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Impaired Affective and Cognitive Theory of Mind and Behavioural Change in Amyotrophic Lateral Sclerosis

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Key words: Motor Neurone Disease, Social cognition, Behaviour, Frontotemporal Dementia.

Word count (excluding title page, abstract, references, figures, tables): 4646

Number of References: 39

ABSTRACT

Objectives. Executive and behavioural changes are well-recognized in classical Amyotrophic Lateral Sclerosis (ALS), indicating a subclinical behavioural-variant FTD (bvFTD) in some patients. Social cognitive deficits in ALS have been recently described and an impairment was identified on a simple Theory of Mind (ToM) test, which assesses the judgement of the preference of another through direction of eye gaze. The present study further delineated this deficit, by distinguishing between Affective and Cognitive subcomponents, and determining the relationship to behavioural change, levels of empathy and self-awareness.

Methods. The Cognitive-Affective Judgement of Preference Test was administered to 33 ALS-patients and 26 controls. Furthermore, a comprehensive neuropsychological battery and detailed behavioural assessment, with measures of empathy and awareness, were included.

Results.
ALS-patients showed a significant impairment in Affective ToM only when compared with healthy controls, with a deficit in 36% of patients 12% showed an isolated Affective ToM deficit while 24% showed more generic ToM dysfunction. A Cognitive ToM deficit was found in 27% of patients with 3% showing an isolated Cognitive ToM deficit. The ALS patients showed reduced Empathy (Fantasy scale) and increased behavioural dysfunction with high levels of Apathy. In addition, patients with either an Affective and/or Cognitive ToM deficit exhibited poor self-awareness of their performance and abnormalities on verbal fluency, while those with an Affective ToM Deficit also displayed higher levels of apathy and a naming deficit.

Conclusions. Dysfunctional ToM is a prominent feature of the cognitive profile of ALS. This specific difficulty in identifying and distinguishing the feelings and thoughts of another from a self-perspective may underpin the social behavioural abnormalities present in some ALS patients, manifest as apathy and loss of awareness.

INTRODUCTION

The overlap between ALS and frontotemporal dementia (FTD) is well established on a neuropathological, genetic and clinical level.[1] ALS patients with mixed features most commonly resemble *behavioural variant FTD* (bvFTD), characterized by abnormal personality, behaviour, and executive dysfunction. Severity of cognitive and behaviour change may range from intact to FTD, with 'subclinical bvFTD' in a significant proportion of cases. The cognitive profile of these patients is characterised by verbal fluency dysfunction,[2 3] linked to abnormalities in the dorsolateral prefrontal cortex,[3 4] although impairments in other executive and language functions have also been described.[3 5]

Social and emotional cognition in ALS has only recently become the focus of research despite dysfunction of these processes being an early diagnostic feature of bvFTD [6]. Patients with bvFTD typically display deficits in Theory of Mind (ToM), empathy and emotion recognition.[7-9] ToM refers to a person's ability to infer mental states of oneself and others such as beliefs, preferences and intentions, and aids the understanding of other people's behaviour. Recent evidence indicates some dysfunction in ALS,[5 10 11] and deficits in ToM have now been reported using relatively complex cartoons and stories[5 11 12 13] (see [14] for a review). In parallel with FTD, ALS-patients have also shown impairment on a simple test of social cognition, the judgement of another's preference using the direction of eye gaze as a cue. Importantly this deficit was dissociated in ALS from the more typically reported executive dysfunction.[11 15] The ToM processes involved in this task have been further fractionated into Cognitive and Affective subcomponents, measuring the recognition of thoughts (beliefs and intentions) and feelings (emotions) of another respectively.[9] Deficits for affective judgement has been found in patients with damage to the ventromedial prefrontal cortex, a region typically showing early atrophy in bvFTD, while cognitive ToM has been suggested to be related to dysfunction of the dorsolateral prefrontal cortex. However it is unclear which of these processes underlie the ToM deficit in ALS[16]

