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A NEUROPSYCHOLOGICAL AND COGNITIVE INSIGHT IN MOTOR NEURON DISEASE/ AMYOTROPHIC LATERAL SCLEROSIS

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1. AN INTRODUCTION TO AMYOTROPHIC LATERAL SCLEROSIS/MOTOR NEURONE DISEASE (MND/ALS):

1.1 TERMINOLOGY

The nomenclature of disorders of the motor system can be confusing. Currently, terminology is based on clinical or pathological descriptions rather than on basing underline mechanism. This terminological difficulty can be resolved by consideration of historical development of the concept of anterior horn cell disease as a cause of muscle wasting. Progressive muscular wasting was a clinical syndrome well known in the early 19th century. The term *Progressive Muscular Atrophy* (PMA) was firstly used by Aran in 1850 (1), who believed that this syndrome was a muscular disorder. Duchenne gave a description of this disorder in 1849 (2). In 1869, Jean Martin Charcot (3,4), the first professor of Neurology at the Salpètriére, and Joffroy, described two cases of the disease, observing lesions in postero-lateral spinal cord. They proposed the name of the new syndrome as *Amyotrophic Lateral Sclerosis* (ALS), and they determined its essential characteristics. During a series of lectures in 1874, Charcot clearly established ALS as a distinct syndrome respect of PMA.

In recognition of the relation between the syndromes of PMA, ALS and Progressive Bulbar Palsy (PBP) Brain (Brain, 1962) introduced the term *Motor Neuron Disease*, as shown by the spectrum of involvement of upper (UMN) and lower (LMN) motor neurones and by topography of the muscular wasting. So, Motor Neuron Disorders (MNDs) are heterogeneous group of disorder (Tab. I) with diverse signs and symptoms, all in the same way affecting the anterior horns cells.

The terms ALS now is more frequently used than before and it is considered to describe the disease more specifically.

Table I: The motor neuron diseases

Idiopatic motor neuron diseases
Amyotrophic lateral sclerosis (ALS)
Progressive Bulbar Palsy (PBP)
Progressive Muscular Atrophy (PMA)
Primary Lateral Sclerosis (PLS)
Familial Amiotrophic Lateral Sclerosis
Juvenile Amiotrophic Lateral Sclerosis
Madras motor neuron disease
Kennedy's disease
Monomelic motor neuron disease (amiotrophy)
Toxin-related motor neuron disease
Lathyrism
Konzo
Gaumann ALS

1.2 EPIDEMILOGY

Amyotrophic Lateral Sclerosis has an incidence similar across the world (range, 1.0 to 2.5/100,000).

The 1990s incidence and mortality rates of MND average at 1.89 per 100,000/year and 1.91 per 100,000/year, respectively, thus yielding increases of 46% and 57% over the 1960s-1970s decades, respectively. This increase appeared mainly due to Southern Europe countries, to female gender and to patients aged 75 years and over. Thus, the results of this analysis confirmed that the incidence of, and mortality from, MNDs continued to increase during the 1990s and, suggest that this increase could be partly due to increased life expectancy. Other factors might also contribute, such as better diagnosis since El Escorial criteria (see paragraph 1.5), and better accuracy of death certificate collection (5). Survival has been observed as affected by age at onset (median survival: 34, 27, and 23 months for onset <60, 60-75, and >75 years, respectively), area of residence (median survival: 24 months in mountainous areas, 32 elsewhere), and type of work (median survival: 25 months in agricultural workers, 33.5 in others). The duration of the disease is defined as interval between the onset of symptoms and death. Gender did not influence survival, whereas percutaneous endoscopic gastrostomy placement and invasive ventilation did (Mandrioli, 2006). Moreover, Forced vital capacity (FVC) is an indicator of survival and disease progression in an ALS clinic population (6). The mean annual incidence adjusted by age and sex to the 2001 Italian population was 1.7/100,000 (1.4 to 2.0) (7).

Beghi and colleagues (8) studied the incidence rate of definite ALS in Northern of Italy: it was 0.93 (spinal-onset ALS 1.35; bulbar-onset ALS 0.74) and observed that was consistently higher in men with spinal-onset ALS vs men with bulbar-onset ALS and women. So the incidence of ALS varied according to age, sex, and site of onset. Specifically to our region, Briani et al (9) evaluated the incidence of the disease in Padua, using a retrospective method to study all MND cases hospitalized in the district from 1980 to 1991: they found that ALS cases were doubled in this decade (from 0,66 new cases to 1,34 per100.000/year).

1.3 CLINICAL FEATURES

Amyotrophic Lateral Sclerosis is the most common form of MND of undetermined cause in adults (85% of cases), affecting not only the anterior horn cells but also the cortical-spinal traits, resulting in a fairly consistent clinical picture and outcome. The disorder is almost asimmetric at onset, and it may be quite focal. ALS is relentlessly progressive, and invariably fatal. Death results usually from ventilatory failure. The clinical features depend on the variable permutations of the combination of LMN and UMN involvement, and these vary not only according to the pattern of onset in any particular patients, but also in relation to the stage of the disease.

By definition, the features of ALS are signs and symptoms of lower motor neuron dysfunction (Tab.III), including focal and multifocal weakness, atrophy, cramps and fasciculations, associated with the cortical spinal signs of spasticity and enhanced and pathologic reflexes, representing Upper Motor Neuron Dysfunction (Tab. II). There is the absence of sensory findings.

The patients present with a history of unexpected tripping, difficult negotiating curbs, dragging of a foot, and ultimately more diffuse weakness of the leg. Difficulties with buttoning clothes, picking up objects, or simply poor coordination while performing fine movements are otherwise the exempla of involvement of the UMN. The cortico-bulbar tracts may be also involved (Table IV), resulting in dysphagia and dysarthria that aggravates the already established lower motor neuron involvement at the brain-stem level.

TableII: Upper motor neurone dysfunction

Symptoms
Weakness (Loss of muscle strength)
Stiffness
Slowing of distal movements
Inco-ordination
Signs
Spasticity
Brisk reflexes
Babisky and Hoffman signs
Weakness
Pathological Hyperryflexia
Tonic-flexors spasm
Pseudobulbar affect

TableIII: Lower motor neurone dysfunction

Symptoms
Fatigue
Weakness (Loss of muscle strength)
Cramps
Twiching of muscles
Inco-ordination
Signs
Weakness
Muscle Atrophy
Fasciculations
Suppression of reflexes
Hyporiflexia
Hipotonia

Table IV: Bulbar dysfunction (due to a upper motor neurone defect)

Signs and Symptoms
Dysathria
Dysphagia
Shalorrea
Aspiration and Laringospasm
Spastic Bulbar Palsy (Pseudobulbar Palsy)

Bulbar features develop during the course of the disease, but may be a presenting feature, especially in middle-age women with ALS. Bulbar involvement leads to difficulty speaking and swallowing, and it is often closely correlated with a weakened of respiratory muscles and a reduced forced vital capacity. Patients with bulbar involvement may have prominent emotional lability characterized by uncontrollable paroxysm of laughing or crying. These features define classic ALS, in the sense that it was described by Charcot (3). In sum, at onset, ALS presents with lower motor neuron involvement (LMN-onset or the PMA for the ALS), upper motor neuron involvement (UMN-onset or the PLS form), or bulbar involvement (bulbar-onset or PBP form). A summarizing scheme is shown below (Fig.1). Description of ALS subsets will be better illustrated in the next paragraph.

Other important observations on the clinical features that have been much remarked over the years include the striking relative resistance of the external ocular muscles to denervation during the course of the disease. The striated urinary and anal sphyncter muscle are also relatively spared until the late stages of the disease. Similarly, the abducor muscle of the larynx and the sphincter muscles, which are in state of continuous tonic contraction, as urinary and anal sphyncter, are also resistant to denervation in ALS. Fasciculation of the tongue is a clinical sign with high diagnostic probably with ALS.

Clear frontal or fronto-temporal dementia appear in about 5% of cases (10). Otherwise, mild cognitive impairment may develop in 47% of cases (11), with characteristically frontal effect. Cognitive deterioration in non demented patients with ALS is relatively slow process. Selective cognitive impairment in the form of verbal fluency deficits, most likely indicating executive dysfunction, appears relatively early on the course of the disease, although language functions may become vulnerable as in the disease progresses (12). A review of the literature shows prevalence rates for depression in ALS patients ranging from 0% to 44%, but studies using the structured interview according to DSM-IV criteria find highly consistent rates of 9-11%. Prevalence rates for anxiety in ALS range from 0% to 30%. Depression and anxiety appear to be not always properly addressed

aspects of ALS, as there are only a few references in the literature about psychological and pharmacological interventions (13).

Both neuropsychological than psychopathological findings in MND/ALS are better explained in next chapters.

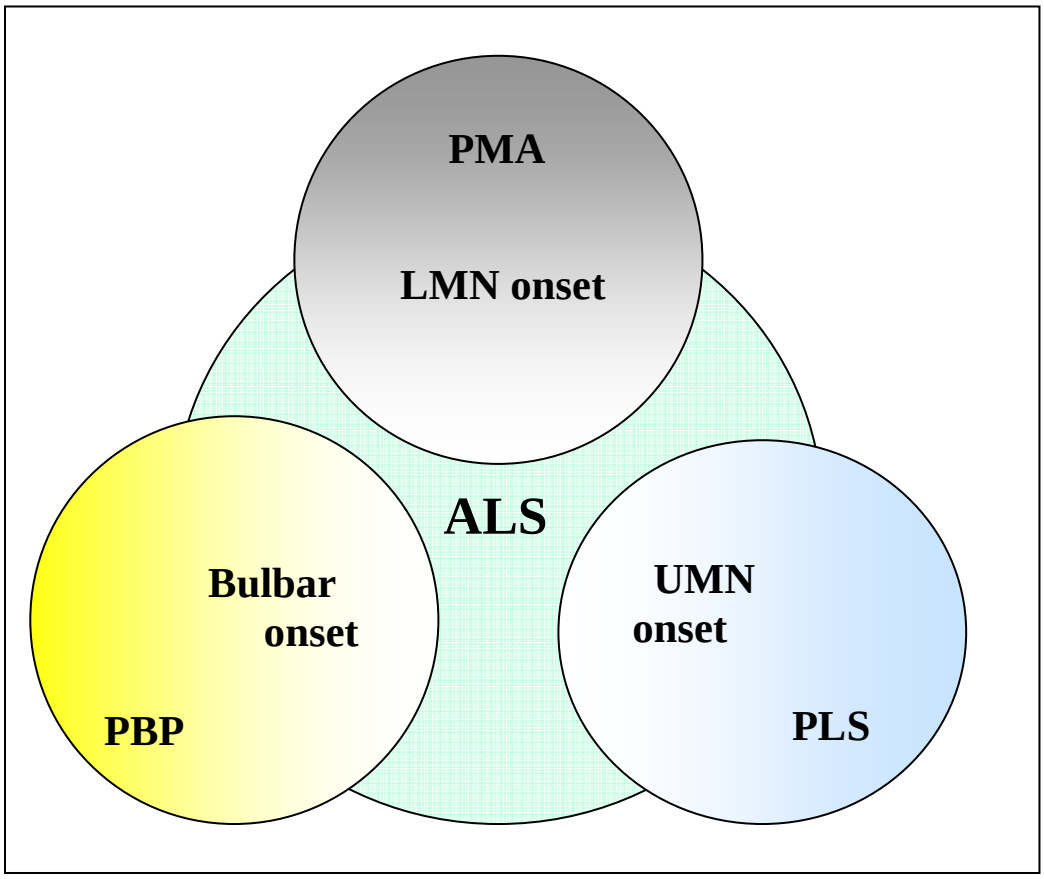

Figure 1: ALS manifests generalized upper motor neuron (UMN) and lower motor neuron (LMN) involvement. At onset may be present only UMN, LMN or bulbar signs. In a small number of patients, the disease remains exclusively in UMN, LMN or bulbar involvement over the entire course of disease (such as in: "Primary Lateral Sclerosis"(PLS), "Progressive Muscular Atrophy", (PMA), "Progressive Bulbar Palsy" PBP

1.4 ALS/MND SUBTIPES

The pattern of onset has been much studied: limb onset is found in 65-80% of cases, and bulbar onset is found in 20-25%. Bulbar involvement carries a poor prognosis, and life expectancy in patients with bulbar onset is worse than in those who present limb onset (14,15). Subsets of ALS such as PMA, PLS and PBP have distinctive clinical pictures, outcomes, and pathologic features. These variations must be recognized when physicians are to tailor advice on disease progression, prognosis, drug therapy, and care to the needs of the individual. Clinical trials of new therapeutic agents have been performed, on the assumption that patients with ALS/MND have the same underlying etiology, addressing the heterogeneous population of the patients under a single diagnostic category. This can be detrimental to the well-being of the individual, because clinical heterogeneity may mask drug effects in clinical trials. The attempt to categorize subgroups based on the clinical and pathological background within the spectrum of ALS/MND may be a critical step in facilitating clinical research in ALS/MND.

