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Deficits in Emotional and Social Cognition in Amyotrophic Lateral Sclerosis

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Abstract

Objective: These studies investigated whether non-demented ALS patients display impairments on tests of emotional decision making and social and emotional cognition, sensitive to frontal variant Frontotemporal Dementia (fvFTD). Previous studies have shown predominant executive dysfunction and dorsolateral prefrontal involvement in ALS, but evidence of other prefrontal dysfunction implicated in fvFTD is sparse. Method: Study A, 19 ALS patients and 20 healthy controls undertook a test of affective decision making, modified Iowa Gambling Task (IGT). Behavioural measures included the Frontal Systems Behaviour Scale. Study B, 14 ALS patients and 20 controls undertook tests of social and emotional cognition (Judgement of Preference based on eye gaze, the Mind in the Eyes, recognition of Facial Expressions of Emotion). Results: Study A, ALS patients demonstrated a significantly different performance profile from healthy controls on the IGT and did not learn to avoid the disadvantageous stimuli (Block 3, d = 0.60, Block 4 d = 0.68). Behaviour ratings showed increased apathy from premorbid levels. Study B, ALS patients were impaired on attentionally demanding (d = 3.12) and undemanding (d=7.52) conditions of the Judgement of Preference task, despite many showing intact executive functions. A smaller subset showed impaired emotion recognition. Behaviour change was also evident. Conclusions: The findings reveal a Theory of Mind deficit on a simple test which was dissociated from the presence of executive dysfunction and suggests a profile of cognitive and behavioural dysfunction indicative of a subclinical fvFTD syndrome. The relative contribution of prefrontal pathways to the cognitive profile in ALS are considered.

Key Words: Motor Neurone Disease, Executive Functions, Theory of Mind, Behaviour

Introduction

Although traditionally characterised as a motor system disorder, amyotrophic lateral sclerosis (ALS) is now recognized to affect multiple systems with a significant proportion of patients displaying a frontotemporal syndrome in addition to motor system pathology (Strong et al. 2009). A subgroup of patients (5-15%) meets criteria for frontotemporal dementia (FTD), typically a frontal variant with predominant executive dysfunction and pattern of behaviour change including disinhibition and apathy (Neary et al. 1990; Snowden, et al. 1996; Neary, et al 2000; Lomen-Hoerth et al. 2002). A further large proportion of non-demented ALS patients (25-50% of cases) have more subtle cognitive impairment of predominantly executive dysfunction (Abrahams & Goldstein, 2002, Strong et al. 2009). This has led to the suggestion of a continuum of cognitive change ranging from those with FTD to those with solely motor system involvement (Kew & Leigh, 1992; Leigh & Ray-Chaudhuri, 1994; Neary et al. 2000; Talbot et al., 1995; Wilson et al, 2001; Murphy et al. 2007) although some have suggested that the evidence for such a continuum is weak (Phukan et al. 2007).

At present evidence of a cognitive continuum rests predominantly on the repeated and striking demonstration of selective letter fluency impairments in non-demented ALS patients (Abrahams et al., 1997; Abrahams et al. 2000; Abrahams et al. 2005b). This test is heavily dependent on executive processes and deficits have been found to occur independent of language or working memory dysfunction and are still present once physical disability has been accommodated (Abrahams et al. 2000). Letter fluency deficits in non-demented ALS patients have been directly related to: underlying cerebral dysfunction of the dorsolateral prefrontal cortex and anterior cingulate gyrus through functional neuroimaging studies

(Abrahams et al. 1996, Abrahams et al. 2004); frontotemporal white matter abnormalities in structural neuroimaging (Abrahams et al. 2005a) and reduced neuronal receptor binding of Flumazenil in the inferior frontal gyrus (Wicks et al. 2008). These cognitive deficits are found early on in the disease process (Abrahams et al. 2005b), are increased in ALS patients with pseudobulbar palsy (Abrahams et al. 1997), correlate with ocular fixation abnormalities (Donaghy et al. 2009) and are absent in patients without upper motor neurone involvement (Wicks et al 2006). Impairments have also been reported on other tests of executive functions including concept formation and mental flexibility, planning and verbal and visual attention, verbal reasoning and sequencing (Abrahams and Goldstein 2002, Evdokimidis et al., 2002; Ringholtz et al. 2006, Pinkhardt et al. 2008; Santhosh, et al., 2004) although these deficits appear to be less consistently described.

However, it is well established that patients with frontal variant FTD (fvFTD) can have a distinctive behavioural syndrome prior to the emergence of executive dysfunction on standard testing, with corresponding early changes in the orbital-medial parts of the frontal lobes. These patients also show impairment on experimental tests of emotional processing and social cognition (Gregory et al., 2002, Lough et al., 2001). Emotional processing may be compromised with impairments in emotional recognition (Lough et al. 2006) and on a widely used test involving affective decision making, the Iowa Gambling Test (IGT, Torralva et al. 2007). Deficits on tests of Theory of Mind (ToM i.e. the ability to understand the thoughts and intentions of others) have been also been frequently described (Gregory et al. 2002, Lough et al. 2006, Snowden et al. 2003, Torralva et al. 2007, Torralva et al. 2009). It is of note that although performance on the IGT is sensitive to lesions of the ventromedial prefrontal cortex (Bechara et al. 1994) deficits on this test have been found not to correlate

with some ToM measures in patients with fvFTD, indicating possible independent functional processes (Torralva et al. 2007).

Evidence of impairments in social and emotional cognition in non-demented ALS patients, reflective of fvFTD and dysfunction of more obribtal and medial prefrontal pathways, is sparse. Recent findings have demonstrated some incidence of behaviour change in ALS (Lomen-Hoerth et al. 2003) with irritability and disinhibtion (Murphy et al. 2007) and apathy (Grossman et al. 2007) although studies have not excluded patients with FTD, moreover behaviour change has been difficult to dissociate from reactions to the disease or the consequences of physical disability. Gibbons et al. (2008) reported carers' descriptions of changes in affect and social behaviour, with self-centeredness/selfishness and loss of interest/apathy being the most frequently described behaviour change. Some evidence of emotional dysfunction has been described with a failure to show enhanced recall of emotional words (Papps et al. 2005) and impairments in facial recognition of emotions (Zimmerman et al. 2007) and one study has demonstrated evidence of a deficit on ToM in some ALS cases (all of whom had bulbar signs) with an impairment in interpreting humorous cartoons and story comprehension (Gibbons et al., 2007), although due to the demanding nature of the tasks executive dysfunction may have been at the root of the deficit seen. In the current studies social and emotional cognition in non-demented ALS patients is investigated using a range of experimental tests, previously shown to be sensitive to impairment in fvFTD and the relative contribution of prefrontal pathways to the profile seen is considered further.

Study A: Affective Decision Making and Behaviour

In this first study we investigated whether there was evidence of a deficit in non-demented ALS patients on a modified version of the IGT, a test of affective decision making which has been previously shown to be impaired in fvFTD. The relationship of performance to behaviour change was also investigated.

Method

Participants

The patient group consisted of a sample of 19 non-demented patients (12 male, 7 female) with sporadic ALS recruited through the regional ALS service at Western General Hospital, Edinburgh. All had clinical and electrophysiological evidence of combined upper and lower motor neurone involvement and fulfilled the revised criteria for clinically definite or probable ALS (Brooks et al. 1998). None of the patients fulfilled the diagnostic criteria for FTD according to the core and supportive diagnostic features of FTD as detailed by the Lund Manchester consensus (Neary et al., 1998). The patients' mean time since symptom onset was 33.22 months (SD 29.01). Patients mean rating on the ALS Functional Rating Scale-R was 29.37 (SD10.50) (Cederbaum et al. 1999). Patients were excluded if they had any other significant neurological or psychiatric history, or communication difficulties that would compromise their performance.