Behavioural changes in ALS include apathy, disinhibition and irritability, and to a lesser extent, abnormal eating habits, stereotypical behaviours and sensory abnormalities.[5 11 17] Anosognosia (loss of insight) is also a prominent feature in bvFTD,[18] and has likewise been reported in ALS-patients, although may be restricted to those with bvFTD [17 19 20] However, studies have rarely succeeded in demonstrating an association between

abnormal performance on tests of social cognition and behaviour change in ALS or FTD.[21] Empathy and self-awareness are two key components important for effective social and interpersonal functioning.[22 23] Empathy is the capacity to not only recognize but experience the thoughts and feelings being experienced by another[8 15] and is clearly associated with Affective ToM.[9] Snowden et al.[15] posited that a lack of mental state attribution to others and failure to deviate from an egocentric perspective might give rise to abnormal empathy in FTD. ToM is also related to self-awareness,[23] and not only involves ascribing mental states to others but also to *oneself*.[24] Both these components have strong clinical relevance with diminished empathy[25] and loss of insight being associated with increased carer burden in Alzheimer's Disease and traumatic brain injury.[26]

The present study investigated whether the ToM deficit recently described in ALS could be further delineated as one of *Affective* or *Cognitive* ToM and to explore the relationship between this social cognition deficit and the behavioural manifestations of empathy and self-awareness. The study aimed to determine whether this specific deficit was at the root of the clinical behavioural change present in some ALS patients.

MATERIALS & METHODS

Participants

Thirty three ALS-patients were recruited from four Scottish ALS clinics, and 26 healthy control participants through local community centres and the University of Edinburgh subject volunteer panel. All patients had a diagnosis of clinical possible, probable or definite ALS and none presented with overt dementia.[27] Participants were 27-80 years old, with English as a first language, normal or corrected-to-normal vision and hearing. Healthy controls were all screened for cognitive impairment using the Addenbrookes Cognitive Examination – Revised [28] and scored within the normal range (96.6 ± 2.7, range 92 – 100). None of the participants had other neurological, vascular, significant co-morbid medical problems, psychotic, mood (long standing history), substance abuse or developmental disorders. Patients with a poor prognosis or marked respiratory dysfunction were excluded. The Hospital Anxiety & Depression Scale (HADS)[29] measured current depression and anxiety levels. One item ("I feel as if I am slowed down") was removed from analysis following Abrahams et al.[2] to prevent false exaggeration of the score by physical disability. Patients scored 34.7±7.1 on the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALS-FRS-R),[30] but demonstrated normal respiratory function (subscore: 11.1±1.6). The Epworth Sleepiness Scale (ESS)[31] measured the extent of daytime sleepiness due to

nocturnal hypoventilation, and indicated normal levels (ALS: 6.0±5.0, Johns' normative group: 5.9±2.2, t=0.1, p=.93). Mean disease duration, defined as date$_{first\ evaluation}$ - date$_{start\ ALS\ symptoms}$ was 36.7±31.3 months). Disease onset frequencies were as follows: bulbar (n=11, 33.3%), limb (n=22, 66.7%). Informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki. The study was approved by both the National Research Ethics Service (NRES) – Scotland A Research Ethics Committee and the University of Edinburgh Psychology Research Ethics Committee (PREC).

Neuropsychological Evaluation

Background Cognitive Tests

Executive functions were measured with the Brixton Spatial Anticipation Test[32] and the Verbal Fluency Index, both written (letters S-C)[4] and spoken (letters P-R-W), with higher scores indicating longer thinking times and worse performance[2] The two fluency measures were combined into one single performance measure as previous regression analyses supported the legitimacy of the merge. Visuospatial functions were assessed with the subtests Cubes and Number Location (Visual Object and Space Perception battery),[33] and language functions with the Graded Naming Test.[34]

Experimental Paradigm: Cognitive-Affective Judgement of Preference Test

The Judgement of Preference test[9 11] was presented in E-prime 2.0, on a touch sensitive portable tablet PC. Participants, or if not possible, the experimenter touched the screen using a stylus after the participant had given a response. Participants were instructed to respond as accurately and as fast as possible. There were 8 blocks of 12 trials, yielding a total of 108 trials. A fixed sequence of blocks was presented although trials within each block were administered using a random selection without replacement. Six stimulus-categories were used: animals, cartoon-figures, fruits, vegetables, colours and furniture. Each category consisted of two sets of four object-pictures, presented in a fixed position on the screen. White squares demarcated the four response areas on the screen (see Figure 1).

