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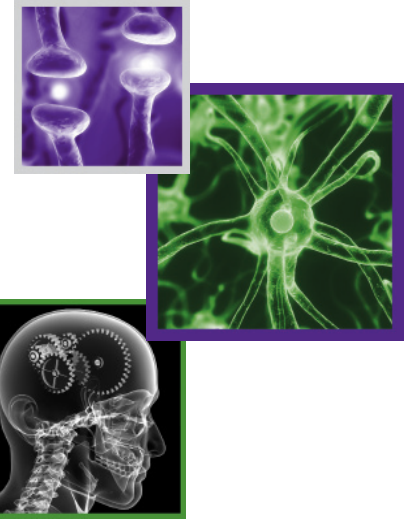
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REVIEW

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Social cognition in amyotrophic lateral sclerosis



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Practice Points

- There is a clinical overlap between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), with 15% of ALS patients suffering from a full-blown FTD.
- A further third of ALS patients will have more subtle cognitive and behavioral change indicative of a 'subclinical FTD' syndrome.
- Executive dysfunction is a predominant symptom, in particular with letter fluency deficits.
- Behavioral change is prevalent with increased apathy and self-centeredness commonly reported.
- Underlying cognitive deficits can be found on tests of social cognition, theory of mind, emotional processing and decision making.
- Some ALS patients may have particular problems in understanding another person's perspective, or interpreting emotions and hence may appear egocentric and unresponsive in their viewpoint.
- It is predicted that some patients may experience a breakdown in social interaction and communication with carers.
- Clinicians should direct education strategies for those involved in the daily care of patients to shed light on this as an integral feature of the disease.

SUMMARY There is an overlap between amyotrophic lateral sclerosis and frontotemporal dementia. Approximately 15% of amyotrophic lateral sclerosis patients suffer from frontotemporal dementia characterized by behavioral change while a further third experience subtle executive dysfunction (typically letter fluency deficits) and corresponding prefrontal changes. Behavior change appears prevalent with apathy being the most prominent feature. Reports of social and emotional cognition deficits are increasing. Deficits have been described on theory of mind tasks including interpretation of stories and cartoons, faux pas detection and in the judgment of preference based on direction of eye-gaze. Impairments in emotional face and prosody perception and emotional enhancement of memory have been reported, and decision making (with and without risk) appears affected. The role of executive dysfunction in this social cognition deficit remains unresolved and more direct evidence of orbitofrontal involvement has yet to be found. Implications for healthcare provision are discussed with deterioration of social interaction with carers predicted.

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Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease, is a rapidly progressive and fatal condition, diagnosed on the basis of upper and lower motor neuron degeneration. The age of onset is typically 58–63 years and patients experience muscle wasting, weakness and spasticity, which is often focal at the beginning, affecting the limbs or bulbar region. The disease typically spreads to encompass other regions and death usually occurs within 30 months of onset of symptoms. The incidence is low at 2.16 per 100,000 and a familial link is found in 5% of patients (three major gene mutations having been identified), although the definition of familial ALS is controversial [1,2]. Traditionally viewed as a disease exclusively of the motor system, there has been a substantial increase in reports of cognitive change in ALS in recent years, and cognitive deficits and behavior dysfunction are now viewed as an integral part of this multisystem disorder [3–6].

Amyotrophic lateral sclerosis to frontotemporal dementia: a clinicopathological spectrum

There is growing evidence of an overlap between ALS and frontotemporal dementia (FTD), the second most common dementia in those under 65 years and a clinico-neuropathological spectrum has been proposed [7]. A small group of ALS patients suffer from a full blown dementia syndrome (ALS-dementia), which is of a frontal type [8]. FTD consists of three distinct clinical syndromes; behavioral variant (bvFTD), progressive nonfluent aphasia and semantic dementia [9]. ALS-dementia most commonly resembles bvFTD. Language dysfunction in ALS has been described [10–12] with symptoms more often of the progressive nonfluent aphasia spectrum [13]. Reports of symptoms of semantic dementia in ALS are rare [14,15]. Estimates of dementia prevalence within the ALS population were at 3–5% [16]; however, these have risen to up to 15% when using more recent FTD diagnostic criteria, which are strongly based on behavior change [17–19]. This new estimation may also be conservative as patients with cognitive impairment have a more rapid disease progression [18,20,21], and therefore studies that recruit from a prevalent rather than an incident population are likely to exhibit lower frequencies of cognitive change. ALS may precede the

dementia, develop concurrently or FTD may be the presenting complaint. ALS is present in up to 10% of FTD cases [8]. Distribution of pathology within ALS-dementia appears to be concentrated in the frontal lobes, (possibly even more prominently than in bvFTD in whom pathological spread also encompasses the temporal lobes [22]). Support for a neuropathological continuum has been strengthened by reports of TDP-43 protein abnormalities in almost all ALS cases, the majority of ALS-FTD cases and up to half of FTD cases [23–25].

