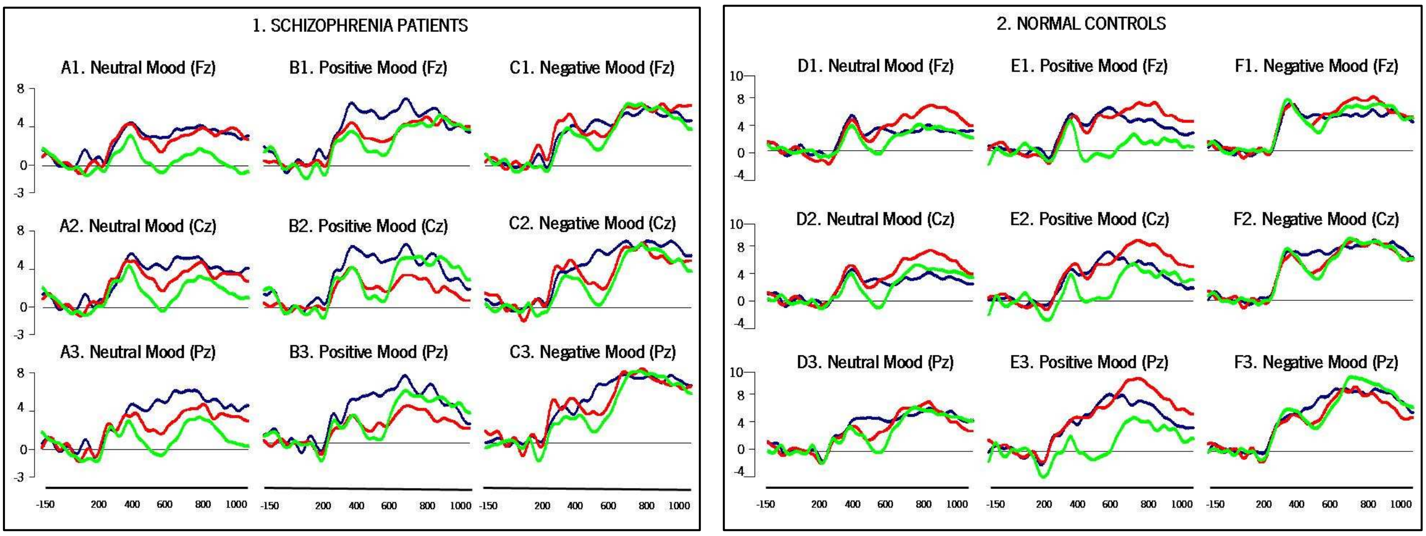
A repeated-measures ANOVA showed an effect of sentence condition (*F*(2, 46) = 65.98, *p* = .000). Planned comparisons revealed more correct responses for EE relative to WCV and BCV, and more correct responses for BCV relative to WCV.

We followed this analysis with subsequent repeated-measures ANOVAs for each mood separately, in order to explore if different response patterns were associated with different moods: an effect of sentence condition was observed in neutral mood (*F*(2, 56) = 24.38, *p* = .000), positive mood (*F*(2, 56) = 36.76, *p* = .000), and negative mood (*F*(2, 56) = 51.33, *p* = .000): for all moods, more correct responses were found for EE, followed by BCV, and then by WCV (see Figure 4).

The groups did not differ in the accuracy rates.

3.3. ERP Results

3.3.1. N400 amplitude



Caption: Blue = EE; Red = WCV; Green = BCV

Figure 4 (4.1.-4.2.). Grand average waveforms to final target words in the second sentence in schizophrenia - SZ (I) and normal controls - NC (II), under affect induction, at frontal, central, and parietal electrode locations.

Panel A & D: in both NC and SZ, under neutral affect induction, N400 was least negative to EE, and most negative to BCV, with WCV in between (similar to Federmeier and Kutas, 1999a, 1999b – for normal controls). Panel B & E: under positive affect induction, NC process WCV like EE: N400 WCV=N400 EE (similar to Federmeier et al., 2001). In SZ, the opposite effect was observed: N400 WCV=BCV. Panel C & F: under negative affect induction, in NC N400 WCV=N400 BCV. In Sz, N400 effects were similar to those found in neutral affect (D).

3.3.1.1. Neutral Mood

General effects

A repeated-measures ANOVA (group x sentence condition x region x electrode site) showed a main effect of sentence condition (F(2, 48) = 10.38, p = .000). N400 amplitudes were more negative for BCV, followed by WCV, and then by EE. Pairwise comparisons revealed a significant difference between BCV and EE (p = .001), and a marginally significant difference between EE and WCV (p = .059). No group effects were observed.

Within-group effects

In schizophrenia, N400 for EE was significantly more positive for EE (*M* = 1.89; *SD* = 0.68) than for WCV (*M* = 0.38; *SD* = 0.61) and BCV (*M* = -0.57; *SD* = 0.62), and more negative for BCV relative to EE only, as evinced by a main effect of sentence condition ($F(2, 24) = 7.81$, $p = .004$).

For normal controls, a main effect of sentence condition was also observed ($F(2, 24) = 3.87$, $p = .035$): more negative N400 was found for BCV (*M* = -0.83; *SD* = 1.21) relative to EE (*M* = 1.55; *SD* = 1.37) ($p = .053$), but not to WCV (*M* = 0.51; *SD* = 0.76).

3.3.1.2. Positive Mood

A significant effect of sentence condition was found for the positive mood ($F(2, 40) = 18.59$, $p = .000$): N400 was significantly more negative for BCV relative to EE ($p = .000$) and WCV ($p = .004$).

In addition, a main effect of group was observed ($F(1, 20) = 5.09$, $p = .035$): N400 was significantly more positive for individuals with schizophrenia relative to normal controls across the three main sentence conditions.

Within-group effects

Within-group analyses revealed different patterns for both groups.

In normal controls, WCV were processed similarly to EE, so that no amplitude difference was observed between both sentence conditions; moreover N400 for BCV was significantly more negative than for EE ($p = .035$) and WCV ($p = .009$), as confirmed by a significant effect of sentence condition ($F(2, 20) = 8.89$, $p = .003$).

In schizophrenia, N400 to EE was significantly more positive than to WCV ($p = .002$) and BCV ($p = .003$), as evinced by a main effect of sentence condition ($F(2, 20) = 13.70$, $p = .000$).

3.3.1.3. Negative Mood

An almost significant effect of sentence condition was found for negative mood ($F(2, 48) = 2.98$, $p = .068$). Means for each sentence condition showed more negative N400 for BCV (*M* = 0.34; *SD* = 0.63), relative to WCV (*M* = 1.06; *SD* = 0.73), and EE (*M* = 1.99; *SD* = 0.78).

Within-group effects

No significant difference between sentence conditions was observed in normal control group. Interestingly, however, the N400 pattern observed for negative mood was different from neutral mood (WCV>BCV>EE), with more negative N400 being observed for WCV (M = 1.24; SD = 1.28), followed by BCV (M = 1.61; SD = 1.08), and then by EE (M = 2.43; SD = 1.36).

A main effect of sentence condition was observed in the schizophrenia group ($F(2, 28) = 4.80$, $p = .021$): N400 tended to be more positive to EE (M = 1.54; SD = 0.89) relative to BCV (M = -0.93; SD = 0.74) ($p = .064$), but not to WCV (M = 0.87; SD = 0.82).

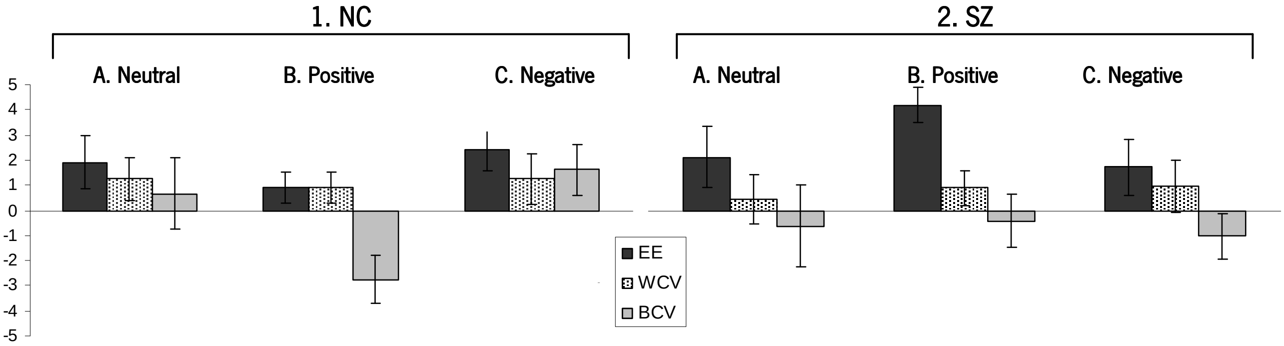


Figure 5. Mean N400 amplitudes (all channels included in ANOVA) for the three ending types as a function of mood state, for both normal controls (1) and schizophrenia participants (2). Error bars indicate standard errors.

3.3.2. N400 Latency

3.3.2.1. Neutral mood

N400 peaked earlier for EE, then for WCV, and finally for BCV. However, no main effects or interactions were found for neutral mood.

Within-group analysis

In schizophrenia patients, a sentence condition effect was found ($F(2, 22) = 3.54$, $p = .055$): N400 peaked significantly earlier for EE relative to BCV only. No main effects or interactions were found for normal controls, although the means for N400 peak latencies showed a different pattern for the three sentence conditions (EE<WCV<BCV) than the one observed in schizophrenia patients (EE<BCV<WCV).

3.3.2.2. Positive mood

A different pattern was observed for positive mood: N400 peaked earlier for WCV, followed by EE, and then by BCV. A main effect of region was observed ($F(2, 44) = 4.78$, $p = .025$). N400 peaked earlier at parietal electrodes relative to central electrode sites.

Within-group analysis

An effect of region was found in controls ($F(2, 24) = 6.30$, $p = .017$): N400 tended to peak earlier at parietal relative to frontal electrode sites (BCV<WCV<EE). No main effects or interactions were found for individuals with schizophrenia (WCV<EE<BCV).

3.3.2.3. Negative mood

For negative mood, means showed earlier N400 peak latency for WCV, then for BCV, and the latest latency for EE. Again, no main effects or interactions were observed.

Within-group analysis

No main effects or interactions were found for schizophrenia (BCV<WCV<EE) or normal controls (WCV<BCV<EE).

4. Discussion

In this study, we explored the effects of induced mood states (positive, negative, and neutral) in semantic processing in schizophrenia, using the ERP technique. Two different questions were addressed: (1) do patients with schizophrenia access semantic categories in the same way as normal controls? (2) in which ways does transient mood impact the access to semantic memory in schizophrenia?

We examined the influence and interaction of mood, contextual congruity, and semantic memory organization, presenting three different types of sentence endings (EE, WCV, BCV), after the presentation of pictures with emotional (positive and negative) and neutral valence. Results showed that the structure of semantic memory affected processing, and that the amplitude of ERP responses (N400) to three ending types (EE, WCV, BCV) was affected by transient induced mood (positive, negative, vs. neutral).

In normal controls, we have replicated the results of Federmeier and Kutas (1999a, 1999b) who reported an incremental increase in the N400 (i.e., getting more negative-going) from EE, to unexpected sentence endings from the same category as expected endings (WCV), and to unexpected sentence endings from a different, but neighbouring category (BCV), where the most negative N400 was observed. Also, we have replicated the effects of a positive affect induction on semantic processing (Federmeier et al., 2001) and showed that words from unexpected words from the same category become processed as if they were expected sentence endings, suggesting that, to some extent, semantic distance was shortened under positive mood. These results are in line with the theoretical view that positive affect influences flexibility in problem solving and performance on semantic memory tasks of remote semantic associates (Isen, 1999; Isen et al., 1985, 1987; Isen & Means, 1983; Kirson, 1990).

Furthermore, we have extended the affect manipulation to negative affect and showed that unexpected sentence endings from the same category (WCV) are processed like unexpected words from a different category (BCV), suggesting a greater semantic distance. Thus, in normal controls, positive affect, as suggested previously (Ashby et al., 1999; Federmeier et al., 1999a, 1999b), contributed to broadening of a semantic network of acceptable sentence endings, while the negative affect contributed to the narrowing of this network.

This hypothesis is corroborated by behavioral data indicating more incorrect responses for WCV relative to EE and BCV. In other words, words from the same semantic category were assumed more frequently to be appropriate endings, which suggest that the structure of semantic memory (i.e., the semantic similarity between EE and WCV that is independent from sentence context) is affecting processing, at the behavioral and electrophysiological level.

Therefore, findings from sentences processing confirm the intricate connections between emotion and cognition during language comprehension, shown by previous behavioral (e.g., Glenberg et al., 2005; Isen et al., 1985) and ERP (e.g., Chung et al., 1996; Federmeier et al., 2001; Pratt & Kelly, 2008; Wiswede, Münte, Goschke, & Rüsseler, 2009) studies with normal population.

Data collected in schizophrenia point to abnormalities in modulating semantic information processing by affect. While in neutral affect induction condition, schizophrenia data are qualitatively similar to normal controls (i.e, in terms of the N400 effect EE<WCV<BCV), showing facilitation for contextually expected items (EE) as compared with unexpected items (WCV and BCV), in the positive affect induction condition the N400 to WCV is the same as to BCV, i.e., it is the opposite effect to that found in normal controls. Data for positive mood suggest that

individuals with schizophrenia were not using context predictively, since they didn't show facilitation for WCV, and little difference was observed between WCV and BCV.

However, contrary to our initial prediction, data from neutral mood suggest schizophrenia sensitivity to semantic relationships in long-term semantic memory, as evinced by smaller N400 to WCV relative to BCV. Differences in experimental stimuli (e.g., strength of sentence context; use of an explicit behavioral task) relative to previous studies may have accounted for these results (see Kreher, Goff, & Kuperberg, 2009).

In the negative affect induction condition, the N400 response in schizophrenia was similar to the N400 response in the neutral affect induction condition. Both the N400 response observed in the positive and negative affect induction condition suggest profound abnormalities in the way semantic information processing is modulated by affect in SZ.

Interestingly, no group differences were observed for behavioral accuracy. In addition, no latency differences were observed, contrary to previous studies (Adams et al., 1993; Koyama et al., 1991; Nestor et al., 1997; Niznikiewicz et al., 1997; Olichney, Iraqui, Kutas, Nowacki, & Jeste, 1997), suggesting that differences do not lie in the timing of the semantic effect, but are essentially differences in the integration of emotion and cognitive processing.

These data are consistent with schizophrenia disturbances in the ability to process sensory information that is emotionally salient (Laviolette, 2007; Rosenfeld, Lieberman, & Jarskog, in press). For example, some studies showed decreased emotional responsivity to positive stimuli in schizophrenia (e.g., Lee et al., 2006; Paradiso et al., 2003; Taylor, Phan, Britton, & Liberzon, 2005). Other studies showed that negative stimuli tended to elicit differential responsivity depending on schizophrenia subtype (Lee et al., 2006). Abnormal emotional-cognition interactions have been described in few previous studies, namely adolescent-onset schizophrenia (e.g., Pauly et al., 2008). Also, the existing evidence indicates schizophrenia abnormalities in brain regions implicated in emotional processing (e.g., Crespo-Facorro et al., 2001; Gur et al., 2002; Paradiso et al., 2003; Schneider et al., 1998; Takahashi et al., 2004). For example, reduced activation of the striatum and amygdala was proposed to lead to a failure in signalling the salience of positive events and to impaired reward prediction (Dowd & Barch, 2009). Therefore, the finding of a different impact of transient mood states on semantic memory access in schizophrenia may be related to the temporo-limbic abnormalities, underlying the abnormal emotional processing that characterizes this disorder.

However, we should note that in spite of abnormalities in emotional processing, normal experiences of positive and negative emotion have been reported (e.g., Burbridge & Barch, 2007; Herbener et al., 2008; Horan, Green, Kring, & Nuechterlein, 2006; see also Gold et al., 2008), indicating a surprising preservation of emotional experience in schizophrenia. Regarding emotional responses elicited by IAPS pictures, similarities were observed between normal controls and individuals with schizophrenia (e.g., Heerey & Gold, 2007; Herbener et al., 2007, 2008). Therefore, we should expect a normal initial response to emotional evocative stimuli. Nonetheless, downstream abnormalities might be expected in the impact of emotional activation in higher-order cognitive processes, such as language processing (see Gold et al., 2008; Herbener, Song, Khine, & Sweeney, 2008). In our study, abnormalities were found particularly in the modulation of semantic information by positive mood. This is consistent with a previous study (Herbener et al., 2007) showing that schizophrenia patients fail to integrate positive emotional experience in memory consolidation processes, in spite of initial preserved response to positive stimuli. Also, deficits in the representation of the reward value of stimuli have been consistently noted (Gold et al., 2008), which is related to deficits in the modulation of motivated behavior (Gold et al., 2008). These data suggest that, even if induced emotional experience is normal, the impact of this experience on subsequent behavior and cognitive functions is abnormal.

In addition, altered semantic representation has already been noticed in schizophrenia, in particular a less organized representation of semantic categories (e.g., Becker et al., 2010; Chen, Chen, & Lieh-Mak, 2000; Kiang, Kutas, Light, & Braff, 2007; Löw, Rockstroh, Elbert, Silberman, & Bentin, 2006; Tallent, Weinberger, & Goldberg, 2001), and abnormal inhibitory processes in semantic networks (Niznikiewicz, 2008; Niznikiewicz, Mittal, Nestor, & McCarley, 2010). This suggests that associative strength within and across semantic categories is different from normal controls, which may give rise to abnormal spreading of activation and thus to abnormal N400 amplitudes during the processing of exemplars taken from the same or from a different semantic category, as observed in our study.