<Insert Figure 1 about here>

Pre-experimental condition: Participants were asked to choose their own favourite object-picture. The aim was to establish object-preference for each of the twelve stimulus-sets.
Experimental condition: Participants were required to make mental inferences during four blocks, varied by Attention (distracter arrow present or absent) and Valence (Cognitive or

Affective). No-distracter blocks were administered before distracter blocks. Valence was counterbalanced; participants either received the two Cognitive blocks before the two Affective blocks, or vice versa. As can be seen in Figure 1, the experimental conditions were similar to the pre-experimental condition, except that a cartoon face was located in the centre, with its gaze directed towards one of the pictures. To minimize memory demands, a question appeared at the top of the screen on each trial, presented simultaneously with the four object-pictures in each corner of the screen for 2000 ms, followed by the cartoon-face and arrow. All stimuli remained on the screen until the participant responded. The cartoon-face displayed one of four gaze directions: towards the upper left, upper-right, bottom left and bottom right corners. In the Affective trials, the face had a happy expression and participants were asked "Which picture does Dina love?", while in the Cognitive trials, the face had a neutral expression and participants were asked "Which picture is Dina thinking of?". In order to successfully complete the trials, participants were required to choose the picture the eye gaze of the cartoon face was directed to. The distracter trials were included to follow the same methodology as previously described.[11] If participants' attention would be captured by the arrow, then this likely indicated attentional or executive problems rather than a primary ToM deficit.

Control condition: After the Experimental condition, participants were required to make judgements regarding physical attributes as opposed to thoughts or feelings. Three blocks were presented in a fixed sequence: Look at, Look at with distracter and Physical. The 'Look at' trials were identical to the Experimental conditions with the exception that the participants were now asked "Which picture is Dina looking at". In the Physical trials participants were asked "Which picture is Dina close to". The Control conditions were crucial to the task since participants may fail the Experimental condition either because of a genuine ToM deficit or attention or visual difficulties. Half of the trials contained a cartoon-face with either a happy or neutral expression.

Outcome measures: Errors were classified as follows: (1) Favourite - participant chooses the picture of his/her own preference as determined in the Pre-experimental condition, (2) Arrow - participant selects the object to which the arrow was pointing at, (3) Other - participant made an incorrect response which could not be classified as either Favourite or Arrow.

Self Awareness Assessment: Immediately after completing the Judgement of Preference test, participants were asked "How do you think you performed on this task?" and required to indicate their answer on a 10 centimetre visual analogue scale, which was divided into two

parts: 'bad to very bad performance' (values between 0-5 cm) and 'good to very good performance' (values between 5-10 cm).

Behavioural Assessment

Participants and their informants (defined as someone who knew the patient very well, e.g. family member, spouse or close friend) completed a set of behavioural measures, including the Frontal Systems Behavior Scale (FrSBe),[35] Neuropsychiatric Inventory – Questionnaire (NPI-Q)[36] to uncover behaviours commonly observed in dementia and the Interpersonal Reactivity Index (IRI)[37] to measure empathy using four scales: Perspective- Taking, Fantasy, Empathic Concern and Personal Distress. The NPI-Q was administered in informants only. In order to assess behavioural change, data on premorbid and post-illness functioning was obtained for the FrSBe and IRI.

Statistical analyses

Skewness of distributions was tested using the Shapiro-Wilk-statistic. Both parametric (Independent samples t-test, ANOVA) and non-parametric tests (Mann-Whitney U, Wilcoxon's signed ranks) were used depending on whether normality was satisfied or violated respectively. Frequency distributions were compared with the Pearson's χ^2-test. A case analysis using z-scores was undertaken to identify patients with abnormal performance, defined as $z \geq 2SD$.

RESULTS

Background Cognitive Tests

The groups did not significantly differ on age, gender, education and HADS anxiety levels (see Table e-1). Although patients displayed more depressive symptoms, the average score was very low, indicating few symptoms of depression. Patients showed normal performance on the Brixton Spatial Anticipation Test, however, deficits were noted for both the Verbal Fluency Index and Graded Naming Tests. Although patients scored significantly lower on Cube Analysis, the group difference was minimal, with patients' scores well above the abnormality cut-off from normative data. In addition, their Number Location performance was normal.

Table 1: Cognitive-Affective Judgement of Preference Test (average number of errors within conditions).

Block	ALS-patients Mean ± SD	Controls Mean ± SD	Statistics
COG	2.6 ± 4.1	.69 ± 1.9	U=339.0, p=.10
COG-D	2.8 ± 4.7	.58 ± 1.8	U=359.0, p=.18
AFF	**3.2 ± 4.7**	**.54 ± 2.0**	**U=302.5, p=.01**
AFF-D	**4.0 ± 5.3**	**.62 ± 1.7**	**U=304.0, p=.02**
LOOK	.06 ± .24	0 ± 0	U=403.0, p=.21
LOOK-D	**0 ± 0**	**.12 ± .33**	**U=379.5, p=.047**
PHYS	0 ± 0	0 ± 0	U=429.0, p=1.0