The healthy control group consisted of 20 participants (9 male, 11 female) recruited from a panel of volunteers at the Department of Psychology, University of Edinburgh. None of the controls had any previous history of head injury or stroke, major neurological or psychiatric illness, or alcohol abuse.

The ALS patients and healthy controls did not significantly differ in terms of age (ALS mean 57.79, SD 15.64, Controls mean 56.80, SD 0.26) or years of education (ALS mean 13.05, SD 3.95, Controls mean 14.87, SD 3.60). The ALS patients showed no evidence of elevated levels of daytime somnolence which may be related to respiratory dysfunction as assessed using the Epworth Sleepiness Scale (Johns, 1991) (ALS Mean 5.9, SD 3.6). Moreover the ALS group showed no evidence of clinical levels of anxiety or depression as revealed by low scores on the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983) (Anxiety – ALS Mean 5.4, SD, 2.6, Depression ALS Mean 4.3, 2.5 SD). Hence it is unlikely that the cognitive impairment revealed in the ALS patients was related to affective disorder or respiratory failure. The study was approved by the local NHS ethics committee and in accordance with the 1964 Declaration of Helsinki and informed consent was obtained for all participants.

Neuropsychological assessment

All participants performed a brief neuropsychological battery to test premorbid intellectual functions, language and executive functions. This included: The National Adult Reading Test–R to estimate of premorbid IQ (NART; Nelson & Willison, 1991); the Graded Naming Test to estimate confrontation naming (GNT; McKenna, & Warrington, 1983); the Written Verbal Fluency Test and Spoken Verbal Fluency Test (in patients in which writing was severely compromised) to assess executive dysfunction, both of which accommodate for physical disability to produce a verbal fluency index (Abrahams et al. 2000); and the Frontal Systems Behaviour Scale to assess behaviour change (FrSBe; Grace, & Malloy, 2001).

Experimental assessment

All participants undertook a version of the IGT (Bechara et al. 2000). The test was presented on a computer screen with participants indicating response either with a mouse or by pointing. A shorter 60 trial version of this task was employed to prevent patient fatigue. In the task the participant selects a card from four separate decks of cards (A, B, C, D). Following selection the participant wins and sometimes loses a certain amount of money. Selection from decks A and B results in high wins, but also high losses and overall accumulative loss and hence selection from these decks is disadvantageous, while selection from decks C and D results in lower wins and lower losses and overall accumulative gain and hence selection from these decks is advantageous.

Statistical analyses

Between group analyses were undertaken comparing the ALS patients to the Controls using analysis of variance (for the IGT and FrSBe data) and parametric *t*-tests, or non-parametric Mann-Whitney U-tests for the background data. Correlational analyses were undertaken using Pearson's Product Moment correlation.

Results

Neuropsychological Assessment

The results of the neuropsychological assessment can be seen in Table 1. The ALS patients differed significantly from controls on scores on the Apathy subscale of the FrSBe only, with increased Apathy in the patient group. A comparison of the ALS patients' self and carer ratings on the FrSBe revealed no significant interactions between Rater (Carer, Patient) and Time (Premorbid, Present) on any of the subscales indicating that carers did not rate the change in the patient's behaviour since the onset of the illness as different from the patients

themselves. All analyses showed an effect of Time, reflecting an increase in carers' and patients' ratings of the patient's behaviour from premorbid to present time (Executive Dysfunction $F=10.77$, df 1, 16, $p<0.01$; Disinhibition $F=7.69$, df 1,16, $p<0.025$; Apathy $F=8.96$, df 1, 16, $p<0.01$; Total Score $F=26.28$, df 1, 16, $p<0.001$). Moreover there was a significant effect of Rater on the Disinhibition subscale with carers rating patients' behaviour as lower than the patients' ratings ($F=6.97$, df 1,16, $p<0.025$). This result may be contrary to that expected and indicates that carers generally rated the patient's behaviour as being less disinhibed than the patients' rated themselves both premorbidly and at present. Of note similar low levels of behaviour change have been reported by carers in other studies (Abrahams et al. 2005b).

[Insert Table 1 here]

Affective Decision Making Test

The selections for the advantageous decks (C+D) and disadvantageous decks (A+B) were computed over 4 blocks of 15 trials. Fig. 1 shows the number of selections from the disadvantageous over the task. Analysis of variance comparing Group (ALS vs Controls) vs Block (1 to 4) on the number of disadvantageous selections revealed a significant effect of Block ($F=3.69$, df 3, 111, $p<0.025$), and of Group x Block ($F= 3.41$, df 3,111, $p< 0.025$). Post hoc comparisons revealed a significant difference between ALS patients and Controls on the number of disadvantageous selections on Block 3 ($t=-2.03$, df 37, $p<0.05$), and Block 4 ($t=-2.20$, df 37, $p<0.05$). Correlational analysis between the total number of selections from the disadvantageous decks and behavioural ratings on the FrSBe revealed a significant correlation with the self rated scores only on Executive Dysfunction ($r=0.65$, $p<0.005$) and

Total Scores ($r=0.52$, $p<0.05$) with increased selections on the disadvantageous decks related to higher rates of behavioural dysfunction. The number of selections from disadvantageous decks did not significantly correlate with the z score of the verbal fluency index.

[Insert Fig. 1 here]

Discussion

The findings from this first study revealed a deficit in this version of the IGT in a group of non-demented ALS patients. The ALS patients showed no adjustment of performance over the course of the task and did not learn to avoid the disadvantageous decks in relation to the negative consequence of losing money. Moreover patients showed evidence of an increase in behavioural dysfunction from premorbid to present time, with significantly greater levels of Apathy than controls and poor performance on the IGT related to overall level of behaviour dysfunction in daily life (Total Scores FrSBe). A failure to learn to avoid disadvantageous decks on the IGT has been found in patients with ventromedial lesions (Bechara et al. 1994) and patients with fvFTD (Torralva et al. 2007). However of note ALS patients did not show a tendency to increase selection from disadvantageous decks during the course of the task as has been shown in patients with fvFTD (Torralva et al. 2007). In contrast ALS patients performance remained stable across the blocks. This may indicate a failure to learn the win-lose contingencies rather than a tendency to engage more in risky decision making (see Clark, & Manes, 2004). It has been suggested that performance on the IGT may also be affected by more dorsal prefrontal dysfunction and have a high learning demand (Clark et al. 2003). It is well established that ALS patients have such dysfunction and associated executive deficits (e.g. Abrahams et al. 2004), and although the current study did not reveal a deficit in verbal fluency in the sample studied, poor performance on the IGT correlated with ratings of

Executive Dysfunction (FrSBe) in daily life. In order to investigate whether there is any further evidence indicative of a subclinical fvFTD profile of dysfunction in the ALS patients a second study was undertaken which focuses on tests of emotional and social cognition including Theory of Mind.