Interestingly, both Federmeier et al. (2001) and other authors (Ashby, 1999; Allman, Hakeem, & Watson, 2002; Laviolette, 2007) link positive affect to dopaminergic regulation and neural emotional learning circuits, and dopamine has been one of the target neurotransmitter systems in terms of neurochemical dysfunction in schizophrenia (Laviolette, 2007). Disturbances in dopaminergic transmission (e.g., involved in emotional processing, emotional learning, and motivation) may be related to abnormalities in emotional processing and perception, namely regulation of positive and negative mood, which can have a differential impact on discourse and meaning processing. For example, reduced ventral striatal activation in schizophrenia was proposed to reflect a failure of dopamine firing to unpredicted positive stimuli, leading to impaired reward prediction and incentive salience (Dowd & Barch, 2009).

Also, dopaminergic transmission was shown to play a role in the modulation of semantic memory function in schizophrenia (Condray et al., 2008; Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003). For example, modulatory effects of dopamine have been found in a N400 task (Condray et al., 2008).

Therefore, even though the relationship between dopamine and cognition is far from straightforward, we note this hypothesis as a potentially rich source of future investigative ideas, interpretative venue for these results, and an additional motivation for careful characterization of medication effects.

Conclusions

Together, these findings confirm that there is a complex interaction between affect processing and the way it regulates cognition, in this specific case, semantic processing (Pessoa, 2008). Since both effective affect regulation and its interaction with cognitive processes are critically important for effective social functioning, we regard these results as very exciting and important for understanding affective abnormality in schizophrenia. These results suggest that while appropriate, activation of semantic information in semantic networks is critical for effective on-line language processing and social communication, and that the appropriate modulation of mood and its effects on higher-order cognitive processes, such as language, is also a crucial mechanism of social interaction and communication.

Since no females were included in our study, these interpretations must be restricted to males. Future studies should include participants from both genders to explore the possibility of gender-specific effects.

Finally, the current results underline the importance of targeting emotional regulation in the context of therapy or cognitive remediation programs in schizophrenia.

Chapter IV

GENERAL DISCUSSION

GENERAL DISCUSSION

1. Event-related potentials studies of prosody and semantic processing in Williams Syndrome and schizophrenia: assembling a jigsaw puzzle

The studies described in the above sections aimed at investigating the electrophysiological (ERP) signatures of semantic and prosody processing in two atypical developmental pathways: Williams Syndrome and Schizophrenia.

Since both disorders present with language and communication abnormalities (e.g., Jarrold, Hartley, Phillips, & Baddeley, 2000; Karmiloff-Smith et al., 1998; Kuperberg, Kreher, & Ditman, 2010; Levy et al., 2010; Li, Branch, & DeLisi, 2009; Nestor et al., 2006; Niznikiewicz et al., 1997; Niznikiewicz, Mittal, Nestor, & McCarley, 2010; Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006; Robinson & Temple, 2009; Tarling, Perkins, & Stojanovik, 2006; Tyler et al., 1997; Volterra, Capirci, Pezzini, Sabbadini, & Vicari, 1996), these studies provided electrophysiological evidence for a better understanding of language function (semantics and prosody) in Williams Syndrome and Schizophrenia. On one hand, Williams Syndrome was previously proposed as evidence for a modular preservation of language (e.g., Bellugi et al., 1990). On the other hand, schizophrenia has been consistently characterized by abnormalities in semantic memory and context processing (e.g., Nestor et al., 1997, 2001; Niznikiewicz, Mittal, Nestor, & McCarley, 2010).

Two language subcomponents were examined: prosody and semantic processing. It is well known that effective communication includes both linguistic (written or spoken words), supra-linguistic (intonation) and non-linguistic (body language, facial expression, gaze) elements (e.g., Schirmer & Kotz, 2006). In addition, effective communication depends on proper regulation of affect so that interpretation of semantic content is close to the reality this content describes (e.g., Diamond & Aspinwall, 2003; Gray, Braver, & Raichle, 2002; Ochsner & Gross, 2005). While studies on language abnormality in Williams Syndrome and schizophrenia abound, studies on supra-linguistic and non-linguistic aspects of communication in Williams Syndrome and schizophrenia are lagging behind. This dissertation tried to fill this gap by proposing to examine abnormalities in processing supra-linguistic elements of communication (in both Williams Syndrome and schizophrenia) and the relationship between affect and processing of semantic content (in schizophrenia).

Table 1

Summary of behavioral and ERP findings in Williams Syndrome (WS) and Schizophrenia (SZ)

Study	Behavior	ERP
1. Prosody study in WS	More errors for angry sentences in the WS group.	Reduced N100 for prosody sentences with semantic content, but more negative N100 for pure prosody sentences; more positive P200 for both pure prosody sentences and sentences with semantic content, in particular for happy intonations; reduced N300.
2. Semantic processing study in WS	Trend for more errors in WS.	No difference between congruent and incongruent sentence endings for N100 amplitude in WS; trend for more positive P200 for incongruent sentence endings; no group differences for N400; more positive P600 in WS.
3. Prosody study in SZ	More errors in SZ.	Reduced N100 and P200 to all prosody types in sentences with semantic content only; no P200 modulation as a function of prosody in SZ.
4. Affective modulation of semantic processing in SZ	No differences between groups.	Enhanced rather than reduced N400 to WCV in positive mood for SZ; in negative mood, N400 to three types of endings similar to neutral mood (EE < WCV < BCV) for SZ.

First, studies of prosody processing in both disorders were developed. Prosody can be viewed as a probe into one aspect of social cognition: the ability to process and interpret tone of voice, which is crucial to social interactions and, in particular, to social reciprocity (e.g., Schirmer & Kotz, 2006; Wildgruber, Ackermann, Kreifelts, & Ethofer, 2006). Notably, no event-related potentials (ERP) studies of prosody processing have been conducted before in schizophrenia or Williams Syndrome.

Second, two studies on the electrophysiological correlates of semantic processing were developed. On the one hand, in spite of several studies suggesting semantic dysfunction in WS, the electrophysiological correlates of semantic processing are not yet fully understood, and no ERP study has been conducted using European Portuguese language. On the other hand, in spite of abundant research on semantic processing in schizophrenia, none has investigated the effects of mood on semantic processing at the electrophysiological level, in this disorder.

In Study 1 and Study 3, we aimed at (1) characterizing the electrophysiological responses (ERP) to three emotional intonation patterns (neutral, happy, and angry) in both groups; and at (2) examining ERP correlates of prosody processing and their interactions with semantic content (see Figure 1).

Results of study 1 (*Electrophysiological correlates of prosody processing in Williams Syndrome*) suggest that prosody processing in WS is supported by dysfunctional early ERP components, which are differentially modulated by the presence or absence of semantic content when taking typical development as reference. In particular, reduced N100 for prosody sentences with semantic content but more negative N100 for pure prosody sentences, and more positive P200 for both pure prosody sentences and sentences with semantic content, were observed in WS. On the one hand, reduced N100 for sentences with semantic content suggests an impairment that is likely mediated by the impact of semantic channel on the efficient processing of prosodic cues. On the other hand, P200 amplitude enhancement to both sentences with semantic content and pure prosody sentences suggests that heightened sensitivity to prosodic cues is present regardless of whether WS individuals need to process semantic information or not. In particular, more positive P200 for happy emotional prosody may be associated with the behavioral components of heightened sociability in WS. Interestingly, group differences for happy sentences seem to be consistent with previous studies showing a bias in WS for rating emotional stimuli as positive and a heightened reactivity/attention to positive social stimuli (Bellugi, Adolphs, Cassady, & Chiles, 1999; Haas et al., 2009). Finally, abnormal N300 in WS (reduced N300 peak amplitude at parietal electrodes and enhancement at frontal electrodes) suggests abnormal processes of cognitive evaluation of emotional significance of acoustic signal and its potential integration with semantic information. Together, these data showed deficits in early sensory stages of prosody processing, suggesting that dysfunction in prosody processing is influenced by altered bottom-up (sensory) mechanisms and it is not be entirely mediated by higher order cortical deficits. Therefore, these ERP findings don’t provide evidence for a relative preservation of the ability to interpret "pure" affective prosody in WS, as proposed by other authors (Skwerer et al., 2007). This study provided, for the first time, electrophysiological evidence for abnormal processing of social cues in WS at the prosody level.

Study 3 (*Electrophysiological correlates of prosody processing in schizophrenia*) provided ERP evidence for abnormal prosody processing in schizophrenia. Differences between schizophrenia patients and healthy controls were observed especially for prosodic sentences with semantic content, as indexed by reduced N100 and P200 amplitude. These results suggest sensory abnormality in processing auditory signal for all prosody types (reduced N100), and a failure to extract emotion specific information from the auditory signal (reduced P200 and absence of emotion effect for sentences with semantic content), but only when prosody is embedded in intelligible semantic information. These results complement previous studies suggesting dysfunctional early auditory processing in schizophrenia (e.g., Butler et al., 2009; Javitt, 2009a, 2009b; Leitman et al., 2006), extending these abnormalities to the prosody domain. This study tried to fill the gaps in research on affective processing in schizophrenia, presenting, for the first time, evidence on the electrophysiological correlates of extracting emotional information from the auditory signal (speech).

In studies 2 and 4, we aimed at examining electrophysiological correlates of semantic processing in Williams Syndrome and schizophrenia (see Figure 1). Study 3 examined the electrophysiological correlates of semantic processing in WS, using a classical N400 task, consisting of the presentation of sentence contexts ending with an expected (congruent condition) or anomalous word (see Kutas & Hillyard, 1980). Abnormalities in sensory (N100 and P200) components and semantic integration ERP indexes (N400) were expected.

Study 4 analyzed the electrophysiological correlates of affective modulation of semantic information processing in schizophrenia. Semantic abnormalities in schizophrenia have been a subject of intense inquiry in recent years. The interest in semantic processing was extended to modulatory effects of affect in these processes. Abnormal modulation by both positive and negative affect in schizophrenia was predicted.

Study 2 (*Electrophysiological correlates of semantic processing in WS*) tried to shed light on the specificities of semantic processing in WS, looking at its ERP correlates. This study extended previous studies (Mills et al., 2003; Neville, Mills, & Bellugi, 1994), using for the first time stimuli in European Portuguese language. Results suggest abnormal semantic processing in Williams Syndrome which is supported by abnormal sensory ERP components (N100 and P200) and by abnormal ERP index of late integrative (syntactic and semantic) processes (enhanced P600), in spite of an apparently preserved N400 amplitude and latency, which is associated with semantic integration operations. Our findings are consistent with previous studies suggesting early dysfunctional ERP components, in particular N100 and P200 (Mills et al., 2003; Neville et al., 1994). However, they don't confirm an enhanced N400 response in WS (i.e., larger amplitude difference between congruent and incongruent sentence endings), as suggested previously (Neville, Mills, & Bellugi, 1994). Differences in the experimental sentences (e.g., sentence length; strength of contextual constraint) may explain these apparently contradictory findings. The finding of an increased P600 for WS may thus suggest difficulties in higher-order processes, namely the integration of semantic and syntactic information, or reanalysis processes, which is consistent with findings from behavioral studies suggesting abnormal semantic and contextual processing (e.g. Tyler et al., 1997).

Study 4 (*The effects of transient mood states on semantic processing in schizophrenia*) confirm the view of N400 as a probe of the structure of semantic memory and its interactions with emotional processing (Federmeier, Kirson, Moreno, & Kutas, 2001; Federmeier & Kutas, 1999a, 1999b). Results of this study suggest that modulation of language (semantic) processes by affect is abnormal in schizophrenia, as indexed by N400 amplitudes to three types of sentence endings: expected exemplars (EE), within-category violations (WCV), and between-category violations (BCV). Results for normal controls fully replicated Federmeier and Kutas (1999a) and Federmeier et al. (2001). Furthermore, affect manipulation was extended to negative affect, showing that WCV words were processed like BCV words. Thus, in normal controls, positive affect broadened the semantic network of acceptable sentence endings (Ashby, 1999; Federmeier et al., 2001), while the negative affect narrowed this network (novel finding). Results for schizophrenia participants suggest profound abnormalities: while in the neutral affect condition SZ data resembled normal controls (N400 effect: EE<WCV<BCV), in the positive affect condition schizophrenia patients processed similarly WCV and BCV (N400 WCV = N400 BCV), the effect opposite to that found in normal controls, suggesting narrowing rather than broadening of the semantic network. Under negative affect, the N400 in SZ resembled the N400 in the neutral affect condition (again different than in normal controls). Together, these results and the

evidence of SZ sensitivity to affect induction on self-report suggest an abnormal and complex interaction between affect processing and the way it influences semantic processing.

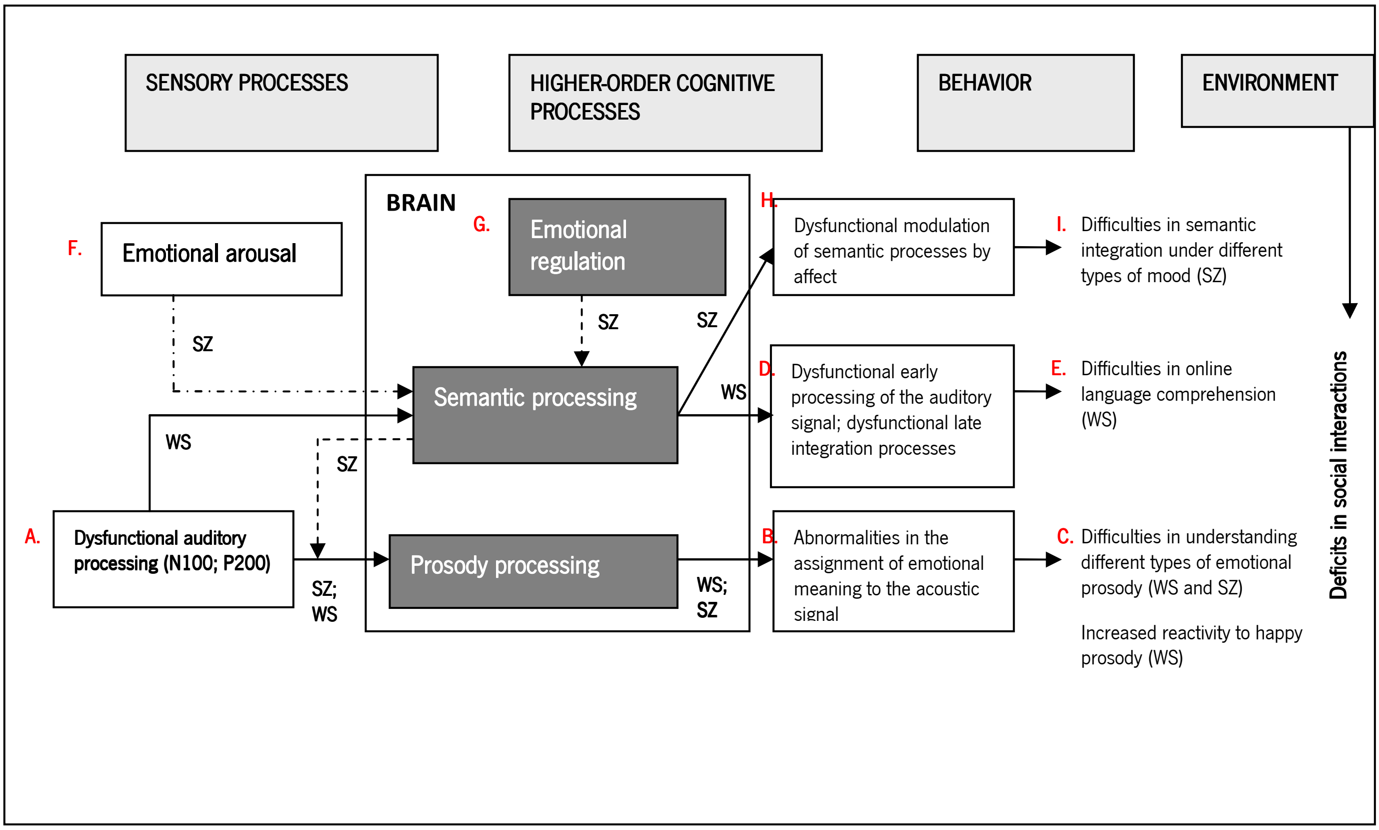


Figure 1. Summary of main findings from studies on the electrophysiological correlates of language processing in Williams Syndrome and Schizophrenia. The figure sums up main findings from studies 1 to 4, on semantic and prosody processing in Williams Syndrome and Schizophrenia. Dysfunctional early sensory (auditory) processing (A) was observed in both Williams Syndrome and Schizophrenia, as indexed by N100 and P200 amplitude. This finding suggests dysfunctional prosody processing and deficits in the extraction of emotional information from the auditory signal (B), underlying deficits in prosody comprehension at the behavioral level (C). Processing of auditory semantic information was related with dysfunctional early ERP components (A) in WS, and with dysfunctional late integration processes, as indexed by P600 (D). Behaviorally, difficulties in online language comprehension (E) may be supported by abnormalities at the electrophysiological level. In Schizophrenia, transient mood states modulated semantic processing differently from normal controls (F), suggesting a differential impact of affect on language processes (G and H). This may be related with altered semantic representation and activation (which is related with aberrant associations in schizophrenia discourse and with dysfunctional semantic integration at the behavioral level), and with disturbances in the ability to process sensory information that

is emotionally salient. Dysfunctional ERP components, underlying prosody and semantic processing, seem to be related with difficulties in social interactions in both Williams Syndrome and Schizophrenia.

