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Multidimensional apathy and executive dysfunction in amyotrophic lateral sclerosis

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ABSTRACT

Apathy and cognitive dysfunction are prominent symptoms of Amyotrophic lateral sclerosis (ALS). More specifically ALS patients show increased Initiation apathy-a lack of motivation for self-generation of thoughts as assessed by the Dimensional Apathy Scale. This study aimed to investigate the cognitive underpinnings of apathy subtypes in ALS. We hypothesized that increased Initiation apathy would be associated deficits on tests of intrinsic response generation, such as verbal fluency. We also explored the relationship of other apathy subtypes to cognitive processes, in particular emotional apathy with emotional and social cognition deficits and executive apathy with planning and goal management deficits. ALS patients, and their carers ($N = 30$), and healthy matched controls, and their informants ($N = 29$) were recruited. All participants completed self- and informant/carer-rated Dimensional Apathy Scale, to quantify apathy subtypes (Executive, Emotional and Initiation), along with standard apathy and depression measures. Patients and controls completed the Edinburgh Cognitive and behavioural ALS Screen, and a comprehensive neuropsychological battery including emotional recognition, social cognition, intrinsic response generation tasks (verbal fluency and random number generation) and a new ecologically valid, computerised measure of planning and goal management. The results demonstrated that increased Initiation apathy was the only significantly elevated subtype in ALS (self-rated $p < .05$, informant/carer-rated $p < .01$). Initiation apathy was found to be significantly associated with verbal fluency deficit, while Emotional apathy was significantly associated with emotional recognition deficits. No associations were found between apathy subtypes and depression or in controls. This is the first study to show specific associations between apathy subtypes (Emotional and Initiation) and executive and emotional cognitive dysfunction, indicating possible distinct underlying mechanisms to these demotivational symptoms.

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1. Introduction

Amyotrophic lateral sclerosis (ALS), the most common type of motor neurone disease, is a rapid, terminal neurodegenerative disease characterised by a deterioration of upper and/or lower motor neurones. Up to 50% of ALS patients also display a profile of cognitive impairments and behavioural changes (for review see Goldstein & Abrahams, 2013). This is characterised by as executive dysfunction and social cognition deficits, with additional changes in language, while the behaviour profile is one of apathy (Abrahams, 2011; Beeldman et al., 2016).

Executive dysfunction is the most prominent cognitive impairment and presents in about 40% of ALS patients (Murphy et al., 2016; Phukan et al., 2012; Raaphorst, De Visser, Linssen, De Haan, & Schmand, 2010). This is primarily characterised by a verbal fluency deficit, with a lack of intrinsic response generation (Abrahams et al., 2000). However different types of executive function deficits have also been described where patients have difficulty in concept formation with increased errors on card sorting tests (Gordon et al., 2010; Libon et al., 2012) and impaired performance on dual tasking paradigms (Pettit et al., 2013). Furthermore, ALS patients have shown impairment on more ecologically valid executive functioning tasks of planning and goal management (Meier, Charleston, & Tippett, 2010; Štukovnik, Zidar, Podnar, & Repovš, 2010). Emotional processing and social cognition deficits have also been reported in ALS (Abrahams, 2011; Elamin, Pender, Hardiman, & Abrahams, 2012; Sedda, 2014). In one study, ALS patients rated extreme emotional stimuli more neutrally and other pleasant or unpleasant stimuli more positively (Lulé et al., 2005). When recognising emotions, ALS patients were found to perform significantly worse than controls (Girardi, MacPherson, & Abrahams, 2011; Zimmerman, Simmons, & Barrett, 2007). This deficit extends to emotional memory, where ALS patients failed to show enhanced memory for emotional material (Cuddy, Papps, Thambisetty, Leigh, & Goldstein, 2012; Papps, Abrahams, Wicks, Leigh, & Goldstein, 2005). Social cognition and theory of mind deficits have also been observed, where patients have difficulty inferring what someone is feeling or thinking (Abrahams, 2011; Cavallo et al., 2011; Gibbons et al., 2007; Girardi et al., 2011). Two studies revealed that ALS patients were impaired in theory of mind tasks assessing understanding of social scenarios (Cavallo et al., 2011; Gibbons et al., 2007). More recent studies have used the Judgement of Preference task where patients have impaired mental state inference compared to controls which encompasses both affective and cognitive theory of mind (Girardi et al., 2011; van der Hulst, Bak, & Abrahams, 2015).

Behaviour change is a prominent feature of ALS, with apathy being the most frequently reported symptom occurring in around 50% of patients (Girardi et al., 2011; Grossman, Woolley-Levine, Bradley, & Miller, 2007; Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011; Witgert et al., 2010) and is associated with negative prognosis (Caga et al., 2016). These studies have measured apathy as a single one-dimensional construct, although it is well established that apathy is a complex syndrome composed of demotivational subtypes (Levy, 2012; Levy & Dubois, 2006; Marin, 1991, 1996; Stuss, Van Reekum, & Murphy, 2011). The Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014) uses a triadic dimensional apathy framework assessing Executive, Emotional and Initiation apathy (Radakovic et al., 2016). Executive apathy, relates to a lack of motivation for attention, planning and organization, Emotional apathy, a lack of emotional motivation, as an emotional neutrality or indifference and, finally, Initiation apathy, a lack of motivation for self-generation of thoughts. Recent research has suggested that Initiation apathy is the characteristic apathy subtype observed in ALS (Radakovic et al., 2016; Santangelo et al., 2017), with a different profile of Initiation and Executive apathy being characteristic in Parkinson's disease (Radakovic, Davenport, Starr, & Abrahams, 2017). Notably the DAS also measures apathy independent of motor disability, which is important as apathy is prominent in neurodegenerative movement disorders.

Apathy and verbal fluency deficits are the most prominent features of the cognitive and behavioural profile of ALS and previous study has shown some evidence of a linkage between the two, albeit only through a unidimensional concept structure of apathy (Grossman et al., 2007). The present study aimed to delineate the cognitive processes underlying apathy in ALS. Specifically we hypothesize that it is Initiation apathy which may be linked to verbal fluency deficits as both appear to a common characteristic of the internal generation of response, thought or action (Abrahams et al., 2000; Stuss, 2011). Given that ALS patients also show difficulties with emotional and social cognition and interpreting thoughts or feelings of another individual as a theory of mind impairment (Girardi et al., 2011; van der Hulst et al., 2015), and also executive dysfunction (Meier et al., 2010; Štukovnik et al., 2010), it is possible that there may be some linkage with emotional and executive apathy, respectively.

This study aimed to investigate the cognitive underpinnings of apathy in ALS. Primarily, we hypothesised that the presence of Initiation apathy was associated with deficits on tests of intrinsic response generation such as verbal fluency, and the generation of random responses. Furthermore, secondary exploratory associations were investigated between emotional apathy and deficits in emotional and social cognition, and between executive apathy and difficulties in key executive functions of planning and goal management.

2. Materials and methods

2.1. *Participants*

30 ALS patients (without dementia) and their carers were recruited from the Scottish Motor neurone disease Audit Research Trials (SMART) register. Patient's ALS Functional Rating Scale-Revised scores (Cedarbaum et al., 1999) were accessed from the SMART register. 29 Healthy Controls and their informants were recruited from the University of Edinburgh Departmental Volunteer Panel. Patients and controls were excluded if they had severe disability that would hinder participation, pre-existing dementia, severe diabetes, epilepsy, alcohol/substance-related disorders, severe head injury (that required intensive care setting hospitalisation),