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# Overview of Cognitive Function in ALS, with Special Attention to the Temporal Lobe: Semantic Fluency and Rating the Approachability of Faces

Heike Schmolck[1,3], Paul Schulz[1,2,4] and Michele York[1,2]
*[1]Baylor*
*[2]Veterans Hospital*
*[3]Ruan Neuroscience Center*
*[4]University of Texas*
*USA*

## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects upper and lower motor neurons and is more recently known to be associated with declines in cognitive and behavioral functions for a subset of patients (Strong, et al., 1996; Strong et al., 2009). The cognitive changes associated with ALS can vary from mild impairments that may or may not affect the individual's daily functioning to more severe cognitive and behavioral changes that meet criteria for a diagnosis of frontotemporal dementia (ALS-FTD). There are at least mild cognitive changes in 40 to 60% of sporadic and familial ALS patients (Massman et al., 1996; Phukan et al., 1996; Ringholz et al., 2005; Wheaton et al., 2007). The cognitive and behavioral changes associated with ALS follow a pattern consistent with involvement of the frontal and temporal lobes (Strong et al., 2009, Hodges et al., 2004), presenting as difficulties with attention, working memory, verbal fluency, and semantic abilities (Abe et al., 1997; Ringholz et al., 2005; Rippon et al., 2006, Schmolck et al., 2007; Strong et al, 1999; Strong et al., 2009). Furthermore, 15% of ALS patients demonstrate more severe cognitive and behavioral changes consistent with ALS-FTD (Lomen-Hoeth et al., 2002; Ringholz et al., 2005; Wheaton et al., 2007), presenting as declines in judgment, problem solving, and reasoning, which are more frontally mediated cognitive functions. In addition to cognitive changes, up to 25% of patients with ALS may also experience significant changes in their behavior, mood, and personality characteristics (Hodges et al., 2004; Kertesz et al., 2005), including a loss of empathy, problems with organization and planning, changes in social behavior and personality, difficulties with impulse control, and apathy.

The temporal lobes are purported to be involved in auditory perception, language comprehension, naming, processing of semantic knowledge and long-term memory storage, high-level visual processing of complex stimuli such as faces and scenes, and episodic memory (Lezak, 1995). In addition, they contain the amygdala and associated limbic areas, which are key structures for processing emotional stimuli and detecting threat from the environment, and are of particular interest for ALS patients. ALS patients show a lack of

memory enhancement for highly emotional stimuli (Abrahams et al., 2005). Furthermore, social judgment was found to be decreased in individuals with ALS as compared to healthy controls (Flaherty-Craig et al., 2011). Behavioral dysfunction has been linked to decreased performance on cognitive measures; however it is unclear if these changes present and/or progress independently (Wooley et al., 2009). The relationship between the fontal and temporal cognitive and behavioral changes in ALS is not well understood. Here, we report on two studies examining temporal cognitive changes in ALS.

Indentifying and acknowledging that ALS patients may also be dealing with cognitive and/or behavioral changes in addition to their debilitating motor declines may help their physicians and caregivers to better care for the individual with ALS and anticipate problems that they may experience throughout the disease progression (Hecht et al., 2003). These cognitive changes can affect the everyday social interactions of ALS patients, and they are vital for the execution of more complex tasks such as decision-making, problem solving, and management of occupational demands (e.g., multi-tasking). Patients with these types of impairments have significantly shorter survival than other ALS patients and are twice as likely to be noncompliant with interventions (Woolley et al., 2008). Safety, financial planning, driving, and occupational performance can be of concern in patients who demonstrate impairments in these cognitive domains. Consequently, the predictive value of these cognitive abilities may aid in the clinical management of ALS patients, aiding physicians in making decisions concerning the overall safety of their patients and their patients' ability to work, drive, and manage their medication regimen. Educating the patients and family members to better understand these cognitive and behavioral changes as part of the disease process can help improve the patient's quality of life and reduce the feelings of caregiver burden (Murphy et al., 2009).

## 2. Rating the approachability of faces in ALS – Too much or not enough fear?

We hypothesize that alterations in emotional cognition indicative of amygdala dysfunction occur in ALS, but are often unrecognized. Changes in the emotional expression of ALS patients are reported by clinicians, and often by patients themselves. Pseudobulbar affect is a common problem. ALS patients also have a lower incidence of depression than patients afflicted with similarly debilitating diseases (Rabkin et al., 2005), and many have a stunning lack of concern regarding their grave illness. They often have a very pleasant personality, which has lead clinicians to call ALS the "nice guy's disease". Emotional lability and mild disinhibition are commonly found.