A clinical ALS-FTD spectrum has been further supported by the finding of executive dysfunction and corresponding prefrontal (predominantly dorsal) changes in a significant proportion of patients who do not have a full-blown dementia syndrome. These studies have consistently found that approximately a third (38 [26], 33 [27], 37 [19] and 36% [18]) of nondemented ALS patient samples show cognitive deficits on testing. Deficits have been found on a range of tasks including those tapping rule deduction, cognitive flexibility, attention, switching and monitoring (e.g., Wisconsin Card Sorting Test and Trail Making Tests) and letter and category fluency [19,20,28–31]. Strong and colleagues have proposed that these patients can be classified as ALS-cognitive impairment, diagnosed on the basis of impairment on two distinct tests of executive functions [6]. Language changes have also been described with evidence of aphasia and naming impairment [20,26,29], while some reports have suggested that multiple domains are compromised, including memory [18,32]. Deficits on letter fluency (rapid word generation beginning with a given letter) have been the most striking and consistently reported in ALS [18,20,28–31,33,34]. Using a version of this task, which incorporates a writing/motor condition and the production of a Verbal Fluency Index (average time to think of each word) this deficit was shown to be independent of physical disability [28,34]. Such slowed word generation has been shown in patients in the absence of language (naming) deficits, working memory problems of the phonological loop or store, and has been related to executive dysfunction of rapid intrinsic response generation [34]. This deficit is present early in the disease course [30], is more pronounced in ALS patients with pseudobulbar palsy [28], and in some familial forms of the disease (non-SOD1 but is absent in SOD1) [35] and in those with progressive muscular atrophy [36]. This deficit has also been shown to correlate with

eye-movement abnormalities (ocular fixation) a neurological marker [37]. Moreover, evidence of a prefrontal substrate to this cognitive profile has come from a range of brain imaging techniques further strengthening the view of an ALS-FTD spectrum [38]. Predominant dysfunction of the dorsolateral prefrontal cortex and anterior cingulate gyrus has been revealed using functional brain imaging [29,33,39]; reduced neuronal receptor binding of Flumazenil has been shown in the inferior frontal gyrus [40] and frontotemporal white matter abnormalities were found through structural neuroimaging [41] while recent studies have in particular highlighted callosal involvement [42].

Although executive dysfunction is characteristic of typical bvFTD (without ALS), diagnosis is based on behavior change and there has been considerable documentation of the predominant and early disruption in social and personal conduct [9,43]. Patients show emotional blunting, lack of insight, loss of empathy, selfishness, disinhibition and apathy [7,44], and such changes may be apparent prior to the development of deficits on traditional tests of executive functions [21–23]. Despite this absence of overt executive dysfunction, impairments have been shown on more experimental tests of social cognition, emotional processing and emotional decision making [45–49]. Effective social interaction is dependent on the interpretation and exchange of specific social signals such as facial expression, body movement and direction of eye gaze [50] and changes to these processes may underlie the behavior changes evident in bvFTD [51]. Other abilities under the umbrella of ‘theory of mind’, involving inferring and representing others intentions and beliefs and attributing mental states to others that are independent from our own, have also been demonstrated to be affected in bvFTD [45,51,52]. Tasks tapping these functions may be sensitive to more medial and orbito frontal regions that are affected early in bvFTD [51,53,54]. In support of an ALS-FTD spectrum, parallel profiles of cognitive and behavior change should be present in ALS.

Social cognition in amyotrophic lateral sclerosis

■ Behavior change

Within ALS, the primary profile of cognitive involvement has been one of executive dysfunction and corresponding changes in the more dorsolateral and anterior medial prefrontal cortex.