Significant group differences are highlighted in bold. Experimental Conditions:- COG: Cognitive, -D: with distractor arrow, AFF: Affective. Control Conditions:- LOOK: Look at, PHYS: Physical

ALS-patients made significantly more errors in the Affective and Affective − Distracter conditions (see Table 1). Healthy controls not patients, made marginally significantly more errors in the Look at − Distracter condition, although barely any errors were made. Within-subjects analyses revealed no differences between distractor and non-distractor trials and therefore this data was collapsed to produce four conditions: Affective, Cognitive, Look At and Physical. The comparisons revealed a significant difference between patients and controls for only the Affective conditions (3.6 ± 4.8 vs. .58 ± 1.8, U=285, p=.01), see Figure 2.

<Insert Figure 2 about here>

Analyses of the types of error committed revealed that ALS-patients made significantly more Favourite, Other and Arrow errors than controls in the Affective condition only (see Table e-2).

Self-Awareness of Performance: Despite committing more errors than controls ALS-patients exhibited similar scores on the self-rating of their performance as healthy controls (7.9 ± 2.1 vs. 8.1 ± 1.7; U=343.5, p=.91).

Behavioural Assessment

Frontal Systems Behaviour Scale

ALS vs. Healthy controls: A repeated measures ANOVA on the FrSBe self-rated questionnaires with one between-subjects factor of Group (ALS-patients, controls) and one within-subjects factor of FrSBe-Scale (Apathy, Disinhibition, Executive Dysfunction) showed significant effects of Group (F=4.6, df=1, p=.037), with ALS-patients exhibiting a significantly higher total FrSBe score than controls (86.6 ± 17.4 vs. 77.2 ± 13.4), indicative of greater behavioural dysfunction, and of FrSBe-scale (F=24.4, df=2, p<.001), with a significant FrSBe-scale x Group interaction (F=7, df=2, p=.002); patients self-reported significantly more Apathy than controls only (t=3.5, df=48, p=.001).

ALS vs. Informants: For the ALS group alone a repeated measures ANOVA with Time (pre-illness, post-illness) and FrSBe-scale as factors, revealed a significant effect of Time (F=20.7, df=1, p<.001), FrSBe-scale (F=7.6, df=2, p=.003), and a significant Time x FrSBe-scale interaction (F=19.1, df=2, p<.001). Compared to pre-illness ratings, post-illness ratings in the patient group were significantly higher for Apathy (t=-5.9, df=24, p<.001) and Executive Dysfunction (t=-2.4, df=24, p=.025). The informant group reported a significant pre-illness to post-illness increase in all scores: Total (Z=-3.7, p<.001), Apathy (t=-3.3, df=22, p=.004), Disinhibition (Z=-3.2, p=.001) and Executive Dysfunction (Z=-2.4, p=.016). See Table e-3.

Interpersonal Reactivity Index: Empathy

ALS vs. Healthy controls: There was only one significant group difference on the cognitive factor Fantasy; patients scored lower than controls (t=-2.0, df=47, p=.048). Further inspection revealed that 5 ALS-patients (20.8%) scored more than 2SD lower than the control mean, as opposed to none of the healthy controls.

ALS vs. Informants: None of the comparisons between pre- and post-illness ratings of informants, nor between informants' and patients' post-illness ratings about patients themselves, were significant. See Table e-3.

Neuropsychiatric Inventory – Questionnaire (NPI-Q)

Changes in Appetite/Eating (45.5%) were most frequently noted by informants in ALS-patients, followed by Depression/Dysphoria (31.8%), as well as a triad of symptoms: Night-time Behaviours, Agitation/Aggression and Apathy/Indifference (27.3% each). Other symptoms included Irritability/Lability (22.7%) and Anxiety (18.2%). Some symptoms were hardly reported, for instance Elation/Euphoria (9.1%), Delusions and Motor Disturbance (both 4.5%), or absent, including Hallucinations and Disinhibition. The majority of patients (81.7%) showed at least one behavioural abnormality on the NPI-Q.

Subgroup Comparison AFF- and AFF+

To explore the association between behavioural dysfunction, awareness and the social cognition deficit and due to the heterogeneity of performance on the Judgement of Preference task, ALS-patients were divided into two groups based on the errors made in the Affective conditions. The raw scores were subsequently converted into z-scores, and patients were classified as unimpaired affective ToM (AFF+, within 1SD from control mean) or impaired affective ToM (AFF-, greater than 2SD from control mean).