None of the above observations can be explained satisfactorily by behavioral changes commonly seen with frontal dysfunction alone. Thus, while examining frontal contributions to social and emotional cognitive changes in ALS has been fruitful, other areas that have been implicated in social cognition have not been studied much. In one study, ALS patients have been found to show a lack of memory enhancement for highly emotional stimuli, which is consistent with amygdala dysfunction (Abrahams et al., 2005). We have previously shown in a small group of patients that ALS patients have a tendency to rate faces inappropriately approachable compared to normal controls (Schmolck et al., 2007); this behavior is also consistent with amygdala dysfunction. Lastly, a study by Zimmerman and colleagues (2007) found that over 62% of patients with bulbar ALS had deficits in their ability to properly recognize the emotions of others (emotional perceptual deficits).

Few neuropathologic studies have examined non-frontal areas in ALS brains. In the ALS-Parkinson-dementia complex of Guam, tau and alpha-synuclein aggregates are a common

finding in the amygdala (for example, Yamazaki et al., 2000). Case series of sporadic ALS patients with and without dementia have demonstrated ubiquitinated intraneuronal inclusions and spongiform changes in the amygdala and other limbic structures (Kawashima et al., 2001; Kato et al., 1994; also Tsuchiya 2002).

The amygdala is a key structure for processing emotional stimuli and detecting threat from the environment (e.g., Adolphs 2003a; Adolphs 2003b). Patients with bilateral amygdala damage are impaired at recognizing negative basic emotions in facial expressions, most notably fear (e.g., Adolphs et al., 1994; Broks et al., 1998;, Schmolck & Squire 2001) . In a much broader sense, they also have difficulties making social judgments, and interpreting social signals about intentions and internal states (e.g. Adolphs 2003b); for example, patients are differentially impaired at recognizing complex social emotions relative to complex non-social emotions (Adolphs et al., 2002), and assigning emotional states to people (e.g. Fine et al., 2001) and objects (anthropomorphizing; Heberlein & Adolphs, 2004). This is also seen clinically when patients get themselves into unfavorable situations because they are unable to correctly read and act on threatening environmental and social stimuli. Adolphs et al. (1998) replicated this observation most closely in a laboratory experiment, showing that patients indiscriminately rated unfamiliar faces as approachable and trustworthy while controls did not.

We administered the same task to ALS patients hypothesizing that their "nice" personalities and strikingly good morale in facing a debilitating disease might be due, at least in part, to amygdala dysfunction as part of a broader multi-system disorder.

### 2.1 Participants

91 ALS patients were recruited from the MDA-ALS clinic and the ALSA clinic at Baylor College of Medicine. 78 age and gender matched controls were recruited from 2 groups – family members and friends of ALS patients, as well as patients from the Baylor Cardiology CHF clinic (n = 24). The latter group was chosen to control for the effects of living with a serious life threatening chronic illness. Data from both control groups were combined in the final analysis, as there were no significant differences between groups. Please see Table 1 for demographic characteristics for both groups.

|  | ALS | CON |
|---|---|---|
| **Gender** | | |
|     Male | 54.9% | 54.3% |
|     Female | 45.1% | 45.7% |
| **Age** | | |
|     Mean | 50.4 | 58 |
|     Range | 22-78 | 30-84 |
| **Disease Type** | | |
|     Limb onset | 61.5% | |
|     Bulbar onset | 27.5% | |
|     No information | 10.9% | |
| **Disease Duration** | | |
|     Mean | 2.5 years | |
|     Range | 0.5 – 14 years | |

Table 1. Demographic Characteristics of Participants

## 2.2 Methods

Participants viewed 60 images of faces (Adolphs et al., 1998) in a pseudo-random order on a computer screen. 40 faces were excluded to reduce testing time. We chose the 20 most approachable, the 20 least approachable, and the 20 intermediate faces. Faces expressed a mix of neutral or emotional expressions. Before viewing, participants were given the following case scenario:

*"Imagine you are in a city you do not know well, you are by yourself, it is getting dark and you have lost directions. You see many people on the street. You need to decide who you would like to approach to ask for directions.*

*We will show you 60 faces. For each face, we would like you to decide how approachable that person is in the particular situation that you are in."*

Participants were then instructed to respond with an answer between –3 and 3, and were given examples of what each rating would mean. There was no time limitation. Answers were recorded by the examiner. To minimize gender effects, all faces that had received different ratings (p < .10) from male and female controls were eliminated from further analysis; 51 faces remained.

As part of their initial ALS evaluation in the MDA-ALS or ALSA Clinic, several patients (n = 49) were given a comprehensive neuropsychological interview and testing battery and received a cognitive diagnosis: cognitively intact, subtle deficits, mild-to-moderate or severe (FTD) deficits (see Table 2).

## 2.3 Results

For each participant, three means were calculated – overall mean rating, mean rating for the 10 most approachable faces, and mean rating for the 10 least approachable faces. We then divided participants into Trusters, Suspicious Responders (SR) and Conventional Responders (CR). Participants were labeled Trusters if their average rating for the 10 least approachable faces was above zero; i.e. they regarded even those faces as approachable that controls would not have approached. They were labeled Suspicious Responders if their average rating for the 10 most approachable faces was lower than 1, indicating that they felt faces difficult to approach that controls found very approachable.