2. From genes, to brain, to language: insights from atypical developmental pathways

Together, these different studies point to several major conclusions:

1. Same behavioral scores do not necessarily mean same brain/cognitive processes. In study 1 (*Electrophysiological correlates of abnormal prosody processing in WS*), differences between WS and a typically developing group were only observed for angry prosody, at the behavioral level. However, performance in the same task was supported by distinctive brain processes in WS and in a typically developing group. This suggests that the idea of "preserved modules" is not adequate to describe Williams Syndrome, or developmental disorders in general. Also, in study 4 ("The effects of transient mood on semantic processing in schizophrenia: electrophysiological (ERP) evidence"), no differences between schizophrenic patients and healthy controls were found in the number of correct responses in a sentence comprehension task, in spite of abnormal ERP correlates of semantic processing modulated by mood. Together, these findings suggest the importance of combining methodologies for a better understanding of specific cognitive processes, indicating that behavioral measures are limited when trying to understand atypical developmental pathways. Since the often divergent behavioral and function results may lead to contrasting theoretical conclusions, both sources of data provide the most accurate description of processes under study, elucidating whether overt behavior is normal or underpinned by atypical brain processes.

2. Findings from WS and schizophrenia also suggest the robust character of the language acquisition process, despite atypical development constraints, as proposed by Brock (2007) regarding WS:

"...the significance of WS is not that it demonstrates how language can develop independently of cognition, or that it provides an example of a radical departure from normal language development. Rather, WS illustrates quite how robust the language acquisition process is. In any complex system (including language), robustness is achieved through redundancy, ensuring that subtle malfunctioning of a component is not catastrophic for the system" (p. 120). Language abilities are thus the product of altered constraints on general cognitive, linguistic, and brain development. In other words, language acquisition is heavily constrained by the brain that is acquiring the language (Fowler, 1998).

Therefore, contrary to initial claims proposing the modularity of language and its independence from general cognition in Williams Syndrome, our findings are consistent with previous studies that show that children and adolescents with WS perform well on some language tasks but they rarely, if ever, perform at their chronological age level (Karmiloff-Smith et al., 1995, 1997), which suggests the interdependence of language and cognition (Mervis & Becerra, 2007).

3. Moreover, findings from studies 1 and 2 point to the need of tracing full developmental trajectories, to a better understanding of behavior and brain activity over time. Future studies should include different typically developing groups of different chronological ages in order to better understand what changes from one developmental stage to another in WS, electrophysiologically and behaviorally: the end states of cognition are not necessarily identical to its starting point, since development is dynamic and brain systems are interactive (e.g., Karmiloff-Smith, 1998; Mareschal et al., 2007).

4. Both studies on Williams Syndrome and schizophrenia provide additional evidence for the complex interactions between genes, brain, and environment, arguing in favour of an interactive specialization view of functional brain development and demonstrating how differences in genotype are related to phenotype differences. Several levels of analysis and complex developmental interactions lie between genes and behavior (Karmiloff-Smith, 1998; Pennington, 2001). In fact, due to the interactive properties of brain development processes, it is implausible that specialized systems in the brain could develop normally and the surrounding ones atypically. This is supported by studies showing that a specific functional brain system develops in the context of other brain systems (Mareschal, Johnson, Sirois, Spratling, Thomas, & Westermann, 2007).

Williams Syndrome represents a case of development that is atypical since the beginning. In spite of early claims defending the modularity of language in this syndrome (Bellugi, Marks, Bihrle, & Sabo, 1988; Bellugi, Bihrle, Neville, Jernigan, & Doherty, 1992; Pinker, 1994), both studies on semantic and prosody processing suggest atypical brain processes related with language processing.

Schizophrenia is also an example of the complex interplay of genes, brain and behavior, and of the importance of timing in key neural developmental events (in this case, the end of adolescence), which can lead to atypical cognitive outputs. According with more recent conceptual models of schizophrenia, namely the neurodevelopmental model (see Rapoport, Addington, & Frangou, 2005), an atypical developmental pathway underlies this disorder, with progressive brain changes and subtle cognitive, motor, and behavioral deviations seen before illness onset. The structural brain abnormalities that characterize schizophrenia, related to susceptibility genes interacting with environmental factors (e.g., Tsuang, 2000), are thus linked to brain function atypicalities, as evinced by our studies on prosody processing and on the effects of mood on semantic processing.

In sum, these findings show the dynamic nature of the brain system that, in spite of developmental constraints, tends to adapt and generate appropriate behaviors (Ashby, 1952).

Since the major disadvantage of ERP is its lack of spatial resolution (compensated by its advantageous temporal resolution), future studies should integrate spatial and temporal information (fMRI studies are warranted) in order to get a more comprehensive view of brain processes during cognitive operations in both atypical developmental pathways, in particular semantic and prosody processing.

We believe that insights gained from this investigation will significantly improve our understanding of language and communication dysfunction in both WS and schizophrenia, providing impetus for further studies on language and social cognition, and serving as springboard for therapeutic interventions.

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APPENDIX

Appendix 1

A PRELIMINARY STUDY FOR THE DEVELOPMENT OF EXPERIMENTAL STIMULI

Sentence final word completion norms for European Portuguese children and adolescents: effects of age and sentence context

Abstract

This study presents a set of sentence contexts and their cloze probabilities for European Portuguese children and adolescents. Seventy-three sentence contexts (35 low- and 38 high-constraint sentence stems) were presented to 90 children and 102 adolescents. Participants were asked to complete the sentence contexts with the first word that came to their mind. For each sentence context, responses were listed and cloze probabilities of the words chosen to complete that sentence context were computed. Additionally, idiosyncratic and incorrect responses (structural and semantic errors) were analyzed. A high degree of consistency in responses among the two age samples (children and adolescents) was found, along with a decrease of idiosyncratic and incorrect responses in older participants. Differences were more evident in responses to low contextually constraining sentences.

These results shed light on age-related changes in the effects of linguistic context (high and low constraining) on word production, and also in knowledge's representation.

Key-words: cloze probability, sentence constraint, semantic memory, development

1. Introduction

How do we know that a cat can eat a mouse, but not a shark? The answer would depend on whether a shark in question is an ocean dwelling predator or a biscuit for cats in the shape of a shark. Also, for the following sentence context – "They immediately swam to shore because they thought it was a…", the word "shark" would be expected if the subject was provided in first place with the context "Two teenage boys were swimming off the coast of Florida when they noticed a suspicious looking dorsal fin". Semantic context has, thus, a crucial role in language comprehension. The way that language helps to organize the knowledge of the world, representing objects, events and relationships, arranging items in categories and providing meaning tools, seems to be a unique human legacy and an evolutionary advantage (Lieberman, 2000).

Specifically, the ability to use sentence context in order to constrain semantic choices (words) is a crucial process in sentence comprehension, allowing the listener/reader to determine meanings and solve potential ambiguities. For example, classical models of semantic processing (e.g., Collins & Loftus, 1975; Collins & Quillian, 1969; Loftus, 1973) suggest that words are organized in a semantic network of interconnected nodes of related meanings. During sentence processing, components of the lexical network are activated by the phonological or orthographic input that the person is processing, as well as by the context that these words create. As the sentence progresses and the context emerges, inhibitory mechanisms suppress those nodes that were previously activated but no longer appropriately complete the sentence (Kimble et al., 2002; Stanovich & West, 1981). More recent models, as the Parallel Distributed Processing (PDP) approach (Rogers & McClelland, 2004), go further saying that a system of massively interconnected processing units underlies semantic processing. The pattern of activation between these units is then ruled by weighted connections among units. In addition, changes in these weights, as a consequence of daily experience or learning, are the basis for the development of semantic knowledge.

The basic assumptions of activation models of semantic memory are supported by several studies suggesting that human beings, besides being meaning creators, also generate expectations based on the linguistic input they are receiving (DeLong, Urbach, & Kutas, 2005; Federmeier et al., 1999 a, 1999 b; Hagoort, Hald, Bastiaansen, & Petersson, 2004; Kamide, Altmann, & Haywood, 2003; Neely, 1991; Otten, Nieuwland, & Van Berkum, 2007; Otten & Van Berkum, 2007; Pickering & Garrod, 2007; Taraban & McClelland, 1988; Van Berkum, Brown, Zwitserlood, Kooijman, & Hagoort, 2005; Van Berkum, Hagoort, & Brown, 1999; Van Berkum, Zwiserlood, Hagoort, & Brown, 2003; Wicha, Bates, Moreno, & Kutas, 2003).

One task that has been widely used for testing the effects of semantic expectation (Williams & Colombo, 1995), as well as the effects of semantic context (Bloom & Fischler, 1980; McDonald & Tamariz, 2002), is the sentence completion task. The pioneer work of Bloom and Fischler (1980) contributed to a better understanding of how word associations can be constrained by linguistic context. Traditionally, this task consists of asking subjects to read a set of sentence contexts and to complete the last fragment with the first word that comes to their mind (Taylor, 1953). The responses obtained through this task allow the computation of cloze probabilities, i.e., the probability that a word can appropriately complete a given sentence context (Taylor, 1953). This process reflects the effects emerging from multiple-level constraints (syntactic, semantic and pragmatic) and that will govern the choice of a word for a specific context (Connoly, Phillips, & Forbes, 1995; Kohn & Cragnolino, 1998; Lahar, Tun, & Wingfield, 2004; van den Brink, Brown, & Hagoort, 2001). If the sentence context is highly constraining (i.e., allowing one or very few plausible completion words), the cloze probability of that word is going to be higher than if the context provides low constraint (allowing several possible completions) (Schwanenflugel & LaCount, 1988; Schwanenflugel & Shoben, 1985).

Norms for sentence completion are currently available for English (e.g., Bloom & Fischler, 1980; Schwanenflugel, 1986; Towse, Hamilton, Hitch, & Hutton, 2000), French (Robichon, Besson, & Faita, 1996), and Spanish (McDonald & Tamariz, 2002), although no similar norms exist for European Portuguese.

These norms constitute a valuable resource for several areas of research, including psycholinguistics, human memory, and neuroscience (e.g., Federmeier, McLennan, Ochoa, & Kutas, 2002; Griffin & Bock, 1998; Kleiman, 1980; Lahar, Tun, & Wingfield, 2004; Stanovich & West, 1983), allowing us to understand the cognitive and neurocognitive mechanisms underlying processes of language comprehension and production (e.g., Cramer, 1968). Also, they have been used for the study of clinical populations, namely aphasia (Berndt, Mitchum, Haendinges, & Sandson, 1997), Alzheimer's disease (Nebes & Brady, 1991), schizophrenia (Kircher et al., 2001) and posttraumatic stress disorder (Kimble et al., 2002). These norms are also useful for event-related potentials (ERP) studies of language aiming to understand the neural processes underlying language comprehension. Results of these studies show that expected sentence endings elicit smaller N400 amplitudes (an index of semantic integration and expectedness) than unexpected endings (e.g., Curran, Tucker, Kutas, & Posner, 1993; Kutas & Hillyard, 1980; Federmeier & Kutas, 1999 a,b).

The importance of these norms for studies on semantic memory structure is also well documented (e.g., Federmeier et al., 2002; Federmeier, Kirson, Moreno, & Kutas, 2001; Federmeier & Kutas, 1999a, 1999b, 2001; Kounios & Holcomb, 1992). Developmentally, differences in the words chosen to complete a given context (as in a sentence completion task) may be explained by changes in the structure and process of semantic memory. For example, studies showed that the number of words produced in verbal fluency tasks increases with age (e.g., Bjorklund, 1987; Bjorklund, & Marchena, 1984), indicating an increase in vocabulary size (Kausler & Puckett, 1980). Other studies showed lexical and conceptual changes around 7-8 years of age (Carneiro, Albuquerque, Fernandes, & Esteves, 2004; Cronin, 2002; Francis, 1972; Nelson, 1977; Petrey, 1977), in particular a higher number of syntagmatic responses (words that are associated in a syntactic sequence – e.g., *cold - outside*) than paradigmatic responses (associates from the same grammatical class– e.g., *cold – hot*) in younger than in older children. A raise in the commonality of responses and paradigmatic responding, in both older children and adults, has also been reported (Rosenzweig, 1964; Sharp & Cole, 1972).

Moreover, the organization of knowledge seems to change from thematic (items that share an interactive or functional relationship – e.g., "*dog-bone*") to taxonomic (items that belong to the same category - e.g., "*river-lake*") relationships (Markman, 1990; Markman & Dietrich, 2000; Markman & Hutchinson, 1984; Nelson, 1977; Sell, 1992; Smiley & Brown, 1979), and lexical representations tend to become more segmental and less holistic, as vocabulary increases (Elbro, 1996; Storkel, 2002, 2009). There is also evidence pointing to changes in the relative influence of contextual and stimuli factors on word recognition as reading fluency develops, with young children relying more on contextual information to aid word recognition and adults showing increased automatic word processing abilities (Schwantes, Boesl, & Ritz, 1980; West & Stanovich, 1978; West, Stanovich, Feeman, & Cunningham, 1983).

Together these findings suggest that, throughout development, the structure of semantic memory undergoes changes not only in terms of the number of items in semantic networks, but also in terms of the richness of representations and items' accessibility (e.g., Bjorklund, 1984, 1987; Chi & Ceci, 1987; Gathercole, Willis, Emslie, & Baddeley, 1992; Munson, Swenson, & Manthei, 2005; Schneider & Pressley, 1997; Storkel, 2002, 2009; Swingley, 2003; Vicente, Castro, & Walley, 2003). Also, they indicate that these changes are supported by the dynamic interaction of individual factors (e.g., maturation) and environmental variables (e.g., education) (see Thomas & Karmiloff-Smith, 2002, 2003).

Because of the utility of sentence completion norms for several research domains, studies have already been conducted in different languages with the aim of developing these norms with an adult population (e.g., Bloom & Fischler, 1980), but few have been conducted with children (Towse, Hutton, & Hitc, 1997, 1998), and none in Portugal.

The utility of age-adjusted norms is critical for the development of reliable research in psycholinguistics, as well as in developmental and neurolinguistics research (see also Lahar, Tun, & Wingfield, 2004).

This study describes a set of 73 sentence contexts (varying from highly to low constraining contexts) and their cloze probabilities for European Portuguese children and adolescents. In addition, one of its aims was to compare the responses of children and adolescents to the sentence completion task, analyzing potential developmental changes in the number of correct and incorrect responses, as well as in the number of singular words produced by each group for each sentence context. Three measures were used: (a) cloze probability (the number of times the same word was chosen by a specific group for a given sentence context, considering the size of that group); (b) idiosyncratic responses (the number of correct responses produced by only one individual of a given group for a specific sentence context); and (c) incorrect responses (the number of inappropriate responses, at a structural or semantic level, produced by a given group for a specific sentence context). Age-related changes were expected. These changes would be consistent with the developmental pathway that corresponds to vocabulary growth and to the construction of semantic associations, related with the developmental course of schematic and taxonomic knowledge.

2. Methods

2.1. Participants

Ninety children (*Mean age* = 9.19; *SD* = 1.35; age range: 6-11) and 102 adolescents (*Mean age* = 14.69; *SD* = 1.94; age range: 12-18) participated in this study. All participants were European Portuguese native speakers from both genders (children: 50 females and 40 males; adolescents: 73 females and 29 males). They were recruited in elementary and high schools in the North of Portugal. All participants were monolingual or had knowledge in other languages equivalent to their educational level. None of them were identified by their teachers as having learning or intellectual disabilities.

2.2. Materials

Seventy three sentence contexts were developed. All sentences had the same syntactic structure (subject and direct verb in the present tense - SVO). The number of words per sentence context was kept constant (4).

Sentences were coded by two adult independent judges, graduates in Portuguese Literature, as *low contextual constraint sentences* (e.g., *"The woman smells a..."*), if they allowed for several appropriate endings, or as *high contextual constraint sentences* (e.g., "*The girl is curling the*..."), if the semantic context was sufficiently restrictive in order to allow only one or two plausible endings. Differences in judges' assessment were resolved by consensus. However, in the situations when there was no agreement between them, a third independent judge (also graduated in Portuguese Literature) decided the final rating. For all the sentences, inter-rater agreement was higher than 90%. Thirty five sentences were classified as low-constraint and thirty eight sentences were judged as high-constraint (see Appendix 1A).

A booklet with 73 sentence contexts was used to collect responses from participants. Sentence contexts from which the last word was missing were printed in white paper (Arial Narrow font, size 13), with a blank space in the end of each context where subjects could write down their responses. The order of the sentence contexts was pseudo-randomized before presentation to the groups (in order to avoid potential effects of lexical or semantic association between one sentence and the following one), but the order of these sentences remained constant across participants.

2.3. Procedure

All children and adolescents were tested in the classroom. They were told to read the sentences and complete each one with the first word that came to their mind and that made sense, writing down the response in the booklet. The instructions emphasised that they did not have to think much about it. Also, they were encouraged to complete all items and not to look at what their classmates were writing. Younger participants were told to skip a sentence context if they had difficulties in completing it. The second graders were helped with the task, so that when they had difficulties in reading and/or writing, it was the experimenter who wrote the words in the booklet.

All legible responses were registered in the dataset. The words chosen by the participants were ranked for each sentence context, in an ascending order, according to its frequency (the number of times each word was used to complete a given sentence context relative to the total number of responses for that context). Sentence completion norms for children and adolescents are provided in Appendix 1A. For each correct response, cloze probability (the number of times the same word was chosen by a specific group for a given sentence context) was computed.

Additionally, in order to understand how the production of less common words and incorrect responses differs across groups, the number of idiosyncratic (correct words generated by only one individual) and incorrect responses (words that do not appropriately complete the sentence) was computed. Incorrect responses were classified as structural or semantic errors. Structural errors were defined as final words that do not fit the previous context in a syntactically appropriate way (e.g., disagreement in number or gender, as in "*The lady smells a perfumes*"). Semantic errors represent sentence endings that do not fit the previous context in a semantically correct way (e.g., the final word doesn't have any semantic relationship with the subject and/or the verb of the sentence, as in "*The grandmother prays a story*"). Correct and inappropriate responses were identified after the classification made by three judges (those who have also classified sentence contents as low or high-constraint). Words were classified as incorrect when at least two agreed that the word was not appropriate given the syntactic structure or semantic context of the sentence.