Evidence of behavior change and impairments in social and emotional cognition and involvement of more orbital prefrontal pathways typical of bvFTD has only recently become a focus for investigation within the disorder [55]. In an influential paper, Lomen-Hoerth and colleagues highlighted that behavior change similar to that found in bvFTD was prevalent in ALS [27]. New-onset personality changes that met the criteria for FTD was found in all cases in which letter fluency deficits were present. Using the Neuropsychiatric Inventory, apathy, disinhibition and poor social monitoring were commonly reported. Moreover, a substantial number of patients with normal word generation also showed behavior change [27]. The estimated prevalence of behavior change in ALS may have been exaggerated somewhat in this study owing to the referral patterns to this particular clinic, but nevertheless the findings strengthened the view of a clinical overlap between ALS and FTD. Other studies have similarly reported behavior changes of apathy, irritability, aggression, stereotypy and disinhibition using the Neuropsychiatric Inventory [56,57]. Changes in apathy appear to be one of the most prominent features within ALS. This is commonly reported using the Frontal Systems Behavior Scale (FrSBe) [58,59], which is designed to assess three domains (apathy, executive dysfunction and disinhibition). Moreover increased apathy in ALS using the FrSBe has been related to involvement of the anterior cingulum as measured by diffusion tensor MRI [60]. A recent study of a large cohort of ALS patients (n = 225) revealed changes in at least one domain of the FrSBe in up to 39% of cases [61]. However, a difference appears to emerge between ALS and FTD cases in levels of insight with those ALS patients with mild behavior change showing insight with no significant difference between carer and self-ratings of the FrSBe [62]. A criticism of such studies is the use of questionnaires developed and standardized for the head injury population, in whom physical disability is a less prominent feature. Several items on the FrSBe are confounded by motor disability, such as “is slow moving”, “lacks energy” and “is inactive”, which may exaggerate scores on the apathy scale. Measuring behavior change in ALS is further complicated by emotional reactions and coping with physical disability and terminal illness, and apathy may be a symptom of both an FTD-type behavior change and depression. However, studies that

have used more appropriate interview-based techniques have also revealed high levels of apathy within this population. A more detailed case-by-case carer interview was undertaken by Gibbons *et al.* [63]. Self-centeredness/selfishness was reported as the most prominent symptom in 11 of 16 patients and loss of interest/apathy was found in six of 16. Other symptoms included aggression, loss of insight and social disinhibition described in two of 16 cases. A direct comparison of behavior dysfunction in ALS and bvFTD (without ALS) was undertaken by Lillo *et al.* using the Cambridge Behavior Inventory [64]. A total of 41% of ALS patients showed moderate-severe apathy. Depression was present in 30% of cases but regression analysis revealed that it did not significantly contribute to the presence of behavior symptoms [64]. As the majority of ALS patients do not meet the criteria for FTD, Strong and colleagues have proposed that ALS patients who show behavior change may be classified as ALS-behavioral impairment, diagnosed on the basis of two nonoverlapping supportive diagnostic features from either the Neary or Hodges' criteria [6].

■ Theory of mind

In parallel to the FTD literature deficits on theory of mind tests have now been reported in a significant proportion of ALS patients. Gibbons *et al.* investigated the interpretation of cartoons and stories that involved understanding a character's mental state (including false belief and deception) and revealed a spectrum of impairment ranging from normal to abnormal scores in 16 ALS patients [65]. Deficits were more prominent in those with bulbar symptoms. However, ALS patients did not only have difficulties with the 'social' components of this task but deficits were found in understanding physical scenarios in which humor was based on the physical properties of the scene. The same profile has been shown in FTD and, similarly, ALS patients also show an increase in concrete responses [46]. These tasks have a strong reasoning and inferential component and hence executive dysfunction may have been a contributing factor if not at the root of this deficit. This was further supported by the finding that poor performance on the Wisconsin Card Sorting Task correlated with deficits on these tasks in the ALS group. More recently, Meier and colleagues employed the Faux Pas test to investigate theory of mind in ALS [66]. The test involves recognizing that a

character in a particular scenario has said something that they should not have said. The test has been shown to be sensitive to FTD and to lesions to the ventromedial prefrontal cortex [45,67]. Nine of 18 ALS patients were impaired at identifying a faux pas when compared with controls. No difference was found between groups when using control stories that did not contain a faux pas element [58]. By contrast to the Gibbons *et al.* study, some independence from executive dysfunction was revealed as the deficit remained relatively unchanged with covarying performance on letter fluency [66].

A more selective 'social' deficit in ALS has been recently revealed by Cavallo *et al.* [68]. Here the understanding of social contexts was investigated using a cartoon-based story task that distinguished between inferring private (nonsocial) intentions versus social intentions. A private intention involves a goal that is only relevant to that one person, by contrast to a social intention that involves a social goal. Functional brain imaging has revealed greater prefrontal involvement in the processing of social intentions as compared with the private intentions [69]. In keeping with this, ALS patients were significantly worse at the 'social' items in contrast to controls who showed no significant difference between social and nonsocial items. A significant difference between these processes has also been reported in FTD patients [70].