While 65.4% of participants in the control group were CR, 62.6% in the ALS group were either Trusters or Suspicious Responders (Figure 1 "minority responders"; Chi square test p < .001).

Thirty-one ALS patients were Trusters, 26 were SR, and 34 were CR (34.1%, 28.6% and 37.4%, respectively). In the control group, 16 were Trusters, 11 SR and 51 CR (20.5%, 14.1% and 65.4%, respectively). Both Trusters (34.1% vs. 20.5%) and Suspicious Responders (28.6% vs. 14.1%) were significantly more common in the ALS group (Chi Square tests; both ps < .01) than in the control group.

We previously reported results on 26 patients (Schmolck et al., 2007); only Trusters were identified in that subgroup (n = 14) since that was a common response pattern. In retrospect, the SR pattern was present in 3 patients but not recognized at the time. Our finding in a large group of ALS patients thus not only confirms our earlier results, but also expands them to describe a new common response pattern in the ALS group.

In the subgroup of 49 patients with neuropsychological testing, there was no clear correlation between cognitive diagnosis and performance on the faces task (Table 2). In the small number of patients with FTD (n = 8), half of patients were CR and half of patients were Trusters (Table 2).
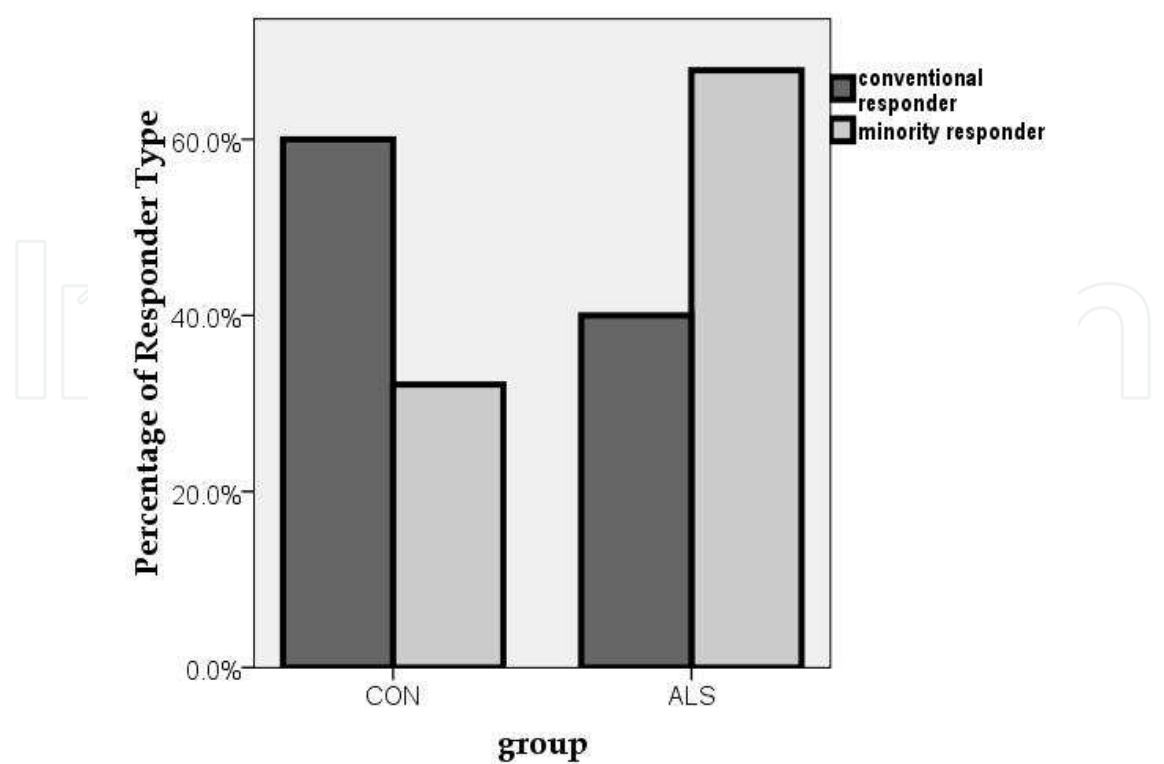
Fig. 1. Significantly more ALS patients were minority responders (Trusters and Suspicious Responders combined)

| | Cognitive Diagnosis | | | | |
|---|---|---|---|---|---|
| | Intact | Subtle | MiMo | FTD | Total |
| Conventional Responder | 10 | 3 | 3 | 4 | 20 |
| Truster | 10 | 1 | 1 | 4 | 16 |
| Suspicious Responder | 5 | 2 | 6 | 0 | 13 |
| Total | 25 | 6 | 10 | 8 | 49 |