Study B: Social Cognition and Behaviour

This study aimed to undertake a more in depth analysis of social and emotional cognition in ALS, its relation to executive function and behaviour. One previous study which has shown a deficit in ToM tasks in ALS employed relatively highly demanding tasks (interpretation of stories and humorous cartoons) which raised the possibility that executive dysfunction may underlie the deficit (Gibbons et al. 2007). This was supported by the finding that poor performance on the Wisconsin Card Sorting Task correlated with deficits on these tasks. The current study included a version of a simple ToM task in which preference judgements are made on the basis of the direction of eye gaze of a face. The task has low executive demands and has been previously shown to be sensitive to fvFTD (Snowden et al. 2003). Complex and simple emotional understanding of expression was also investigated using the Reading the Mind in the Eyes Test and the Facial Expressions of Emotions Test, both of which have also been shown to be affected in fvFTD (Lough et al. 2006, Torralva et al. 2007). Moreover as previous studies have revealed an association between cognitive impairment and bulbar pathology (Abrahams et al. 1997) and this has been found in relation to ToM deficits (Gibbson et al. 2007) the presence of bulbar dysfunction was also investigated.

Method

Participants

The patient group consisted of a non-demented sample of 14 patients (10 male, 4 female) with sporadic ALS recruited through the regional ALS service at Western General Hospital, Edinburgh. All had clinical and electrophysiological evidence of combined upper and lower motor neurone involvement and fulfilled the revised criteria for clinically definite or probable ALS (Brooks et al. 2000). None of the patients fulfilled the criteria for diagnosis of FTD according to the core and supportive diagnostic features of FTD as detailed by the Lund Manchester consensus (Neary et al., 1998). Seven patients had bulbar symptoms at the time of testing, while 7 patients had limb involvement only. The patients' mean time since symptom onset was 38.07 months (SD 29.56). Patients mean rating on the ALSFRS-R was 29.79 (SD 10.58) (Cederbaum et al. 1999). Patients were excluded if they had any other significant neurological or psychiatric history, or communication difficulties that would compromise their performance.

The healthy control group consisted of 20 participants (15 male, 5 female) recruited from a panel of volunteers at the Department of Psychology, University of Edinburgh. None of the controls had any previous history of head injury or stroke, major neurological or psychiatric illness, or alcohol abuse. The patients and controls were a separate group from that recruited for Study A, i.e no participant was recruited into both studies. The ALS patients and healthy controls did not significantly differ in terms of age (ALS Mean 57.4, SD 16.0, Controls Mean 54.8, SD 11.5) or years of education (ALS Mean 14.4, SD 5.4, Controls Mean 15.1, SD 3.2). In addition there was no significant difference between groups on the Epworth Sleepiness Scale (ALS Mean 5.1, SD 5.2, Controls Mean 7.6, SD 4.2). Moreover the two

groups did not significantly differ in estimates of anxiety and depression using the HADS, (Anxiety – ALS Mean 6.5, SD 2.6, Controls Mean 6.9, SD 4.1; Depression – ALS Mean 3.9, SD 2.7, Controls Mean 2.8, SD 2.8). Hence it is unlikely that abnormalities in social and emotional cognitive processes and behavioural profiles in the ALS patients were related to affective disorder or respiratory failure. The study was approved by the local ethics committee and in accordance with the 1964 Declaration of Helsinki and informed consent was obtained for all participants.

Neuropsychological assessment

All participants performed a standard neuropsychological battery to test intellectual, memory, language and executive functions. An estimate of current Verbal IQ was produced using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Memory was assessed using immediate and delayed story recall from the Wechsler Memory Scale-III (WMS-III; Wechsler, 1999) and the Kendrick Object Learning Test (KOLT; Kendrick, 1985). The Graded Naming Test was used to estimate confrontation naming (GNT; McKenna, & Warrington, 1983). Three tests were used to assess executive function: the Hayling Sentence Completion Test and Brixton Spatial Anticipation Test (Burgess, & Shallice, 1997), and the Written Verbal Fluency Test or Spoken Verbal Fluency Test (Abrahams et al. 2000) which produced the verbal fluency index. A more extensive investigation of behaviour change was undertaken in this study using the Manchester Behavioural Questionnaire (MBQ, Bathgate et al., 2001) the Cambridge Behavioural Inventory (Bozeat et al. 2000) and the Frontal Systems Behaviour Scale (FrSBe; Grace, & Malloy, 2001). Both patients and carers also completed the Emotional Lability Questionnaire

(ELQ; Newsom-Davis et al. 1999) to assess the patient's frequency of laughter and crying in the four weeks prior.

Experimental tasks

Judgement of Preference. The task assesses the ability to make a preference judgement based on eye gaze. A computerised version of the task was created in E-Prime (E-Prime, 2000) based on the paper and pencil version previously described by Baron-Cohen et al. (1995) and Snowden et al. (2003). In all trials, four pictures of objects belonging to the same semantic category (animals, cartoon characters, colours, furniture, fruits or vegetables) were positioned in each of the four corners of the computer screen (upper left, upper right, lower left and lower right). The task consisted of a pre-experimental condition, an experimental condition and a control condition. In the pre-experimental condition, participants were asked to choose their personal favourite of the 4 objects. In the following conditions, a cartoon face was also presented in the middle of the computer screen and the eye gaze of the face was directed towards one of the four objects (see Fig. 2). In the experimental condition the following question appeared at the top of each screen, "Which picture does the face like best?" In the control condition the stimuli were identical but the question at the top of the screen was "Which picture is the face looking at?" For half of the trials in both the experimental and control conditions a distracter arrow was also presented which pointed towards a different object to the one that the face's eye gaze was directed at. Participants who failed the task for reasons of attention/executive dysfunction would be more likely to make errors related to the distracter arrow. The task involved a structured forced-choice response where participants had to press the button on the keyboard corresponding to the position of the object on the screen. For each condition, there were 12 trials and each

semantic category was presented twice (2 x 6 categories) with the exemplars in the same position. Participants were instructed to respond as fast but as accurately as possible. The number of correct responses was recorded. Errors were categorized as: “favourite”, in which participants chose their personal favourite object (as determined in the pre-experimental condition; “arrow” in which participants chose the object indicated by the distracter arrow; or “unclassified” if they did not fit into either of the other two error types.

[Insert Fig. 2 here]

Reading the Mind in the Eye (MIE). A computerised version of the task was developed in E-prime (2000) using the stimuli from Baron-Cohen et al. (2001). In each trial, a photograph of the eye region of a face was presented with four words describing complex mental states. The target word and the three foil words had the same emotional valence but did not describe semantic opposites (e.g. concerned vs. unconcerned). Before each trial, participants were shown a display cross in the middle of the computer screen with the 4 mental states below. Participants were asked whether they knew the meaning of all 4 words and if they did not, a definition was read to them from a glossary of words. Once participants were sure they knew the meaning of each word, the cross was replaced by a picture of the eye region. Participants then had to press a button on the keyboard corresponding to the word that best described what the person in the picture was feeling or thinking. The picture remained on the computer screen until a response was made. There were 36 trials in total and the number of correct responses was recorded.

Facial Expressions of Emotions. The Ekman 60 item subtest from the Facial Expression of Emotion: Stimuli and Test (FEEST; Young et al. 2002) was administered. Participants were presented with black and white photographs of faces in the middle of the computer screen and underneath each face was a list of adjectives describing the 6 possible emotions: anger, disgust, fear, sadness, happiness or surprise. From this list, participants had to choose the adjective that best described the emotion portrayed on the face in the photograph. Each photograph remained on the computer screen until the participants made their decision. Ten stimuli of each emotion were presented, resulting in a total of 60 trials. Prior to performing the task, participants were given 6 practice trials consisting of an example of each emotion using an individual who did not appear in the test phase.

Statistical analyses

The data were analysed in terms of group and individual scores. The groups were compared using parametric *t*-tests, analysis of variance or non-parametric Mann-Whitney U-tests. The performance of each individual ALS patient was also compared against the healthy control means using *z*-scores where performance is considered abnormal if a patient performs 2 or more standard deviations above or below the control group mean i.e. $z > 2$.