Progressive Muscular Atrophy (PMA) is characterized by pure LMN findings only over the entire course of the disease. Patients who present with LMN signs and later develop features of classic ALS are considered to have *LMN-onset ALS* or the PMA form of ALS. PMA is rare: it showed (16) in only 2,4% of ALS patients. Its duration is longer than that of ALS. Based on El Escorial diagnostic criteria for ALS, PMA is not synonymous of ALS and should be considered an independent entity (M:Fratio 3-4:1).

Primary Lateral Sclerosis (PLS) is characterized by pure UMN findings and should be considered an independent condition. PLS is found in 2% to 3.7% of all patients with ALS (16). Patients who present with signs of UMN findings and later develop features of classic ALS are considered to have *UMN-onset ALS* or the PLS form of ALS.

Progressive Bulbar Palsy (PBP) is characterized by progressive paralysis of muscles because of involvement of UMNs and LMNs separately or in combination. By definition, the disease must be strictly limited to the bulbar muscles during its entire course. Patients who presents with signs of bulbar palsy and later develop features of classic ALS are considered to have *bulbar-onset ALS*. Even in its early stages, most patients with bulbar onset ALS have evidence of LMN involvement outside the bulbar musculature. Therefore, PBP is extremely rare and should be considered as one type of presentation of ALS (16 Cognitive deficit in ALS appear more prominent in patients with pseudobulbar palsy (17) (M:F ratio 1:1)

Sporadic ALS is nonfamilial; ALS is identified in only one member of entire family. It constitutes more than 90% of all ALS cases. When the family history is uncertain or the parents of the patient died at an early age, the possibility of familial ALS cannot be excluded. Autopsy findings may not be specific enough to distinguish familial forms, and the clinical features are identical both in sporadic then in familial. (M:F ratio 3:2)

Familial ALS (fALS) constitutes about 10% of ALS cases. It is typically autosomal-dominant; one additional affected family members needs to be identified in the preceding or successive generation. Generation skipping is rare in fALS (17). When a medical history of the family members, particularly the parents, is not available, fALS cannot be excluded. The superoxyde dismutase mutation (SOD1) is approximately present in 15% of fALS patients (18). The prevalence and pattern of cognitive impairment in familial ALS is similar to that of sporadic ALS (19).

"Flail arm syndrome", "man in a barrel syndrome", "progressive amyotrophic diplegia" or "Bernhard-Vulpian syndrome" is characterized by a predominant LMN weakness of both arms. UMN signs develop in 50-70% of cases. The progression of the disease is often slow, prognosis is better than in typical ALS. It

is more common in people of African and Asian origin. This syndrome represents about 10% of all cases at presentation (20).

MND-Dementia syndrome (MND-D) it has classically frontal or fronto-temporal involvement, and it is present in 5% of cases, even though 20-50% of patients have subtle cognitive change of “frontal” type. MND-D may present first with dementia or with MND progressing to dementia, or with a combination of both.

1.5 DIAGNOSIS

Criteria for clinical and pathological diagnosis have been defined at consensus conference held in El Escorial, Spain, in 1994 (21), and at Airle House, Virginia, in 1998 (22). In these criteria, the clinical diagnosis is based on the clinical, electrophysiological, and neuroradiological features. Currently there is not surrogate marker for the diagnosis of ALS.

The El Escorial World Federation of Neurology (WFN) criteria individuated five features to make the diagnosis of ALS, showed in Table V.

Table V: El Escorial world federation of neurology criteria for the diagnosis of ALS

Features Present	Features Absent
• Signs of lower motor neuron degeneration by clinical, EMG, or neuropathological examination	• EMG evidence of other disease processes that might explain signs of lower motor neuron or upper motor neuron degeneration
• Signs of upper motor neuron degeneration by clinical examination	• Neuroimaging evidence of other disease processes that might explain observed clinical and EMG signs
• Progressive spread of signs within a region, or two other regions	

Because the progressive spread of signs from region to region is so critically important in the diagnosis of ALS, the El Escorial WFN conference provided guidelines based on topographic criteria to establish the diagnosis with varying degrees of certainty, as shown in Table VI. The four cardinal regions are also defined in Table VI.

TableVI: Levels of certainty in the clinical diagnosis of ALS according to the World Federation of Neurology guidelines

Level of certainty	Characteristic features
Suspected ALS	• Only lower motor neuron signs in two or more regions
Possible ALS	• Upper motor neuron and lower motor neuron signs are in only one region; or, • Upper motor neuron signs alone are present in two or more regions; or, • Lower motor neuron signs are rostral to upper motor neuron signs
Probable ALS	• Upper and lower motor neuron signs in at least two regions; although the regions may be different, some upper motor neuron signs must be above the lower motor neuron signs
Definite ALS	• Upper motor neuron as well as lower motor neuron signs in the bulbar region and at least two other spinal region; or, • Upper motor neuron motor and lower neuron signs in three spinal regions

TableVII: The four region ascertained in the diagnosis of ALS

Region	Specific Muscle group
Bulbar	Jaw, Face, Palate, Tongue, Larynx
Cervical	Neck, Arm, Hand, Diaphragm
Thoracic	Back, Addomen
Lombosacral	Back, Addomen, Leg, Foot

1.6 PATHOLOGY

The typical clinical picture of combined upper motor neuron (UMN) and lower motor neuron disease (LMN) signs are predominant in classical ALS and are reflected in the anatomical distribution of degenerative changes in the motor systems. This changes have been documented since the studies of Charcot (3). The major UMN pathological features, which correlate with the principal clinical manifestation, are:

a) a reduction in both the number of size of lower motor neurones (anterior horn cells) in the spinal ventral horns and bulbar motor nuclei; and
b) myelin pallor in the cortico-spinal projection pathway, a secondary consequence of axonal loss in this region.

UMN (Betz cell) soma abnormalities are much more variable, and many additional pathological features have been described using conventional and immonocytochemical stains. The most severely affected cases show an obvious absence of giant Betz cells in cortical layer 5^2 accompained by reactive gliosis, which is demonstrable by astrocitosis (e.g. by glial fibrillary acid protein (GFAP) imunocitochemestery) and as a diffuse microgliolisis (e.g. using immunocitochemestery against antigens such as CD68 and HLA-DR). Unfortunately such findings are not direct evidence that the Betz cells have actually dispeared, and there is no molecular marker that exclusively labels UMNs. Phenotypically, these large glutamatergic neurones have molecular characteristics that are similar to other pyramidal cells in the cortex. The extent to which appear the loss of Betz by conventional method (Nissl staining) is due to in part to neurological shrinkage, so that the Betz cells becomes indistinguishable by size criteria alone from neighbouring piramidal cells, is unknown and probably varies from case to case.

Patients who have symptomatic disease that begins in the arm, leg or bulbar regions may show progression of symptomatic involvement to other regions on topographically-based patterns that are consistent with more rapid progression of

the disease to anatomically contiguous areas before developing rostral or caudal symptoms throughout the neuraxis. The cerebral pathology of ALS with frontotemporal dementia-up to 5% of patients with typical motor features of ALS develops it (23,24) - includes several non-specific features. There is diffuse atrophy of the cerebral hemispheres with frontotemporal accentuation (25), together with microvacualation of cortical Lyer two in the worst affected areas (26). Another non specific feature is the presence of variable, but usually intense, subcortical gliosis of white matter in the frontotemporal regions; this may extent into caudate nucleus (25). More recent stereological works have indicated that diffuse cortical neuronal loss can be widespread even in non-demented patients with ALS (27). Substantia nigra degeneration in the absence of Lewy body formation is another common finding. The most specific feature of the pathology of these patients is the presence of ubiquitinated neuronal inclusions bodies in a more widespread distribution han is seen in typical ALS (28); these are characteristically present in hippocampal denatate granule cells. Moreover, neurofilament (NF) aggregate formation within motor neurons is a pathological hallmark of both the sporadic and familial forms of amyotrophic lateral sclerosis (ALS). The relationship between aggregate formation and both microglial and astrocytic proliferation, as well as additional neuropathological features of ALS, is unknown (29).

1.7 PATHOGENESIS

Swash and Ingram, firstly, (30) raised an important issue regarding the preclinical stages of ALS: according to them, ALS probably begins a long time, months or even years, before it manifests clinically. The onset of symptoms seen in ALS patients is assumed to occur when approximately an 80% loss of motor neurons has been achieved, as is the case of polyomelitis (31). More recent literature confirm these intuition: growing evidence from animal models and patients with amyotrophic lateral sclerosis (ALS) suggests that distal axonal degeneration begins very early in this disease, long before symptom onset and motor neuron death (32).

Over the years, many pathogenic mechanisms have been proposed. Amongst others these include: excitotoxicity and oxidative stress, aggregate formation, inflammation, growth factor deficiency and neurofilament disorganization (33). This multitude of contributing factors indicates that ALS is a complex disease and also suggests that ALS is a multifactorial disorder. Excitotoxicity is not the newest hypothesis in the ALS field, but it is undoubtedly one of the most robust pathogenic mechanisms supported by an impressive amount of evidence. Two factors make glutamate a prime candidate as a cause of motor neuron excitotoxicity in ALS. First, it is the principal excitatory neurotransmitter in the human motor system, including the corticospinal tract, spinal cord interneurons and cortico-cortical association pathways. Second, the normal concentration of glutamate is approximately 20,000-fold higher intracellulary than it is extracellulary. Plaitakis and Caroscio (34) found that fasting plasma glutamate levels in patients with motor neurone disease were twice normal levels. Moreover, cerebrospinal fluid glutamate and aspartate levels have been reported to be four times higher than in normal individuals (35). The mode of neuronal degeneration in ALS appears to be predominantly by shrinkage, so this careful examination reveals a proportion of surviving small dark motor neurones (36). These neurones have been shown to display many biochemical features of ‘programmed cell death’, or apoptosis (37). Apoptosis mediates the precise and programmed natural death of neurons and is a physiologically important process in neurogenesis

during maturation of the central nervous system. So, premature apoptosis and/or an aberration in apoptosis regulation is probably implicated in ALS and SMA, as in other pathogenesis of neurodegeneration, such as Alzheimer's (AD), Parkinson's (PD), Huntington's (HD) diseases, diabetic encephalopathy (38).

Data relating ALS to apoptosis have been generated in studies that examine the role of Cu-Zn superoxide dismutase (SOD1) (see also paragraph 1.4) in neuronal cell death, support the hypothesis that oxidative stress is one mechanism by which motor neuron death occurs (39). The genetic finding that a subset of cases with familial ALS is associated with mutations in the gene that encodes for SOD1 (18), has provided a useful molecular basis for the study of molecular degeneration in ALS, but the mechanism by which mutant SOD1 promote apoptosis is unclear. There are compelling data favouring the view that the mutant SOD1 protein can be preapoptotic in vitro. By contrast, in ALS mice that express mutant transgenic SOD1, it is by no means clear that death is apoptotic. However, up to 10% of ALS patients have a positive family history, which usually indicates autosomal-dominant inheritance.