Table 2 Subgroup comparison of the AFF- (impaired affective ToM) with AFF+ (unimpaired Affective ToM) on Background Tests

Measure	AFF- Mean ± SD (n=12)	z > 2SD n (%)	AFF+ Mean ± SD (n=21)	z > 2SD n (%)	Statistical Results
Age	63.8 ± 12.7	N/A	56.1 ± 13.2	N/A	t=-1.6, p=.11
Sex (Male – Female)	6/6	N/A	13/8	N/A	χ2=.44, p=.51
Education (Years)	13.9 ± 3.8	N/A	14 ± 2.9	N/A	U=122, p=.90
HADS - Anxiety HADS – Depression (n=25)	5.6 ± 2.8 1.8 ± 1.4	N/A	5.6 ± 4.3 2.6 ± 2.6	N/A	t=.05, p=.96 U=61, p=.56
VFI z-score (n=27)	3.2 ± 2.6	6 (50%)	1.0 ± 1.4	5 (23.8%)	**U=41, p=.027**
Brixton Test (n=32)	16.2 ± 8.4	4 (33.3%)	14.3 ± 4.8	1 (4.8%)	U=120, p=1.0
VOSP - Cube Analysis VOSP - Number Loc. (n=32)	9.75 ± .45 8.8 ± 1.5	3 (25%) 3 (25%)	9.45 ± 1 9.75 ± .55	6 (30%) 1 (5%)	U=109.5, p=.69 U=70, p=.053
Graded Naming Test (n=32)	21.5 ± 3.6	6/12 (50%)	24 ± 2.8	2/20 (10%)	**t=2.2, p=.04**

Significant results highlighted in bold. z>2SD indicate the number of cases falling in the abnormal range as determined by test scores greater than 2SD from control mean

HADS: Hospital Anxiety & Depression Scale, V*fi:* Verbal Fluency Index, (higher scores indicate worse performance), VOSP: Visual Object and Space Perception battery, Number Loc: Location

Twelve out of 33 patients (36.4%) exhibited an abnormal total affective score (AFF-) on the Judgement of Preference test while 21 patients exhibited normal performance (AFF+). AFF-patients' error rates were similar to that of AFF+ patients on the three control conditions: Look at (.17 ± .39 vs. 0 ± 0; U=105, p=.45), Look at with distracter and Physical (0 ± 0 vs. 0 ± 0). On the self-assessment awareness measure AFF- patients rated themselves as

significantly worse than AFF+ patients (6.4 ± 2.4 vs. 8.8 ± 1.3, U=31, Z=-2.9, p=.002), however, the mean value of AFF- patients was still higher than 'neutral' (5), falling within the 'good to very good' performance range. A further case-by-case analysis, of the patients who completed both test and self-ratings, demonstrated that 8 AFF- patients (72.7%) rated themselves as 'good to very good', compared to the remaining 3 patients (27.3%) with a 'bad to very bad' self-rating (Figure 3). All AFF+ patients rated their performance as 'good/very good'. In addition, the only healthy control with poor affective ToM rated themselves as bad to very bad (i.e. score of 4.2). A subgroup of AFF- patients (n=6) demonstrated particularly high error rates (19-23) and self-ratings (in between 6.9 – 9.4). These patients responded correctly in a minority of the Affective trials (≤ 20%), while rating their task performance to a large extent as well executed, (expressed as ≥ 70%), indicating lack of awareness.

The number of bulbar vs. limb-onset patients in the AFF- group was relatively balanced (41.7% vs. 58.3%), but skewed towards limb-onset patients in the AFF+ group (28.6% vs. 71.4%), although frequency distributions did not significantly differ (χ2=.59, p=.44). AFF- and AFF+ patients did not differ on disease duration (46.5 months ± 41.9 vs. 31.1 ± 22.6, U=92.5, p=.61) nor ALS-FRS-R score (32.5 ± 8.1 vs. 36 ± 6.3, t=1.4, p=.18). Table 2 shows that AFF- patients had more pronounced deficits on the Verbal Fluency and Graded Naming Tests than AFF+ patients.