In contrast to such complex social cognitive tasks that involve the understanding of detailed scenarios with multiple characters, behaviors, emotions and subtle nuances, Girardi *et al.* [60] reported deficits on a simple, undemanding theory of mind test. The task previously shown to be sensitive to bvFTD [46] requires the participant to infer the preference of another by using eye-gaze direction as a social cue. In the first phase of the Judgment of Preference task, the participant is asked to choose their own favorite of four pictures. In phase two, a central face appears, which is looking and smiling at one of the objects, and the participant is required to select which picture 'the face likes best'. Attentional demand was manipulated by the presence of a distracting arrow near one of the pictures. Although 64% of ALS patients were impaired on the attentionally demanding condition (with the distracter present), which may have resulted from demands on executive functions, 36% were still impaired when the distracter was not present. An analysis of the errors showed that there was increased

selection of the patients' own favorite object as opposed to that preferred by the face. Hence, on some trials, patients had difficulties in inhibiting egocentric responding and in the use of a simple social cue (eye-gaze) to perform the task effectively. Of note, ALS patients had no difficulties in performing a third control phase in which the stimuli remained unchanged, but the wording was altered from 'Which picture does the face like best?' to 'Which picture is the face looking at?' Hence, the deficit did not appear to result from basic comprehension or primary attentional dysfunction. Deficits on this test were more prevalent than on traditional measures of executive functions in which only 29% of patients were impaired. Moreover, there was a link to increased behavioral dysfunction in this group with increased apathy related to poor performance on the task. By contrast, to the Gibbons *et al.* study, deficits were found in those with and without bulbar involvement, although there was a greater ratio of bulbar to limb patients in the cognitively impaired subset at a 2:1. This is supportive of previously described associations that suggest that those with bulbar involvement are more at risk of cognitive impairment [28].

■ Emotion processing

Effective emotional processing is fundamental to theory of mind and social interaction. Deficits have been typically reported in bvFTD and similar dysfunction has now been described in ALS. Some studies have revealed that standard facial emotion recognition paradigms are sensitive to ALS [60,71], although this has not been consistently reported [72]. Deficits in identifying emotional prosody in speech have also been described [58] although Zimmerman *et al.* demonstrated that this was not as sensitive as the face emotion recognition test [71]. Girardi and colleagues demonstrated a deficit on two tests involving the understanding of both simple (Facial Expressions of Emotion test) and complex (Reading the Mind in the Eyes test) emotional expression. A subgroup of patients performed poorly on both of these measures and the social cognition eye-gaze task reported previously. However, deficits on the more complex Reading the Mind in the Eyes test have not been consistently related to poor performance on other social cognition measures in ALS [68]. Further studies have demonstrated that this emotional processing deficit is selective and is not a manifestation of general cognitive decline or attentional dysfunction. Papps *et al.*

demonstrated that ALS patients failed to show enhanced recognition of emotional words, a phenomena that is apparent in controls. This deficit could not have resulted from general memory dysfunction as ALS patients' performance on recognizing neutral words was superior to that of controls [72].

In terms of the social relevance of emotion perception, Schmlok *et al.* revealed that ALS patients rated faces as more approachable than controls [73], while Lule and colleagues revealed that ALS patients tended to show a more positive valence towards emotive social situations and rated calm pictures as more exciting and *vice versa*, resulting in a more balanced state of arousal than controls [74]. Levels of arousal were subsequently related to patterns of increased and decreased activation using fMRI (increased activation was observed in the supramarginal gyrus and reduced activation in the extrastriate visual areas in ALS patients). Moreover, changes occurred in the anterior insula over time, which correlated with subjective reports of arousal. Further evidence of the cerebral substrate of the emotional processing dysfunction in ALS comes from a recent fMRI study in which during an emotional decision task, participants were asked to select the most unpleasant (or neutral) word from a series of three words and subsequent recognition of this emotional material [75]. Both decision and recognition tasks were associated with reduced activation in the right hemisphere in ALS patients and an increase in the left hemisphere in comparison with controls. This lateralized dysfunction appears consistent with the findings of Murphy *et al.* who found that ALS patient with FTD and more subtle behavioral disturbance had significantly more gray matter volume reductions in the right hemisphere (as revealed through structural MRI) in comparison with ALS patients without cognitive or behavioral abnormalities. The authors proposed that right hemisphere atrophy was a biomarker for behavioral abnormalities in ALS [76].