1.8 RISK FACTORS

Metal ione and trace elements have long been suspected to play a role in the pathogenesis of ALS: lead, mercury, aluminium, selenium, manganese and iron. In particular, lead poisoning may presents clinically as a disorder that closely resembles ALS and the possibility remains that this metal participates in the pathogenesis of the disease in a proportion of cases. In fact an increase in mobilization of lead from bone into blood may play a role in the acute onset of disease (40). The associations of cigarette smoking and alcohol consumption with the risk of amyotrophic lateral sclerosis was investigated by Nelson and colleagues (41): the authors found that alcohol consumption was not associated with the risk of ALS. Ever having smoked cigarettes was associated with a twofold increase in risk. In fact, the finding that cigarette smoking is a risk factor for ALS is consistent with current etiologic theories that implicate environmental chemicals and oxidative stress in the pathogenesis of ALS (see paragraph below) . Another risk factor is represented by sport activities: Chiò's findings (42). seem to indicate that playing professional football is a strong risk factor for ALS. It is not clear if this incidence increase is due to intense physical exercise, to continuous trauma, to illegal drugs or stuff abuse or to weed-killer and fertilizer exposure. However, the new data support the previous conclusions that physical activity and trauma are probably ("more likely than not") not risk factors for ALS (43).

Cases of ALS diagnosed from 1991 through 1998 were collected from military registries and a publicity campaign in late 1998. Expected incidence was estimated from the age distribution of the Gulf War veteran population, weighted by age-specific death rates of the US population. Secular changes in nationwide ALS rates were assessed using calculations of the age-specific US population death rates from vital statistics data of 1979 to 1998. During 8 postwar years, 20 ALS cases were confirmed in approximately 690,000 Gulf War veterans, and 17 were diagnosed before age 45 years. All the observed incidence of ALS in young Gulf War veterans exceeded the expected, suggesting a war-related environmental trigger (44).

1.9 THERAPEUTIC APPROACHES

The treatment of ALS is hampered by a lack of drugs that intervene in the pathogenic mechanism of disorder. Therapeutic options for amyotrophic lateral sclerosis remain limited: only one treatment that tickles the causes and disease mechanism, the antiglutamate drug, Riluzole, is available, which probably exert its effect trough the blocking of the glutamate activity (45). It is a benzhotiazole derivative with complex effects on glutamate neurotransmission including inhibition of pre-synaptic glutamate release. Until the advent of Riluzole, there was no recognized, effective treatment (46). For the treatment of emotional lability due to pseudobulbar syndromes can be used agents that exert their effect through serotoninergic mechanism. Stem cell transplantation might represent actually a promising therapeutic strategy: Mazzini et colleagues in a recent study on 9 patients observed a significant slowing down of the linear decline of the forced vital capacity and of the ALS-FRS score. This results may suggest that MSCs represent a good chance for stem cell cell-based therapy in ALS and that intraspinal injection of MSCs is safe also in the long term. (47).

In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS: cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, drooling and muscle relaxation; (48,49). Marijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival.

The purpose of the vast majority of other possible medical intervention is to maintain or to improve function and well-being, and consequently to have a positive impact upon quality of life. The centrality of quality of life as an outcome measure is highlighted developments in pharmaceutical industry that suggest for the first time a feasible treatment for the disease.

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1. AN OBSERVATIONAL STUDY OF NEUROPSYCHOLOGICAL IMPAIRMENT IN MND/ALS

2.1 NEUROPSYCHOLOGICAL FEATURES IN MND/ALS

Although the causes of Motor neuron disease / Amyotrophic lateral sclerosis are not well understood, recent studies support the view that ALS/MND is a complex genetic disorder (1). Studies on ALS suggest that are structural and pathological changes that extend beyond motor neurons and that some changes correlate with cognitive dysfunction (2). A number of studies have demonstrated impairments in cognitive functioning in MND/ALS, but the prevalence and types of cognitive impairment reported in association with ALS appear to vary greatly. Massman and colleagues (3), in a study on 146 patients, indicated that 36% of them had clinical significant cognitive impairment. More recent studies have described some degree of impairment in 55 to 75% of patients with ALS (4,5). Cognitive impairment has been also demonstrated in a substantial proportion of non-demented patients with ALS (6). Bulbar onset ALS patients performances are reported as consistently poorer in many cognitive tests than spinal-onset (7,21). Ringholz and colleagues (8) underwent comprehensive neuropsychological evaluation on 279 ALS patients. This latter study, that represents the largest study on MND neuropsychological profile nowadays investigated, reported the presence of cognitive impairment in 50% of patients. The frequency of severe cognitive impairment in MND was about 1 to 5% (9-13). Nowadays is well established that MND dementia is characterized by a specific pattern of symptoms developing in a certain sequence in time (14), that most MND patients have mild cognitive impairment with subtle to severe executive deficits, and that 5% have a clinical subtypes of frontotemporal lobar degeneration called frontotemporal dementia (FTLD) (15,16). FTLD, which was originally described as a Pick's disease, is the second most common cause of progressive cognitive impairment after Alzheimer's disease. The three forms of FTLD were described by consensus criteria in 1998 by Neary (17) (Tab I). The form most frequently described is in patients with ALS is frontal variant frontotemporal dementia (fvFTD); the other

two forms are non-fluent progressive aphasia, which is characterized by language impairment, and semantic dementia, which is characterized by loss of conceptual knowledge (18). Although there is a clear link between some forms of ALS and frontotemporal dementia, the frequency, severity, and progression of cognitive impairment in otherwise classic ALS remain unclear. The most consistently reported cognitive changes in ALS relate to dysfunction of the components of the executive systems (eg, verbal fluency and attention), whereas abnormalities in memory and language are less well characterized. Table II summarises some of these findings and most representative ALS study results.

Table I. Variants of frontotemporal lobar dementia

	Neuropathological topography	Cognitive symptoms	Behavioural changes	Neurological findings
Frontal variant of frontotemporal dementia	Frontal atrophy more severe than temporal atrophy. Particularly affected: right dorsolateral and prefrontal cortex, and left premotor cortex	Executive dysfunctions (eg, verbal fluency and attention)	Distractibility, disunhibition, decline in personal hygene, hyperorality, perseveration, apathy, and submissiveness	Frontal release signs and primitive reflexes, motor neuron disease, and possible extrapyramidal features (PSP or CBD)
Non-fluent progressive aphasia	Asymmetric atrophy of left emisphere. Particularly affected: left frontal, insular, anterior parietal, superior temporal, and perysilvian cortex	A disorder of expressive language. Non-fluent spontaneous speech with agrammatism, phonemic paraphasias and anomia. Impaired executive function and working memory	Behavioural changes typically seen late in the course of this illness. Possible social withdraval and depression	Sopranuclear gaze disturbance, axial rigidity, alien limb, and focal dystonias
Semantic dementia	Temporal atrophy more severe than frontal atrophy. Particularly affected: insula, amygdala, and anterior hyppocampus	Impaired understanding of word meaning and object identity, fluent but empty spontaneous speech, semantic paraphasias, long term memory loss, and perceptual disorders (eg, prosopoagnosia, associative agnosia, or both)	Emothional withdraval, depression, rigidity and compulsions	Neurological findings emerge late in the course of this illness

PSP= progressive sopranuclear palsy; CBD= corticobasal degeneration;

Modified from: Phukan et al; *Lancet Neurol* 2007

Table II : ALS/MND neuropsychological tests performance in past literature

	Patients (n)	Neuropsychological test performance that showed impairment	Neuropsychological test performance in the normal range
Gallassi, 1985 (26)	22	Verbal fluency, verbal reasoning, visual attention, short term verbal memory, short term visual recall	Long term verbal memory, memory spans (verbal and spatial)
David, 1986 (25)	14	Set shifting (WCST), episodic memory, picture recall	Attention (digit span), visual recall, prose recall
Neary, 1990 (46)	4	Verbal fluency (letter and category) set shifting (WCST), intelligence (WAIS-R), interpretation of proverbs, episodic memory	Visuoperception, Intelligence, memory, delayed verbal recall
Kew,1993;Kew, 1993 (28;29)	12;16	Verbal fluency (written), free picture recall, recall memory	operceptual battery, set shifting (WCST),
Ludolph, 1992 (20)	18	Verbal fluency	Set shifting (WCST), cognitive inhibition (Stroop), visual recall, attention (digit span), naming, visual concentration
Massmann, 1996 (3)	146	Verbal fluency, immediate free recall, continuous recognition memomry test, Stroop negative priming	Delayed verbal recognition memory, visuoperception, confrontation naming
Abrahahms, 1997 (21)	52	Verbal fluency (written), executive function and intrinsic generation (noted in pseudobulbar palsy only), planning and working memory, set shifting (WCST), word recognition memory test, Stroop negative priming (trend towards significance)	Episodic memory, recall memory
Rakowicz, 1998 (30)	18	Verbal fluency, attention (reverse digit span), conceptual semantic processing, syntatctic comprehension, MMSE, confrontation naming	Attention (forward digit span), picture naming, word picture matching
Moretti, 2002 (47)	14	Verbal fluency (letter), set shifting (WCST), cognitive inhibition (Stroop) , attention (PASAT), interpretation of proverbs, bilingual, aphasia test, MMSE	Intellectual ability (WAIS-R), attention (digit span), story retrieval, past events retrieval, visuoperception
Shreiber , 2005 (7)	52	Verbal fluency, total and perseverative scores of WCST	Visuoperceptual functions
Abrahahms, 2005 (38)	20	Verbal fluency (written and spoken), computerised sentence-completion task	Confrontation naming, fluency, attention (PASAT, letter span), set shifting (WCST), episodic memory, recognition memory test, recall memory, visuoperception, object decision, position discrimination
Ringholz, 2005 (8)	279	Verbal fluency, visual recall, logical memory, confrontation naming	Visuoperceptual ability (Benton facial recognition test), fluency (category and design), attention (PASAT, letter span), MMSE (excepted severerly impaired patients), cognitive inhibition (Stroop)

WCST= Wisconsin Card Sorting Test; PASAT= paced auditory serial addition test; MMSE = Mini Mental State Examination; WAIS-R=Wechsler Adult Intelligence Scale Revised

2.1.1 Executive function

Executive functions are traditionally thought of as higher-level mental process that control and organise other cognitive process (19). They are a heterogeneous set of a skills that facilitate problem solving and responses to novelty. Executive functions are also implicated in behavioural regulation, response initiation, motivation, and elements of memory functioning. Impaired verbal fluency, a sensitive indicator of damage to frontal or striatofrontal areas that are involved in intrinsic initiation of responses, has been reported in almost all studies of cognitive impairment in ALS (20-22). Both letter fluency than category fluency, which require rapid generation of words, can be disturbed. Simultaneous effect on both type of fluency implicate dysfunction in component of the executive system, whereas disappropriate reduction in category fluency would suggest broader semantic impairment. Tests of verbal fluency are sensitive, but they depend on verbal or written responses and the results can be confounded by motor impairments in ALS. However, modifications to control of the speed of response can allow patients with upper limb disabilities, and consequent writing disabilities, to be assess meaningfully. Abrahams and colleagues (23) calculated a verbal fluency index using the times patients took to copy words thy had written previously in fluency tests (the average time taken to think to each word was estimated as the total time allowed for the tests minus the time taken to copy all word generated). Although deficiencies in verbal fluency are commonly believed to result from executive dysfunction, true language dysfunction might also contribute to deficit in verbal fluency in ALS. A functional MRI study lead by Abrahams et al (24) has shown normal activation of the inferior frontal gyrus and Broca's area during verbal fluency and naming tasks in patients who have sporadic ALS without aphasia or dementia. Cerebral structures involved in language seemed to be affected before naming deficits had become clinically significant. Further investigations of the executive systems are needed to identify clearly the nature and range of deficits in patients who have sporadic ALS without aphasia and dementia. David and Gillham (25) and Gallasi (26) and colleagues have reported impaired executive function in patients with ALS using the

Wisconsin Card Sorting Test (WCST), an established measure of rule shifting and mental flexibility, but this finding has not be confirmed in further studies (27, 28). Impairments in the attentional systems are often associated with damage to the frontal lobes, and attention deficits have been reported in ALS (3, 21). Evaluation of attention is important, because disinhibited-type patients might have near-normal results in traditional tests of frontal executive functions but show impaired responses in tests of selective attention. Rakowitcz and Hodges (30) reported a consistent and significant reduction in reverse digit span test, patients must repeat strings of number forwards and backwards, and these sequences become progressively more difficult until nine digits read aloud. Poor reverse digit span often indicates impaired working memory rather than pure attentional impairments.