3. Results

All correct final words, idiosyncratic responses, structural errors, and semantic errors for each sentence context and group are listed in Appendix 1A. Blanks and illegible responses (1.41% for children and 0.42% for adolescents) were excluded from the analyses.

Repeated-measures analyses of variance (ANOVA) were conducted in order to analyze group differences in the mean number of correct responses with higher cloze probability, idiosyncratic responses, and structural and semantic errors.

ANOVAs were calculated with group (children vs. adolescents) as between-subjects factor and sentence condition (low vs. high- constraint) as within-subjects factor, separately for each type of responses (correct responses, idiosyncratic responses, structural and semantic errors), using Bonferroni procedure correction for multiple comparisons. For correct responses with the highest cloze probability, separate analyses were conducted for high- and low-constraint sentence contexts, including sentence condition as within-subjects factor. However, for low-constraint sentences, the second and third words with higher cloze probability were also analyzed since, as expected, low constraining contexts elicited higher responses diversity.

The Geisser-Greenhouse correction (Geisser & Greenhouse, 1959) was applied to all repeated-measures with greater than one degree of freedom in the numerator.

3.1. Correct responses with higher cloze probability

Table 1 shows cloze probability values for the words with the highest cloze probability for both high and low-constraint sentences, and for the words with the second and third higher scores of cloze probability in the latter condition.

Table 1. Mean cloze probability (standard deviation in brackets) for the most selected word in high- and low-constraint sentence contexts, by children and adolescents.

	High-Constraint	Low-Constraint
Children	**Word 1:** 0.804 (0.008)	**Word 1:** 0.496 (0.010)
		Word 2: 0.149 (0.063)
		Word 3: 0.088 (0.046)
Adolescents	**Word 1:** 0.829 (0.007)	**Word 1:** 0.561 (0.009)
		Word 2: 0.147 (0.056)
		Word 3: 0.075 (0.049)

The word with the highest cloze probability for each sentence context was the same in both age groups for the majority of sentences. It is of note that in only five sentence contexts of out 73 (one high-constraint and four low-constraint), the most frequently selected word differed between groups (see Appendix 1A).

Age of acquisition and written frequency of the word with the highest cloze probability were collected from European Portuguese lexical databases (Marques et al., 2007; Nascimento, Casteleiro, Marques, Barreto, & Amaro, no date). Low age of acquisition (*M* = 1.95; *SD* = 0.55) and high written frequency (*M* = 163.45; *SD* = 229.51) characterized these responses.

Despite the fact that the most chosen word was the same in children and adolescents, ANOVAs for words with the highest cloze probability in low- and high-constraint sentence contexts showed differences between groups, as evidenced by a main effect of group ($F_{1, 190}$=20.17, *p*=.000). The cloze probability of these words was higher in the adolescents group, indicating that more subjects in this group selected the same response. A main effect of sentence context was also observed ($F_{1, 190}$=2000.11, *p*=.000), showing that cloze probability was higher for high-constraint than for low-constraint sentences. This effect interacted with group ($F_{1, 190}$= 9.91, *p*=.002): the cloze probability of the most selected word for both types of sentence contexts was higher in the adolescents group relative to children.

No group differences were observed for the second word with the highest cloze probability in low-constraint sentences. Nonetheless, a marginally significant difference was noted for the third word ($F_{1, 190}$=3.58, *p*=.060), indicating higher cloze probabilities in the children group relative to adolescents.

3.2. Idiosyncratic responses

Figure 1 presents the mean number of idiosyncratic responses for children and adolescent groups, in low- and high-constraint sentences (see also Appendix 1A).

1. Idiosyncratic responses

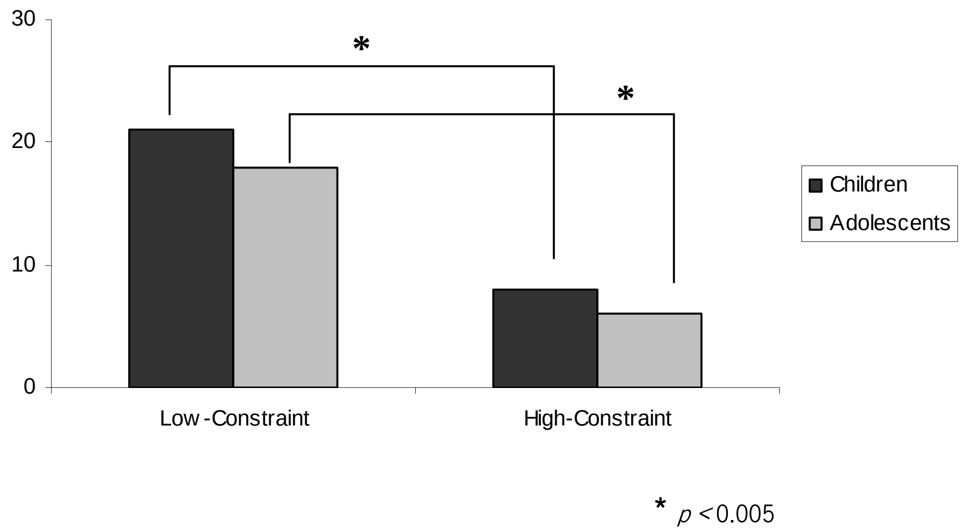

Fig. 1. Mean number of idiosyncratic responses (%) per age group (children and adolescents), for low- (LC) and high- (HC) constraint sentence contexts.

Statistical analysis revealed a main effect of group ($F_{1,\ 190}$=7.12, *p*=.008) and sentence context ($F_{1,\ 190}$=446.16, *p*=.000). A higher number of idiosyncratic responses was observed in children than in adolescents, and in low relative to highly constraining sentence contexts.

3.3. Incorrect responses

Figures 2A and 2B present the percentage of incorrect responses for low and highly constraining sentence contexts (see also Appendix 1A).

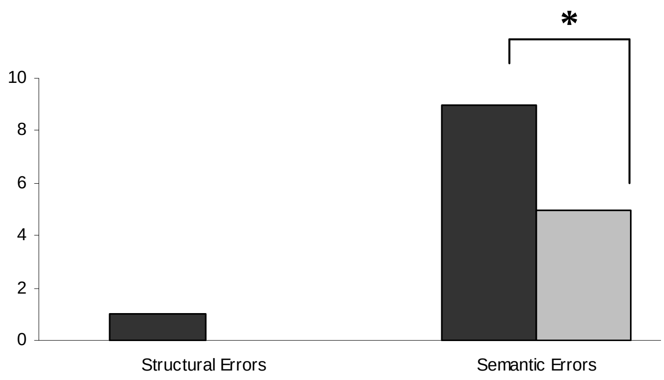

Figure 2-A. Mean number (%) of structural and semantic errors per age group (children and adolescents), for low-constraint sentence contexts.

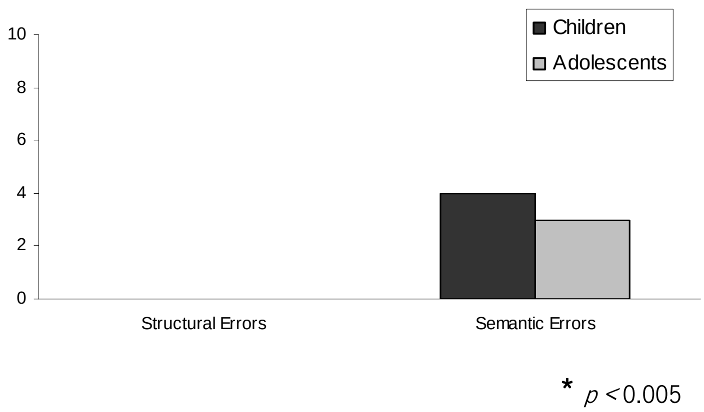

Figure 2-B. Mean number (%) of structural and semantic errors per age group (children and adolescents), for high-constraint sentence contexts.

No differences between groups or sentence conditions were observed for structural errors (see Figures 2A and 2B), which were almost nonexistent.

For semantic errors, a main effect of group ($F_{1,\ 190}$=19.06, *p*=.000) and sentence context ($F_{1,\ 190}$=91.79, *p*=.000) was observed. More errors were found in the younger group than in adolescents. Also, a higher number of semantic errors was observed for low-constraint relative to high-constraint sentence contexts. A significant sentence context x group interaction ($F_{1,\ 190}$=14.94, *p*=.000) was also found. Groups differed but only for low-constraint sentences, for which more semantic errors were found in children.

Summary

Overall, the findings point out that, as age progresses, the number of idiosyncratic and inappropriate responses decreases, while the number of common responses increases, as demonstrated by the cloze probability ratings. However, for the majority of the sentences, the final word most frequently evoked is similar across both age groups.

4. Discussion

The current study aimed to accomplish a double goal: first, to contribute to the development of preliminary completion norms for 73 sentence contexts in European Portuguese that varied from high (38) to low-constraint (35); second, to explore developmental differences, from childhood to adolescence, in the cloze probability of the produced words, as well as in the number of idiosyncratic and incorrect responses (structural and semantic errors).

Regarding developmental changes in the responses for the sentence completion task, the results of this study prompt two major conclusions: (a) during development, there is a reduction in the number of idiosyncratic responses and semantic errors; and, nonetheless, (b) there is an increased consistency in the type of appropriate final words chosen to complete a specific sentence context.

On one hand, the fact that the majority of subjects in each group chose the same word for almost all of the sentence contexts points to some consistency in word selection and seems to support the idea that early in development, humans have powerful learning mechanisms for extracting regularities in the environment and constructing common representations about things in the world and about how things work (Bates, Dale, & Thal, 1995; Bathes, Thal, Finlay, & Clancy, 1992; Thomas & Karmiloff-Smith, 2005).

On the other hand, cloze probability was higher for adolescents, indicating that consistency in word selection tends to increase during development. This tendency was more pronounced for highly constraining sentences than for low constraining sentences, confirming previous studies showing that higher constraint strength leads to higher predictability of the sentence final word, thus reducing uncertainty about possible final word choices, in comparison with low-constraint sentence contexts (Schwanenflugel & LaCount, 1988). Several studies proved that highly constraining semantic contexts facilitate its completion with the most predictable word (e.g., Schwanenflugel & LaCount, 1988; Schwanenflugel & Shoben, 1985), while low constraining sentence contexts facilitate the retrieval of less predictable items. In addition, other studies on sentence comprehension showed that context activates a set of semantic features related with it, as features of the category of the most expected exemplar are activated even before the presentation of the actual final word (e.g., DeLong, Urbach, & Kutas, 2005; Van Petten, Coulson, Rubin, Plante, & Parks, 1999). These results are corroborated electrophysiologically by a reduction of N400 amplitude to within-category violations (unexpected words that belong to the same semantic category of the expected exemplar) than to between-category violations (unexpected words that do not belong to the same semantic category of the expected exemplar) (Federmeier & Kutas, 1999a, 1999b).

A finding worth noting is that the most selected word for each sentence context, in both groups, had a low age-of-acquisition. This finding is consistent with previous studies that suggest that words acquired early in life are processed faster and more accurately than words that are acquired later (e.g., Carroll & White, 1973); arguably, such words can be also activated more quickly in the semantic network.

Moreover, the diversity and number of idiosyncratic responses diminished with age. These findings also corroborate previous studies that documented an increase of commonality of responses and paradigmatic responding with years of education (Rosenzweig, 1964; Sharp & Cole, 1972). Clearly, differences in life experiences of participants can affect the availability of relevant concepts, as proposed by the PDP approach (Rogers and McClelland, 2004). According to this model, daily experience modulates the weights of semantic units and therefore the structure of semantic knowledge. For example, it is known that education exerts its effects on word associations, since schooling promotes the learning of standard definitions of words, reducing the occurrence of atypical and incomplete semantic representations of word meaning (Burke & Peters, 1988). This may explain the higher level of idiosyncratic responses in younger participants. Furthermore, another hypothesis to explain the higher production of uncommon or idiosyncratic responses in younger ages would be the representation of an incomplete or atypical word meaning (Burke & Peters, 1988; Hunt, 1978). In fact, previous studies indicated differences in mental representation of words in the developing lexicon, compared with the fully developed lexicon (Charles-Luce & Luce, 1990, 1995; Dollaghan, 1994; Metsala & Walley, 1998; Storkel, 2002), and also a gradual refinement of conceptual knowledge, which is less based on scripts and is more abstract and categorically organized as age increases (e.g., Nation & Snowling, 1999; Nelson, 1977, 1982). Together, these studies point to the interplay of individual (e.g., maturation) and contextual (e.g., education) factors on semantic and lexical development.

Regarding semantic errors, their number was also different between age groups, indicating that semantic structure is being consolidated throughout development. These result may be explained by previous evidence stating that, during development, weak connections between semantic representations and lexical labels are found in the lexicon of younger children, in comparison with adolescents and adults (e.g., Gershkoff-Stowe, 2001;McGregor, 1997; McGregor, Friedman, Reilly, & Newman, 2002; Plunkett, Karmiloff-Smith, Bates, Elman, & Johnson, 1997). This same trend was found in studies on picture naming performance, which suggested a correlation between the depth of semantic knowledge and the success of word retrieval (Capone & McGregor, 2005; McGregor et al., 2002).

Together, our findings point to developmental differences in word selection during a sentence completion task, in particular, in the number of semantic errors, idiosyncratic responses and cloze probability of the words chosen by the majority of participants. Despite those differences, consistency in word selection was evident especially for high-constraint sentence contexts, as evinced by the fact that the same word was chosen by the majority of subjects in both groups for almost all of the sentence contexts.

These norms are thus expected to contribute to cognitive and neurocognitive research using the European Portuguese language, either in the selection of stimuli for experimental paradigms, or in the assessment of responses provided by participants.

In spite of these contributions, some limitations might be taken into account. First, due to the size of our samples, normative data are still preliminary, so that more participants are needed in future studies, including samples from other regions of the country. Second, caution is needed when generalizing the norms for other Portuguese-speaking populations in Africa and America, because cloze probabilities can be influenced by cultural and linguistic specificities, as pointed out by previous studies (see also Arcuri, Rabe-Hesketh, Morris, & McGuire, 2001; Carneiro et al., 2004).

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Appendix 1A

Note: Numbers indicate cloze probabilities.

SENT NR	SENTENCE	GROUP	CORRECT RESPONSES	IDIOSYNCRATIC RESPONSES	INCORRECT RESPONSES	
			Most frequent (descending order)		**Syntactic errors**	**Semantic errors**
I. High-constraint Sentences						
1	A menina penteia o... (*The girl curls the...*)	*Children*	Cabelo (*Hair*): 0.99	Bebé (0.01)	0	0
		Adolescents	Cabelo (*Hair*): 0.96	0	0	Cão (*Dog*): 0.04
2	A cozinheira acende o... (*The cook lights the...*)	*Children*	Fogão (*Cooker*): 0.74 Forno (*Oven*): 0.11 Fósforo (*Match*): 0.03 Lume (*Fire*): 0.09	Candeeiro (*Lamp*): 0.01	0	Jantar (*Dinner*): 0.01
		Adolescents	Fogão (*Cooker*): 0.85 Lume (*Fire*): 0.06 Forno (*Oven*): 0.04 Fósforo (*Match*): 0.04	0	0	Feijão (*Beans*): 0.01
4	A criança bebe o... (*The child drinks the...*)	*Children*	Leite (*Milk*): 0.75 Biberão (*Bottle*): 0.07 Sumo (*Juice*): 0.18	0	0	0
		Adolescents	Leite (*Milk*): 0.95 Sumo (*Juice*): 0.03	Biberão (*Bottle*): 0.01 Refrigerante (*Soda*): 0.01	0	0
5	A galinha põe um... (*The chicken lay a..*)	*Children*	Ovo (*Egg*): 0.99	0	0	Pintainho (*Chick*): 0.01
		Adolescents	Ovo (*Egg*): 1	0	0	0
8	A pulseira enfeita o... (*The bracelet decorates the...*)	*Children*	Pulso (*Wrist*): 0.44 Braço (*Arm*): 0.41 Menino (*Boy*): 0.03	Filho (*Son*): 0.01 Boneco (*Doll*): 0.01	0	Cão (*Dog*): 0.01 Quarto (*Room*): 0.01 Fato (*Suit*): 0.01 Bolo (*Cake*): 0.01 Colar (*Necklace*): 0.02 Diário (*Diary*): 0.01 Pescoço (*Neck*): 0.01
		Adolescents	Pulso (*Wrist*): 0.60 Braço (*Arm*): 0.40	0	0	0
9	A meia aquece o...	*Children*	Pé (*Foot*): 0.93	0	0	Arroz (*Rice*): 0.01

