



Research report

Neural substrate of cognitive theory of mind impairment in amyotrophic lateral sclerosis

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ABSTRACT

We now know that amyotrophic lateral sclerosis (ALS) is not restricted to the motor system. Indeed, a large proportion of patients with ALS exhibit cognitive impairment, especially executive dysfunction or language impairment. Although researchers have recently turned their attention to theory of mind (ToM) in ALS, only five studies have been performed so far, and they reported somewhat contradictory results. Moreover, the neural basis of the potential ToM deficit in ALS remains largely unknown. The present study was therefore designed to clarify whether a cognitive ToM deficit is indeed associated with ALS, specify the putative link between cognitive ToM deficits and executive dysfunction in ALS, and identify the dysfunctional brain regions responsible for any social cognition deficits. We investigated cognitive ToM and executive functions in a group of 23 patients with ALS and matched healthy controls, using an original false-belief task and a specially designed battery of executive tasks. We also performed an ¹⁸F-fluorodeoxyglucose positron emission tomography examination. Results confirmed the presence of cognitive ToM deficits in patients compared with controls, and revealed significant correlations between ToM and executive functions, although the cognitive ToM deficit persisted when a composite executive function score was entered as a covariate. Using statistical parametric mapping, we calculated positive correlations between tracer uptake and false-belief scores on a voxel-by-voxel basis in the patient sample. Results showed that the cognitive ToM deficit correlated with the dorsomedial and dorsolateral prefrontal cortices, as well as the supplementary motor area. Our findings provide compelling clinical and imaging evidence for the presence of a genuine cognitive ToM deficit in patients with ALS.

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Abbreviations: ALS, amyotrophic lateral sclerosis; ¹⁸FDG-PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; FTD, fronto-temporal dementia; SMA, supplementary motor area; ToM, theory of mind; VBM, voxel-based morphometry.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive paralysis, owing to loss of both upper and lower motor neurons. It causes weakness, muscular wasting, and spasticity, starting segmentally before becoming widespread and resulting in death from respiratory failure at a median of 3 years after onset.

1.1. Beyond the motor deficit: cognitive and behavioural impairment

There is an acknowledged clinical, pathological and genetic link between ALS and frontotemporal dementia (FTD). A subgroup of patients with ALS (5–15%) meets the criteria for FTD, typically a frontal variant that predominantly causes executive dysfunction and a pattern of behavioural change (Lomen-Hoerth et al., 2003; Neary, Snowden, & Mann, 2000; Phukan et al., 2012; Ringholz et al., 2005). Previous studies suggested that 35–50% of patients with ALS without FTD exhibit mild cognitive and behavioural impairments. Despite some discrepant findings, probably due to the variety of neuropsychological tasks used, the most commonly reported deficits concern executive functions (Phukan et al., 2012; Ringholz et al., 2005) and language. Executive dysfunction in ALS patients affects mental set shifting, action planning and sequencing (Abrahams et al., 2000; Phukan, Pender, & Hardiman, 2007; Pinkhardt et al., 2008; Ringholz et al., 2005), resulting in reduced word fluency (Abrahams et al., 2000). Language impairments have also been reported in a significant percentage of ALS patients (35%), and these deficits may indeed be more common than executive dysfunction itself (Abrahams, Newton, Niven, Foley, & Bak, 2014). Impairments in memory and, less frequently, in visuoconstructional, visuo-perceptual and visuospatial abilities, have also been found (Bak & Hodges, 2004; Flaherty-Craig, Eslinger, Stephens, & Simmons, 2006; Massman et al., 1996; Phukan et al., 2012; Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010; Ringholz et al., 2005; Strong et al., 1999; Taylor et al., 2013). Regardless of cognitive impairment, nondemented patients with ALS may exhibit behavioural changes characterized by irritability, disinhibition and apathy (Gibbons, Richardson, Neary, & Snowden, 2008; Grossman, Woolley-Levine, Bradley, & Miller, 2007; Lomen-Hoerth et al., 2003; Murphy, Henry, & Lomen-Hoerth, 2007; Phukan et al., 2007), the latter being regarded as the most common feature. All these findings reflect the heterogeneity of the cognitive and behavioural changes in ALS, probably due to a variable involvement of the temporal and frontal structures subserving executive functions, language and behaviour (Abrahams et al., 2014). The cognitive and behavioural changes described in patients with ALS are, to a great extent, also found in FTD, leading to the now largely acknowledged notion that the two diseases - ALS and FTD - lie at either end of a continuum (Goldstein & Abrahams, 2013; Murphy, Henry, Langmore, et al., 2007; Wilson, Grace, Munoz, He, & Strong, 2001).

1.2. Theory of mind (ToM), ALS and FTD

ToM is defined by the ability to infer and understand the mental states of self and others. This understanding refers not only to how other people are feeling emotionally, but also to the realization that they may have different beliefs in given situations and thus behave differently. A distinction has been made between so-called *cognitive ToM* (also known as *mentalizing*), which deals with the cognitive states, beliefs, thoughts or intentions of other people (Coricelli, 2005), and *affective ToM*, which concerns their affective states, emotions or feelings (Brothers & Ring, 1992). In day-to-day social interactions, ToM enables us to constantly consider perspectives distinct from our own, and to describe, explain and predict behaviour based on the mental states of others (Baron-Cohen, 1995).

The neural network underlying successful ToM performance includes the temporoparietal junction (Saxe & Wexler, 2005), posterior superior temporal sulci, precuneus, anterior temporal lobes (Olson, Plotzker, & Ezzyat, 2007) and medial prefrontal cortices (Amodio & Frith, 2006). The importance of the prefrontal cortex for cognitive ToM is supported both by lesion studies, in which selective damage to this area impaired the capacity to understand and infer thoughts and beliefs of others (Lee et al., 2010; Roca et al., 2011; Stuss, Gallup, & Alexander, 2001), and then by functional neuroimaging studies in healthy individuals (Amodio & Frith, 2006; Gallagher & Frith, 2003). Recent neuroimaging studies have suggested that cognitive ToM mainly recruits the dorsomedial and dorsolateral prefrontal cortices, whereas affective ToM mainly depends on the ventromedial prefrontal, orbitofrontal and inferior frontal cortices (Abu-Akel & Shamay-Tsoory, 2011; Gallagher & Frith, 2003). Neuroimaging data highlight an extensive neural network, suggesting that ToM is not a single process, and that other cognitive functions are also involved when a person reasons about the mental states of others.

Although the nature of the link between cognitive ToM and executive function is still a matter for debate, ToM and executive function have been shown to be closely related in developmental experiments both in children (Carlson & Moses, 2001) and in adults (Qureshi, Apperly, & Samson, 2010; Rakoczy, Harder-Kasten, & Sturm, 2012). Specifically, executive function has been found to be involved in ascribing beliefs that aim to represent the world truthfully, because ascribing such beliefs requires the inhibition of the default assumption that beliefs are true (Sabbagh, Moses, & Shiverick, 2006). According to recent models, belief reasoning can be subdivided into three distinct components: representation of reality, belief inference and self-perspective inhibition (Leslie, Friedman, & German, 2004; Samson, Apperly, & Humphreys, 2007; Van der Meer, Groenewold, Nolen, Pijnenborg, & Aleman, 2011). The first component corresponds to the representation of the true state of reality, that is, the individual's own belief, and involves general cognitive functions (attention, perception, and semantic and episodic memory). Belief inference, the second component, is thought to be specific to ToM and independent of executive function, whereas the third component (self-perspective inhibition) is thought to be

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