2.1.2 Memory

There has been disagreement about memory deficits in ALS. Studies of cognition have shown that memory impairments in patients with ALS usually involve immediate recall. Deficits in delayed recall are highly variable, which suggests that the abnormality lies in the encoding of the information rather than in the speed of forgetting (14). These results are consistent with current theories that encoding is an executive component of memory and involves a neuronal circuit that arises in the left frontal lobe (31). Anyway, not all authors have interpreted memory failures in terms of frontal lobe dysfunction. Impairements in delayed recall, were assumed by some authors (32) to reflect medial temporal lobe pathology, on the basis of the established role of the medial temporal lobes in recall of learned informations. Moreover, the impairment of the central executive system contribute to disturbance on tests of memory and new learning which invariably occur.

2.1.3 Language

Language networks seems to be impaired in MRI and PET studies of ALS patients (23), which lends support to the aforementioned findings that ALS affects extramotor pathways. Language deficits noted in studies of ALS have included reduced verbal output (33,34), deficits in naming of objects (3,21,42), perseveration, echolalia (repetition of words said by other people), stereotypic expression (30) and semantic paraphasias (substitution of words that relate closely to one other, eg, sock for glove) (30,33). Patients with ALS can have features of progressive non-fluent aphasia, semantic dementia that is often atypical, or both (35-37). Rakowicz and Hodges (30) reported significant language deficits in patients with ALS and dementia, particularly on tests of naming and syntactic comprehension. Patients with ALS who did not have dementia have a language output disorder characterised by difficulties with word findings and naming, with a tendency to make category coordinate semantic errors or circomloctions. Both groups performed well on tests of non verbal-semantic knowledge and grammar. Naming deficits have been reported in other studies of ALS (3, 21, 38), which suggests that a language dysfunctions underlies basic word –finding processes. However, in some patients, confrontation naming ability is intact (29, 22). Processing of verbs has been reported to be greater than that of nouns in patients that have primary progressive aphasia (39) or ALS with dementia (34). Hillis and colleagues (2004) suggest that such differences in the patterns of language deterioration might relate to degeneration of different brain areas, which implicates the posterior inferior frontal cortex and insula and motor speech and naming actions. Results from other studies have suggested that language deficits such as progressive slowing of words retrieval form a continuum with aphasia in ALS (14,21,30). The possibility that deficits in executive functions, such as verbal fluency, are related to language deficits needs to be explored further. Whether aphasia in patients with ALS is an early stage of an aphasic type is unclear. Another possibility is that language deficits occur independently of cognitive impairment, and that patients with such deficits have distinct subtype of ALS-related dementia.

2.1.4 Visuoperceptual function

Visuoperceptual functions are heterogeneous set of process that include attention, object identification, and object recognition. Visuoperceptual processes are largely preserved in many patients with MND (40-42), but Strong and colleagues (1999) have noted some visuopreceptual deficits. It is reported that ALS patients with frontotemporal dementia often have little difficulty in navigation around their own home environment, in location of objects, in coping of non-representational hand postures, and in identification of their home town on a map (43).

2.2 STUDY PORPUSES

The ability of neuropsychological tests to identify cognitive impairment in MND in its mildest ‘subliclinical’ forms suggests an important role of neuropsychology in the early detection of cognitive impairment and dementia. The aims of the study were to conduct a neuropsychological investigation on MND to determine:

1) the incidence of dementia in our MND sample

2) the incidence of mild cognitive impairment in our MND sample (according to criteria explained in ‘diagnostic procedure’, paragraph 2.3.4)

3) differences in cognitive performance in bulbar vs spinal onset in MND patients

4) which are cognitive functions more impaired in MND and which are the most adequate tests to investigate them.

With regard to this latter point, it appear as a necessity to individuate clinical neuropsychological test sensitive to MND impairments that can contemporarily be available in most of neurological departments. In fact, even with moderate motor impairment, the assessment of the accompanying cognitive impairment in MND is a difficult problem.

2.3 METHODS AND MATERIALS

2.3.1 Setting and participants

Between February 2005 and March 2008, 128 MND patients (89M, 39F; mean age: 58.96, sd=12.6) were consecutively recruited from Motor Neuron Disease Centre of Padova, Department of Neurosciences. Thirty-two of these patients (20M, 12F) showed a bulbar onset, 96 (69M, 27F) a spinal-onset of the disease. Inclusion criteria were history and neurological examination findings consistent with motor neuron disease in patients older than 20 years, supplemented by confirmatory electromygraphic findings. Neurological examination established that all participants fulfilled the El Escorial criteria for 'possible', 'probable' or 'definite' MND (44). We excluded individuals with sensory abnormalities, results of nerve conduction studies suggestive of neuropathy, and serious concomitant conditions, including stroke, severe depression, and other psychiatric disease. Patients with a ALS family history of neurodegenerative disease were eligible for inclusion. All participants were Italian speaking. Informed consent was obtained from all patients, and institutional review board was obtained for the protocol. Controls were obtained from surgery department of Aosta, between March 2007 until March 2008 and were matched 1:1 to patients with MND for age, sex and education level. Controls with concomitant conditions that may affect test performance (eg, stroke, depression, and other psychiatric disease) were excluded before sampling. Participants characteristics are presented in Table III.

2.3.2 Data collection

Subjects with marked bulbar symptoms were unable to complete the comprehensive neuropsychological battery, as well as patients unable to move dominant superior art. The neuropsychological exam took an average of 1.5 hours to complete. All the information was collected in a standardized manner and entered into a database at the time of clinical evaluation. The comprehensive neuropsychological battery was administered exclusively to subjects who were perfectly able to speak and to write.

Table III: PARTICIPANTS CHARACTERISTICS

	MND (n=128)	Controls (n=113)	Significant (p<0.05)
Age (SD)	58.96(12.6)	57.76 (14.46)	no
Males (n)	89	83	no
Educational Level (years)(SD)	9.22	10.29 (4.93)	no
Bulbar (n)	32		
Mean ALSFRS-R (SD)	34.59 (3.3)		
Mean MRC upper (SD)	39.3 (6.65)		
Mean MRC lower (SD)	30.26 (9.63)		
Forced Vital Capacity (SD)	84.58 (27.2)		
Time since diagnosis in months (SD)	40.95 (18.6)		

SD =Standard Deviation. FVC: Forced Vital Capacity. ALSFRS-R: Amyotrophic Lateral Sclerosis functional Rating Scale Revised. MRC upper and lower= Medical Research Council scale applied to upper districts (maximum score=50) and applied to lower districts(maximum score=40)

2.3.3 Diagnostic Evaluations and employed measures

Clinical interview included inquiry into the approximate date and location of symptom onset, the nature of the first symptoms, clinical features, and medical and family history. Clinical and laboratory evaluations, such as biopsy hystochemical analysis, were performed by two neuromuscular specialists.

The *Amyotrophic lateral Sclerosis Functional Rating Scale Revised* (ALSFRS-R) was employed to assess physical functionality (45). *Medical Research Council* (MRC) scale was used to evaluate patients motor disability we used the measure of muscle strength by the limb muscles (score from 0, absence of movement to 5, full strength). Muscles evaluated were: deltoids, triceps and biceps brachii, finger extensor, thumb adductor, thigh flexor, knee extensor, ankle extensor and flexor. We considered the total MRC score (megascore) of both upper and lower limbs which respectively ranged from 0 to 50 and from 0 to 40. *Forced vital capacity* (FVC) was assessed by a standard manual spirometer (CYTEC 60) and expressed as a percentage of the expected value. Neuropsychological assessment focused on

cognitive domains considered to represent prefrontal (executive) functions and temporal lobe (memory) functions as well as attentional control. The test battery included the investigation of the following functions, with well-known individual tests:

2.3.3.1 General Screening

- *Mini Mental State Examination (MMSE)* (48): it was employed to assess general mental status. Although insensitive to frontal dysfunction, the MMSE is used routinely both clinically and in research. It is rapid to administer and gives a single score out of 30, weighted in favour of orientation. A score <24 30 is generally taken to indicating dementia.

2.3.3.2 Intelligence

- *Brief Intelligence Test (TIB)*(49) *:* it is the Italian version of NART (National Adult Reading Test), the purpose of the test is to provide an estimate of premorbid intellectual ability. It is a reading test of 50 irregularly spelled words, assuming that the patient is familiar with the word, accuracy of pronunciation is used to predict QI.
- *Coloured Raven's Progressive Matrices (CRPM)* (50): it is used to assess reasoning in the visual modality, and it was also selected because it is less vulnerable to the effects of physical disability. The tests consists of 36 items, grouped into three sets (A, Ab, B). Set A consists of problems in the forms of the continuous patterns. As one progresses in the set, the items are increasingly perceptual difficulty. Items in the Ab and the B series are made up four elements or parts, three of which are given and done to be selected among the response alternatives. There is a gradual shift trough the Ab and b sets from four parts, which form a coherent whole or gestalt to problems in which each part is a symbol in an analogies test and there is no perceptual gestalt per se. The number of correctly matched items was used as the measure.

2.3.3.3 Executive functions and attention

- *Trail Making Test (TMT)* (51): the TMT is a measure of attention, speed, and mental flexibility. Hartikonen and colleagues (52) showed the importance of this test to investigate cognitive impairment in ALS. It requires the subject to connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in proper order (part A) and 25 encircled numbers and letters in alternating order (part B). Participants who not completed part B in 5 min (300 sec) are assigned a time of 301. Scoring is expressed in terms of the time in seconds required for completion of each of the two parts of the test. Because of the difference in cognitive tests demands between part A and part B, we calculated also derived scores : the Trails B - Trails A difference score, as introduced by Lamberty (53).
- *Modified Wisconsin Card Sorting Test (MWCST)* (54): the purpose of this test is to assess the ability to form abstract concepts, to shift and maintain set, and to utilize feedback. Impairment in MND have been highlight thanks to this measure in some studies (3, 5, 21, 25), but not in others (20, 27, 29). This test consists of four stimuli cards, placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses and the fourth with the four blue circles on them. The examiner instructs the subject to place each response cards in piles below one of the four stimulus key cards, wherever he or she thinks it should go, and it is told that experimenter will then inform him or her whether the choice is right or wrong. Because standard version includes some ambiguous stimuli that can be classed according the more than one category, we used Nelson's version, a modified version without the response cards that share more than one attribute with the stimulus cards, thus eliminating ambiguity. Performance can be scored in a number of ways: we took under consideration numbers of completed categories, percent of errors and percent of perseverative errors.