	(*The sock warms the ...up*)					Comer (*Food*): 0.02 Forno (*Oven*): 0.01 Lavadouro (*Desk*): 0.01 Pente (*Comb)*: 0.01
		Adolescents	Pé (*Foot*): 0.93	0	0	Almoço (*Lunch*): 0.01 Café (*Coffee*): 0.01 Leite (*Milk*): 0.01 Pão (*Bread*): 0.01 Corpo (*Body*): 0.01
10	A noiva compra um... (*The bride buys a...*)	*Children*	Vestido (*Dress*): 0.87 Anel (*Ring*): 0.06 Ramo (*Bunch*): 0.06	Véu (*Veil*): 0.01	0	Fato (*Suit*): 0.01
		Adolescents	Vestido (*Dress*): 0.87 Anel (*Ring*): 0.07 Ramo (*Bunch*): 0.03 Véu (*Veil*): 0.03	0	0	0
14	A menina cala a... (*The girl shuts her...*)	*Children*	Boca (*Mouth*): 0.59 Gata (*Cat*): 0.06 Irmã (*Sister*): 0.08 Bebé (*Baby*): 0.05 Mãe (*Mother*): 0.03 Colega (*Colleague*): 0.02 Cadela (*Dog*): 0.06	Outra (*Other*): 0.01 Amiga (*Friend*): 0.01 Professora (*Teacher*): 0.01 Empregada (*Waitress*): 0.01 Criança (*Child*): 0.01 Matraca (*Mouth*) [Colloquial]: 0.01	0	Montanha (*Mountain*): 0.01 Boneca (*Doll*): 0.02
		Adolescents	Boca (*Mouth*): 0.76 Irmã (*Sister*): 0.02 Mãe (*Mother*): 0.03 Colega (*Colleague*): 0.03 Amiga (*Friend*): 0.04 Cadela (*Dog*): 0.04	Gata (*Cat*): 0.01 Bebé (*Baby*): 0.01 Outra (*Other*): 0.01 Criança (*Child*): 0.01	0	Boneca (*Doll*): 0.02 Folha (*Leaf*): 0.02
17	A avó reza uma... (*The grandmother says a...*)	*Children*	Oração (*Prayer*): 0.53 Avé-Maria (*Hail Mary*): 0.29 Vez (*Once*): 0.04	Reza (*Prayer*): 0.01 Santa-Maria (*Saint Mary*): 0.01	0	Cantiga (*Song*): 0.01 Planta (*Plant*): 0.01 Filha (*Daughter*): 0.01 Quadra (*Poem*): 0.01 Missa (*Mass*): 0.02 Promessa (*Promise*): 0.01 Lenda (*Legend*): 0.01

						História (*Story*): 0.01 Cruz (*Cross*): 0.01
		Adolescents	Oração (*Prayer*): 0.54 Avé-Maria (*Hail Mary*): 0.24 Vez (*Once*): 0.02	Prece (*Prayer*): 0.01	0	Missa (*Mass*): 0.17 Coisa (*Something*): 0.01 Bênção (*Blessing*): 0.01 História (*Story*): 0.01
18	A torneira deita muita…	*Children*	Água (*Water*): 0.99			Salada (*Salad*): 0.01
	(*The tap pours lots of…*)	*Adolescents*	Água (*Water*): 0.99		Pinga (*Drop*): 0.01	
22	A abelha procura uma… (*The bee looks for a…*)	*Children*	Flor (*Flower*): 0.46 Casa (*House*): 0.15 Colmeia (*Beehive*): 0.32 Caixa com mel (*Box with honey*): 0.02	Árvore (*Tree*): 0.01 Coisa (*Thing*): 0.01	0	Pessoa (*Person*): 0.01
		Adolescents	Flor (*Flower*): 0.67 Casa (*House*): 0.02 Colmeia (*Beehive*): 0.24	0	0	Pessoa (*Person*): 0.03 Toca (*Burrow*): 0.01 Fábula (*Fable*): 0.01 Agulha (*Needle*): 0.01
23	A chave fecha a… (*The key closes the…*)	*Children*	Porta (*Door*): 0.98 Casa (*House*): 0.02	0	0	0
		Adolescents	Porta (*Door*): 0.95 Casa (*House*): 0.02 Fechadura (*Lock*): 0.02	Gaveta (*Drawer*): 0.01	0	0
27	O cofre guarda o… (*The safe saves the…*)	*Children*	Dinheiro (*Money*): 0.74 Tesouro (*Treasure*): 0.14 Ouro (*Gold*): 0.08	Segredo (*Secret*): 0.01 Anel (*Ring*): 0.01	0	Motor (*Engine*): 0.01
		Adolescents	Dinheiro (*Money*): 0.73 Tesouro (*Treasure*): 0.11 Ouro (*Gold*): 0.15	Segredo (*Secret*): 0.01 Anel (*Ring*): 0.01	0	0
28	O mecânico compõe o… (*The mechanic repairs the…*)	*Children*	Carro (*Car*): 0.86 Pneu (*Tyre*): 0.02 Camião (*Truck*): 0.02 Motor (*Engine*): 0.03 Automóvel (*Car*): 0.02	Jipe (*Jeep*): 0.01 Autocarro (*Bus*): 0.01 Triciclo (*Tricycle*): 0.01	0	Parafuso (*Screw*): 0.01
		Adolescents	Carro (*Car*): 0.88 Pneu (*Tyre*): 0.02 Motor (*Engine*): 0.05	Camião (*Truck*): 0.01 Jipe (*Jeep*): 0.01 Automóvel (*Car*): 0.01	0	Parafuso (*Screw*): 0.01 Óleo (*Oil*): 0.01
29	O motorista conduz o… (*The driver drives the…*)	*Children*	Autocarro (*Bus*): 0.40 Carro (*Car*): 0.26 Camião (*Truck*): 0.11	Comboio (*Train*): 0.01	Veículo (*Vehicle*): 0.01	Avião (*Airplane*): 0.02

			Táxi (*Taxi*): 0.09 Automóvel (*Car*): 0.10			
		Adolescents	Autocarro (*Bus*): 0.38 Carro (*Car*): 0.25 Camião (*Truck*): 0.24 Táxi (*Taxi*): 0.05 Automóvel (*Car*): 0.05	Comboio (*Train*): 0.01	Veículo (*Vehicle*): 0.02	0
30	O padeiro faz o… (*The baker cooks the…*)	*Children*	Pão (*Bread*): 0.98	Molete (*Bread*) [regionalism]: 0.01 Bolo (*Cake*): 0.01	0	0
		Adolescents	Pão (*Bread*): 0.95 Bolo (*Cake*): 0.04	Bolo-rei (*Christmas Cake*): 0.01	0	0
32	O rapaz calça o… (*The boy wears the…*)	*Children*	Sapato (*Shoe*): 0.93 Ténis (*Sneakers*): 0.03	Calçado (*Footwear*): 0.01 Chinelo (*Slipper*): 0.01 Pé(*Foot*): 0.01	0	0
		Adolescents	Sapato (*Shoe*): 0.90 Calçado (*Footwear*): 0.03 Chinelo (*Slipper*): 0.02 Ténis (*Sneakers*): 0.03	24 [shoes' size]: 0.01 38 [shoes' size]: 0.01	0	0
33	O bombeiro apaga o… (*The fireman puts the …out*)	*Children*	Fogo (*Fire*): 0.91 Incêndio (*Fire*): 0.09	0	0	0
		Adolescents	Fogo (*Fire*): 0.96 Incêndio (*Fire*): 0.04	0	0	0
34	O gato caça um… (*The cat hunts a…*)	*Children*	Rato (*Mouse*): 0.84 Coelho (*Rabbit*): 0.04 Pássaro (*Bird*): 0.04	0	0	Lanche (*Snack*): 0.01 Cão (*Dog*): 0.02 Insecto (*Insect*): 0.01 Sapato (*Shoe*): 0.01 Peixe (*Fish*): 0.01
		Adolescents	Rato (*Mouse*): 0.95	Coelho (*Rabbit*): 0.01	0	Cão (*Dog*): 0.03 Pão (*Bread*): 0.01
35	O menino joga um… (*The boy plays a…*)	*Children*	Jogo (*Game*): 0.87 Bocadinho/bocado (*Little*): 0.03	Desporto (*Sport*): 0.01	Baralho de cartas (*Playing cards*): 0.01 Balão (*Ballon*): 0.01 Tazo [A kind of playing card]: 0.01 Pião (*Spinning top*): 0.01 Berlinde (*Marble*): 0.01	Golo (*Goal*): 0.01 Gato (*Cat*): 0.01 Limão (*Lemon*): 0.01
		Adolescents	Jogo (*Game*): 0.92	Bocadinho/bocado (*Little*): 0.01	Dado (*Dice*): 0.01 CD-Rom (*CD-Rom*): 0.01	0

					Pião (*Spinning top*): 0.03 Berlinde (*Marble*): 0.01 Xadrez (*Chess*): 0.01	
38	O pescador apanha um... (*The fisherman catches a...*)	*Children*	Peixe (*Fish*): 1.00	0	0	0
		Adolescents	Peixe (*Fish*): 0.97 Tubarão (*Shark*): 0.02	Robalo (*Sea bass*): 0.01	0	0
40	O pasteleiro dá um... (*The confectioner gives a...*)	*Children*	Bolo (*Cake*): 0.57 Pastel (*Cake*): 0.19 Pão (*Bread*): 0.17 Doce (*Sweet*): 0.02 Pastelão (*Big cake*): 0.02	Croissant (*Croissant*): 0.01 Rebuçado (*Sweet*): 0.01	0	0
		Adolescents	Bolo (*Cake*): 0.72 Pastel (*Cake*): 0.19 Pão (*Bread*): 0.02 Biscoito (*Biscuit*): 0.02	Doce (*Sweet*): 0.01 Pretzel: 0.01 Palito (*Toothpick*): 0.01 Grito (*Yell*): 0.01	0	Carro (*Car*): 0.01 Balão (*Balloon*): 0.01
41	O aluno afia o... (*The student sharpens the...*)	*Children*	Lápis (*Pencil*): 1.00	0	0	0
		Adolescents	Lápis (*Pencil*): 1.00	0	0	0
42	O coelho come uma... (*The rabbit eats a...*)	*Children*	Cenoura (*Carrot*): 0.88 Erva (*Grass*): 0.02	Alface (*Lettuce*): 0.01 Couve (*Cabbage*): 0.01 Flor (*Flower*): 0.01 Refeição (*Meal*): 0.01 Palha (*Straw)*: 0.01	0	Lebre (*Hare*): 0.02 Formiga (*Ant*): 0.02
		Adolescents	Cenoura (*Carrot*): 0.85 Couve (*Cabbage*): 0.02 Flor (*Flower*): 0.02 Erva (*Grass*): 0.02	Alface (*Lettuce*): 0.01 Planta (*Plant*): 0.01	0	Lebre (*Hare*): 0.03 Carne (*Meat*): 0.01 Coelha (*Rabbit*): 0.01 Perna (*Leg*): 0.01 Casca (*Peel*): 0.01
46	O jogador chuta a... (*The player shoots the...*)	*Children*	Bola (*Ball*): 1.00	0	0	0
		Adolescents	Bola (*Ball*): 1.00	0	0	0
47	O vendedor varre a... (*The seller sweeps up the...*)	*Children*	Loja (*Shop*): 0.60 Casa (*House*): 0.04 Cozinha (*Kitchen*): 0.07 Lixeira (*Trash*): 0.02	Sujeira (*Dirt*): 0.01 Manta (*Blanket*): 0.01 Sala (*Room*): 0.01 Carrinha (*Truck*): 0.01 Relva (*Grass*): 0.01 Pastelaria (*Confectionery*): 0.01	Vassoura (*Broom)*: 0.01	Secretária (*Desk*): 0.01 Estrada (*Road*): 0.02 Feira (*Fair*): 0.01 Rua (*Street*): 0.06 Roupa (*Clothes*): 0.01 Mesa (*Table*): 0.01

				Terra (*Ground*): 0.01		Banca (*Desk)*: 0.01 Poeira (*Dust*): 0.01 Mota (*Motorcycle*): 0.01 Praça (*Square*): 0.01 Tralha (*Stuff*): 0.01
		Adolescents	Loja (*Shop*): 0.44 Casa (*House*): 0.02 Cozinha (*Kitchen*): 0.03 Lixeira (*Trash*): 0.03 Entrada (*Entry*): 0.03 Varanda (*Balcony*): 0.05	Sala (*Room*): 0.01 Carrinha (*Truck*): 0.01 Barraca (*Tent*): 0.01 Sujidade (*Dirt*): 0.01 Papelaria (*Stationery*): 0.01 Calçada (*Sidewalk*): 0.01	0	Estrada (*Road*): 0.08 Rua (*Street*): 0.21 Banca (*Desk)*: 0.01 Porta (*Door*): 0.01 Desarrumação (*Mess*): 0.01 Colina (*Hill*): 0.02 Barreira (*Barrier*): 0.01
49	O trolha constrói uma... (*The builder builds a...*)	*Children*	Casa (*House*): 0.85 Parede (*Wall*): 0.06 Vivenda (*Villa)*: 0.02 Muralha (*Wall*): 0.02	Pensão (*Inn*): 0.01 Oficina (*Garage*): 0.01	0	Mesa (*Table*): 0.01 Bicicleta (*Bike*): 0.01
		Adolescents	Casa (*House*): 0.91	Parede (*Wall*): 0.01 Empresa (*Company*): 0.01 Obra (*Work*): 0.01 Habitação (*Housing)*: 0.01 Fábrica (*Factory)*: 0.01 Varanda (*Balcony*): 0.01 Escola (*School*): 0.01 Cozinha (*Kitchen)*: 0.01	0	0
50	O porteiro abre a... (*The porter opens the...*)	*Children*	Porta (*Door*): 0.92 Caixa (*Box*): 0.02	Mala (*Bag*): 0.01 Cancela (*Gate*): 0.01 Janela (*Window*): 0.01 Portela (*Little door*): 0.01 Portaria (*Entrance*): 0.01	0	0
		Adolescents	Porta (*Door*): 0.79 Portaria (*Entrance*): 0.05 Fechadura (*Lock*): 0.04 Casa (*House*): 0.02	Cancela (*Gate*): 0.01 Escola (*School*): 0.01 Caixa (*Box*): 0.01 Entrada (*Entrance*): 0.01 Garagem (*Garage*): 0.01 Cabine (*Cabin*): 0.01	0	0
52	O varredor utiliza a... (*The road sweeper uses the...*)	*Children*	Vassoura (*Broom*) 0.97	Escova (*Brush*): 0.01	0	Calculadora (*Calculator*): 0.01 Renda (*Rent*): 0.01
		Adolescents	Vassoura (*Broom*) 0.99	Pá (*Shovel*): 0.01	0	0

53	O espelho mostra a… (*The mirror shows the…*)	*Children*	Cara* (*Face*): 0.54 Imagem (*Image*): 0.16 Menina (*Girl*): 0.08 Figura (*Figure*): 0.06 Pessoa (*Person*): 0.07	Beleza (*Beauty*): 0.01 Estrada (*Road*): 0.01 Cidade (*City*): 0.01 Senhora (*Lady*): 0.01	0	Reflexão (*Reflection*): 0.06
		Adolescents	Cara* (*Face*): 0.37 Imagem (*Picture*): 0.37 Menina (*Girl*): 0.03 Figura (*Figure*): 0.02 Pessoa (*Person*): 0.13 Face (*Face*): 0.03	Parede (*Wall*): 0.01 Sombra (*Shadow*): 0.01 Criatura (*Creature*): 0.01 Realidade (*Reality*): 0.01 Verdade (*Truth*): 0.01	0	0
55	O árbitro segura o… *(The referee holds the…)*	*Children*	Apito (*Whistle*): 0.58 Cartão (*Card*): 0.13 Assobio (*Whistle*): 0.03 Jogador (*Player*): 0.07	Boné (*Cap*): 0.01 Horário (*Schedule*): 0.01	0	Barulho (*Noise*): 0.01 Futebol (*Football*): 0.04 Jogo (*Game*): 0.08 Treino (*Training*): 0.01 Poste (*Pole*): 0.01 Regador (*Watering Cane*): 1
		Adolescents	Apito (*Whistle*): 0.81 Cartão (*Card*): 0.07 Jogador (*Player*): 0.03	0	0	Jogo (*Game*): 0.06 Resultado (*Result*): 0.02 Campeonato (*Championship*): 0.01
60	O rádio faz muito… *(The radio makes lots of/very …)*	*Children*	Barulho (*Noise*): 0.92	Sucesso (*Success*): 0.01 Ruído (*Noise*): 0.01 Som (*Sound*): 0.01 Relato (*Report*): 0.01 Bem (*Good*): 0.01 Trabalho (*Work*): 0.01	0	Exercício (*Exercise*): 0.01
		Adolescents	Barulho (*Noise*): 0.86	Anúncio (*Advertising*): 0.01	Publicidade (*Advertising*): 0.01	0
62	O cachecol aquece o… (*The scarf warms the…*)	*Children*	Pescoço (*Neck*): 0.80 Menino (*Boy*): 0.06 Corpo (*Body*): 0.06	João [a person's name]: 0.01 Senhor (*Sir*): 0.01 Aluno (*Pupil*): 0.01 Miguel [a person's name]: 0.01 Rapaz (*Boy*): 0.01	0	Pão (*Bread*): 0.02 Ovo (*Egg*): 0.01
		Adolescents	Pescoço (*Neck*): 0.91 Menino (*Boy*): 0.02 Corpo (*Body*): 0.06	Ouvido (*Ear*): 0.01	0	0
65	O dentista trata o… *(The dentist takes care of the…)*	*Children*	Dente (*Tooth*): 0.94 Menino (*Boy*): 0.03	Cliente (*Client*): 0.01 Doente (*Patient*): 0.01	0	0
		Adolescents	Dente (*Tooth*): 0.96	Menino (*Boy*): 0.01	0	0