Results

Neuropsychological assessment

Table 2 demonstrates the means and standard deviations for the ALS patients and healthy controls on the standard neuropsychological tests. The individual scores of ALS patients are shown in Tables 3 and 4. There was no significant difference between the groups

in current Verbal IQ. In terms of verbal memory, there was a significant difference between the ALS patients and healthy controls in immediate verbal recall, with the four of the ALS cases (three without bulbar signs) performing in the abnormal range. Although there was no significant difference between groups in the percentage of information retained over a delay, three of the ALS patients without bulbar signs scored in the abnormal range. There was a trend towards ALS patients naming fewer items on the Graded Naming Test and two ALS patients without bulbar signs showed an abnormal level of naming ability. Moreover two patients scored within the abnormal range on the Hayling Sentence Completion Test, one patient on the Brixton Spatial Anticipation Test and two on the letter fluency although group differences were not found.

On the Self rated FrSBe scores a Group (ALS patient vs. healthy control) x Time (Premorbid vs Present) analysis of variance revealed a significant interaction between Time and Group ($F=5.38$, df 1, 31, $p< 0.05$) and a near significant effect of Group ($F=4.17$, df, 1, 31, $p = 0.05$). Contrary to expectation the controls rated themselves as having a higher level of behaviour dysfunction than the ALS patients, but they showed less change from premorbid to present ratings. A breakdown of scores across the three components of the questionnaire (Apathy, Disinhibition, Executive Dysfunction) indicated that the interaction was primarily driven by the Apathy subscale which tended towards significance Time x Group ($F= 3.29$, df 1, 31, $p = 0.079$) with a greater increase in Apathy in ALS patients from premorbid levels. Neither of the other two subscales produced a significant or near significant interaction. A comparison of the ALS patients' self ratings and their family ratings revealed no significant main effect of Rater (Carer or Patient) or interaction between Rater and Time (Premorbid, Present). Patients' families did not rate their relatives' behavioural changes over time worse

than the patients rated themselves. Analysis of the ELQ revealed a significant difference between the ALS patients and controls on the total score. A comparison of Carer and Patient ratings of the ELQ revealed a significant effect of Rater (F=10.46, df 1, 13, p = 0.007), with patients rating themselves as more emotionally labile than carers had rated them (patients mean 14.43, SD 10.53, carers mean 8.36, SD 9.83). Scores on the MBQ and CBI (see Table 4) show varying levels and types behavioural dysfunction in daily life as rated by a carer. On the CBI no patient was above the cut-off score for dementia (Hancock and Larner 2008).

A comparison between the two patient groups in Study A and Study B revealed no significant difference between the patient groups on letter fluency z scores, [Study A 1.27 (2.6), Study B 3.81 (8.2), t=-9.45, df 10.3, p =0.37)] or on the Graded Naming Test [Study A 23.22 (3.2), Study B 21.75 (3.5), t=1.20, df 29, p = 0.239)]. Hence the two groups appear comparable in terms of background measures which have been previously found to be sensitive to impairment in ALS in other studies.

[Insert Tables 2, 3 and 4 here]

Experimental tasks

Judgement of Preference. Fig. 3 shows mean and standard errors for the number correct responses for the ALS patients and controls. The analysis revealed that the ALS patients produced significantly fewer correct responses than healthy controls in the experimental “like best” with and without distractor conditions (U = 45.5, p < .001 and U = 99.0, p <.05 respectively). The ALS patients also performed more poorly than controls in the control “look at” condition without a distractor, (U = 111.0, p < .05) although as can be seen

from the Fig. they are very close to ceiling on this measure (Without Distracter ALS mean 11.43, SD 1.6). Moreover, no significant difference was found between the two groups in the control “look at” with-distracter condition.

Individual performance can be seen in Table 5 in which 9/14 of the ALS patients performed in the abnormal range for the experimental “like best” with distracter condition (6 bulbar, 3 non-bulbar), while 5 performed in this range in the without distracter condition (3 bulbar, 2 non-bulbar).

[Insert Fig. 3 here]

The means and standard deviations for each error type in each of the 4 conditions are shown in Table 6. Nonparametric analysis revealed that the ALS patients made significantly more “favourite”, “arrow” and “unclassified” errors, than the healthy controls in the Experimental ‘like best’ with distracter condition. In the Experimental without distracter condition, the ALS patients also made significantly more “favourite” and “unclassified” errors. The two groups did not significantly differ in the number of errors made in either of the control conditions.

[Insert Tables 5 and 6 here]

Correlational analyses between performance on the Judgement of Preference task and behavioural measures (FrSBe) revealed that the number of correct responses in the Experimental with distracter condition correlated significantly with the change in self rated

Apathy scores on the FrSBE, in that poor performance on the test was related to an increase in Apathy from premorbid to the present time ($r=-0.56$, $p<0.05$). Moreover the relationship to measures of executive functions was explored and performance on the Experimental with distracter condition showed a trend only towards a significant correlation with z scores on verbal fluency tests ($r=0.-60$, $p=0.07$). No significant correlation was found between performance on this test and the WMS-III immediate memory score.

Reading the Mind in the Eye. Fig. 4 demonstrates the mean accuracy scores and standard error for both groups. The number of correct responses tended towards a significant difference in the ALS patients compared with controls once unequal variances were corrected for (t 2.08, df 17.3, $p=0.05$). Three ALS patients performed within the abnormal range (2 bulbar and 1 non-bulbar).

[Insert Fig. 4 here]

Correlational analyses revealed no significant relation with behavioural measures, although the number correct significantly correlated with z scores of verbal fluency performance ($r = -0.66$, $p< 0.05$) only. No significant correlation was found between performance on this test and the WMS-III immediate memory score.

Facial Expressions of Emotions Test. The mean accuracy scores and standard errors for the ALS patients and controls performing the emotion recognition test are displayed in Fig. 5. A Group (ALS vs Controls) x Emotion (Anger, Sadness, Happiness, Disgust, Fear, Surprise) ANOVA comparing the accuracy scores showed a significant main effect of Group,

(F (1, 32) = 4.34, p < .05), where the ALS patients recognised significantly fewer emotions than the healthy controls. Two ALS patients (both with bulbar signs) performed within the abnormal range on the total score.

[Insert Fig. 5 here]

The FEEST did not significantly correlate with any behavioural measures. Correlational analyses revealed a significant correlation with number correct on the Reading the Mind in the Eyes Test (r-0.76, p<0.005). Moreover the FEEST significantly correlated with verbal fluency performance (r = -0.83, p< 0.005) only.

Discussion

The findings of the second study revealed that a substantial proportion of patients were impaired at inferring the mental state of another as determined by eye gaze in the Judgement of Preference task. This resulted in overall significant differences between ALS patients and healthy controls on this simple ToM task. Although more ALS patients (64%) showed difficulties on the distracter condition which had greater attentional demand, just over a third of cases (36%) were in the abnormal range in the less executively demanding condition, when the distracting information was not present. In addition, errors produced by ALS patients did not only include selecting the item indicated by the distracting arrow, but also included increased selection of their own personal favourite item relative to controls. This suggests that on some trials performance decrements resulted from a misdirection of attention towards irrelevant information, while on other trials there had been difficulties in inhibiting egocentric processing of the stimuli, both of which have lead to impairments in inferring the

mental state of another. Of note ALS patients had little difficulty during the control task which was identical to the experimental task other than the wording of the question “Which picture does the face like best?” to “Which picture is the face looking at?” This demonstrates that ALS patients were able to attend and process the stimuli presented, but had difficulties with inferring the mental state of the face based on a simple social cue, eye-gaze.