- *Spoken Verbal Fluency Test:* tests of verbal fluency have been traditionally employed in clinical setting to measure executive dysfunctions. Test of verbal fluency is reported in literature as the most sensitive to detect the impairment of ALS patients (3, 4, 5, 22, 55). Two versions of the verbal fluency test were used: 1)letter fluency in which subjects were asked to produce as many novel words as possible, excluding proper names, within one minute beginning with a given letter (F, A, S). 2) Category fluency in which subjects are asked to generate words from given categories -in this case animals, fruits and cars. To exclude the effect of dysarthria on verbal fluency, both phonemic than semantic, patients were asked to read aloud all the words generated during the task as quickly as possible and the examiner recorded the time taken to perform this phase, called *control condition*. The control condition was conducted following a delay, as to provide a rest for patients. The difference between the specified time for the generation condition and the time taken for the control condition, the fluency index (*fi*) was calculated according to guidelines of Abrahams et al.(*Neuropsychologia*, 38:734-747, 2000) as mentioned in the introduction of this chapter. It consists in the following formula:

$$fi = \frac{\textit{time for items generation} - \textit{time for control condition}}{\textit{total numbers of items generated}}$$

- *Written verbal fluency test:* it is reported as particularly sensitive to detect impairment in ALS, as well as spoken verbal fluency (21, 23, 29). It is an Abraham's and colleagues adaptation (23) of Thurstone's world fluency test. During the generation condition the participant was required to write as many words as possible beginning with the letter M in 5 min and with four-letter words beginning with letter C in 4 min. Following a delay the participant conducted the control condition from which a written verbal fluency index was calculated, in the manner of verbal fluency index (see above).

2.3.3.4 Memory

- *Digit Span*: it is a traditional measure to assess verbal short-term memory: Gallassi and colleagues (55) found significant results to detect cognitive impairment in MND also in this test. So, forward and reverse digit span were assessed to investigate selective verbal attention according to standardised methods from the Wechsler Adult Intelligence Scale (56). The subject is asked to repeat strings of digit increasing length said by the examiner in the same (forward) and in reverse (backward) order. The highest direct or reverse span achieved was used as the measure.
- *Corsi Blocks tapping Test*: it represent gold standard measure to detect visuo-spatial short term memory, it is employed in the assessment of the capacity of the visual short-term memory and of the implicit visual-spatial learning. The theoretical background is characterized by Baddeley's concept of the working memory. The examiner displays 9 randomly positioned dice and with his/her hand points on a certain number of these dice. The respondent is then asked to point at the dice in the same order.
- *Words Span test*: it is a sequence of between two and eight bisillabic words that are read to participants. It reflects analogous functions than traditional digit span: we introduced this variant to detect eventually differences between number and words short-term memory.
- *Prose Memory Test (Logical memory)* (51): It involves free recall following auditory presentation of a short prose story and is considered a measure of verbal memory. Such prose stories are considered to have increased ecological validity compared to other memory measures. It consists in listening to a short prose passage and recalling its elements immediately and after 10 minutes. An impairment in prose recall was yet reported in some previous studies (32) but not in the others (52, 25).
- *Serial position curve test* (51): this test reflects the free recall of the serial presentation of the items as a function of each items position in a item list. The curve was dived into two positions: recency, which refers to the enhanced recall of the last few items on the list, and the primacy, which

refers to the enhanced recall of the first few items of the list. It is documented that there is a great disparity between performance of MND/ALS patients and normal controls in the immediate recall rather than delayed recall condition. So distinguish between recency and prmacy effect it was considered to be interesting with this measure.

2.3.3.5 Language

- *Token Test* (51): This test is employed to assess comprehension of verbal commands of increasing complexity. It uses 20 plastic tokens in five colours (red, white, yellow, blue and green) two sizes (small and large) and two shapes (circles and squares) arranged in a fix order in front of the patient. Several studies have demonstrated impaired performance on language tasks, such as sentence comprehension (27, 37) in MND patients.
- *Boston Naming Test* (57): The purpose of the test is to assess visual naming ability using 60 black and white drawings of common objects. Scores include the number of produced spontaneously correct responses, the numbers of cues requested in terms of semantic cueing and phonemic cueing, that are given if patient is not able to individuate correct response after semantic cueing. The total correct is the sum of the number of spontaneously given correct responses.

2.3.3.6 Visuospatial function

- *Rey-Osterrieth Complex Figure Test* (58): the purpose of this test is to assess visuo-spatial constructional ability and visual memory. The traditional measure of performance include a copy score (which reflects the accuracy of the original copy) and the time required to copy the figure, and 3 min delayed recall scores (which assess the amount of information retained over time). For our study we took under consideration only accuracy scores because of motor impairment of some patients.

2.3.4 Diagnostic Procedure

The diagnosis of MND was made at the time of clinical evaluation by experienced neuromuscular specialists conforming to El Escorial criteria (44). Because no measure of functional limitation due to cognitive impairment was available (thus precluding *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (59), diagnosis of dementia, which requires impairments in social or occupational functioning), we operationally defined dementia on the basis of neuropsychological testing, as has been described previously. This approach has previously been shown to reliably correlate with physician diagnosis of dementia (60), especially in a well educated sample such as in the study group. The neuropsychological paradigm considers memory impairment to be the key defining feature of dementia and defines memory impairment as impairment into two or three memory domains (short and long term verbal memory, and short and long term non verbal memory). So, a diagnosis of dementia was given to individuals who exhibited memory dysfunction and impaired performances in at least two additional domains (executive functioning, attention, language, or visuo-spatial ability). Fronto-temporal lobar dementia diagnosis was attribute according to Neary's criteria (17). Individuals characterized as mildly impaired exhibited impaired neuropsychological test performance insufficient for a diagnosis of dementia, defined as scoring below criterion levels on two or more individuals tests. We also observed cognitive performance according to MMSE results: cutting scores based on MMSE was considered as intact if < 27 ; mild impairment if included between 25 - 27; moderate to severe impairment was defined as <= 25.

2.3.5 Statistical analysis

All analyses were performed using the psychometric package as provided in the R language and environment for statistical computing -R Development Core Team, 2005- (61).

Differences in parametrically distributed variables between subjects and controls groups were analyzed using Student's *t* test for unpaired variables. Non-parametrically distributed variables were analyzed using the Mann-Witney U Test. Significance was defined as a p value of < 0.01.

2.4 RESULTS

2.4.1 Overall Data

The population under study consisted in 128 MND patients with mean age as 58.9 (sd=12.6); 69% were men; 96 had limb onset, and 32 had bulbar onset. The mean education was, in years, 9.22; MMSE mean score was 27.51 (sd= 2.5) and the mean scale of premorbid IQ was 106.7 (sd= 8). ALSFRS-R mean total score was 34.6 (sd=8.12), which is in the mild to moderately impaired range. More detailed data are shown in Table III. Both groups were highly comparable with respect to age, gender, and years of education. With regard to neuropsychological diagnoses, 73 (57%) patients were intact; 42 patients (32%) had cognitive impairment but did not meet criteria for dementia. As noted above, these individuals were classified as mildly impaired. twelve patients (9.4%) were diagnosed with dementia: out of them, 9 (7%) met traditional criteria of FTD, as described by Neary (1998). Global cognitive function as judged by MMSE on 81 patients (all the patients able both to speak than to write) showed 12 patients with score lower than 25 (representing moderate to severe impairment); 20 patients reached a score between 25 to 27 (representing a mild impairment) and 49 patients appeared as intact (MMSE score > 27). Comparisons were made between the patients and the control group; general results are discussed below and are reported in Table III.

2.4.1.1. General Screening

The differences in performance of the patient group on the mini mental state examination reached significance at $p<0.01$ level: mean scores revealed a better performance in patients than controls.

2.4.1.2 Intelligence

On measures of intellectual function there were no significant differences between the groups in premorbid full IQ, as estimated by the TIB, and the

Raven's CPM score (p>0.01). However, we observed a trend toward impairment in this latter performance in patients respect of controls, that did jnot reach statistic significance.

2.4.1.3 Executive functions and attention

Trail making test A, B and A-B performances of MND patients were compared with controls: no significant differences were found between the two groups. Also numbers of errors made in A and B tasks were compared and no significant differences were observed.

Wisconsin card sorting test performance presented a significant different mean scores, qualitatively better in patients than controls, for number of categories individuated (U=657.5, p=0.000), number of errors (U=1556.5.5, p=0.000), and percentage of perseverative errors on total number of errors (U=1469.5, p=0.005).

The analyses of the numbers of words generated both in semantic (animals, fruits, vehicles) than in phonemic (F.A.S.) spoken verbal fluency task revealed significant differences between patients and controls (respectively U=2075.5, p=0.002 and U=2143.5, p=0.000). Spoken verbal fluency index, both in semantic than in phonemic tasks, revealed as well as significant better performance in patients than in controls (respectively U=2235.5, p=0.000; U=1941.5, p=0.000). These results indicate that the inclusion of control condition, which corrects for motor speed disabilities, can confirm the deficit of MND patients, that appear as independent of bulbar impairment.

The analysis of the written verbal fluency test word generation ('C' and 'M') revealed, similarly, a significant difference between patients and control (respectively U=1469.5, p=0.005 and U=1469.5, p=0.005). Written verbal fluency indices, both for 'C' and 'M' , were significantly different (respectively U=1227.5 with p=0.000 and U=1278.5, p=0.000): on average the patient group revealed a slowdown to think of the words than the control group. These results indicate that the inclusion of the control condition and the subsequent analyses of the written

fluency indices confirmed a performance decrement independently of variation in speed of writing.

2.4.1.4 Memory

There was a significant difference on Digit Span, both forward (U=2208.5, p=0.001), than backward (U=1263.5, p=0.000), in patients group compared to controls. Mean group scores on visuo-spatial short-term memory, assessed with Corsi Blocks tapping Task, prose memory test, assessed with Logical Memory test, words span, assessed with bisillabic words, primacy and recency effect assessed with positional serial curve, appeared not significantly different from controls (p>0.001).

2.4.1.5 Language

Neuropsychological assessment did not show significant differences in mean score of syntactic comprehension, assessed with Token Test (p>0.001), nor in semantic denomination on visual presentation, assessed with Boston Naming Test (p>0.001): nevertheless, a trend toward impairment was found in this latter test, although it did not reach statistical significance. There were no significant differences between patients and controls neither in numbers of requested semantic and phonemic cues (p>0.001).

2.4.1.6 Visuoperceptual function

The mean scores of visuoconstructional abilities assessed with Rey-Osterreith complex figure (copy and re-call) did not differ between patients and controls.

2.4.2 Relation between cognitive dysfunction and pseudobulbar palsy

Patients subgroup with limb-onset disease and subgroup with bulbar-onset disease were very comparable with respect to age, gender, level education and premorbid IQ, but not in number of subjects, because patients with bulbar onset were sensitively fewer.

Patients with bulbar vs limb onset MND were not sostantially different in either level of impairment and pattern of performance, with the exception of Trail making test A, in terms of time employed ($U=407.5$, $p=0.009$). The analyses of the numbers of the spontaneous correct responses in Boston Naming Test revealed a trend effect of deterioration in denomination ability on visual presentation in bulbar-onset respect to limb-onset patients ($U= 114$, $p=0.023$): however, it did not reach statistical significance.