			Doente (*Patient*): 0.02	Cliente (*Client*): 0.01		
68	O livro conta uma... (*The book tells a ...*)	*Children*	História (*Story*): 0.94 Lenda (*Legend*): 0.02	Anedota (*Joke*): 0.01 Aventura (*Adventure*): 0.01 Parábola (*Parable*): 0.01	0	0
		Adolescents	História (*Story*): 0.95	Anedota (*Joke*): 0.01 Lenda (*Legend*): 0.01 Aventura (*Adventure*): 0.01 Acção (*Action*): 0.01 Prosa (*Prose*): 0.01	0	0
69	A galinha come o... *(The chicken eats the...)*	*Children*	Milho (*Corn*): 0.72 Farelo (*Bran*): 0.02 Grão (*Grain*): 0.03 Ovo (*Egg*): 0.09 Trigo (*Wheat*): 0.02	Almoço (*Lunch*): 0.01 Penso (*Feed)*: 0.01 Vegetal (*Vegetable*): 0.01 Alimento (*Food*): 0.01	0	Dedo (*Finger*): 0.01 Pintainho (*Chick*): 0.02 Peixe (*Fish)*: 0.01 Insecto (*Insect*): 0.01 Coelho (*Rabbit*): 0.01
		Adolescents	Milho (*Corn*): 0.61 Ovo (*Egg*): 0.21 Grão (*Grain*): 0.07 Pão (*Bread*): 0.02	Farelo (*Bran*): 0.01 Centeio (*Rye*): 0.01	0	Pintainho (*Chick*): 0.01 Feno (*Hay)*: 0.01 Farnel (*Package-meal*): 0.02 Cão (*Dog*): 0.01 Galo (*Cock*): 0.02
70	O papagaio diz uma... (*The parrots says a...*)	*Children*	Palavra (*Word*): 0.57 Frase (*Sentence*): 0.11 Letra (*Letter*): 0.06 Asneira (*Nonsense*): 0.07 Coisa (*Thing*): 0.09	Mentira (*Lie*): 0.01	0	Piada (*Joke*): 0.04 Canção (*Song*): 0.01 Anedota (J*oke*): 0.02 Loucura (*Insanity*): 0.01 Papelaria (*Stationer's shop*): 0.01
		Adolescents	Palavra (*Word*): 0.62 Frase (*Sentence*): 0.07 Asneira (*Nonsense*): 0.19 Repetição (*Repetition*): 0.02	Mentira (*Lie*): 0.01 Parvoíce (*Stupidity*): 0.01	0	Piada (*Joke*): 0.04 Anedota (J*oke*): 0.04 Gargalhada (*Laugh*): 0.01
73	A almofada enfeita a... *(The pillow ornaments the..)*	*Children*	Cama (*Bed*): 0.94 Sala (*Living-room*): 0.04	0	0	Cabeça (*Head*): 0.01
		Adolescents	Cama (*Bed*): 0.95 Sala (*Living-room*): 0.02 Cadeira (*Chair*): 0.02	Janela (*Window*): 0.01	0	0

II. Low-constraint Sentences

3	A girafa levanta o... (*The giraffe raises the...*)	*Children*	Pescoço (*Neck*): 0.88	Filho (*Son*): 0.01 Nariz (Nose): 0.01	0	Menino (*Boy*): 0.02 Bebé (*Baby*): 0.01

				Corpo (*Body*): 0.01 Pau (*Stick*): 0.01 Corno (*Horn*): 0.01		Trompete (*Trumpet*): 0.01 Gato (*Cat*): 0.01
		Adolescents	Pescoço (*Neck*): 0.92	Filho (*Son*): 0.01 Joelho (*Knee*): 0.01 Rabo (*Tail*): 0.01 Pé (*Foot*): 0.01	0	Bebé (*Baby*): 0.01 Casco (*Hoof*): 0.01 Homem (*Man*): 0.01 Caderno (*Notebook*): 0.01
6	A senhora cheira um… (*The lady smells a…*)	*Children*	Perfume (*Perfume*): 0.48 Bolo (*Cake*): 0.03 Ramo (*Bunch*): 0.04 Cão (*Dog*): 0.02 Gladíolo (*Gladiolus*): 0.02 Sapato (*Shoe*): 0.02 Manjerico (*Basil*): 0.02 Malmequer (*Daisy*): 0.02	Sabonete (*Soap*): 0.01 Jasmim (*Jasmine*): 0.01 Cravo (*Carnation*): 0.01 Girassol (*Sunflower*): 0.01 Arranjo (*Bunch*): 0.01 Texugo (*Badger*): 0.01 Bacalhau (*Cod*): 0.01 Pastel (*Cake*): 0.01 Sabão (*Soap*): 0.01 Pão (*Bread*): 0.01 Lenço (*Tissue*): 0.01 Sumo (*Juice*): 0.01 Chocolate (*Chocolate*): 0.01 Chouriço (*Chorizo*): 0.01 Prato (*Plate*): 0.01 Cabrito (*Kid*): 0.01 Fruto (*Fruit*): 0.01 Frango (*Chicken*): 0.01 Peru (*Turkey*): 0.01 Alecrim (*Rosemary*): 0.01 Aroma (*Flavour*): 0.01 Tomate (*Tomato)*: 0.01 Cozinhado (*Meal*): 0.01 Limoeiro (*Lemon tree*): 0.01 Homem (*Man*): 0.01 Café (*Coffee*): 0.01 Rato (*Mouse*): 0.01 Tacho (*Saucepan*): 0.01	0	Almoço (*Lunch*): 0.01
		Adolescents	Perfume (*Perfume*): 0.67 Bolo (*Cake*): 0.02 Ramo (*Bunch*): 0.05 Cravo (*Carnation*): 0.05	Cão (*Dog*): 0.01 Sapato (*Shoe*): 0.01 Malmequer (*Daisy*): 0.01 Pão (*Bread*): 0.01	0	Filho (*Son*): 0.01

			Tomate (*Tomato*): 0.02 Eucalipto (*Eucalyptus*): 0.02 Alimento (*Food*): 0.02	Lenço (*Tissue*): 0.01 Fruto (*Fruit*): 0.01 Alecrim (*Rosemary*): 0.01 Bife (*Steak*): 0.01 Cozinhado (*Meal*): 0.01 Champô (*Shampoo*): 0.01 Doce (*Sweet*): 0.01 Copo (*Glass*): 0.01 Biscoito (*Biscuit*): 0.01 Incenso (*Incense*): 0.01 Pano (*Cloth*): 0.01		
7	A secretária atende o… (*The secretary answers/serves the…*)	*Children*	Telefone (*Phone*): 0.47 Cliente (*Client*): 0.40 Senhor (*Man*): 0.09 Telemóvel (*Mobile phone*): 0.02	Menino (*Boy*): 0.01 Aluno (*Student*): 0.01	0	0
		Adolescents	Telefone (*Phone*): 0.83 Cliente (*Client*): 0.09 Telemóvel (*Mobile phone*): 0.06	Telefonema (*Phone call*): 0.01 Aluno (*Student*): 0.01	0	0
11	A raposa persegue a… (*The fox chases a…*)	*Children*	Lebre (*Hare*): 0.35 Galinha (*Chicken*): 0.31 Cadela (*Bitch*): 0.04 Menina (*Girl*): 0.06 Perdiz (*Partridge*): 0.02 Presa (*Prey*): 0.03 Coelha (*Rabbit*): 0.02	Cabra (*Goat*): 0.01 Raposa (*Fox*): 0.01 Ovelha (*Sheep*): 0.01 Doninha (Wease*l*): 0.01 Rã (*Frog*): 0.01 Carne (*Meat*): 0.01	0	Gaivota (*Seagull*): 0.03 Folha (*Leaf*): 0.01 Ratazana (*Rat*): 0.01 Cobra (*Snake*): 0.02 Águia (*Eagle*): 0.01
		Adolescents	Lebre (*Hare*): 0.43 Galinha (*Chicken*): 0.37 Ovelha (*Sheep*): 0.02 Gata (*Cat*): 0.02 Coelha (*Rabbit*): 0.04	Cadela (*Bitch*): 0.01 Menina (*Girl*): 0.01 Presa (*Prey*): 0.01 Criança (*Child*): 0.01	0	Ratazana (*Rat*): 0.01 Cobra (*Snake*): 0.01 Borboleta (*Butterfly*): 0.01 Tartaruga (*Turtle*): 0.01 Girafa (*Giraffe*): 0.02 Lagarta (*Caterpillar*): 0.01 Cabaça (*Calabash*): 0.01 Toupeira (*Mole*): 0.01
12	A mãe lê um… (*The mother reads a…*)	*Children*	Livro (*Book*): 0.90 Jornal (*Journal*): 0.06	Conto (*Tale*): 0.01 Relatório (*Report*): 0.01 Diário (*Diary*): 0.01	0	Concurso (*Contest*): 0.01
		Adolescents	Livro (*Book*): 0.88 Jornal (*Journal*): 0.08	Panfleto (*Handout*): 0.01	0	Colar (*Necklace*): 0.01

			Texto (*Text*): 0.02			
13	A costureira usa o... (*The dressmaker uses the...*)	*Children*	Dedal (*Thimble*): 0.40 Casaco (*Jacket*): 0.06 Tecido (*Fabric*): 0.11 Fato (*Suit*): 0.02 Alfinete (*Pin*): 0.16 Vestido (*Dress*): 0.05 Linho (*Linen*): 0.02 Fio (*Thread*): 0.06 Pano (*Cloth*): 0.02	Anel (*Ring*): 0.01 Roupeiro (*Wardrobe*): 0.01 Livro (*Book*): 0.01	0	Avental (*Apron)*: 0.02 Açúcar (*Sugar*): 0.01 Pente (*Comb*): 0.01 Cravo (*Carnation*): 0.01
		Adolescents	Dedal (*Thimble*): 0.60 Casaco (*Jacket*): 0.02 Tecido (*Fabric*): 0.03 Alfinete (*Pin*): 0.13 Vestido (*Dress*): 0.05 Linho (*Linen*): 0.02 Fio (*Thread*): 0.03 Pano (*Cloth*): 0.03 Botão (*Button*): 0.06	Fato (*Suit*): 0.01 Novelo (*Ball*): 0.01 Metro (*Metre*): 0.01	0	Carro (*Car*): 0.01
15	A mulher veste uma saia (*The woman puts on s a...*)	*Children*	Saia (*Skirt*): 0.40 Roupa (*Cloth*): 0.18 Camisola (*Shirt*): 0.32	Rapariga (*Girl*): 0.01 Camisa (*Shirt*): 0.01 Túnica (*Tunic*): 0.01 Casaca (*Coat*): 0.01	0	Meia (*Sock*): 0.03 Écharpe (*Scarf*): 0.01 Fada (*Fairy*): 0.01
		Adolescents	Saia (*Skirt*): 0.61 Roupa (*Cloth*): 0.02 Camisola (*Shirt*): 0.19 Camisa (*Shirt*): 0.14	Farda (*Uniform*): 0.01	Cueca (*Pants*): 0.02	Meia (*Sock*): 0.02
16	A comida enche a... (*The food fills the...*)	*Children*	Barriga (*Tummy*): 0.40 Boca (*Mouth*): 0.06 Panela (*Pot*): 0.10 Travessa (*Dish*): 0.02	Galinha (*Chicken*): 0.01 Rapariga (*Girl*): 0.01 Mãe (*Mother*): 0.01	0	Sopa (*Soup*): 0.01
		Adolescents	Barriga (*Tummy*): 0.61 Boca (*Mouth*): 0.02 Panela (*Pot*): 0.09	Travessa (*Dish*): 0.01 Pança (*Paunch*) [colloquial]: 0.01 Colher (*Spoon*): 0.01	0	0
19	A escritora escreve uma... (*The writer writes a...*)	*Children*	Carta (*Letter*): 0.26 História (*Story*): 0.25 Folha (*Sheet*): 0.02 Frase (*Sentence*): 0.13	Notícia (*News*): 0.01 Anedota (*Joke*): 0.01 Peça (*Play*): 0.01 Curiosidade (*Curiosity*): 0.01	0	Escrita (*Writing*): 0.01 Agenda (*Diary*): 0.01 Bíblia (*Bible*): 0.01

			Canção (*Song*): 0.02 Leitura (*Reading*): 0.05 Poesia (*Poetry*): 0.03 Revista (*Magazine*): 0.02 Obra (*Work*): 0.02 Página (*Page)*: 0.03 Biografia (*Biography*): 0.03	Lenda (*Legend*): 0.01 Letra (*Letter*): 0.01 Fábula (*Fable*): 0.01 Composição (*Essay*): 0.01 Assinatura (*Signature*): 0.01		
		Adolescents	Frase (*Sentence*): 0.21 História (*Story*): 0.20 Carta (*Letter*): 0.18 Poesia (*Poetry*): 0.17 Lenda (*Legend*): 0.02 Letra (*Letter*): 0.02 Página (*Page*): 0.03 Dedicatória (*Dedication*): 0.04 Prosa (*Prose*): 0.03	Notícia (*News*): 0.01 Peça (*Play*): 0.01 Biografia (*Biography*): 0.01 Fala (*Talk*): 0.01 Epopeia (*Epic*): 0.01 Quadra (*Poem*): 0.01 Crónica (*Chronicle*): 0.01 Redacção (*Essay*): 0.01 Palavra (*Word*): 0.01 Bibliografia (*Blibliography*): 0.01	0	Ficha (*Test*): 0.01
20	A batedeira mexe a… (*The mixer stirs the…*)	*Children*	Massa (*Pastry*): 0.20 Farinha (*Flour*): 0.05 Mousse (*Mousse*): 0.02 Gema (*Yolk*): 0.08 Fruta (*Fruit*): 0.02	Laranja (*Orange*): 0.01 Banana (*Banana*): 0.01 Maçã (*Apple*): 0.01 Água (*Water*): 0.01 Amora (*Blackberry*): 0.01	0	Palheta (*Straw*): 0.01 Batata (*Potato*): 0.07 Sopa (*Soup*): 0.18 Tarte (*Pie*): 0.01 Comida (*Food*): 0.19 Omolete (*Omolette*): 0.02 Colher (*Spoon*): 0.01 Mão (*Hand*): 0.02 Mesa (*Table*): 0.01 Salada (*Salad*): 0.01 Cabeça (*Head*): 0.01 Tampa (*Top*): 0.01
		Adolescents	Massa (*Pastry*): 0.41 Farinha (*Flour*): 0.12 Gema (*Yolk*): 0.02 Fruta (*Fruit*): 0.03 Clara (*Egg white*): 0.03 Nata (*Cream*): 0.02 Mistura (*Mixture*): 0.02	Banana (*Banana*): 0.01 Água (*Water*): 0.01	0	Sopa (*Soup*): 0.14 Comida (*Food*): 0.14 Omolete (*Omolette*): 0.01 Ventoinha (*Fan*): 0.01 Panela (*Pot*): 0.01 Carne (*Meat*): 0.02 Bebida (*Drink*): 0.01
21	A empregada arruma a…	*Children*	Casa (*House*): 0.57 Mesa (*Table*): 0.11	Sala-de-estar (*Sitting room*): 0.01 Secretária (*Desk*): 0.01	0	0

	(*The waitress tidies up the...*)		Cozinha (*Kitchen*): 0.11 Sala (*Sitting room*): 0.10 Loiça (*Crockery*): 0.02 Cama (*Bed*): 0.02	Boneca (*Doll*): 0.01 Livraria (*Bookshop*): 0.01 Vassoura (*Broom*): 0.01 Prateleira (*Shelf*): 0.01		
		Adolescents	Casa (*House*): 0.60 Mesa (*Table*): 0.11 Cozinha (*Kitchen*): 0.11 Sala (*Sitting room*): 0.08 Cama (*Bed*): 0.02 Loja (*Store*): 0.02	Secretária (*Desk*): 0.01 Loiça (*Crockery*): 0.01 Banca (*Worktop*): 0.01 Gaveta (*Drawer*): 0.01 Despensa (*Larder*): 0.01 Casa-de-banho (*Bathroom*): 0.01 Roupa (*Clothes*): 0.01	0	0
24	A mão espreme uma... (*The hand squeezes the ... out*)	*Children*	Laranja (*Orange*): 0.47 Bolha (*Blister*): 0.05 Esponja (*Sponge*): 0.13 Espinha (*Pimple*): 0.05 Fruta (*Fruit*): 0.01 Saia (*Skirt*): 0.01 Camisola (*Sweater*): 0.01	Manga (*Mango*): 0.01 Tangerina (*Tangerine*): 0.01 Azeitona (*Olive*): 0.01 Borbulha (*Spot*): 0.01 Esfregona (*Mop*): 0.01 Uva (*Grape*): 0.01	0	Folha (*Leaf*): 0.01 Letra (*Letter*): 0.02 Toalha (*Towel*): 0.08 Maçã (*Apple*): 0.02 Palmada (*Smack*): 0.01 Leitura (*Reading*): 0.01 Latada (*Slap*): 0.01 Flor (*Flower)*: 0.01
		Adolescents	Laranja (*Orange*): 0.63 Esponja (*Sponge*): 0.04 Espinha (*Pimple*): 0.06 Fruta (*Fruit*): 0.01 Uva (*Grape*): 0.02 Verruga (*Wart*): 0.02 Toalha (*Towel*): 0.02 Camisa (*Shirt*): 0.01	Azeitona (*Olive*): 0.01 Borbulha (*Spot*): 0.01 Cereja (*Cherry*): 0.01	Calça (*Pants*): 0.01	Maçã (*Apple*): 0.01 Flor (*Flower)*: 0.01 Alface (*Lettuce*): 0.01 Banana (*Banana*): 0.01 Coisa (*Thing*): 0.01
25	A bicicleta atravessa a... (*The bike crosses the...*)	*Children*	Rua (*Street*): 0.58 Ponte (*Bridge*): 0.09 Passadeira (*Pedestrian crossing*): 0.04 Estrada (*Road*): 0.26	0	0	Terra (*Soil*): 0.01 Pedra (*Stone*): 0.01 Corrente (*Chain*): 0.01
		Adolescents	Rua (*Street*): 0.48 Ponte (*Bridge*): 0.06 Passadeira (*Pedestrian crossing*): 0.07 Estrada (*Road*): 0.36 Cidade (*City*): 0.02	0	0	Casa (*House*): 0.01 Fonte (*Fountain*): 0.01
26	A cama tem uma... (*The bed has a...*)	*Children*	Almofada (*Pillow*): 0.67 Coberta (*Bedspread*): 0.03	Grade (*Grill*): 0.01 Dona (*Owner*): 0.01	0	0