Table 2. Cognitive Performance and Responder Type in the subgroup of patients with neuropsychological testing results. MiMo – Mild to moderate impairment

## 2.4 Discussion

We have shown that more than half of our patients with ALS have an abnormal response pattern. One response pattern (Trusters) shows similar behavioral characteristics to patients with bilateral amygdala damage on a paradigm asking participants to judge the approachability of unfamiliar faces. This difficulty can be generalized as an inability to correctly recognize threat in a given social context. A person with this behavioral pattern would be expected to be trusting, friendly and open to cooperation, and show very little hostility or suspicion. Many clinicians caring for ALS patients have noted this type of personality in ALS patients. The second response pattern is that of overly suspicious behavior (SR). These patients will be overly reluctant to approach unfamiliar faces, also showing poor discrimination between approachable and less approachable faces. These

patients show a response pattern that might be seen in autism (e.g. Baron-Cohen et al., 2001), or patients with anxiety disorder or social phobia, which have both been linked to hyperactivity of the amygdala (e.g. Freitas-Ferrari et al., 2010; Blair et al., 2011). Clinically, this patient population might not be easily recognized if not specifically probed by the examiner during history taking.

There are some clues regarding the basic mechanism by which amygdala damage leads to impairments making social judgments from faces. Complex mental states are recognized disproportionately from the eye region of the face, and when making judgments about mental states from the eye region, healthy controls activate the amygdala in functional imaging studies (Baron-Cohen et al., 1999; Baron-Cohen et al., 2001). Bilateral damage to the amygdala has been shown to impair the recognition of negative basic emotions in facial expressions, notably fear (e.g. Adolphs et al., 1994; Calder et al., 1996; Broks et al., 1998; Anderson et al., 2000). Investigating the first patient reported to show this deficit (S.M.), Adolphs and colleagues (2005) demonstrated that her impairment stems from an inability to make normal use of information from the eye region of faces when judging emotions. They traced this deficit to a lack of spontaneous fixations on the eyes during free viewing of faces. Although SM fails to look normally at the eye region in all facial expressions, her selective impairment in recognizing fear is explained by the fact that the eyes are the most important feature for identifying this emotion. It is thus likely that inadequate evaluation of the eye region leads to impairments in the Approachability Task, and perhaps in some real life situations. While this mechanism may explain some of the impairments in social cognition seen in patients with amygdala damage, it would not explain others, such as detection of fear and anger from voices (Scott et al., 1997) impaired anthropomorphizing (Heberlein et al., 2004), or inferring internal mental states (Fine et al., 2001).

Performance on the Approachability Paradigm was not related to frontal dysfunction. While we cannot be certain, this suggests that the response pattern seen in the patients without frontal dysfunction was more likely to be due to amygdala involvement. Healthy volunteers judging the trustworthiness of faces activate the amygdala bilaterally for faces judged untrustworthy in an fMRI paradigm (Winston et al., 2002). Also, even in the presence of overt FTD, only half of the patients had abnormal performance on the Approachability Paradigm.

## 3. Phonemic and semantic verbal fluency in ALS

Verbal fluency tasks, which require an individual to generate words starting with a specified letter (phonemic fluency) or in a specified category (semantic fluency), have been shown to be sensitive tools for identifying cognitive dysfunction in neurologically impaired populations (Canning, Leach, Struss, Ngo, & Black, 2004; Ho et al., 2002; Fangundo et al., 2008; Libon et al., 2009). Phonemic fluency involves prefrontal and frontal functions because it requires strategic processes for searching the lexicon (Leggio, Silveri, Petrosini, & Molinari,, 2000; Martin, Wiggs, Lalonde, & Mack, 1994), while semantic fluency localizes more to the left anterior temporal lobe, where representations are categorized by meaning (Pihlajamki et al., 2000). Recent functional magnetic resonance imaging (fMRI) studies have verified the neuroanatomical locations involved in phonemic fluency in the left premotor and inferior frontal gyrus and for semantic fluency in the left fusiform and left middle

temporal gyrus (Bim et al., 2009; Meinzer et al., 2009). Consequently, by evaluating ALS patient performances on phonemic and semantic fluencies, we were able to investigate frontal and temporal function in ALS patients.

The cognitive substrates underlying verbal fluency have been examined further in neuropsychological studies (Baldo, Schwartz Wilkins & Dronkers, 2006; Troyer, Moscovitch, & Winocur, 1997). Clustering and switching have been shown to be components that underlie verbal fluency performance (Troster et al., 1998; Troyer et al., 1997). Clusters are groups of related words, accessed through memory stores, in which intact performance is purported to rely on temporal lobe functioning. Switching refers to the process of changing from one cluster to another, which has been associated with frontal-lobe-mediated abilities (Troyer et al., 1998). We investigated differences in phonemic and semantic fluency between ALS patients, classified into neurocognitive subgroups, and healthy participants and whether these declines in verbal fluency were due predominantly to changes in clustering, switching, or a combination of the two component processes (Lepow et al., 2010).