A subset of the patients performed poorly on the Judgement of Preference task and in complex and simple emotion recognition. Three of the patients performed within the abnormal range on the MIE test, leading to a strong trend towards a significant difference between the two groups. Moreover two of these patients were in the abnormal range on both the MIE and the FEEST. On the latter the ALS patient group as a whole were significantly worse at recognising emotions than controls. The findings extend previous work implicating emotional processing systems in ALS (Papps et al. 2005), to emotional stimuli which are relevant to social interactions and are consistent with reports of emotional dysfunction in FTD (Keane et al., 2002; Rosen et al., 2002; Lough et al., 2006, Torralva et al. 2007).

In investigating the effect of executive dysfunction on performance we found that verbal fluency indices (time taken to ‘think’ of a word) significantly negatively correlated with the number correct on the MIE and FEEST, with longer thinking times related to poorer performance. Moreover there was also a trend towards a significant correlation with performance on the Judgement of Preference Task indicating some evidence of a relationship. However fewer patients were impaired on tests of executive functions, which identified a deficit in only four of 14 cases, as compared with the social cognition measure. Of note one case showed evidence of a deficit in executive functions, but not on any test of social and

emotional cognition. Conversely six of the 14 cases who were impaired on the Judgement of Preference test showed intact executive functions. It should be noted that not all of the tests of executive functions could be performed on the ALS patients due to varying disability affecting performance, but at least one standard executive test was undertaken on each case. The findings demonstrate that this simple ToM task detects a deficit in more ALS patients than standard tests of executive function and implies an impairment in inferring the mental state of another on the basis of a simple social cue which is over and above a deficit in executive functions.

It has been suggested that poor performance on the MIE task may be due to poor language functions (Gregory et al., 2002). Indeed, although participants were asked to acknowledge that they knew each word's meaning before performing the trial, some words in this task were complex and abstract. However, the two groups did not significantly differ in Verbal IQ and no significant correlation was found between the correct number of responses on the MIE and the Graded Naming task. Therefore, at least in the current study, the poorer performance of the ALS patients on the MIE task cannot be explained by language dysfunction.

The ALS patients group showed an increase in behaviour dysfunction on the FrSBe from premorbid levels, although the patients did not rate their level of dysfunction highly compared to controls. This was particularly evident in changes in Apathy which significantly related to poor performance on the Judgement of Preference task, but not to the emotional tests. Moreover there was evidence of behaviour change in 10/14 cases as determined by carers' descriptions using the MBQ and CBI including; exaggerated emotional display, irritability, loss of emotional insight and embarrassment, selfishness, excessive worrying,

inappropriate behaviour, loss of interest, a change in eating behaviour and in sense of smell and adherence to routine. The presence of behaviour dysfunction strongly overlapped with the social cognition impairment, with five patients (36%) showing deficits on the Judgement of Preference task and behaviour change. However three cases with social cognition deficits showed no signs of behaviour change, while four cases showed some behaviour dysfunction but no social cognition impairment. It should be recognized that behaviour change can result from a number of factors including those related to the pathology of the disease (e.g. disinhibition, apathy and emotional lability) and those related to the impact of the disease (e.g. coping with disability).

In relation to the investigation of bulbar involvement, it should be highlighted that cognitive deficits and behaviour change were found in those with and without bulbar involvement. Nevertheless there was a preponderance of bulbar cases in the cognitively impaired subset at a ratio of approximately 2:1 (Judgement of Preference with distracter 2:1, without distracter 3:2, MIE 2:1, FEEST 2:0). This finding is supportive of previously reported associations and suggests that those with bulbar involvement are more at risk of developing cognitive change (Abrahams et al. 1997, Gibbons, et al. 2007).

General Discussion

These studies demonstrate evidence of deficits in affective decision making, Theory of Mind and complex and simple emotional recognition in ALS. The profile of impairment is similar to that found in fvFTD and hence appears supportive of a subclinical syndrome in a significant proportion of ALS cases. However there are a number of issues which need to be considered in relation to this assumption.

The effect of executive dysfunction on affective decision making and ToM has undergone much debate and raises the question of whether the deficits shown here are simply a manifestation of executive impairment in ALS. Performance on the IGT varies with executive demands (Hinson et al. 2002) and has a high learning and working memory component (see Clark, &Manes, 2004). The profile of choice selection in the current ALS group may therefore reflect an executive failure to learn rather than a tendency towards risk taking behaviour. In relation to ToM some argue for a dissociation from executive functions, (Lough et al., 2001; Gregory et al., 2002), while others suggest that the two show strong interdependence and impairments on ToM tasks may result from executive deficits (Channon, & Crawford, 2000). The second study showed a deficit in a simple undemanding test of social cognition which in 43% of ALS cases were found with intact executive functions. This finding suggests that the most prominent impairment in ALS is one of ToM (up to 64% of ALS), while a subset have executive dysfunction and a subset of these have additional emotional processing difficulties. This dissociation of ToM and executive dysfunction is similar to that found in the early stages of fvFTD when the pathology of the disease is more confined to orbitofrontal regions (Gregory et al. 2002, Snowden et al. 1996, 2003).

However, the demonstration of ToM and IGT deficits in ALS do not necessarily imply involvement of orbitofrontal regions. The possibility that different underlying causes resulted in deficits on the ToM tasks and the IGT in ALS is supported by the finding that performance on the two tasks have been shown not to correlate in patients with fvFTD (Torralva et al. 2007). It is recognized that dysfunction to dorsal and medial prefrontal cortex may be related to impairment on the IGT (Ernst et al. 2002, Manes et al. 2002), regions which have been

implicated in functional imaging studies in ALS (Abrahams et al. 1996, Abrahams et al. 2004). Moreover the integrity of the medial prefrontal cortex has also been shown to be vital for effective ToM (Bird et al. 2004). The limbic system is clearly involved in the interpretation of emotional facial expressions and the amygdala has been implicated in ALS (Anderson et al. 1995). Hence it is possible that the current pattern of impairment may be produced without direct involvement of the orbitofrontal cortex, but through dysfunction of other regions (dorsolateral and medial prefrontal and limbic) which link into this system, producing dysfunction along this pathway.

One of the key behavioural symptoms which emerged was an increase in Apathy from premorbid levels. Some caution needs to be taken here as Apathy items on the FrsBe load on mobility which may exaggerate scores for disabled patients. Nevertheless apathy has been related to dysfunction of medial prefrontal cortex implicated in ALS (Abrahams et al. 2004, Kew et al. 1993). Moreover a significant subgroup of patients showed evidence of a social cognition deficit and corresponding behaviour change similar to that found in fvFTD and so provide further support for a subclinical fvFTD syndrome in ALS.

The current findings have implications for the care and management of ALS patients in daily life. ALS patients may have difficulties in social interaction with carers, with problems using social cues to understand the emotions and intentions of others and difficulty in attributing to others a mental state that differs from their own. This may be seen as egocentric/selfish perspective, and a lack of concern for partners' views and feelings. Educational strategies for those involved in the care of ALS patients should be adopted.