Of note, up to half of ALS patients show a dysregulation of emotional expression termed emotional lability. The relationship of this loss of emotional control to the deficit in emotional processing has not yet been investigated, although recent studies have demonstrated that lability does not appear to be directly related to other cognitive deficits present in ALS and suggests differing neuronal pathways underlying these symptoms [77].

■ Decision making

There is now growing evidence to suggest that the cognitive impairment in ALS encompasses decision-making processes including those reliant on more orbitomedial prefrontal functions. A typical paradigm involves reward learning and deficits have been revealed in a modified version of the Iowa gambling task [60], which has been shown to be sensitive to ventromedial lesions [78] and FTD [79], although no deficits were reported on a probabilistic reversal learning task [58] also sensitive to ventromedial lesions. Using a version of the Iowa gambling task, Girardi and colleagues revealed that ALS patients made no adjustment to their performance in response to the negative consequences of losing money and continued to select from high-risk decks in comparison with controls [60]. Poor performance was also related to overall behavioral change as measured by the FrSBe. However, it should be noted that performance of ALS patients did not resemble that of FTD in whom there appears to be an increased selection from high-risk decks as the task continues [79]. By contrast, ALS patients' performance remained stable throughout the test, indicating a failure to learn that may have resulted from more executive dysfunction. This is consistent with the finding that poor performance may also be affected by dorsolateral prefrontal dysfunction [80]. Further evidence of affected decision-making processes in ALS comes from a recent study that employed an attribute-based decision-making task [66]. In the Holiday Apartment task, the participant must select a suitable apartment on the basis of assessment of multiple attributes. It has previously been demonstrated that patients with ventromedial lesions use different search strategies (apartment by apartment) than those of dorsolateral prefrontal damage who use an attribute-based strategy. A total of 44% of ALS patients showed a more apartment based search strategy on more complex trials, similar to that of patients with ventromedial lesions. This is of particular interest as the affective and risk component of decision making has been removed and hence has clear implications for decision making within everyday life.

Conclusion & future perspective

A subgroup of ALS patients appear to show dysfunction in social cognition and corresponding behavior change that is parallel to that found in

bvFTD. Dysfunction ranges in severity from a full-blown dementia syndrome characterized by marked behavior change to a more subtle impairment. The latter reflects a profile of 'sub-clinical' FTD in a significant proportion of cases and provides further support for a clinico-pathological spectrum. Several unresolved issues remain – most prominently, to what extent these changes can be related or explained by executive dysfunction, which is clearly present in the disease. Executive dysfunction and more dorsal prefrontal involvement are known to produce impairments on some of these experimental cognitive tasks. Moreover, there is still an absence of direct evidence of changes to the orbitomedial cortex as found in early changes in bvFTD. If executive dysfunction and social cognitive deficit emerge as independent features, the question arises of whether these deficits are reflective of different subphenotypes with separable distribution of prefrontal pathology. Longitudinal studies in ALS are notoriously difficult to perform owing to progressive disability and high attrition rates; however, these are necessary to determine the course of these changes and shed further light on heterogeneity of impairment. Poor prognosis has been associated with cognitive change in ALS [18,20,21]. If this is also true of those with a social cognition deficit, the question arises of whether this is a primary consequence of disease progression with those with associated cognitive symptom experiencing a more aggressive disease, whether this is a secondary consequence of different treatment strategies being offered to those with cognitive dysfunction, or whether this is a factor of those cognitively impaired ALS patients not adhering to treatment.

The impact of such changes on daily life is yet to be investigated and has clear implications for the daily management of ALS patients. Potential problems may emerge in using social cues to guide behavior in interpreting the emotions and the intentions of others resulting in problems with social interaction. Some ALS patients may fail to see another person's perspective and appear self-centered with a loss of concern for their partner's/families' feelings, resulting in deteriorating social relationships with carers. An ALS patient during the course of their illness becomes increasingly dependent on those in their immediate environment and hence a breakdown in effective social interaction is likely to have considerable impact on

the everyday life of the family. Further problems may emerge in decision making in fully understanding the consequences of their own actions. This has particular relevance for decision making over disease-specific issues such as treatment and end-of-life care, in addition to secondary issues such as organizing finances and planning for the future of the family. Where dysfunction in social cognition is suspected, clinicians should use education strategies to inform those involved in the direct care of the patient (including healthcare professionals and family and friends) of the range of potential symptoms (e.g., inability to see another's perspective and apathy) and the impact that these changes may

have on relationships and social interactions with those around them. Most importantly, carers should be educated that these symptoms are an integral part of the disease and often not a symptom of other secondary factors associated with their relationship.

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