## 3.1 Participants

A total of 49 ALS patients and 25 healthy control participants (HC) were recruited from the Baylor College of Medicine (BCM) ALS Association Clinic. The HC participants were caregivers or family members of the ALS patients who participated in this study. ALS patients' motor functioning was evaluated by the ALS Functional Rating Scale (ALS-FRS), and their site of onset (limb vs. bulbar) was recorded at their initial clinic visit.

A subset of these ALS patients ($N$ = 36) underwent a comprehensive neuropsychological assessment, and these data were used to classify participants as cognitively intact (ALS-intact), mildly impaired (ALS-mild), or FTD (ALS-FTD). Patients were coded as ALS-FTD using Strong et al.'s (2009) criteria. Patients were coded as ALS-mild if their neuropsychological evaluation, excluding their performance on phonemic and semantic fluency measures, revealed cognitive deficits (<1.5 $SDs$ below the mean for the appropriate normative sample) in one cognitive domain. The ALS cognitive impaired classification (ALSci) described by Strong et al. (2009) is based on impairments in executive functioning only; however, we excluded both phonemic and semantic fluency so as not to classify patients based on the measures under investigation. Hence, additional measures of executive functioning were limited. Consequently, patients were classified based on their entire comprehensive evaluation.

## 3.2 Methods
### 3.2.1 Neuropsychological evaluation

The comprehensive neuropsychological assessment examined basic orientation (Mini Mental Status Examination [Folstein Folstein & McHugh, 1975]), attention/ information-processing speed (Wechsler Adult Intelligence Scale-3rd Edition, [WAIS-III; The Psychological Corporation, 1997], Digit Span, Trail Making Test Part A, and Verbal Sustained Attention Test), verbal learning (Rey Auditory Verbal Learning Test [Schmidt, 1996], visual learning (Brief Visual Memory Test-Revised), language (Boston Naming Test [Kaplan, Goodglass, & Weintraub, 1983]), visual-spatial abilities (Rey-Osterrieth Complex Figure Test [Meyers, & Meyers 1995], WAIS-III Block Design), and executive function (Wisconsin Card Sorting Test [Heaton, 1981], Trail Making Test Part B).

### 3.2.2 Fluency scoring methods

Verbal fluency tests were administered to ALS patients and HC in the following manner: Patients were asked to generate a list of words that began with a specific letter (F, A, & S was used for phonemic fluency) or category (Animals was used for semantic fluency) in a 1-minute period. Prior to administering the test, patients were told that proper nouns and root words with different suffices were not allowed. Words generated (including repetitions and rule breaks) were recorded verbatim. The total number of words generated, excluding repetitions and rule breaks, was the standard measure of analysis and Troyer's (Troyer et al, 1997) scoring methods for clustering and switching were utilized.

### 3.2.3 Verbal fluency components

*Phonemic fluency.* Clusters are scored for groups of phonemic words, or words that are similar based on phonemic rules for each letter. Troyer and colleagues (1997) defined parameters for scoring clusters, including: (a) words beginning with the same first two letters, (b) rhyming words, and (c) words that are the same syllabic length and differ only by a vowel sound. For example, *follow, fog, fond, foster, forget* is a cluster of four because the words all begin with the same phoneme, and the cluster size begins with the second word of a cluster. Each word that is not classified in a group of related phonemic words is scored as a cluster of zero. The *number of clusters* is defined as the total sum of individual clusters, including clusters of zero. The *cluster value* is defined as the sum number of consecutive related words excluding the first word of each grouping, or the sum of the values assigned to the clusters. *Switches* are defined as any break between clusters, including clusters of zero.

*Semantic fluency.* In the semantic fluency task, clusters are composed of words that are semantically related. Troyer's method defines the categories for finding semantic clusters in "Animals" as living environments, zoological categories, and human use, with each supraordinate category containing specific exemplars. The *cluster size* begins with the second word of a cluster. For example the group, *cow, horse, chicken,* and *rooster,* is scored as a cluster of three because they are all farm animals. Number of clusters, cluster value, and switches were calculated as discussed above.

### 3.3 Results

### 3.3.1 Participant characteristics

The 49 ALS patients and the 25 HCs did not differ in age or education level (Table 1). There were significantly more female HCs than female ALS patients (p=0.006). Gender correlated significantly with Troyer's average number of switches for phonemic fluency; thus, gender was entered as a covariate in this analysis. There were no significant demographic differences between the three groups of ALS patients coded for degree of cognitive dysfunction (Table 1), including site of onset (p = 0.36) and total ALS-FRS scores (p = 0.34).