Conclusions

These studies demonstrated evidence of deficits in ALS in social and emotional cognition on tests sensitive to the early changes in fvFTD. The findings may underlie the behaviour change seen in some ALS patients. The profile of cognitive and behaviour change is indicative of a subclinical fvFTD syndrome in a significant proportion of patients with classical ALS although the relative contribution of different prefrontal pathways to this syndrome may vary. Future research may shed light on a) the relationship between this social cognition deficit and other cognitive deficits in ALS to determine whether the impairment is specific to the processing of social cues b) the relationship of this social cognition deficit to changes in every day behaviour and social interaction and c) the cerebral underpinnings of this impairment and whether the deficit is produced from dysfunction of the orbitofrontal cortex or through disruption to other prefrontal-limbic pathways.

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Fig. Captions

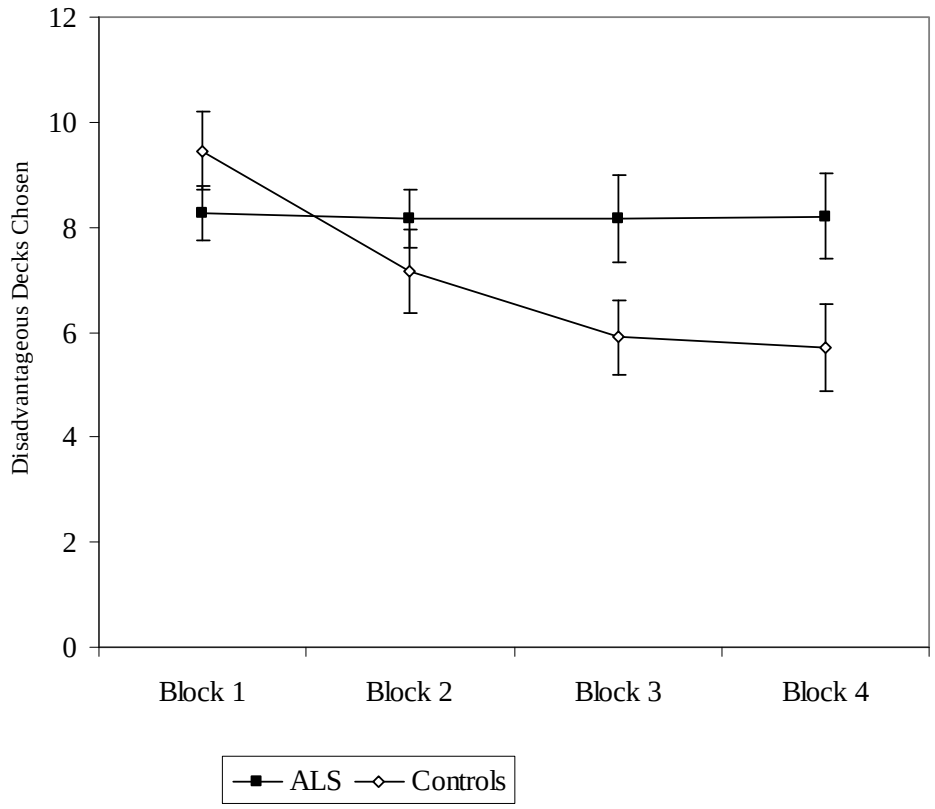
Fig. 1. Number of selections from disadvantageous decks on a version of the IGT. Maximum number of selections per block is 15.

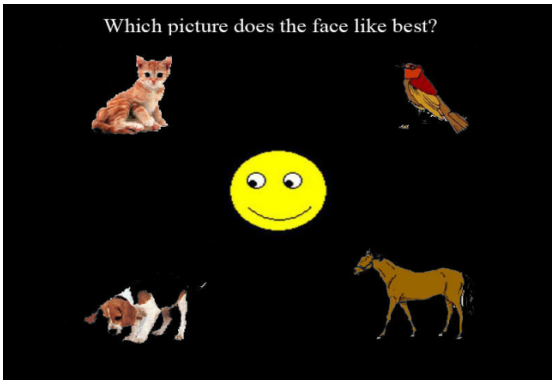
Fig. 2. Judgement of Preference Test. (a) Top 'Like Best', (b) Middle, 'Like Best with Distracter' (c) Bottom 'Look At'.

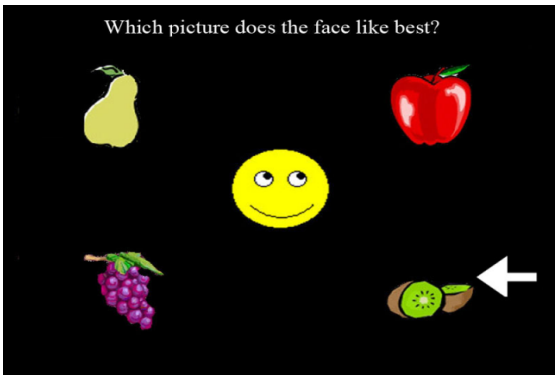
Fig. 3. Judgement of Preference Test: Mean and standard errors of the number of correct choices for the ALS patients and Healthy Control groups in the (a) Experimental 'like best' Condition (top) and (b) Control 'look at Condition (bottom).

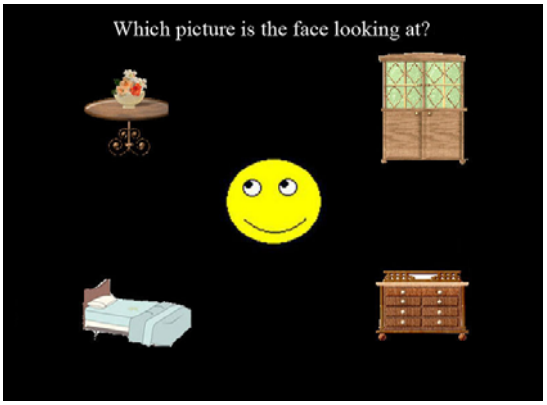
Fig. 4. Reading the Mind in the Eye Test: Means and standard errors of the number of correct choices (max 36) for the ALS patients and control groups.

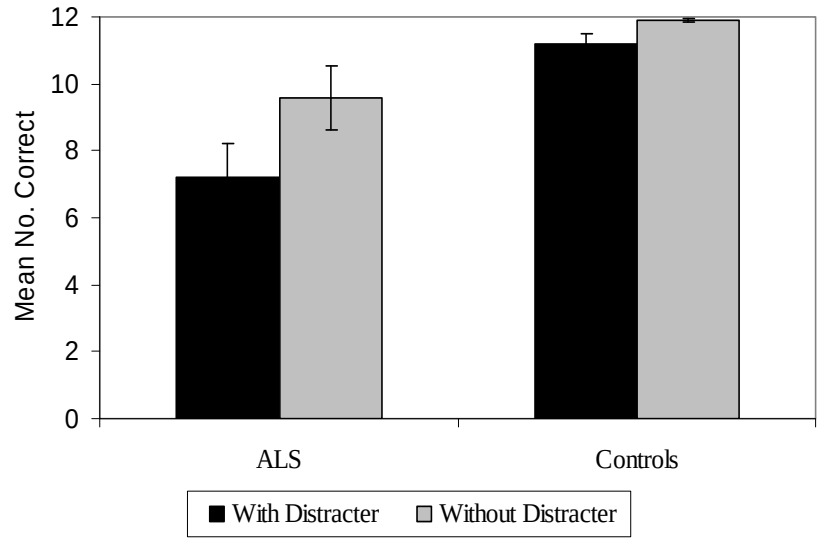
Fig. 5. Emotion Recognition Test: Means and standard errors of the number of correct choices (max 12 per emotion) for the ALS patients and control groups.