Table 3 – Performance of patients with AFF- (n=12) and AFF+ (n=21) on behavioural measures

Measure	AFF- z > 2SD n (%)	AFF+ z > 2SD n (%)	Fisher's Exact p (2-sided / 1-sided)
IRI Patient (n=24)			
• Total score	0	3 (14.3%)	p=.53 / p=.28
• PT	1 (8.3%)	3 (14.3%)	p=1.0 / p=.54
• FS	2 (16.7%)	3 (14.3%)	p=1.0 / p=.56
• EC	0	2 (9.5%)	p=.52 / p=.40
• PD	0	0	--
IRI Informant (n=22)			
• Total score	0	2 (9.5%)	p=.52 / p=.39
• PT	1 (8.3%)	2 (9.5%)	p=1.0 / p=.71
• FS	1 (8.3%)	1 (4.8%)	p=1.0 / p=.61
• EC	1 (8.3%)	1 (4.8%)	p=1.0 / p=.59
• PD	0	0	--
FrSBe Patient (n=25)			
• Total score	3 (25%)	2 (9.5%)	p=.31 / p=.23
• **Apathy**	**5 (41.7%)**	**2 (9.5%)**	**p=.058 / p=.034**
• Disinhibition	2 (16.7%)	4 (19%)	p=1.0 / p=.64
• EF	1 (8.3%)	1 (4.8%)	p=1.0 / p=.60
FrSBe Informant (n=23)			
• Total score	0	3 (14.3%)	p=.53 / p=.26
• Apathy	1 (8.3%)	2 (9.5%)	p=1.0 / p=.73
• Disinhibition	0	4 (19%)	p=.26 / p=.15
• EF	0	3 (14.3%)	p=.53 / p=.26

AFF- =patients with impaired Affective ToM; AFF+ =patients with unimpaired Affective ToM; FrSBe= Frontal Systems Behavior Scale; IRI= Interpersonal Reactivity Index; EF=Executive Dysfunction; PT=Perspective-Taking; FS=Fantasy; EC=Empathic concern; PD=Personal Distress; Behavioural measures are all 'current, post-illness ratings; Performance of >2SD than control mean for FrSBe measures indicates abnormality, while for IRI, abnormality is defined by performance < 2SD, indicating less empathy; For Informant z-scores, healthy control data from 'current self-ratings' was used.

Subgroup analyses of the behaviour data revealed that compared to AFF+ patients, only abnormally self-rated Apathy on the FrSBe was more prevalent in the AFF- group (see Table 3). The NPI-Q was completed by two-thirds of informants in either subgroup. No significant differences emerged between the subgroups' frequency distributions on any of the NPI-Q items.

<Insert Figures 3 and 4 about here>

Subgroup Comparison COG- and COG+

For comparative purposes, ALS-patients were also divided into unimpaired cognitive ToM (COG+, within 1SD from control mean) or impaired cognitive ToM (COG-, greater than 2SD from control mean). Nine out of 33 patients (27.3%) displayed an abnormal total cognitive score (COG-), while 24 patients were unimpaired (COG+). The COG- and COG+ groups did not significantly differ on error rates on the Look at (.22 ± .44 vs. 0 ± 0; U=84.0, Z=-2.3, p=.35), Look at with distracter and Physical control conditions (both 0 ± 0 vs 0 ± 0). Results obtained on the self-awareness measure showed no significant difference between the COG- and COG+ groups, with both classifying themselves on average in the 'good to very good' range: 7.3 ± 2.4 vs. 8.1 ± 2.0 (U=58.0, Z=-1.1, p=.28). Of the patients who completed both test and self-ratings, 7 COG- patients (87.5%) rated themselves in the 'good to very good' range, whilst only 1 patient (12.5%) as 'bad to very bad'. Nearly all COG+ rated themselves as 'good/very good' (n=18, 90%), except for 2 patients (10%). One healthy control demonstrated poor cognitive ToM and rated themselves as 'bad/very bad'. A subgroup of COG- patients (n=6) made a high number of errors (18-24) and of these patients, 4 also produced high self-ratings (in between 6.9 - 9.4), showing lack of awareness. The COG- and COG+ subgroups did not differ with respect to bulbar vs. limb onset distributions: 3 vs. 6 and 8 vs. 16 (Fisher's Exact p=1.0), nor with regards to the total ALS-FRS-R score (31.2 ± 8.0 vs. 36.0 ± 6.4; U=69.5, z=-1.6, p=.12). In contrast, COG- patients experienced a significantly longer disease duration than the COG+ patients (65.8 ± 37.4 vs. 26.2 ± 21.1 months; U=24.5, z=-3.0, p=.002), as well as longer thinking times on the VFI (see Table e-4). None of the behavioural variables on the FrSBe, IRI or NPI-Q yielded significant group differences (see Table e-5).