*Phonemic fluency.* ALS patients generated fewer numbers of clusters than did HCs (p = 0.04; Figure 1). ALS patients also generated fewer switches between clusters; however, once gender was entered as a covariate in the analysis, this difference was no longer significant (p =0.14). The number of clusters differed significantly between the ALS groups, with the ALS-intact group scoring higher than the ALS-mild and the ALS-FTD groups (p = 0.004; Table 2). The number of switches also differed between the ALS cognitive groups, with the ALS-

intact patients switching more often than both the ALS-mild and the ALS-FTD groups (p =0 .004; Table 2). The cluster value scores did not differ significantly between the ALS groups (p=0 .13).

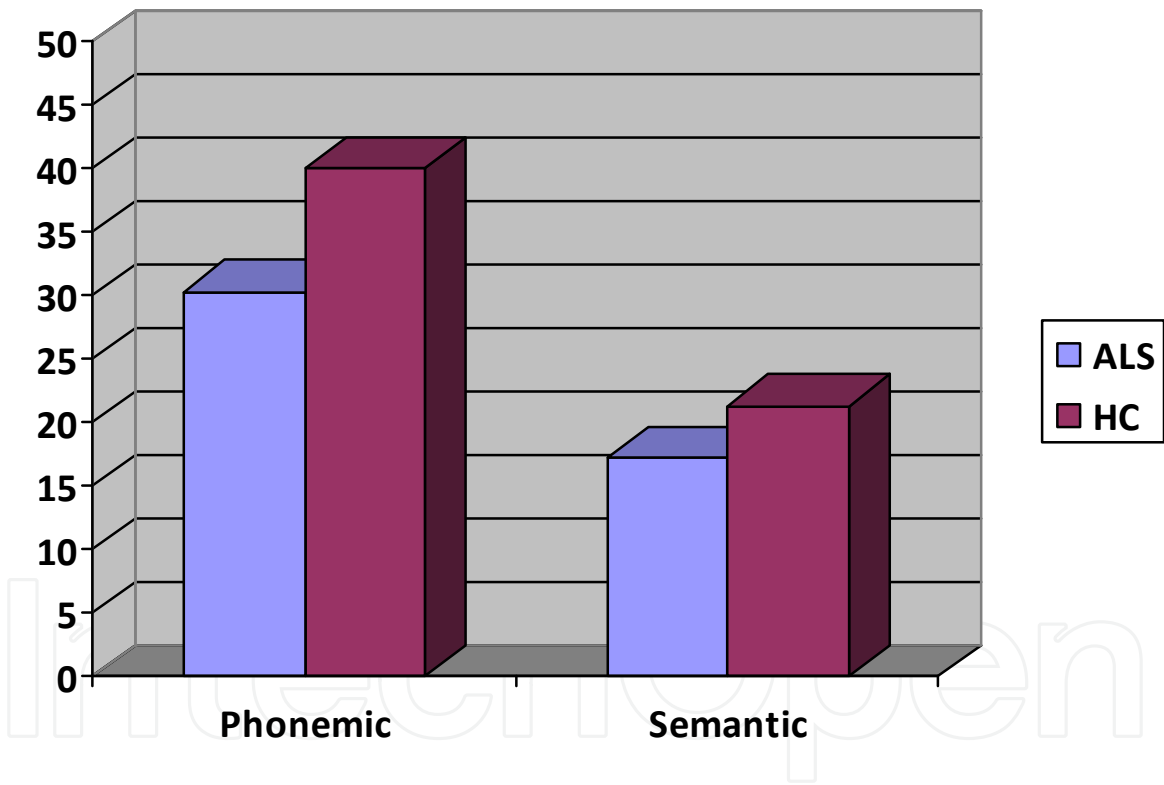| Table 1 | ALS | | | | HC (n=25) | p-value |
|---|---|---|---|---|---|---|
| | Intact (n=13) | Mild (n=17) | FTD (n=7) | Total (n=49) | | |
| Gender (M/F) | 8/5 | 10/7 | 3/4 | 28/21 | 6/19 | **0.006** |
| Age (yrs) | 54.2 (8.96) | 58.1 (12.1) | 61.4 (14.2) | 56.1 (11.3) | 52.7 (13.0) | 0.28 |
| Education (yrs) | 14.1 (2.95) | 13.3 (1.32) | 12.9 (3.44) | 13.8 (2.71) | 15.2 (2.99) | 0.07 |



Fig. 1. Total Phonemic and Semantic Fluency Scores for ALS and HC groups

*Semantic fluency.* The total group of ALS patients generated fewer numbers of clusters (p = 0.01) and made significantly fewer switches between clusters (p =0.03) than did the HCs. The total groups did not differ significantly on the number of words within semantic clusters (cluster value=0.15). The ALS-FTD patients generated a smaller cluster value score than did ALS-intact and ALS-mild groups (p=0.03). The number of clusters and number of switches demonstrated trends toward significant differences between the groups (p=0.07, p= 0.06, respectively; Table 2).