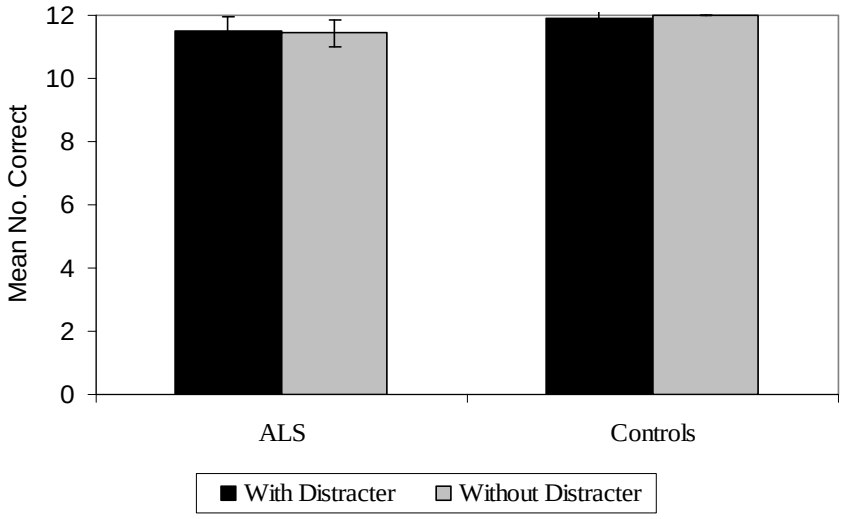

12
10
8
6
4
2
0
Disadvantageous Decks Chosen
Block 1
Block 2
Block 3
Block 4
ALS
Controls

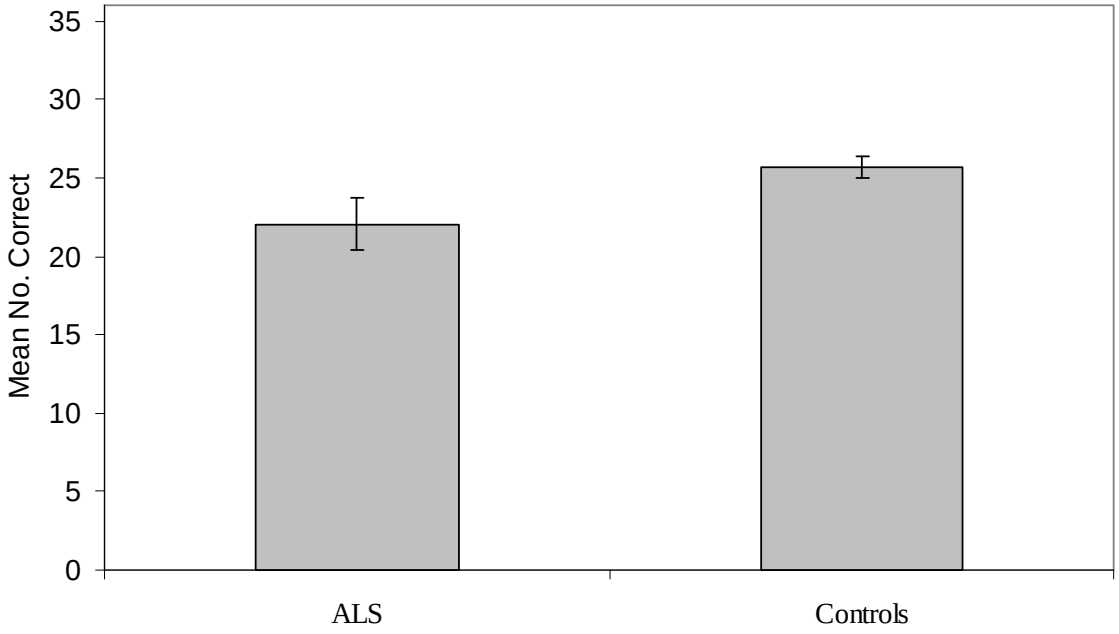

Which picture does the face like best?


Which picture does the face like best?


Which picture is the face looking at?


12
10
8
6
4
2
0
Mean No. Correct
ALS
Controls
With Distracter
Without Distracter


12
10
8
6
4
2
0
Mean No. Correct
ALS
Controls
With Distracter
Without Distracter


35
30
25
20
15
10
5
0
Mean No. Correct
ALS
Controls

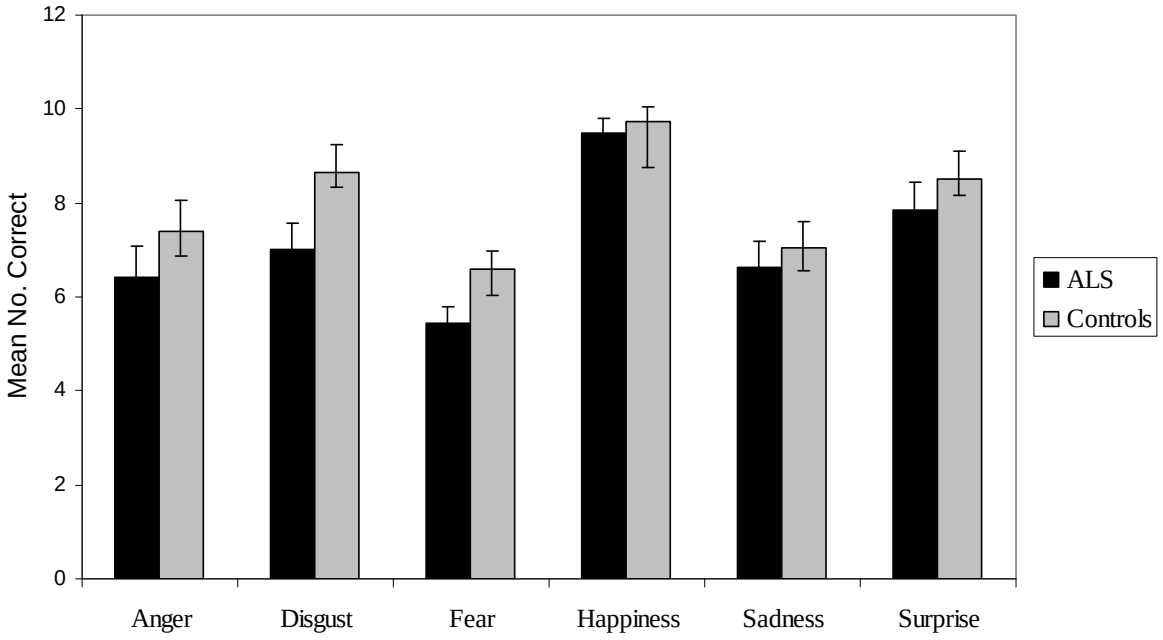

12
10
8
6
4
2
0
Mean No. Correct
Anger
Disgust
Fear
Happiness
Sadness
Surprise
ALS
Controls

Table 1: Study A. Comparison of ALS vs Controls on standard neuropsychological tests

	ALS Mean (SD)	*Healthy Controls* Mean (SD)	*T value*	*P*
NART-R Full Scale IQ (ALS n = 17)	113.43 (7.81)	112.43 (11.42)	-0.31	0.76
Graded Naming Test (max = 30) (ALS n = 19)	23.21 (3.19)	23.95 (3.75)	0.66	0.51
VF Index (z score) (ALS n = 19)	1.27 (2.62)	0.92 (1.42)	-0.50	0.62
FrSBe Self Rated (present) (ALS n = 17)				
Total (T) Score	56.47 (14.71)	51.12 (14.21)	-1.11	0.27
Apathy	57.12 (16.20)	45.94 (8.31)	-2.56	**0.02**
Disinhibition	54.82 (13.85)	53.05 (12.09)	-0.41	0.66
Executive Dysfunction	54.76 (14.12)	47.36 (9.19)	-1.88	0.07

NART-R – National Adult Reading Test-Revised; VF - Verbal Fluency; FrSBe - Frontal Systems Behaviour Scale, Healthy controls were asked to rate their behaviour at the present time only.