Relationship of Affective and Cognitive ToM

Figure 4 shows that 4 patients (12.1%) had an impaired affective ToM only. Patient 1 showed VFI and GNT deficits in keeping with the AFF- group but no behavioural data was available for this patient. Patient 2 only showed behavioural impairments only with reduced awareness of performance (i.e. a 'good to very good' awareness score) and impaired IRI scores for Empathic Concern and Perspective-Taking with the latter empathy score corroborated by the carer. Patient 3's profile was characterised by abnormal performance on scores on some cognitive tests including the VOSP Number Location and GNT in addition to behavioural impairments on all self-rated FrSBe-scores except for 'Executive Dysfunction', with increased Apathy also rated by the carer. Patient 4 had a mixture of cognitive and behavioural deficits on the Brixton test, and self-rated Apathy on the FrSBe, with poor self-awareness of performance. The four patients with an isolated affective ToM deficit had shorter disease duration (7 to 16 months) in comparison to those with the combined affective and cognitive ToM deficit (n=8, mean 66.4, sd 40.4) but with a similar ALS-FRS-R scores and included two bulbar and two limb patients. One patient (3%) had impaired cognitive ToM only, indicating some dissociation between the two ToM subcomponents. This patient did not display any other cognitive deficits, however showed abnormal scores for self-awareness and for FrSBe self-rated Disinhibition. This patient had a long disease duration of 61 months, with an ALS-FRS-R score of 41.

DISCUSSION

This study revealed deficits in Affective and Cognitive ToM in a proportion of patients with ALS on a simple social cognition test designed to be less dependent on executive functions than more traditional ToM tests. The most prominent deficit was in Affective ToM with 36% of patients showing impairment, while 27% a Cognitive ToM impairment. This frequency of impairment is relatively comparable with previous studies of ToM in ALS. In our own previous investigation which did not distinguish between affective and cognitive components, although 9/14 showed some deficit on the judgement of preference task, 5/14 (36%) showed dysfunction in the less executively demanding condition.[11]. In the current study 10/33 patients (31%) had deficits on a similar condition. Meir et al.[5] demonstrated that 33% of their 18 patients showed a deficit on the Faux Pas test, while in the study by Gibbons et al.[13] only 2 of the 16 patients were explicitly impaired (>2sd) on the experimental theory of

mind tasks. Given the small sample sizes recruited through clinic rather than population based techniques, combined with the heterogeneity of presentation in ALS with the majority of patients not showing a deficit, these studies produce remarkably consistent findings indicating that a deficit in ToM is a key feature of the cognitive profile in this disease.

Furthermore there was some heterogeneity in performance with several types of ToM dysfunction emerging. The most common type of dysfunction was a combined generalised Cognitive and Affective ToM deficit which occurred in 24% and only small subsets of patients exhibited isolated Affective and Cognitive ToM deficits, 12% and 3% respectively. Impaired Affective and Cognitive ToM has been noted in patients with ventromedial and dorsolateral prefrontal lesions respectively [9 16] indicating variability in the spread of frontal lobe changes in ALS. The profile of these patients with isolated ToM deficits generally included a range of cognitive and behavioural dysfunction, although those with the affective ToM deficits tended to have had a shorter disease duration at testing than those with the combined ToM deficit indicating that they may be at an earlier stage of frontal lobe changes. However a comparison of those with impaired versus unimpaired affective ToM revealed more widespread deficits, not only in verbal fluency but also in naming and on a behavioural level, with 42% of this subgroup of patients more frequently self-reporting abnormal levels of Apathy, a feature commonly noted in ALS.[11 20]. Those with impaired cognitive ToM displayed verbal fluency deficits and a longer disease duration, indicating that these ToM components may be affected differentially in different disease subtypes.

The profile of performance deficits was characterized by an abnormally high number of Favourite errors detected in one-third of patients, and an overall significantly reduced 'Fantasy' score on the IRI. These findings indicate that some patients had difficulty disengaging themselves from an egocentric viewpoint or in identifying themselves with characters from cultural artefacts (e.g. movies). This finding is consistent with empathic dysfunction reported in patients with ventromedial lesions,[9] FTD[8 15] and more recently in ALS.[10 11] The process of disengaging oneself from an egocentric perspective in order to shift attention to another also involves an 'executive' set-shifting component and it is possible that this is underling or exaggerating the impairment in ALS. The present study encouraged an egocentric perspective by incorporating the Favourite condition. Given the nature of this question "Which picture is your favourite" it is possible that this

disproportionately influenced the subsequent affective as opposed to cognitive attribution, producing the disproportionate deficit in Affective ToM. .