| Table 2 | ALS intact Mean (SD) | ALS mild Mean (SD) | ALS FTD Mean (SD) | p-value |
|---|---|---|---|---|
| **Total** | | | | |
|   **Phonemic** | 37.2 (10.9) [1,2] | 30.1 (9.76) [1] | 23.3 (6.54) [2] | **0.009** |
|   **Semantic** | 19.0 (5.29) [1,2] | 18.3 (5.72) [1] | 12.9 (4.05) [2] | **0.02** |
| **Troyer** | | | | |
| **Phonemic Fluency** | | | | |
|   Number of Clusters | 9.84 (2.34)[1,2] | 7.15 (2.79)[1] | 6.43 (2.17)[2] | **0.004** |
|   Cluster Value | 3.20 (1.77) | 2.72 (1.62) | 1.67 (1.12) | 0.13 |
|   Switches | 8.84 (2.34) [1,2] | 6.15 (2.81) [1] | 5.43 (2.17) [2] | **0.004** |
| **Semantic Fluency** | | | | |
|   Cluster Value | 10.94 (3.78)[1] | 8.85 (3.83) | 6.43 (3.41)[1] | **0.03** |
|   Number of clusters | 10.59 (3.73) | 8.54 (3.26) | 7.29 (1.98) | 0.07 |
|   Switches | 9.59 (3.73) | 7.46 (3.20) | 6.29 (1.98) | 0.06 |

### 3.4 Discussion

These results support the findings that ALS patients demonstrate cognitive impairment localizing to both the frontal and temporal lobes, highlighting the frontotemporal neurocognitive phenotype of this disease (Lepow et al., 2010). ALS patients exhibited decreased phonemic and semantic fluency performances as compared to healthy non-neurologically impaired controls. Furthermore, in comparison to ALS patients whose cognition was intact, the subset of ALS patients with mild cognitive dysfunction or ALS-FTD demonstrated performance declines on standard measures of verbal fluency and the component processes of these measures. The component processes of verbal fluency provide a unique opportunity to further evaluate the ALS frontotemporal neurocognitive phenotype from slightly different perspective (Troyer et al., 1997). For phonemic fluency, the intact ALS sample generated fewer clusters and more switches than the ALS-mild and ALS-FTD patients, suggesting temporal involvement in ALS patients, with increasing frontal lobe involvement in patients with greater cognitive dysfunction. For semantic fluency, similar results were obtained with a greater emphasis on declines in clustering or increased temporal lobe dysfunction. These results suggest that verbal fluency measures identify frontal and temporal lobe involvement in the cognitive decline associated with ALS, particularly when the component processes are evaluated.

As a group, the ALS patients demonstrated temporal lobe involvement as compared to individuals without ALS. However, when the ALS patients were stratified based on their level of cognitive dysfunction, the influence of the frontal lobe involvement became more pertinent to their ability to perform this task. In conclusion, the differences in phonemic and semantic fluency scores between ALS patients and HCs suggest temporal lobe involvement in ALS patients with increasing frontal lobe involvement across the neurocognitive spectrum of the disease. A frontotemporal neurocognitive phenotype is revealed in ALS patients who demonstrate cognitive changes.

## 4. General discussion

Up until the late 1980s, the prevalent view in the neurological literature was that ALS was a pure motor neuron disease only infrequently affecting cognitive function. This view has

changed in the last decade with several neuropsychological and functional imaging studies confirming common involvement of cortex outside the motor strip. The concept of primarily frontal lobe dysfunction in motor neuron disease was introduced by Montgomery and Erickson (1987) as well as Iwasaki et al. (1990). Several studies have since confirmed the association between FTLD, executive dysfunction, and ALS (eg. Massman et al., 1996; Strong et al., 2009). The largest study examining cognitive function in ALS to date found that 51% of patients had varying degrees of executive dysfunction (Ringholz et al., 2005; n = 279). These numbers confirmed an earlier study by Lomen-Hoerth and colleagues (2003) who had found evidence for frontal executive deficits in half of their patients, many of whom met criteria for Frontotemporal Lobar Degeneration.

Whereas frontal pathology has become the focus of cognitive investigation in ALS patients, the integrity of temporal structures (apart from the hippocampal formation) in ALS has not received much attention. Temporal pathology is a hallmark of FTLD, and several behavioral observations in ALS patients could suggest temporal pathology.