Table 2: Study B - Comparison of ALS patients vs Controls on standard neuropsychological tests

	ALS Mean (SD)	*Healthy Controls* Mean (SD)	*T value (U or F)*	*P*
WASI Verbal IQ	110.25 (13.05)	117.60 (7.92)	1.49	0.17
WMS-III Immediate Recall	46.42 (13.45)	55.85 (7.05)	2.25	**0.04**
WMS-III % Delayed Recall	85.39 (21.90)	91.82 (7.0)	0.99	0.34
KOLT Total (max = 70)	46.67 (12.25)	44.0 (7.33)	-0.77	0.45
Graded Naming Test (max = 30)	21.75 (3.5)	24.4 (3.72)	2.0	**0.06**
Hayling Errors (Total)	4.45 (3.30)	3.35 (2.08)	93.0 (U)	0.48
Hayling Response Time Section 2 – 1	31.94 (46.0)	25.01 (11.2)	-0.49	0.63
Brixton Spatial Anticipation Test (Errors)	18.86 (6.94)	16.70 (7.34)	-0.86	0.40
VF Index	18.28	4.29	-1.61	0.17

	(21.23)	(2.15)		
FrSBe Self Rated Total Score	61.85	74.95		
(premorbid)	(21.26)	(10.25)	5.38 (F)	**0.03**
FrsBe Self Rated Total Score	67.46	74.85		
(present)	(16.94)	(10.74)		
ELQ Self Rated Total Score	13.69	6.15	-2.35	**0.03**
	(10.58)	(5.57)		

WASI - Wechsler Abbreviated Scale of Intelligence; WMS-III - Wechsler Memory Scale – III; KOLT - Kendrick Object Learning Test; VF - Verbal Fluency; FrSBe - Frontal Systems Behaviour Scale Healthy controls were asked to rate their behaviour at the present time and 2 years prior; ELQ – Emotional Lability Questionnaire.

Table 3: Study B - Individual scores of ALS patients on standard neuropsychological tests.

Patient		WMS-III	WMS-III					
(bulbar-b)		Immediate	% Delayed	KOLT		Hayling	Brixton	VF Index
		Recall	Recall	Total	GNT	Errors	Errors	(spoken/written)
1	(b)	43	94	70	25	11*	26	N/A
2	(b)	51	78	48	25	3	18	3.04 (s)
3	(b)	27*	100	30	20	1	20	37.69* (w)
4	(b)	60	100	60	22	3	7	3.91 (s)
5	(b)	N/A	N/A	N/A	N/A	N/A	18	N/A
6	(b)	61	100	40	24	N/A	14	N/A
7	(b)	N/A	N/A	N/A	N/A	N/A	36*	52.22* (w)
8		49	49*	58	16*	8*	10	N/A
9		28*	46*	51	19	6	24	4.0 (s)
10		36*	100	51	26	5	19	4.82 (w)
11		33 *	100	41	21	0	20	7.50 (w)
12		44	58*	46	25	7	19	5.08 (s)
13		66	100	32	22	0	18	2.15 (w)
14		59	100	34	16 *	0	16	5.31 (w)

*= Score greater than 2sd outside of mean of healthy control group ($z > 2$)

Patients with bulbar signs are represented by (b). WMS-III = Wechsler Memory Scale-III; KOLT = Kendrick Object Learning Test; GNT = Graded Naming Test; N/A = data not available. VFI = written verbal fluency index; FrSBe = Frontal Systems Behaviour Scale; Present – Premorbid - Present minus the Premorbid Total Self Rated scores to give an estimate of change; ELQ – Self, Emotional Lability Questionnaire Self Rated Total Score.

Table 4: Study 2- Emotional Lability and Behaviour Change in ALS patients

Patient (bulbar – b)		ELQ-Self Total	FrSBe Present – Premorbid	Manchester Behaviour Interview	Cambridge Behaviour Inventory Total
1	(b)	27*	-5	Exag Emotion, Irritability, Loss of Emotional Insight, Change in Smell	75
2	(b)	0	3	No Change	10
3	(b)	7	24*	No Change	16
4	(b)	30*	3	Irritability, Inapp. Behaviour, Eating Behaviour	45
5	(b)	0	NA	NA	NA
6	(b)	29*	6	Exag. Emotion, Loss of Emotional Insight, Ex. Worry, Inapp. Behaviour, Eating Behaviour	55
7	(b)	16	0	Loss of Emotional Insight, Loss of interest, Eating Behaviour, Adhere to Routine.	73
8		15	0	Loss of Emotional Insight, Ex. Worry	74
9		19*	3	Irritability, Selfishness, Ex. Worry, Inapp. Behaviour, Loss of Interest, Adhere to Routine,	76
10		13	1	No Change	51

11	9	2	No Change	5
	0	14	Exag. Emotion, Loss of Embarrassment,	33
12			Irritability, Loss of Interest, Ex. Worry	
13	13	2	Loss of Embarrassment, Selfishness, Change	23
			in Smell,	
14	0	20*	Adhere to Routine	21

* = Score outside normal range ($z > 2$). Patients with bulbar signs are represented by (b).

Exag Emot: Exaggerated emotional display, Ex Worry: Excessive worrying, Inapp. Behaviour: Inappropriate Behaviour.

Table 5: Means and standard deviations (SD) for the types of errors made by ALS patients and healthy controls performing the Judgement of Preference Task.

	ALS Mean (sd)	Controls Mean (sd)	U	P
Like best with Distracter				
Favourite	1.93 (2.02)	0.50 (1.15)	75.5	**0.01**
Arrow	2.29 (3.12)	0.40 (0.68)	67.0	**0.005**
Unclassified	1.0 (1.3)	0.15 (0.49)	82.5	**0.009**
Like best without Distracter				
Favourite	1.14 (1.88)	0.0 (0.0)	90.0	**0.005**
Unclassified	1.29 (2.23)	0.1 (0.31)	100.0	**0.048**
Look at with Distracter				
Favourite	0.07 (0.27)	0.0 (0.0)	130.0	0.232
Arrow	0.29 (0.83)	0.10 (0.45)	127.0	0.355
Unclassified	0.21 (0.58)	0.0 (0.0)	120.0	0.086

Look at without Distracter

Favourite	0.14	0.0	120.0	0.086
	(0.36)	(0.0)		
Unclassified	0.43	0.0	120.0	0.086
	(1.34)	(0.0)		

Table 6: Individual scores (total correct) for ALS patients performing the Social and Emotional Cognition tests.

Patient (bulbar – b)	Like best with distracter (max = 12)	Like best without distracter (max = 12)	Mind in the Eye (max = 36)	FEEST (max 60)
1 (b)	8 *	12	26	51
2 (b)	4 *	4 *	24	51
3 (b)	3 *	12	25	38
4 (b)	11	12	26	54
5 (b)	8 *	12	9 *	34 *
6 (b)	0 *	4 *	26	48
7 (b)	4 *	4 *	10 *	18 *
8	12	12	21	46
9	11	12	25	39
10	10	12	28	56
11	5 *	9 *	17 *	43
12	5 *	5 *	20	40
13	12	12	26	44
14	8 *	12	26	48

* = Score outside normal range (z >2). Patients with bulbar signs are represented by (b).