			Boneca (*Doll*): 0.02 Travesseira (*Pillow*): 0.05 Colcha (*Bedspread*): 0.05 Perna (*Leg*): 0.03 Menina (*Girl*): 0.02	Mola (*Spring*): 0.01 Beirada (*Edge*): 0.01 Falha (*Fault*): 0.01 Ervilha (*Pea*): 0.01 Alcofa (*Hamper*): 0.01 Cobertura (*Covering*): 0.01 Tábua (*Board*): 0.01 Pessoa (*Person*): 0.01 Roupa (*Clothes*): 0.01		
		Adolescents	Almofada (*Pillow*): 0.61 Coberta (*Bedspread*): 0.02 Travesseira (*Pillow*): 0.03 Colcha (*Bedspread*): 0.11 Perna (*Leg*): 0.06 Tábua (*Board*): 0.03 Manta(*Blanket*): 0.05 Roda (*Wheel*): 0.02	Grade (*Grill*): 0.01 Mola (*Spring*): 0.01 Cabeceira (*Headboard*): 0.01 Pessoa (*Person*): 0.01 Mala (*Suitcase*): 0.01 Aranha (*Spider*): 0.01 Fronha (*Pillowcase*): 0.01	0	Frincha (*Slit*): 0.01
31	O professor ensina o... (*The teacher teaches the...*)	*Children*	Aluno (*Student*): 0.69 Abecedário (*Alphabet*): 0.06 Alfabeto (*Alphabet*): 0.05 Menino (*Boy*): 0.02	Estudante (*Student*): 0.01 Texto (*Text*): 0.01 Corpo humano (*Human body*): 0.01 Exercício (*Exercise*): 0.01 Diogo [man's name]: 0.01 Miguel [man's name]: 0.01 Estudo do Meio (*Natural Sciences*): 0.01 Português (*Portuguese Language*): 0.01 João [man's name]: 0.01 A,e,i,o,u (*Alphabet*): 0.01 Estudo do Meio (*Natural Sciences*): 0.01 Círculo (*Circle*): 0.01 Trabalho (*Work*): 0.01	Tudo (*Everything*): 0.01	0
		Adolescents	Aluno (*Student*): 0.71 Texto (*Text*): 0.02 Abecedário (*Alphabet*): 0.08 Alfabeto (*Alphabet*): 0.03 João [man's name]: 0.02 Livro (*Book*): 0.04 Dever (*Homework*): 0.02	Português (*Portuguese Language*): 0.01 Francês (*French*): 0.01 Menino (*Boy*): 0.01 Provérbio (*Proverb*): 0.01 Verbo (*Verb*): 0.01 Projecto (*Project*): 0.01 Romantismo (*Romanticism*): 0.01	0	Cão (*Dog*): 0.01
36	O jardineiro rega o... (*The gardenerwaters*	*Children*	Jardim (*Garden*): 0.90 Quintal (*Back yard*): 0.02	Vaso (*Flowerpot*): 0.01 Parque (*Park*): 0.01	0	Ramo (*Bunch*): 0.01

	the...)			Relvado (*Lawn*): 0.01 Canteiro (*Flower bed*): 0.01 Pimenteiro (*Pepper tree*): 0.01 Repolho (*Cabbage*): 0.01		
		Adolescents	Jardim (*Garden*): 0.94 Canteiro (*Flower bed*): 0.02	Relvado (*Lawn*): 0.01 Campo (*Field*): 0.01 Cravo (*Carnation*): 0.01 Malmequer (*Daisy*): 0.01	0	0
37	O pintor pinta um... (*The painter paints a..*)	*Children*	Quadro (*Painting*): 0.74 Hotel (*Hotel*): 0.02 Carro (*Car*): 0.06 Muro (*Wall*): 0.03 Móvel (*Piece of furniture*): 0.03 Quarto (*Room*): 0.03	Casarão (*Big house*): 0.01 Poste (*Pole*): 0.01 Balde (*Bucket*): 0.01 Telhado (*Roof*): 0.01	Chão (*Floor*): 0.01	0
		Adolescents	Quadro (*Painting*):0.87 Carro (*Car*): 0.04 Muro (*Wall*): 0.02 Portão (*Gate*): 0.02 Desenho (*Drawing*): 0.04	Quarto (*Room*): 0.01 Retrato (*Portrait*): 0.01 Tecto (*Ceiling*): 0.01	0	0
39	O carteiro entrega um... (*The postman delivers a...*)	*Children*	Postal (*Postcard*): 0.30 Envelope (*Envelope*): 0.22 Cartão (*Card*): 0.06 Correio (*Mail*): 0.15 Jornal (*Journal*): 0.04 Recado (*Message*): 0.04 Cartaz (*Poster*): 0.04	Bilhete (*Ticket*): 0.01 Convite (*Invitation*): 0.01 Anúncio (*Advertisement*): 0.01 Documento (*Document*): 0.01 Pacote (*Packet*): 0.01 Presente (*Gift*): 0.01 Papel (*Paper*): 0.01 Telegrama (*Telegram*): 0.01 Prémio (*Prize*): 0.01 Tupperware (*Tupperware*): 0.01 Livro (*Book*): 0.01	0	Carro (*Car*): 0.01 Pão (*Bread*): 0.01
		Adolescents	Postal (*Postcard*): 0.35 Envelope (*Envelope*): 0.33 Bilhete (*Ticket*): 0.02 Correio (*Mail*): 0.06 Jornal (*Journal*): 0.03 Pacote (*Packet*): 0.08 Presente (*Gift*): 0.02 Embrulho (*Package*): 0.02	Jogo (*Game*): 0.01 Cartão (*Card*): 0.01 Recado (*Message*): 0.01 Telegrama (*Telegram*): 0.01 Folheto (*Brochure*): 0.01 Colar (*Necklace*): 0.01 Apito (*Whistle*): 0.01	0	0

43	O músico toca a... (*The musician plays the...*)	*Children*	Música (*Music*): 0.42 Viola (*Guitar*): 0.09 Flauta (*Flute*): 0.18 Guitarra (*Guitar*): 0.18 Canção (*Song*): 0.03 Bateria (*Drums*): 0.03 Melodia (*Melody*): 0.02	Concertina (*Concertina*): 0.01 Pandeireta (*Tambourine*): 0.01	Trompete (*Trumpet*): 0.01 Orquestra (*Orchestra*): 0.01	0
		Adolescents	Música (*Music*): 0.47 Viola (*Guitar*): 0.06 Flauta (*Flute*): 0.12 Guitarra (*Guitar*): 0.23 Melodia (*Melody*): 0.06	Canção (*Song*): 0.01 Pandeireta (*Tambourine*): 0.01 Partitura (*Score*): 0.01 Pauta (*Tariff*): 0.01 Peça (*Play*): 0.01	0	Letra (*Lyrics*): 0.01
44	O cão sacode a... (*The dog shakes the...*)	*Children*	Cauda (*Tail*): 0.22 Pulga (*Flea*): 0.13 Pata (*Paw*): 0.21 Mosca (*Fly*): 0.03 Terra (*Land*): 0.07 Água (*Water*): 0.04	Areia (*Sand*): 0.01 Relva (*Turf*): 0.01 Lixarada (*Garbage*): 0.01 Chuva (*Rain*): 0.01	0	Perna (*Leg*): 0.04 Barriga (*Belly*): 0.03 Cabeça (*Head*): 0.03 Manta (*Blanket*): 0.01 Raça (*Race*): 0.01 Orelha (*Ear*): 0.02 Roupa (*Clothes*): 0.02 Coleira (*Leash*): 0.01 Pele (*Skin*): 0.01 Pessoa (*Person*): 0.01 Menina (*Girl*): 0.01 Meia (*Sock*): 0.01
		Adolescents	Cauda (*Tail*): 0.47 Pulga (*Flea*): 0.20 Pata (*Paw*): 0.07 Mosca (*Fly*): 0.02 Água (*Water*): 0.02 Carraça (*Tick*): 0.02	0	0	Perna (*Leg*): 0.03 Cabeça (*Head*): 0.05 Manta (*Blanket*): 0.01 Orelha (*Ear*): 0.05 Galinha (*Chicken*): 0.01 Pessoa (*Person*): 0.01 Cadela (*Dog*): 0.01 Boca (*Mouth*): 0.01 Melga (*Pisser*): 0.01 Lata (*Tin*): 0.01
45	O coelho ultrapassa a... (*The rabbit overcomes the...*)	*Children*	Tartaruga (*Turtle*): 0.32 Gata (*Cat*): 0.02 Raposa (*Fox*): 0.07 Lebre (*Hare*): 0.16 Cobra (*Snake*): 0.02	Lesma (*Slug*): 0.01 Cadela (*Dog*): 0.01 Bicicleta (*Bike*): 0.01 Vaca (*Cow*): 0.01 Pata (*Duck*): 0.01	0	Grade (*Railing*): 0.01 Poça (*Puddle*): 0.02 Passadeira (*Pedestrian crossing*): 0.02 Rede (*Wire netting*): 0.01 Vedação (*Fence*): 0.02

			Meta (*Finishing line*): 0.03 Galinha (*Chicken*): 0.05 Rã (*Frog*): 0.04 Coelha (*Rabbit*): 0.03 Formiga (*Ant*): 0.02	Menina (*Girl*): 0.01 Pessoa (*Person*): 0.01		Erva (*Grass*): 0.01 Porta (*Door*): 0.01 Árvore (*Tree*): 0.02 Água (*Water*): 0.01
		Adolescents	Tartaruga (*Turtle*): 0.26 Raposa (*Fox*): 0.09 Lebre (*Hare*): 0.11 Cobra (*Snake*): 0.02 Meta (*Finishing line*): 0.04 Galinha (*Chicken*): 0.02 Coelha (*Rabbit*): 0.03 Formiga (*Ant*): 0.03 Perdiz (*Partridge*): 0.02	Gata (*Cat*): 0.01 Bicicleta (*Bike*): 0.01 Lagarta (*Caterpillar*): 0.01 Minhoca (*Worm*): 0.01 Ratazana (*Rat*): 0.01	0	Passadeira (*Pedestrian crossing*): 0.02 Rede (*Wire netting*): 0.02 Vedação (*Fence*): 0.04 Árvore (*Tree*): 0.01 Estraa (*Road*): 0.04 Ponte (*Bridge*): 0.01 Toca (*Burrow*): 0.01 Rua (*Street*): 0.06 Cerca (*Fence*): 0.02 Casa (*House*): 0.01 Mata (*Wood*): 0.01 Estação (*Station*): 0.01 Quinta (*Farm*): 0.01 Selva (*Jungle*): 0.01 Barreira (*Barrier*): 0.01 Lura (*Nest*): 0.02 Pastagem (*Pasture*): 0.01 Floresta (*Forest*): 0.02
48	O homem pendura a... (*The man hangs up the...*)	*Children*	Camisa (*Shirt*): 0.17 Roupa (*Clothes*): 0.15 Casaca (*Tails*): 0.15 Camisola (*Sweater*): 0.07 Mala (*Bag*): 0.04 Carne (*Meat*): 0.02 Gabardina (*Raincoat*): 0.02 Gravata (*Tie*): 0.04 Moldura (*Frame*): 0.02 Vassoura (*Broom*): 0.03	Placa (*Plate*): 0.01 Fotografia (*Photo*): 0.01 Chouriça (*Sausage*): 0.01 Bengala (*Walking stick*): 0.01 Saca (*Bag*): 0.01 Caneta (*Pen*): 0.01 Gaiola (*Cage*): 0.01 Carta (*Letter*): 0.01 Lebre (*Hare*): 0.01 Galinha (*Chicken*): 0.01 Perna do porco (*Pig's leg*): 0.01 Tela (*Screen*): 0.01 Telha (*Tile*): 0.01 Bicicleta (*Bike*): 0.01 Cruz (*Cross*): 0.01 Pintura (*Painting*): 0.01	Calça (*Trousers*): 0.03	Porta (*Door*): 0.01 Janela (*Window*): 0.01 Salsicha (*Sausage*): 0.01

				Chave (*Key*): 0.01 Meia (*Socks*): 0.01 Loiça (*Tableware*): 0.01		
		Adolescents	Camisa (*Shirt*): 0.21 Roupa (*Clothes*): 0.14 Casaca (*Tails*): 0.16 Camisola (*Sweater*): 0.09 Chave (*Key*): 0.08 Mala (*Bag*): 0.02 Chouriça (*Sausage*): 0.02 Gabardina (*Raincoat*): 0.03 Gravata (*Tie*): 0.03 Tela (*Screen*): 0.02 Mola (*Spring*): 0.02 Meia (*Socks*): 0.02	Fotografia (*Photo*): 0.01 Carne (*Meat*): 0.01 Bengala (*Walking stick*): 0.01 Saca (*Bag*): 0.01 Moldura (*Frame*): 0.01 Pintura (*Painting*): 0.01 Lâmpada (*Lamp*): 0.01 Cortina (*Curtain*): 0.01 Cara (*Face*): 0.01 Bata (*White coat*): 0.01 Corda (*Rope*): 0.01 Boina (*Beret*): 0.01 Tabuleta (*Tablet*): 0.01 Corrente (*Chain*): 0.01	Calça (*Trousers*): 0.02	Salsicha (*Sausage*): 0.01 Mulher (*Woman*): 0.01
51	O agricultor planta uma... (*The farmer plants a...*)	*Children*	Planta (*Plant*): 0.27 Batata (*Potato*): 0.02 Flor (*Flower*): 0.20 Árvore (*Tree*): 0.23 Couve (*Cabbage*): 0.03 Cebola (*Onion*): 0.03 Alface (*Lettuce*): 0.03 Laranjeira (*Orange tree*): 0.02 Rosa (*Rose*): 0.02	Macieira (*Apple tree*): 0.01	0	Semente (*Seed*): 0.10 Erva (*Grass*): 0.01 Plantação (*Plantation*): 0.01
		Adolescents	Árvore (*Tree*): 0.19 Batata (*Potato*): 0.05 Flor (*Flower*): 0.16 Árvore (*Tree*): 0.19 Couve (*Cabbage*): 0.15 Cebola (*Onion*): 0.04 Alface (*Lettuce*): 0.06 Laranjeira (*Orange tree*): 0.02 Rosa (*Rose*): 0.02 Macieira (*Apple tree*): 0.03 Batateira (*Potatoes plant*): 0.02	Abóbora (*Pumpkin*): 0.01 Videira (*Vine*): 0.01	0	Semente (*Seed*): 0.06 Erva (*Grass*): 0.01 Banana (*Banana*): 0.01 Horta (*Vegetable garden*): 0.01
54	O turista faz uma... *(The turist does a...)*	*Children*	Viagem (*Trip*): 0.69 Paragem (*Stop*): 0.03	Entrega (*Delivery*): 0.01 Pergunta (*Question*): 0.01	Féria (*Vacation*): 0.01	Parede (*Wall*): 0.01 Admiração (*Wonder*): 0.01

			Visita (*Visit*): 0.09 Pesquisa (*Research*): 0.02 Caminhada (*Walk*): 0.02	Asneira (*Nonsense*): 0.01 Corrida (*Race*): 0.01 Pausa (*Pause*): 0.01 Música (*Song*): 0.01		Pistola (*Gun*): 0.01 Tourada (*Bullfight*): 0.01 Janela (*Window*): 0.01
		Adolescents	Viagem (*Trip*): 0.76 Visita (*Visit*): 0.13 Caminhada (*Walk*): 0.04 Excursão (*Tour*): 0.02	Pergunta (*Question*): 0.01 Análise (*Analysis*): 0.01 Bebida (*Drink*): 0.01 Peregrinação (*Pilgrimage*): 0.01 Expedição (*Expedition*): 0.01	0	0
56	A avestruz esconde a… *(The ostrich hides the…)*	*Children*	Cabeça (*Head*): 0.21 Filha (*Daughter*): 0.17 Comida (*Food*): 0.08 Cria (*Young*): 0.15 Pata (*Paw*): 0.06 Ave pequena (*Small bird*): 0.03 Cauda (*Tail*): 0.05 Ninhada (*Litter*): 0.03 Pena (*Feather*): 0.03	Gruta (*Cave*): 0.01 Asa (*Wing*): 0.01 Fêmea (*Female*): 0.01 Cara (*Face*): 0.01 Bola (*Ball*): 0.01 Carne (*Meat*): 0.01 Planta (*Plant*): 0.01 Avestruz (*Ostrich*): 0.01	0	Bebé (*Baby*): 0.01 Bolacha (*Cookie*): 0.01 Perdiz (*Partridge*): 0.01 Galinha (*Chicken*): 0.01 Taça (*Cup*): 0.01 Senhora (*Lady*): 0.01 Pintainha (*Chick*): 0.01
		Adolescents	Cabeça (*Head*): 0.45 Filha (*Daughter*): 0.02 Asa (*Wing*): 0.03 Comida (*Food*): 0.04 Cria (*Young*): 0.15 Pata (*Paw*): 0.09 Pena (*Feather*): 0.04 Cara (*Face*): 0.05 Família (*Family*): 0.02 Perna (*Leg*): 0.03	Cauda (*Tail*): 0.01 Bola (*Ball*): 0.01 Minhoca (*Worm*): 0.01 Barriga (*Belly*): 0.01	0	Bebé (*Baby*): 0.01 Pele (*Skin*): 0.01 Galinha (*Chicken*): 0.01
57	O menino esvazia o… *(The boy empties the…)*	*Children*	Balde (*Bucket*): 0.24 Balão (*Baloon*): 0.11 Pote (*Pot*): 0.03 Pneu (*Tire*): 0.03 Quarto (*Room*): 0.03 Prato (*Plate*): 0.03 Copo (*Cup*): 0.09 Pacote (*Package*): 0.03 Saco (*Bag*): 0.04 Garrafão (*Carboy*): 0.09 Caixote (*Bin*): 0.02	Cesto (*Basket*): 0.01 Azeite (*Olive oil*): 0.01 Contentor (*Container*): 0.01 Bidé (*Bidet*): 0.01 Barril (*Barrel*): 0.01 Frasco (*Flask*): 0.01 Cantil (*Cantil*): 0.01 Regador (*Watering Cane*): 0.01	Garrafa (*Bottle*): 0.01 Banheira (*Bath tube*): 0.01	Vinho (*Wine*): 0.02 Campo (*Field*): 0.01 Lixo (*Waste*): 0.01 Ar (*Air*): 0.01 Leite (*Milk*): 0.01 Poço (*Well*): 0.01