Several imaging studies and neuropathological investigations suggest that involvement of the temporal cortex, as well as the amygdala and other limbic structures in the disease process is very likely. Kew et al. (1993) showed reduced blood flow (rCBF) in the anterior cingulate cortex, the medial prefrontal cortex (Brodmann area 9 and 10), parahippocampal gyri and the anterior thalamic nuclear complex. Abrahams and colleagues (1995) observed decreased activity across a wide area of the frontal lobes, which also included the insular cortex and thalamic nuclear complex. In a small sample of clinically non-demented patients, there was a decrease in cerebral blood flow of the frontal and temporal lobes, despite normal MR imaging (Kokubo et al., 2003). Recently, a morphometric study of gray matter volume on MR scans revealed significant differences between patients with ALS and normal controls, predominantly in fronto-temporal areas, regardless of cognitive status; that is, the differences in gray matter volume between the ALS group as a whole and the control group were much more extensive than differences between cognitively normal and demented ALS patients (Chang et al., 2005).

There have been a limited number of neuropathological studies looking at frontal and temporal pathology in ALS. Wilson et al. (2001) found changes that where overall more pronounced for cognitively affected patients (ubiquitin positive, alpha-synuclein-negative, and tau-negative neuronal inclusions), most pronounced in the cingulate cortex. Cognitive impairment was uniformly associated with superficial linear spongiosis, a pathologic feature common to several forms of frontotemporal dementia. Wilson and colleagues did not study temporal structures in more detail. In a group of ALS patients with cognitive impairment, and decreased frontal blood flow on SPECT, neuropathologic examination showed spongy degeneration and neuronal loss in the frontal lobe (Abe et al., 1997).

Pathologically, there is also a special tie between semantic dementia, or temporal variant FTD, and ALS. Both FTD-MND (or FTD-ALS) and semantic dementia are characterized by ubiquinated inclusions (FTD-U); the clinical spectrum of patients seen with this histopathological finding varies from ALS, ALS with FTD and semantic dementia without ALS (Davies & Xuereb, 2007). This suggests that patients with ALS caused by this histopathological subtype would be expected to have overt or subtle features of temporal involvement, especially impairments in semantic processing and amygdala function.

Some studies have specifically evaluated the limbic system in sporadic ALS. In the ALS-Parkinson-dementia complex of Guam, tau and alpha-synuclein aggregates are a common

finding in the amygdala (e.g., Yamazaki et al., 2000). Case series of sporadic ALS patients with and without dementia have demonstrated ubiquitinated intraneuronal inclusions and spongiform changes in the neostriatum, the amygdala and the parahippocampal gyrus, as well as the temporal pole, anterior cingulate, orbitofrontal cortex and insula (Kawashima et al., 2001; Kato et al., 1994, also Tsuchiya et al., 2002).

We assume that the cognitive findings of decreased semantic fluency and abnormal approachability are the clinical correlate of the changes seen neuroradiologically and neuropathologically and suggest that many ALS patients may, in fact, have both clinically relevant amygdala dysfunction and difficulties with semantic processing.

Performance on the Approachability Paradigm was not related to frontal dysfunction. A similar lack of correlation between amygdala dysfunction and frontal cognitive changes was reported by Zimmerman and colleagues (2007). In their study, among the 8 patients with emotional perceptual impairment, one-half did not have depressive, or memory or cognitive symptoms on screening, whereas the remainder showed dementia symptoms alone or together with depressive symptoms. This finding is important in two ways: First, it suggests the response pattern seen in ALS patients in both studies was in fact due to amygdala involvement as hypothesized and was less likely to be the result of frontal dysfunction

Second, FTLD is known to have several subtypes with variable sites of onset, all of which can be seen in conjunction with ALS. Thus, it is not surprising to find that amygdala dysfunction and frontal dysfunction are not associated. It may be that there are groups of ALS patients that have predominantly temporal dysfunction at onset, while other groups have predominantly frontal onset. This also suggests that more ALS patients have clinical involvement outside the motor strip than the rough estimate of 50% percent from prior studies, which mainly concentrated on frontal cognitive dysfunction.

## 5. Conclusion

We have shown that more than half of patients with ALS have unusual response patterns on a paradigm asking participants to judge the approachability of unfamiliar faces, suggesting amygdala dysfunction. Performance on this task did not correlate with frontal-executive dysfunction on cognitive testing. Patients also had significantly reduced semantic fluency suggesting involvement of the temporal cortex. Disease involvement outside the motor cortex in ALS is common, and can manifest as frontal, temporal or frontal and temporal dysfunction. Further studies need to be done to clarify the relationship between histopathological subtypes and cognitive patterns.

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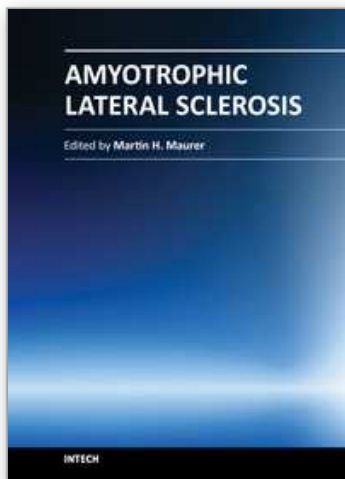
**Amyotrophic Lateral Sclerosis**

Edited by Prof. Martin Maurer

Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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