Table IV: Mean Neuropsychological scores in MND patients and controls

	Patient's score mean (SD) n=128	Controls Mean (SD) *n=98*	Mann-Witney U coefficient	P Value
General Screening				
MMSE	**22.26 (1.77) *n=93***	**28.51(1.79) *n=98***	**1491.5**	**0.002**
Intelligence				
TIB	106.7 (5.6) *n=60*	108.67 (4.9) *n=60*	659	0.742
Rs CPM	28.41 (5) *n=120*	31.91 (2.9) *n*=98	2260	0.023
Executive function/Attention				
Trail Making Test A	56.88 (40.4) *n=77*	44.88 (22) *n=70*	2227	0.051
Trail Making Test A errors	0.22 (0.7) *n=77*	0.11 (0) *n=70*	1968	0.174
Trail Making Test B	120.35 (55.8) *n=77*	102.16 (38.50) *n=70*	1687	0.038
Trail Making Test B errors	0.66 (0.9) *n=77*	0.33 (1.4) *n=70*	1617.5	0.049
Trail Making Test A-B	80.7 (57.2) *n=77*	77.2 (80.7) *n=70*	1687	0.038
WCST (n categories)	**3.92 (1.7) *n=55***	**4.41 (1.5) *n= 60***	**657.5**	**0.000**
WCST (errors)	**16.67 (12.4) *n=55***	**13.37 (8.3) *n= 60***	**1556.5**	**0.000**
WCST (% perseverations)	**52.4 (13) *n=55***	**39.8 (7.5) *n= 60***	**1469**	**0.005**
Spoken Semantic Fluency	**38.56 (12.28) *n=103***	**44.54 (12.1) *n= 100***	**2075.5**	**0.002**
Spoken Semantic Index (*SSfi*)	**4.04 (2.4) *n=84***	**2,15 (1,4) *n= 100***	**2235.5**	**0.000**
Spoken Phonemic Fluency	**27.7 (11.2) *n=103***	**35.15 (13.4) *n= 100***	**2143.5**	**0.000**
Spoken Phonemic Index (S*Pfi*)	**6.48 (4.7) *n=83***	**2.77 (1.96) *n= 100***	**1941.5**	**0.000**
Written verbal fluency "C"	**8.85 (5.9) *n=48***	**15.63 (5.9) *n = 48***	**3323.5**	**0.000**
Written verbal fluency Index (WVfi) "C"	**32.51 (12.9) *n=48***	**13.04 (5.6) *n=48***	**1227.5**	**0.000**
Written verbal fluency "M"	**22.75 (11.2) *n=48***	**36.24 (12.3) *n = 48***	**323**	**0.005**
Written verbal fluencyIndex (WVfi) "M"	**13.45 (11) *n=48***	**6.80 (3.1) *n=48***	**1278.5**	**0.000**
Memory				
Digit span forward	**5.43 (0.91) *n=102***	**5.94 (1.6) *n=100***	**2208.5**	**0.001**
Digit span backward	**3.16 (0,9) *n=102***	**3.72 (1.4) *n=100***	**1263.5**	**0.000**
Words span	4.47 (0,8) *n=100*	4.6 (0.9) *n=100*	1388	0.537
Corsi Blocks Tapping Test	5.13 (0,9) *n=80*	5.39 (1.3) *n=80*	2458.5	0.129
Prose	11.15 (2,4) *n=93*	10.1 (2.4) *n=93*	2527	0.351
Primacy effect	4.89 (1.9) *n=30*	4.41 (2.1) *n=30*	847	0.292
Recency effect	13.84 (2) *n=30*	17.58 (2.3) *n=30*	714	0.052
Language				
Token Test	4.18 (5.3) *n=25*	2.18 (4.3) *n=23*	345.5	0.136
Boston Naming Test (n. errors)	4.45(4.9) *n=36*	3.01(1.2) *n=36*	663	0.023
Boston Naming Test semantic cues	1.71(0.4) *n=36*	1.54 (0.3) *n=36*	798	0.4164
Boston Naming Test phonemic cues	3.28(1.7) *n=36*	2.44 (0.9) *n=36*	715	0.051
Visuospatial function				
Rey copy	30.97 (4.92) *n=25*	32.58 (0.7) *n=25*	207	0.221
Rey memory	12(6.7) *n=25*	14.3 (8.2) *n=25*	322	0.215

p<0.01 is highlighted in bold;
MMSE=Mini Mental State Examination; RsCPM=Raven's Coloured Matrices; TIB=Brief Intelligence Test; WCST=Wisconsin Cards Sorting Test Modified Version (Nelson)

Table V: Mean Neuropsychological scores in MND patients with limb-onset and bulbar onset disease

	Limb patient's score mean (SD)	Bulabr patients score mean mean (SD) *n=32*	Significant (P<0.01)
General Screening			
MMSE	27.71 (2.26) *n=70*	26.91(1.79) *n=23*	n.s.
Intelligence			
TIB	106.76 (9.89) *n=42*	106.28 (9.05) *n=18*	n.s.
Rs CPM	28.60 (4,54) *n=89*	27.82 (3.82) *n=29*	n.s.
Executive function/Attention			
Trail Making Test A	**51.76(20.92) *n=49***	**79.76(12.72)*n=28***	**P<0.01**
Trail Making Test A errors	0.26 (1.1)*n=49*	0.12 (0.11) *n=28*	n.s.
Trail Making Test B	116.74 (55.55) *n=49*	128.52 (56.94) *n=28*	n.s.
Trail Making Test B errors	0.83 (0.9) *n=49*	0.46 (1) *n=28*	n.s.
Trail Making Test A-B	82.28 (106.37) *n=24*	78.71 (60.23) *n=28*	n.s.
WCST (n categories)	3.97 (1.77) *n=38*	3.76 (1.32) *n=17*	n.s.
WCST (errors)	16.30 (13.75) *n=38*	17.92 (11.55) *n=17*	n..s
WCST (%perseverations)	49.16 (18.68) *n=38*	54.4 (14.91) *n=17*	n.s.
Spoken Semantic Fluency	38.60 (12.33) *n=85*	38.33 (11.15) *n=18*	n.s.
Spoken Semantic Index (*SSfi*)	3,92 (2,12) *n=70*	4,87 (13,58) *n=14*	n.s.
Spoken Phonemic Fluency	28.15 (11.16) *n=84*	25.8 (12.40) *n=18*	n.s.
Spoken Phonemic Index(S*Pfi*)	6.04 (2.50) *n=69*	8.42 (2.31) *n=14*	n.s.
Written verbal fluency "C"	9.63 (0.7) *n=26*	7.47 (4.83) *n=22*	n.s.
Written verbal fluency Index(WVfi) "C"	37.6 (15.7) *n=26*	51.57(60.6) *n = 22*	n.s.
Written verbal fluency "M"	25.14 (2.82) *n=26*	18.56 (9.04) *n=22*	n.s.
Written verbal fluencyIndex(WVfi) "M"	11.33 (12.24) *n=26*	18.74 (16.47) *n=22*	n.s.
Memory			
Digit span forward	5.47 (0.95) *n=81*	5.37 (0.75) *n=21*	n.s.
Digit span backward	3.15 (1.76) *n=81*	3.18 (0.2) *n=21*	n.s.
Bisillabic words span	4.47 (1.4) *n=79*	4.5 (0.83) *n=21*	n.s.
Corsi Blocks Tapping Test	5.18 (1.77) *n=50*	5.03 (0.93) *n=30*	n.s.
Prose	11.22 (3.3) *n=78*	10.91 (2.4) *n=15*	n.s.
Primacy effect	4.91(2.39) *n=19*	4.75 (1.7) *n=11*	n.s.
Recency effect	14 (4.54) *n=19*	12.5 (2.3) *n=11*	n.s.
Language			
Boston Naming Test	4.59 (2.94) *n=27*	3.2 (2.74) *n=9*	n.s.
Boston Naming Test sementic cues	0.95 (1.43) *n=27*	0 (0) *n=9*	n.s.
Boston Naming Test phonemic cues	3.47(2.81) n=27	2.83 (1.9) n=9	n.s.
Token Test	3.71(2.16) n=10	5.12 (2.29) n=15	n.s.
Visuospatial function			
Rey copy	32.6 (4.92) *n=15*	27.93 (2.19) *n=10*	n.s.
Rey memory	19(6.95) *n=15*	18.5 (8.4) *n=10*	n.s.

p<0.01 is highlighted in bold;
MMSE=Mini Mental State Examination; RsCPM=Raven's Coloured Matrices; TIB=Brief Intelligence Test; WCST=Wisconsin Cards Sorting Test Modified Version (Nelson)

2.5DISCUSSION

Prevalence and types of cognitive impairment and dementia reported in association with MND vary greatly, as mentioned in the 2.1 chapter. Despite that the majority of studies have focused on the overlap between MND/ALS and FTD (62), there are also descriptions of less severe cognitive impairment associated with MND, such as impairment of attention, working memory, verbal fluency, and other frontal executive functions (3,38,63). Clinical evidence that cognitive dysfunction in ALS forms a continuum, from mild impairment to frontotemporal lobar dementia (63) remains weak. Currently, the frequency of impaired cognitive functions in patients with MND cannot be established definitively, but formal mechanism to evaluate the significance of clinical findings are not in place. In order to better address the issues of prevalence and patterns of performance respect disease onset, we conducted detailed clinical and neuropsychological examinations on a large sample of patients tested across a wide range of cognitive dysfunctions. Other than to detect cognitive functions and decline in these patients, our aim was to put the basis for a formal and reproducible battery of neuropsychological tests in MND, using cognitive tests available in most of Neurology Department.

The findings of our study support the view that cognitive deficits hits more than 40% of our MND/ALS patients. Out of them, 12 patients (10%) appeared as clinically affected by generic dementia as described in DSM-IV (60), and 9 patients out of this smaller group presented typical FTD characteristics according to Neary's criteria (17).

Interestingly, MMSE, performed on all the MND patients able both to speak than to write, showed 12 patients with score lower than 25, representing moderate to severe impairment: the same patients were assessed as affect by clinical dementia according to DSM IV criteria. This data could support the importance of MMSE in a rapid screening to individuate eventually severe cognitive deficits, even if current literature is inclined to ascribe it to a quite insensitive diagnostic measure.

In our MND sample we observed functional executive impairment, working memory impairment and language deficits. In particular, were found as significantly impaired performance on MND patients respect to controls in modified Wisconsin card sorting test (which implicates abstract reasoning, concept generation and perseverative respondings), in spoken phonemic and semantic fluency, that underlines a selective deficit in spoken and verbal language (when speech and writing abilities were taken into account). Short term memory was also revealed as impaired: forward digit span, a measure of elementary attention or span of apprehension, and backward digit span, a measure of mental manipulation or control, both requiring working memory that, as observed in some previous studies (30,55) can be ascribed to prefrontal lobe functioning (64,65). A trend toward impairment in patients respect to controls was observed in naming task (Boston naming test) and recency effect in memory recal.Performance not significantly different respect to controls were found in attentional control (TMT A, B and A-B), words short-term memory, visuo-spatial short term memory, long-term memory, syntactic comprehension primacy effect in memory recall, visuoconstructional abilities and visuo-spatial recall (Rey complex figure). So, given that visuoperception function appear as spared in the great majority of our sample, the pattern of cognitive impairment can be viewed primarily but not exclusively as frontotemporal, although frontal impairment appear as prominent, as confirmed by current literature. This pattern of impairment appeared as consistent with dysfunction of the 'supervisory attentional system' (SAS) (66), attributed mainly to frontal lobe functioning. A disruption of the SAS, as observed by Abrahams (22), would results in dysfunction in the initiation of responses which are not externally cued, resulting in deficits in tasks as fluency procedures. As a strumental diagnostic confirm of this datum, Abrahams and colleagues (24) studied with a functional magnetic resonance the performance of MND sample group during a confrontation naming task, revealing abnormalities in regions associated with simple word retrieval and semantic processing, including inferior frontal gyrus and temporal cortex. Frontal lobe frequent impairment is supported also by a recent pathologic study of tau-positive neuronal and astrocytic inclusions in the frontal cortex of patients with

ALS. These inclusions were found to greater extent in those patients with cognitive impairment than in those who were cognitively intact. This suggests that patients with and without cognitive impairment represent a disease continuum (66). On the other hand, some memory functions, that can be ascribed to temporal function, appear as impaired or there is a trend to impairment, such as in recency effect. The role of temporal pathology in ALS remains controversial, since the reported alterations are non-specific, limitated to subgroups and difficult to distinguish from health-related changes. Moreover, it is widely accepted that the frontal lobes themselves plays an important role in memory processing. Consequently, memory functions may be affected by primary prefrontal dysfunction, and, vice versa, the degeneration of the temporo-limbic areas may exert a secondary influence on frontal lobe functioning. So, our large-scale study confirmed the presence of cognitive impaired in approximately 40% of patients with MND. Mild executive dysfunction typified by impairment of attention, short term memory, abstraction, and verbal fluency appeared as the most frequent features. Eight percent of them displayed typically FTD, as mentioned before. In particular, we confirm previous findings of predominant deficits of verbal and non-verbal fluency as well as set-shifting and attention (3,20,21,26,68).

