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A systematic linguistic profile of spontaneous narrative speech in pre-symptomatic and early stage Huntington's disease

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ABSTRACT

Cognitive decline accompanying the clinically more salient motor symptoms of Huntington's disease (HD) has been widely noted and can precede motor symptoms onset. Less clear is how such decline bears on language functions in everyday life, though a small number of experimental studies have revealed difficulties with the application of rule-based aspects of language in early stages of the disease. Here we aimed to determine whether there is a systematic linguistic profile that characterizes spontaneous narrative speech in both pre-manifest and/or early manifest HD, and how it is related to striatal degeneration and neuropsychological profiles. Twenty-eight early-stage patients (19 manifest and 9 gene-carriers in the pre-manifest stage), matched with 28 controls, participated in a story-telling task. Speech was blindly scored by independent raters according to fine-grained linguistic variables distributed over 5 domains for which composite scores were computed (Quantitative, Fluency, Reference, Connectivity, and Concordance). Voxel-based morphometry (VBM) was used to link specific brain degeneration patterns to loci of linguistic decline. In all of these domains, significant differences were observed between groups. Deficits in Reference and Connectivity were seen in the pre-manifest stage, where no other neuropsychological impairment was detected. Among HD patients, there was a significant positive correlation only between the values in the Quantitative domain and gray matter volume bilaterally in the putamen and pallidum. These results fill the gap of qualitative data of spontaneous narrative speech in HD and reveal that HD is characterized by systematic linguistic impairments leading to dysfluencies and disorganization in core domains of grammatical organization. This includes the referential use of

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noun phrases and the embedding of clauses, which mediate crucial dimensions of meaning in language in its normal social use. Moreover, such impairment is seen prior to motor symptoms onset and when standardized neuropsychological test profiles are otherwise normal.

1. Introduction

Huntington's disease (HD) is an autosomal dominant genetic neurodegenerative disease that involves cognitive and psychiatric disorders in addition to motor impairment. Cognitive decline can precede motor impairments by several years (Stout et al., 2011; 2016). The earliest cognitive impairments in clinically manifest HD have been found to implicate attention, executive functions, memory, and social cognition (Caine, Ebert, & Weingartner, 1977; Foroud et al., 1995; Ho et al., 2003; Papoutsi, Labuschagne, Tabrizi, & Stout, 2014). Some of these impairments, including deficits in social cognition (Bora, Velakoulis, & Walterfang, 2016), can characterize, in milder forms, the pre-manifest stage.

Since the discovery of the genetic polyglutamine expansion as the cause of the disease (Gusella et al., 1983), an increasing amount of research has focused on detecting biomarkers that would allow tracking disease progression before the onset of the clinical manifestations, which usually start in the late thirties or forties of affected individuals. The potential of language as such a biomarker has barely been explored, though Vogel, Shirbin, Churchyard, and Stout (2012) suggested that markers of speech in the acoustic domain related to speech timing could be potential signals in the early symptomatic and perhaps the prodromal stage. While cognitive dysfunction has been extensively studied in HD, only a handful of studies have investigated the effects of the disease on language function (De Diego-Balaguer et al., 2008; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Sambin et al., 2012; Teichmann et al., 2005, 2006; Teichmann, Dupoux et al., 2008; Teichmann, Gaura et al., 2008; Ullman et al., 1997). This is despite the fact that, cognitive, behavioral and motor dysfunctions are expected to be reflected in the language use of patients and to affect their everyday social interactions. Normal language use requires the interaction and integration of a myriad of cognitive systems, including memory, perception, attention, and the various subsystems of language itself. Furthermore, language is a primary tool used for conveying mental states and determining them in others, and hence may relate to the early impairments in the ability to understand the mental states of others (theory of mind', ToM) noted in HD (Adenzato & Poletti, 2013; Bora et al., 2016; Brüne, Blank, Witthaus, & Saft, 2011; Eddy, Sira Mahalingappa, & Rickards, 2012; Saft et al., 2013).

HD involves primary neural death in the striatum extending progressively to widespread cortical areas. The striatum forms part of the cortico-subcortical language network, though its functional role and degree of specificity remain unclear. Available evidence supports its role both in the application of syntactic rules in language (Teichmann et al., 2005) and in the access to lexical aspects of grammatical processing (Friederici & Kotz, 2003; Friederici, Steinhauer, & Frisch, 1999; Moro et al., 2001). Striatal damage in early manifest HD has been shown to affect the application of structural rules in different aspects of language, while leaving lexical knowledge unaffected (De Diego-Balaguer et al., 2008; Sambin et al., 2012; Teichmann, Dupoux et al., 2008; Teichmann et al., 2005). In particular, impairments have been reported in sentence comprehension (Sambin et al., 2012; Teichmann et al., 2005) and the perception (Teichmann et al., 2006) and production (Longworth et al., 2005; Ullman et al., 1997) of verbal inflection.

Syntactic structuring and verbal inflection in sentences require temporal processing (Bornkessel-Schlesewsky & Schlesewsky, 2013), just as motor sequencing does. Thus, the linguistic deficits described could derive from a more general role of the basal ganglia shared by different aspects of motor and cognitive functions. As first proposed by Graybiel (1995a, 1995b), the role of the basal ganglia could be that of a more general 'pattern generator', supporting the sequencing of meaningful behavioral repertoires, reiteration, and timing (Kotz & Schwartze, 2010; Kotz, Schwartze, & Schmidt-Kassow, 2009; Lieberman, 2007) in both motor sequences and cognitive sequences. This is consistent with findings of impaired control over the timing and duration of speech units in patients with striatal damage (Hertrich & Ackermann, 1994; Ludlow, Connor, & Bassich, 1987; Vogel et al., 2012). Indeed, temporal processing has been linked to the sequential processing necessary for syntactic structuring (Bornkessel-Schlesewsky & Schlesewsky, 2013) and the motor system appears to sustain this timing function. Thus, given its relation with a variety of cognitive and motor functions, some language changes could serve as an important and sensitive objective behavioral marker of cognitive decline and disease progression in HD, as has been suggested in the case of the schizophrenia prodrome as well (Bedi et al., 2015).

Previous studies on HD have studied language dysfunctions in constrained situations designed to test specific deficits in experimental tasks. Although this effort has helped to pinpoint that HD patients have particular difficulties with different aspects of syntactic processing accompanied by less impairment in lexico-semantic processing, these tasks may not reflect HD speech in more natural situations and in its normal social use. Narrative speech is a more ecologically natural condition, which poses distinctive cognitive challenges. These may in part overlap with, but also add to those of the experimental tasks previously mentioned. Specifically, narrative speech requires introducing story characters and tracking them throughout the story, setting up and developing the story line, and bringing it to a conclusion. Since agents act because of the reasons and intentions that underlie and rationalize their actions, moreover, storytelling depends on

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