			Estômago (*Stomach*): 0.03 Tanque (*Tank*): 0.02			
		Adolescents	Copo (*Glass*): 0.16 Balão (*Baloon*): 0.14 Pote (*Pot*): 0.06 Pneu (*Tire*): 0.05 Copo (*Cup*): 0.16 Pacote (*Package*): 0.02 Saco (*Bag*): 0.07 Garrafão (*Carboy*): 0.02 Caixote (*Bin*): 0.03 Tanque (*Tank*): 0.04 Frasco (*Flask*): 0.06 Bolso (*Pocket*): 0.05 Biberão (*Baby bottle*): 0.02 Porta-lápis (*Pencilcase*): 0.02	Cesto (*Basket*): 0.01 Quarto (*Room*): 0.01 Prato (*Plate*): 0.01 Estômago (*Stomach*): 0.01 Bidão (*Big vessel*): 0.01 Aquário (*Aquarium*): 0.01 Cofre (*Safe*): 0.01 Frigorífico (*Fridge*): 0.01 Mealheiro (*Moneybox*): 0.01 Carrinho (*Cart*): 0.01	Garrafa (*Bottle*): 0.01	Sumo (*Juice*): 0.02
58	O balde transporta muita... *(The bucket carries a lot of...)*	*Children*	Água (*Water*): 0.71 Areia (*Sand*): 0.13 Comida (*Food*): 0.02 Coisa (*Things*): 0.06	Caruma (*Carum*): 0.01 Lenha (*Firewood*): 0.01 Loiça (*Dish*): 0.01 Lixeira (*Waste*): 0.01 Cebola (*Onion*): 0.01 Espuma (*Foam*): 0.01 Batata (*Potato*): 0.01	0	Carga (*Load*): 0.01
		Adolescents	Água (*Water*): 0.63 Areia (*Sand*): 0.22 Coisa (*Things*): 0.02 Massa (*Concrete*): 0.03 Lixívia (*Bleach*): 0.02 Fruta (*Fruit*): 0.03 Terra (*Land*): 0.03	Maçã (*Apple*): 0.01 Cerveja (*Beer*): 0.01	0	0
59	O bar vende muito... (*The bar sells lots of/very...)*	*Children*	Sumo (*Juice*): 0.36 Álcool (*Alcohol*): 0.18 Vinho (*Wine*): 0.14 Café (*Coffee*): 0.08 Farnel (*Packed meal*): 0.02 Pão (*Bread*): 0.06 Chocolate (*Chocolate*): 0.03 Bem (*Well*): 0.02	Pouco (*Little*): 0.01 Sumol [juice's brand]: 0.01 Molho (*Sauce*): 0.01 Doces (*Candies*): 0.01 Chiclets (*Chewing Gum*): 0.01	Chupa (*Lolipop*): 0.01	Grande (*Big*): 0.01 Limão (*Lemon*): 0.02 Dinheiro (*Money*): 0.01
		Adolescents	Álcool (*Alcohol*): 0.38	Licor (*Liquor*): 0.01	0	Líquido (*Liquid*): 0.01

			Sumo (*Juice*): 0.21 Vinho (*Wine*): 0.20 Café (*Coffee*): 0.02 Pão (*Bread*): 0.03 Chocolate (*Chocolate*): 0.03 Bem (*Well*): 0.09 Leite (*Milk*): 0.02	Refresco (*Refreshment*): 0.01		
61	O aluno levanta o... (*The pupil raises the...)*	*Children*	Dedo (*Finger*): 0.56 Livro (*Book*): 0.08 Casaco (*Coat*): 0.02 Caderno (*Notebook*): 0.06 Lápis (*Pencil*): 0.06 Braço (*Arm*): 0.08 Estojo (*Pencilcase*): 0.02 Rabo (*Butt*): 0.06 Porta-lápis (*Pencilcase*): 0.05	Pé (*Foot*): 0.01	Garrafa (*Bottle*): 0.01	Balde (*Bucket*): 0.01
		Adolescents	Dedo (*Finger*): 0.44 Livro (*Book*): 0.09 Caderno (*Notebook*): 0.15 Lápis (*Pencil*): 0.07 Braço (*Arm*): 0.12 Estojo (*Pencilcase*): 0.03 Rabo (*Butt*): 0.02	Pé (*Foot*): 0.01 Prato (*Plate*): 0.01 Pescoço (*Neck*): 0.01 Banco (*Bench*): 0.01 Relatório (*Report*): 0.01	0	Jarro (*Jar*): 0.01 Quadro (*Blackboard*): 0.01 Peso (*Weight*): 0.01 Professor (*Teacher*): 0.01
63	O vento arrasta a... (*The wind drags the...*)	*Children*	Folha (*Leaf*): 0.51 Árvore (*Tree*): 0.11 Toalha (*Towel*): 0.02 Roupa (*Clothe*): 0.07 Folhagem (*Foliage*): 0.05 Terra (*Land*): 0.03 Poeira (*Dust*): 0.03 Menina (*Girl*): 0.01	Planta (*Plant*): 0.01 Mota (*Motocycle*): 0.01 Cabana (*Hut*): 0.01 Borracha (*Rubber*): 0.01 Água (*Water*): 0.01 Manta (*Blanket*): 0.01 Saca (*Bag*): 0.01 Mesa (*Table*): 0.01 Papelada (*Paperwork*): 0.01 Meia (*Sock*): 0.01	0	Nuvem (*Cloud*): 0.03 Chuva (*Rain*): 0.02
		Adolescents	Folha (*Leaf*): 0.42 Árvore (*Tree*): 0.03 Roupa (*Clothe*): 0.03 Planta (*Plant*): 0.05 Folhagem (*Foliage*): 0.02 Terra (*Land*): 0.02	Mesa (*Table*): 0.01 Telha (*Roof-tile*): 0.01 Erva (*Herb*): 0.01 Casota (*Kennel*): 0.01 Palha (*Straw*): 0.01 Pena (*Feather*): 0.01	0	Brisa (*Breeze*): 0.01 Maré (*Tide*): 0.01 Perna (*Leg*): 0.01

			Poeira (*Dust*): 0.10 Saca (*Bag*): 0.02 Semente *(Seed*): 0.02 Areia (*Sand*): 0.12 Casa (*House*): 0.02 Cadeira (*Chair*): 0.02 Raposa (*Fox*): 0.01 Pessoa (*Person*): 0.02 Menina (*Girl*): 0.01	Flor (*Flower*): 0.01		
64	O carpinteiro faz uma... *(The carpenter makes a ...)*	*Children*	Mesa (*Table*): 0.16 Casota (*Kennel*): 0.05 Porta (*Door*): 0.11 Parede (*Wall*): 0.05 Mobília (*Furniture*): 0.02 Cómoda (*Dresser*): 0.03 Tábua (*Board*): 0.05 Cadeira (*Chair*): 0.05 Janela (*Window*): 0.02 Secretária (*Desk*): 0.02 Escultura (*Sculptur*e): 0.02	Corrida (*Race*): 0.01 Carpintaria (*Carpentry*): 0.01 Pausa (*Pause*): 0.01 Cabana (*Hut*): 0.01 Exportação (*Export*): 0.01 Vedação (*Fence*): 0.01	0	Casa (*House*): 0.18 Garagem (*Garage*): 0.02 Habitação (*Housing*): 0.01 Construção (*Construction*): 0.02 Bata (*White coat*): 0.01 Pedra (*Rock*): 0.01 Escola (*School*): 0.01 Folha (*Sheet*): 0.01 Bota (*Boot*): 0.01 Madeira (*Wood*): 0.01 Vivenda (*Villa*): 0.01 Relva (*Grass*): 0.01
		Adolescents	Mesa (*Table*): 0.26 Casota (*Kennel*): 0.02 Porta (*Door*): 0.11 Mobília (*Furniture*): 0.03 Cómoda (*Dresser*): 0.02 Tábua (*Board*): 0.02 Cadeira (*Chair*): 0.09 Janela (*Window*): 0.06 Secretária (*Desk*): 0.03 Caixa (*Box*): 0.02 Estante (*Bookcase*): 0.02 Moldura (*Frame*): 0.02 Cama (*Bed*): 0.08 Cozinha de madeira (*Wooden Kitchen*): 0.03	Parede (*Wall*): 0.01 Gaveta (*Drawer*): 0.01	0	Casa (*House*): 0.08 Cela (*Cell*): 0.01 Pintura (*Painting*): 0.03 Planta (*Plant*): 0.02 Capoeira (*Chicken-house*): 0.01 Obra (*Production*): 0.02 Avenida (*Avenue*): 0.01
66	O desenhador faz um... *(The designer draws a..)*	*Children*	Desenho (*Drawing*): 0.87 Quadro (*Painting*): 0.07 Retrato (*Portrait*): 0.02 Boneco (*Doll*): 0.02	Plano (*Plan*): 0.01	0	Prédio (*Building*): 0.01

		Adolescents	Desenho (*Drawing*): 0.87 Quadro (*Painting*): 0.03 Retrato (*Portrait*): 0.02 Projecto (*Project*): 0.06	Grafitti (*Grafitti*): 0.01 Esboço (*Sketch*): 0.01	0	
67	A esponja absorve a… (*The sponge absorbs the…*)	*Children*	Água (*Water*): 0.75 Sujidade (*Dirtiness*): 0.08 Espuma (*Foam*): 0.08 Gordura (*Grease*): 0.02	Tinta (*Ink*): 0.01 Lixívia (*Bleach*): 0.01	0	Louça (*Tableware*): 0.01 Banheira (*Bathtub*): 0.02 Pele (*Skin*): 0.01
		Adolescents	Água (*Water*): 0.80 Sujidade (*Dirtiness*): 0.06 Espuma (*Foam*): 0.05 Humidade (*Humidity*): 0.05	Gota (*Drop*): 0.01 Chuva (*Rain*): 0.01	0	Casa (*House*): 0.01 Laranja (*Orange*): 0.01
71	A tesoura recorta a… *(The scissors cut the…)*	*Children*	Folha (*Sheet*): 0.56 Página (*Page*): 0.02 Cartolina (*Cardboard*): 0.17 Figura (*Figure*): 0.02	Capa (*Cover*): 0.01 Carta (*Letter*): 0.01 Flor (*Flower*): 0.01	Papel (*Paper*): 0.01	Calça (*Trousers*): 0.01 Roupa (*Clothes*): 0.02 Saia (*Skirt*): 0.02 Camisola (*Sweater*): 0.04 Linha (*Line*): 0.01 Seda (*Silk*): 0.01 Menina (*Girl*): 0.01 Almofada (*Pillow*): 0.01 Cabeleira (*Wig*): 0.01 Idade (*Age*): 0.01
		Adolescents	Folha (*Sheet*): 0.56 Cartolina (*Cardboard*): 0.18 Figura (*Figure*): 0.02 Imagem (*Image*): 0.02 Revista (*Magazine*): 0.02	Página (*Page*): 0.01 Carta (*Letter*): 0.01 Foto (*Photo*): 0.01 Letra (*Letter*): 0.01 Saca (*Saca*): 0.01	Papel (*Paper*): 0.01	Roupa (*Clothes*): 0.01 Camisola (*Sweater*): 0.01 Linha (*Line*): 0.04 Toalha (*Towel*): 0.02 Camisa (*Shirt*): 0.01 Costura (*Sewing*): 0.01 Mão (*Hand*): 0.01 Borracha (*Rubber*): 0.01 Meia (*Sock*): 0.01 Corda (*Rope*): 0.01 Chapa (*Slab*): 0.01

72	A mãe folheia a... *(The mother leafs a...)*	*Children*	Revista (*Magazine*): 0.24 Página (*Page*): 0.20 História (*Story*): 0.08 Carta (*Letter*): 0.03 Caderneta (*Register*): 0.02	Capa (*Folder*). 0.01 Bíblia (*Bible*): 0.01 Receita (*Recipe*): 0.01 Lista (*List*): 0.01 Conta (*Invoice*): 0.01 Ficha (*File*): 0.01 Papelada (*Paperwork*): 0.01	0	Folha (*Sheet*): 0.16 Flor (*Flower*): 0.03 Massa (*Pasta*): 0.01 Casa (*House*): 0.01 Mesa (*Table*): 0.01 Folhagem (*Foliage*): 0.01 Árvore (*Tree*): 0.02 Nota (*Note*): 0.01 Carne (*Meat*): 0.01 Roupa (*Clothes*): 0.01 Livraria (*Bookstore*): 0.01 Manteiga (*Butter*): 0.01 Cozinha (*Kitchen*): 0.01
		Adolescents	Revista (*Magazine*): 0.59 Página (*Page*): 0.05 História (*Story*): 0.04 Capa (*Folder*): 0.03 Carta (*Letter*): 0.03 Receita (*Recipe*): 0.06 Caderneta (*Register*): 0.06	Bíblia (*Bible*): 0.01 Narrativa (*Narrative*): 0.01 Agenda (*Memo-book*): 0.01 Matéria (*Subjects*): 0.01 Fábula (*Fable*) : 0.01	Fotocópia (*Photocopy*): 0.01	Folha (*Sheet*): 0.05 Jarra (*Jar*): 0.01 Gaveta (*Drawer*): 0.01 Vida (*Life*): 0.01

Appendix 2

Informed consent forms

2A. INFORMED CONSENT FOR STUDIES IN WILLIAMS SYNDROME

Version 1

PROJECTO DE INVESTIGAÇÃO: A LINGUAGEM NO SÍNDROME DE WILLIAMS

O Síndrome de Williams é um síndrome raro, sobre o qual muito ainda falta investigar. Um conhecimento mais detalhado das especificidades deste síndrome auxiliará o processo de desenvolvimento de planos de intervenção mais eficazes, dirigidos às características únicas que constituem este síndrome.

Neste sentido, um grupo de investigadores da Universidade do Minho encontra-se a realizar um estudo acerca do processamento da linguagem em pessoas diagnosticadas com este síndrome. Mais precisamente, o objectivo é perceber de que forma é que estas pessoas processam a linguagem (oral e escrita) e de que forma tal poderá estar relacionado com características neurobiológicas.

Esperamos que os conhecimentos resultantes deste estudo nos possam ajudar a compreender melhor o papel da organização cerebral no desenvolvimento da linguagem e da comunicação narrativa, bem como desenvolver programas educacionais e terapêuticos adaptados às potencialidades e limites das pessoas diagnosticadas com este síndrome.

A participação neste estudo implica a realização de um conjunto de tarefas a terem lugar na Universidade do Minho (Braga), com a duração aproximada de 2 horas, e que incluem o registo da sua actividade electroencefalográfica durante a realização de um conjunto de tarefas linguísticas. Este registo é absolutamente indolor, não tem quaisquer efeitos secundários indesejáveis associados e consiste na colocação de alguns eléctrodos no couro cabeludo, juntamente com um gel electrolítico.

Os dados resultantes deste estudo serão mantidos confidenciais, sendo divulgados publicamente apenas os resultados globais por grupos de indivíduos sem qualquer informação que leve à identificação dos respectivos participantes ou suas famílias.

Consentimento

Fui informado e percebi os objectivos e procedimentos do estudo. Por essa razão, aceito participar no projecto, dando a minha autorização para que os dados sejam apresentados de forma completamente anónima e confidencial em apresentações públicas, congressos científicos e publicações.

Nome: ____

Local e data: ____

O investigador: ____

2B. INFORMED CONSENT FOR STUDIES IN WILLIAMS SYNDROME

Version 2

PROJECTO DE INVESTIGAÇÃO: A LINGUAGEM NO SÍNDROME DE WILLIAMS

O Síndrome de Williams é um síndrome raro, sobre o qual muito ainda falta investigar. Um conhecimento mais detalhado das especificidades deste síndrome auxiliará o processo de desenvolvimento de planos de intervenção mais eficazes, dirigidos às características únicas que constituem este síndrome.

Neste sentido, um grupo de investigadores da Universidade do Minho encontra-se a realizar um estudo acerca do processamento da linguagem em pessoas diagnosticadas com este síndrome. Mais precisamente, o objectivo é perceber de que forma é que estas pessoas processam a linguagem (oral e escrita) e de que forma tal poderá estar relacionado com características neurobiológicas.

Esperamos que os conhecimentos resultantes deste estudo nos possam ajudar a compreender melhor o papel da organização cerebral no desenvolvimento da linguagem e da comunicação narrativa, bem como desenvolver programas educacionais e terapêuticos adaptados às potencialidades e limites das pessoas diagnosticadas com este síndrome.

A participação neste estudo implica a realização de um conjunto de tarefas a terem lugar na Universidade do Minho (Braga), com a duração aproximada de 2 horas, e que incluem o registo da actividade electroencefalográfica do seu educando/filho durante a realização de um conjunto de tarefas linguísticas. Este registo é absolutamente indolor, não tem quaisquer efeitos secundários indesejáveis associados e consiste na colocação de alguns eléctrodos no couro cabeludo, juntamente com um gel electrolítico.

Os dados resultantes deste estudo serão mantidos confidenciais, sendo divulgados publicamente apenas os resultados globais por grupos de indivíduos sem qualquer informação que leve à identificação dos respectivos participantes ou suas famílias.

Caso aceite que o seu filho/educando participe neste estudo, pedimos que assine a secção referente ao consentimento informado.

Consentimento

Fui informado e percebi os objectivos e procedimentos do estudo. Por essa razão, autorizo o meu filho/educando a participar no projecto, dando a minha autorização para que os dados sejam apresentados de forma completamente anónima e confidencial em apresentações públicas, congressos científicos e publicações.

O encarregado de educação: ____

Local e data: ____

O investigador: ____