In this study, patients with bulbar onset disease, were not significantly different from limb-onset patients in terms of their level of cognitive impairment. The sole exception is a motor task implicating sustained attention (Trail making test A): the analyses revealed a different, worse performance in patient with bulbar onset respect of limb onset, but the contribution of motor skills in this simple test remains unclear: even if we ruled out all patients ho had motor impairment in graphic performances, it can reflects the presence of initial delay due to muscular atrophy. In fact, this difference it was not statistically significant in A-B ratio, a more reliable index of attentional control, free from heterogeneous aspects of eventual mild motor disabilities. So, our general findings are consistent with the results of Ringholz' and Frank results (5,8), but differs from the results of other studies in which bulbar onset patients had greater cognitive dysfunctions: Many authors have commented on association between cognitive impairment and bulbar

disease in MND (15,21,33,35-37). Some studies specifically looking into this issue found a significant increase in cognitive dysfunction in patient with pseudobulbar palsy compared with those without, although both group were impaired (21). Formal statistical testing of our cohort failed to show such a correlation. The reason of this discrepancy is not completely clear. However, in our sample, patients with bulbar onset disease were the great minority than those with limb onset (32 vs 96), and that could have diminish statistical power. An other interpretation of our findings largely concurs with those of another Strong's findings (33): patients with bulbar onset have more rapid decline of cognitive abilities, a method for controlling for stage of disease will need to be employed before direct comparison of limb-onset and bulbar-onset patients can be made. However these and other authors observed that ALS subjects who were bulbar predominant at clinical presentation, or had bulbar onset, had relatively more cognitive impairment than their limb predominant subjects. Finally, we highlighted, from this extensive battery, the most common test, at least in Italy, in which MND patients have frequently failures: Wisconsin card sorting test, verbal and written fluency adapted to motor and bulbar skills, digit span forward and backward. These data are confirmed by other findings in literature, as mentioned in previous chapters. These test appear as consistant with suggested measures to evaluate cognitive deficit in ALS by second international Frontotemporal Dementia in ALS Research Conference (London, Ontario, june 2007): indeed, despite the current absence of consensus, identification of cognitive impairment in MND has been improved by the use of untimed neuropsychological tests, experimental adjustments to contro for slower motor speed, and use of recognition rather than free recall. The vantage of this selection is that these test are popular and easy to find them, and the adaptation for MND motor impairment are simple to applicate. On the other hand, the limit can be that these measures may be not so sophisticated to investigate subtle impairment in MND . To verify the sensitivity and practical value of our approach from extensive battery to few, selected tests to investigate rapidly MND cognitive impairment need more investigations.

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3. AN FMRI STUDY: LYMBIC INVOLVEMENT IN ALS

3.1 BEHAVIOURAL AN EMOTIONAL CHANGES IN ALS/MND

Emotional perceptual problems, specifically an inability to interpret emotional facial expressions and/or vocal intonations, can occur in many neurological disorders. It has been associated with vascular as well as neurodegenerative neuropathophysiology affecting prefrontal and right posterior cortical regions as well as frontal subcortical circuits (1-6).

Behavioural impairment is known recognised as a feature also of ALS/MND: the deficits can be evident in behavioural domains closely associated with the prefrontal cortex including executive functions and social cognition.

Rating scales such as Neuropsychiatry Inventory, Frontal Behavioural Inventory, and Frontal System Behaviour Inventory (have shown that up to 63% of patients with ALS are apathetic, irritable, inflexible, restless, and disinhibited (7-9). Apathy and difficulties with social judgement seems to be more frequent in patients whose ALS has bulbar onset than in those whose ALS is non-bulbar (8,10). So Apathy, one of the most common findings, should be differentiated from depression, fatigue and respiration dysfunction by careful examination of medical history and use of validated scales. For example, by contrast with apathy, depression can be linked to particular stressors, and it is characteristically associated with pervasive anhedonia, sadness, tearfulness, hopelessness, suicidal ideation, and guilt. Although there is no consensus for behavioural impairments in ALS, the clinical presentation is thought to represent abnormalities that do not meet the Neary criteria for frontotemporal dementia (11). Behavioural impairment in ALS can be classified on the basis of presentation of frontal-lobe type behavioural impairment in two or more areas, as measured from a standardised caregiver interview (12). However, the debate of whether to classify patients with ALS who have cognitive impairment together with or separate from those who have behavioural impairment continues. Although cognitively normal patients with ALS can have profound behavioural abnormalities, (7), cognitive and behavioural impairment can coexist in 25% or more patients (13). Maintenance of

a division between cognitive a behavioural impairment in research studies might be useful identification of different pathogenetic mechanisms and clinical courses, but it is currently insufficient evidence to make this distinction (14).

Social cognition, which is crucial for human interaction, has been reported as impaired in various studies of frontotemporal dementia. Lough and colleagues (15) showed that patients with fvFTD had impaired recognition of all emotions, and particularly anger and disgust, which might partly explain the difficult these patients have with identification of social violations. Empathy, as rated by carers, was also abnormal in these patients. Thus, social reasoning seems to be disrupted in various ways in fvFTD. This possibility has also been examined in ALS. In fact, although cognitive and social emotion deficits have not been associated historically with amyotrophic lateral sclerosis, some studies suggests that such impairments are identifiable and may play an important role in medical decision-making and care-giving issues (7, 16-20). Although patients with ALS/MND are known to suffer from pathological, emotional lability (see chapter 5), it is unclear why whether they had difficulty perceiving and interpreting interpersonal emotional communication. Papps, Abrhahams and colleagues (21) examined the performance of 19 non-demented ALS patients on neuropsychological tests involving emotional perception and memory. These patients demonstrated a failure to show the normative pattern of enhanced recognition memory for emotional words compared to neutral words and produced higher scores than controls on recognition memory for neutral words. This selective failure demonstrated enhanced memory for emotional material as compared to neutral material: this finding may reflects, according to the authors, differences between ALS patients and healthy controls in the encoding, consolidation or retrieval in memory items. This study had also highlighted the different profile associated with ALS by identifying a specific failure to demonstrate normative enhanced memory for emotional material in the patients in the context of both preserved general intellectual functioning and neutral memory.

Lule and colleagues (22) presented 52 emotive picture slides to 12 patients with sporadic ALS. The researchers recorded subjective reports of pleasantness and arousal, and correlated them to psychophysologic (i.e. starle, EEG) and galvanic

skin responses. Verbal emotional judgements of patients were more positive than controls. Regarding arousal, patients neutralized extreme pictures, in that they rated calm pictures as more exciting than controls and exciting picture as more calm. There were no major differences between patients and controls concerning physiological responses to emotional stimuli. The authors concluded that emotional responses in ALS patients tend to be altered towards positive valence and towards a more balanced arousal state in early stage of the disease: it was observed a decrement in excitability for extreme emotional stimuli. An open question remained weather these changes in emotional processing are a result of a persistent neurodegenerative processes sensu stricto or rather a conscious psychological reaction to the changed situation in which the patient find himself.

In a more recent Lulè's study (23), sixty similar emotional slides were presented to 13 ALS patients, 15 controls and 6 tetraplegic patients. The authors measured subjective reports of valence and arousal as well as brain responses to the affective picture using fMRI. Patients presented an increased brain response in the right supramarginal area and reduced brain response in extrastraite visual areas at both measures compared with healthy controls. Within the ALS patients' group a reduction of brain responses in the anterior insula was interpreted as indicating reduced arousal during the course of disease at the neural and behavioural level. The reduction of activity in extrastriate was similarly interpreted. The increased brain response in the right supramarginal area of ALS patients might represent an altered sensitivity to social-emotion cues. On the other hand, tetraplegic patients presented similar changes in physical activity: that may support the notion that the loss of peripheral inflow and changed circumstances in life. Zimmerman et al (24) underwent on 13 ALS bulbar patients standardized tests of facial and prosodic emotional recognition: the patients performed significantly worse than controls on facial emotional recognition but not on prosodic emotional recognition. Sixty-two per cent of them scored below the 95% Confidence Interval of controls in recognizing facial emotion, and 23% also scored lower in prosody recognition.

All these findings expands the scope of cognitive dysfunction detected in MND, and bolsters the view of MND/ALS as a multisystem disorder involving cognitive as well as motor deficit.

3.2 FUNCTIONAL MAGNETIC RESONANCE: GENERAL CONCEPTS

Human brain uses an oxidative glucose metabolism, based on oxygen consumption and ATP production. Given that there is no neuronal glycogen production, metabolic activity is related to the amount of glucose reaching the CNS through the blood flow. Therefore neuroimaging studies are based on the normal coupling between cerebral glucose consumption and regional blood flow, so that an increase in the second reflects a parallel increase in the former; in fact the evaluation of the regional cerebral blood flow (rCBF) depends on pre-synaptic activity.

fMRI is a particular type of MRI, based on the principle of nuclear magnetic resonance. Hydrogen molecules constitute about 10% of human body mass; almost ¾ of it is hold in water molecules and ¼ in lipids. The nucleus of a hydrogen atom is formed by a single proton, that is not still, but owns an intrinsic propriety, called spin, that can be either positive or negative. Generally electrons and protons coexist in the same atom, lowering the global atomic spin. Given that hydrogen is formed by a single proton, its global spin is not null and is responsible of the generation o fan electromagnetic field M, which is aligned to the spin axis. When an external magnetic field B is applied, hydrogen atoms align along the B field direction, but its intrinsic spin properties prevent it from a complete alignment. In fact the spin axis precedes in the direction of the magnetic field, with a precession frequency that is proportional to the intensity B and to the atom type. All these parameters are related in Larmor's equation: $\omega_0=\gamma B_0$, where ω_0 is the precession frequency expressed in rad/s, B_0 is the magnetic field flow density expressed in T and γ is the giro magnetic constant, which depends on the atom type. The precession frequency expressed in Hz (or Larmor's frequency) is then: $\omega_0=2\pi f$. For a hydrogen atom it is $f=42.57\ B_0$.

Therefore protons embedded in an external magnetic field tend to align in a parallel (low energy) or antiparallel direction (high energy) in respect to the magnetic field. In resting conditions the magnetic vector expressing the entire proton population aims at an antiparallel orientation compared with the external

magnetic field; moreover each proton owns a proper magnetic moment which is perpendicular to the external field. Anyway the vector resulting from the sum of the perpendicular magnetic moments aims at zero. Therefore, at the equilibrium, the global magnetization vector is aligned to the axis of the external magnetic field.

MRI imaging is based on the modification of the previously described balance and on the consequent evaluation of the resulting signal. This could be achieved applying an external magnetic field of low intensity (B_1), in the radiofrequency band, perpendicular to the external fixed field B_0. Radiofrequencies are transmitted in short waves and pass part of their energy to the protons embedded in the magnetic field B_0. The application of a variable magnetic field (excitement phase) causes a shift of the global magnetic vector, with a reduction of the vertical component aligned to the B_0 field axis, that is due to an increase of protons' energy, that will then arrange in an antiparralel direction towards B_0 (flipping). Moreover there is a synchronization of the precessation phase of the protons, with generation of a transversal global magnetization vector.

After the perturbation caused by radiofrequency application, protons tend to shift back to the starting orientation. The longitudinal magnetization vector therefore decreases in a constant time T1 (time necessary to reduce the difference between the post-excitation longitudinal magnetization vector and the resting longitudinal magnetization vector by an *e* factor).