The most prominent behavioural abnormality in the study was Apathy, consistent with numerous previous investigations[e.g 11 38). Abnormal levels of apathy were present in 21% of the sample and were disproportionate in those with a deficit in Affective ToM (42%) in comparison to those without (10%). Previous studies have found high levels of apathy with for example Lillo et al.[38] reporting that 41% of their sample displayed moderate-severe apathy. Variance is found between studies in methods of measurement of apathy and of ascribing abnormality. In the current study a closely matched control group was included and conservative thresholds of two standard deviations below the control mean was applied to determine abnormality. This method may have produced a conservative estimate of this symptom. There are some limitations in the use of the behavioural questionnaires with ALS patients. Several items may be misinterpreted for example, FrSBe-item #29 (*'Is slow moving, lacks energy, inactive'*) may signify apathy, but is confounded by disease-related variables, e.g. secondary depression, motor disabilities and fatigue. Although a large proportion (>80%) showed at least one behavioural feature on the NPI-Q, only 50-75% of participants completed inventories due to attrition or reluctance, leaving the behavioural profile of the remainder unclear. More recently designed questionnaires which minimize impairment due to motor dysfunction have been developed and which have revealed a lower rate of behavioural change than previously described[39]. Future studies should aim to develop more appropriate, motor-free questionnaires for a thorough understanding of behavioural functioning in ALS and other movement disorders.

Reduced awareness of cognitive deficit was also a prominent feature of this study. 70-90% of impaired Affective as well as Cognitive ToM patients rated their performance as good to very good on the task with 50-60% showing a particularly pronounced lack of awareness for their deficit, and thus displayed impairments both in ascribing mental states to others and to oneself. Loss of insight is a characteristic symptom of FTD.[18] and which has recently been revealed in ALS patients with cognitive impairment [19]. These results further highlight that a ToM deficit with a failure to recognize the thoughts and feelings of another and differentiate that from one's own, likely contribute to the cognitive underpinning of the behavioural manifestations of apathy and loss of insight in ALS.

On a clinical level, empathy and self-awareness are vital for effective social and interpersonal functioning.[22 23] Deficits may therefore lead to more egocentric and socially inappropriate behaviours. Apathy and executive-linguistic dysfunction can further exacerbate

social and communication difficulties. Diminished empathy and insight have been associated with increased caregiver burden in other clinical populations,[25 26] while lack of initiation, interest or insight may pose problems with compliance to medical and psychological interventions.[26] Increasing awareness of social cognitive and behavioural deficits in ALS-patients, their families and healthcare specialists may help the development of management strategies that improve interpersonal functioning, quality of life and complex care in patients and carers. Potential management strategies may be delivered via individual, group and family approaches consisting of psycho-education on these deficits, techniques to help shift attention away from one's own perspective to others', increasing self-awareness by helping to identify environmental cues and emotions, social problem solving and skills support, as well as behavioural activation to remediate apathy.

CONCLUSIONS

The social cognitive, executive-linguistic and behavioural deficits observed in classical ALS support the presence of subclinical bvFTD and further underscore the heterogeneity of neuropsychological impairment in ALS. ToM dysfunction is a prominent characteristic of the ALS cognitive profile and may contribute to the behavioural features of apathy and loss of insight. Future investigations may improve the evaluation of behavioural change to highlight the cognitive underpinning of these symptoms and explore impact on daily activities with the aim to develop appropriate care strategies.

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LIST OF FIGURES

Figure 1 - Cognitive-Affective Judgement of Preference Test

Legend: Top panel: Pre-experimental Condition, Left Favourite, Right Introduction. Middle panel: Experimental Condition, Left Cognitive, Right Affective. Bottom panel: Control Condition, Left Looking at, Right Physical.

Figure 2 - Mean number of errors within conditions on Cognitive-Affective Judgement of Preference Test

Legend: * significant comparison. Maximum possible errors = 12

Figure 3 - Relationship between total errors on the Judgement of Preference Test and self assessment for AFF- and AFF+ patients

Legend: Dashed line indicates minimum number of errors necessary (8.4 out of 24) to classify as AFF-; alternating dashed and dotted line indicates midpoint (5) between bad and good performance; ellipse indicates patient subgroup with high error rates whose self rating of performance were good to very good indicating poor awareness of deficit.

Figure 4 - Relationship of Affective and Cognitive ToM deficits (patients error rates)

Legend: Black line indicates a z score of 2, cut-off for abnormality.