Moreover, during relaxation, there is also the reduction or disappearance of the transversal magnetic vector, in a constant time T2 (time necessary to reduce the difference between the post-excitation transversal magnetic vector and the resting transversal vector by an *e* factor), depending on energy transferring between protons. Given that magnetic fields created in-vivo are not homogenous, the effective T2 (or T2*) is lower than the real T2, in such a way: $1/T2^*=1/T2(\text{molecular effects})+1/T2(B_0 \text{ field effect})$.

fMRI images are generally acquired using echo-planar images (EPI), that allow the filling of each line in the *k* space simultaneously with just one excitation, even if with a worse anatomical definition. fMRI is based on a T2* effect, which is due

to the interaction between preceding protons and between them and the magnetic field dishomogeneity, due to the different magnetic properties of the surrounding molecules. Some magnetic properties depend on the state of the interested molecules; in particular on hemoglobin. When this molecule is not bearing oxygen (deoxyhemoglobin), it has four uncoupled electrons, generating a magnetic moment that disappears when oxygen binds to the heme-group. That magnetic moment creates a local electromagnetic gradient that contributes to the reduction of the transversal magnetization an of T2*. Therefore variations of the ratio hemoglobin/deoxyhemioglobin (Blood oxygen level dependent effect or BOLD effect) will reflect in a modification of local T2* times. Obviously modifications of hemoglobin ratio depend on the rCBF that is coupled to the neuronal metabolism and activity. It is in fact known that near active brain areas there is a local arteriolar and venular dilation, probably due to astrocytes, that, after glutamatergic stimulation and consequent calcium influx, release prostanoids, NO, K and H in proximity of arteriolar walls, inducing vasodilation. The relationship between neuronal activity and vascular effects (BOLD) is defined by three parameters: rCBF, regional oxygen cerebral metabolism ($CMRO_2$) and cerebral vascular volume (CBV), in such a way that an increase in the former and the latter lead to an increase in BOLD, while an increase of the second leads to a decrease of the BOLD.

Generally immediately after an increase in neuronal activity, there is a reduction of BOLD effect, probably due to the metabolic response with an increase of $CMRO_2$ (“initial dip”). After 300-500 msec the vascular response begins with vasodilation and increase in BOLD.

Finally it is important to state that the BOLD effect is associated to an increase of pre-synaptic activity and therefore it cannot discriminate between excitatory or inhibitory activities.

3.2 STUDY PORPUSES

Several brain imaging studies had previously linked components of emotional behaviours to limbic and paralimbic structures (insula, amygdala, medial temporal cortex, anterior cingulate) and to subcortical regions (thalamus, caudate, hypothalamus), as well as to medial, dorsolateral, and orbito frontal regions (24-27). Despite that, only two studies have been –apparently- devoted so far to investigate cognitive or emotional performances of ALS patients with functional magnetic resonance. The first was due by Abrahams and colleagues (28): they investigated executive functions of a sample of 28 ALS patients. Interesting, it was revealed significantly impaired, if compared to healthy controls, the activation in the middle and inferior frontal gyri and anterior cingulated gyrus during the letter fluency task and confrontation naming task. This study provided evidence of cerebral abnormalities in ALS in the network of regions involved language and executive functions. The second was due by Lulè's et al. (23), as mentioned before, who noted in fMRI greater responses in the right supramarginal area in patients with ALS than control patients during an emotional task: this datum might represent an altered sensitivity to social and emotional cues.

The aim of this study is to further investigate brain region mediating negative emotions in ALS patients with unpleasant vs neutral material with fMRI. This technique permit to conduct a systematic evaluation of functional cortical and subcortical changes beyond the motor system, as a possible source for ALS behavioural changes, such as the impression that ALS patients are positive-minded, or apathetic, despite their fatal diagnosis (29). Subcortical and cortical networks such as the limbic system, in particular the amygdala, are crucial for the processing of the emotional stimuli. So, we selected Tabert's paradigm (30) to focus on the activation of amygdala and lymbic structures during an emotional linguistic task and a recognition memory task for emotional words, demenstrated as impaired by in ALS Papps (21). During the first scan, patients and controls were required to explicity evaluate the relative emotional significance of highly unpleasant vs. neutral words sets. During the second scan, which immediately followed the first scan, memory for the words presented the first scan was assessed.

3.4 METHODS AND MATERIALS

3.4.1 Participants and controls

Nine patients (7 male, 2 female; mean age 50.7, sd 11.46; mean educational level in years= 10.2, sd=4.8; 1 had bulbar onset, 8 had limb onset) were recruited from Padova' Motor Neuron disease Centre. All patients had undergone full clinical assessment under supervision of a panel of specialists. Neurological data were taken from the records of the patients' clinic visit nearest to the time of testing. All had clinical and electrophysiologal evidence of combined upper and lower motor neurone involvement in at least one region. No patients had a history of cerebrovascular disease, hypertension, or diabetes. Patients were excluded if they severity of upper limb involvement prevented them from undertaking manual task, and if they performed a score higher than clinical cut-off for suspected presence of depression on Beck depression inventory questionnaire. Also patients with more severe bulbar involvement, which would make it uncomfortable to speak whilst lyng supine, were excluded from this study.

Ten healthy controls, comparable for age and educational level, were recruited from a local voluntary group and from friends of patients with ALS. None had a history of neurological disorders or previous significant head injury. All subjects were fluent in Italian and right-handed as judged by the Edinburgh handedness Inventory (31) and had normal or corrected-to-normal visual acuity. After a complete description of the study to the subjects, written informed consent was obtained.

3.4.2Neuropsychological and Psychopathological measures

At the time of initial screening, as mentioned above, patients and controls mood was assessed with the Beck depression inventory (BDI)(32). Anxiety was assessed with Spielberger's State Anxiety (STAI-Y1) (33) both immediately before and immediately after fMRI scanning, to exclude the possibility that an abnormal cognitive profile might be related to emotional state. During the second administration, subjects were instructed to complete the STAI in terms of their experience inside the scanner. Newsome-Davis Emotional lability questionnaire (ELQ) (34) was used to assess the paresence of pathological laughing, crying or smiling in ALS patients. Italian validation of this measure is just completed and the procedure, as well as the measure, are detailed explained in chapter 5.

To exclude the presence of cognitive impairment we perfomed also an extensive neuropsychological battery. Intellectual abilities was assessed with an extensive neuropsychological battery underwent at least two months before functional imaging study. We used the Brief Intelligence Test (TIB) (35) to estimate premorbid full scale IQ and Raven's Satandard Progressive Matrices (SPM) (36) to estimate current intellectual functioning. For a general screening was also employed MMSE (37).

Executive functions were assessed with four test of fluency, adapted from Abrahams and colleagues (38) to control for individual variations in motor speed: the spoken verbal fluency test (F.A.S.)(39), the spoken semantic fluency test (animals, fruits and vehicles)(39), the written verbal fluency test with C and M beginning letter. From these a fluency index was calculated a fluency index (*fi*) was calculated for each measure (Spoken verbal fluency index SV*fi*, Category fluency index C*fi* Written verbal fluency index WV*fi*). Executive functions were also explored using the *Modified Wisconsin Card Sorting Test* (40), *Trail Making Test A and B*. The latter was performed according to Reitan's protocol (41). Long and short-tem Memory were respectively investigated with *Babcock's Prose* (39), *Verbal Digit Span Forward and Backward* (42) and *Corsi Blocks tapping test* (39). Visuo-constructional abilities were assessed with *Rey-Osterreith complex figure* (43), copy and recall task. Language, in terms of syntactic comprehension

and naming ability, was assessed respectively with *Token test* (39) and *Boston Naming test* (44). These measures and their adaptation for MND patients are detailed shown in previous chapter 2.

3.4.3 Study design

3.4.3.1 Words selection process

The words used in this study came from Dictionary of word frequency in spoken Italian language [De Mauro, Mancini, Vedovelli and Voghera (45)] which includes 10561 words that have been rated for use frequency in Italian spoken language. We selected a large group of words (161) similar for high frequency of use and for length. After that, we recruited a group of 50 volunteers (32 male, 18 female), which have rated these words on concreteness [from 1 (low concreteness) to 7 (high concreteness)], imagery [from 1 (low imagery) to 7 (high imagery)], and unpleasantness [from 1 (unpleasent) to 7 (neutral)]. For the current study, were selected 30 unpleasant words and 30 neutral words (mean unpleasantness ratings = 1.9 vs 5.4) that did not differ significantly for word length (mean word length=6.4 vs 6.33, p= 0.912), word frequency (45) (mean frequency of occurrence=7.33 vs 7.06, p= 0.715), concreteness ratings (mean concreteness ratings= 3.8 vs 4.2, p= 0.554) and imagery (mean imagery ratings=5.5 vs 4.2, p= 0.117). Although words were not specifically matched for part of speech, both lists contained nouns, verbs, adjectives and adverbs.
Unpleasent and neutral words selected and employed in the paradigm are shown in Appendices I and III.

3.4.3.2 fMRI Emotional Decision Scan

The generated words were used to generate unpleasant and neutral words sets, where each word set comprised a unique combination of three words. Word sets were presented in eight alternating unpleasant and neutral blocks (Four cycles, exemples in Fig 1 (a) and (b)). Each block began with a 2-second cue indicating whether the block consisted of unpleasant or neutral trials (Fig 1b). Five word set trials were presented during each block, each appearing for 4-seconds with a 2-second inter-stimulus interval (ISI). Thus, the BOLD response was recorded to four bloks of neutral words. During each ISI, a centrally placed fixation cross replaced the word set. A 11-seconds resting baseline preceded the first block trials, and a 24-seconds resting period separated all subsequent blocks of trials, during which subjects also viewed a central fixation cross. During each trial, a word set was projected to the centre of the subject's field of view via a computer-controlled projection system that presented stimuli to a rear-projection screen located at the entrance of the magnetic bore. Subjects viewed stimuli projected to the screen via a 4 x 10 cm^2 mirror attached to the head coil and positioned about 6 cm from and directly above the subject's eyes. Each words appeared twice over the course of the scan (i.e., first presentation occurred during the first two blocks, and the second presentation during the last two blocks of each stimulus type) within unique words set. Words set were presented in a fixed pseudo-randomized order across the blocks with the condition that a word did not reappear until all words had been presented once. The position of a word within a word sets was counterbalanced across presentation of that word. The sequence in which blocks of unpleasant and neutral trials was counterbalanced across subjects by reversing the trial order for four of the nine subjects.

Immediately before the scanning began, subjects were given ten practice trials (5 unpleasent and 5 neutral). The negative and neutral words presented during practice did not overlap with the experimental words, and were chosen from excluded words from the first selection (see paragraph 3.4.3.1). During the unpleasant blocks, subjects were instructed to select with right hand the most unpleasant or the most threatening word from the three negatively valenced words

(word set) presented on each trial. Subjects were instructed to base their decision on their personal knowledge of and experience with the concept and connotations conveyed by the words. Similarly, during neutral blocks, subjects selected with right hand the word they deemed to be the most neutral (i.e., non emotional or non threatening). From each word set. Subjects indicated their responses indicating the ordinal position of word in the screen (1, 2 or 3): a colleague from our team, seated at him or her right, noted on a protocol the choice.

3.4.3.3 fMRI Recognition memory scan

Immediately following the first scan (described above), a second scan was performed to assess recognition memory for the words presented (targets) during the emotional decision task. Sixty additional new words were selected from the excluded valenced word group in the first phase of selection task (see paragraph 3.4.3.1) to serve as foils or distractors in the memory scan (30 highly unpleasant and 30 neutral), matched for lengths and frequency. Additional words are shown in appendix I and II. Together, 120 words (60 previously seen and 60 not previously seen) were presented one at time in the centre of the subject's field of view on 12 alternating unpleasant and neutral blocks (6 cycles, Fig 2 (a)). Each block consisted of a fixed random sequence of 10 words, within a 0.50 probability of being a previously seen word (Fig 2 (b)). Each word was presented for 2 seconds and was immediately followed by the next word. A 20-second resting period preceded the first block of trials and separate successive blocks, during which time subjects viewed a central fixation cross. The sequence in which blocks of unpleasant and neutral trials were presented was counterbalanced across subjects by reversing the trial order for four of the nine subjects. Subjects were instructed to indicate with a little movement with index finger of right hand whenever they recognized a word from the previous scan. Similarly to previous task, a colleague from our team, seated at him or her right, noted on a protocol the subject's choice.

3.4.4 Pre-processing of fMRI data

Images were acquired using a 1.5 T Philips MRI scanner, using a block-design matrix adapted from Tabert et al. Briefly, T2*-weighted, echo-planar images (EPI), depicting BOLD contrast, were acquired in a single session for each paradigm. The TR was of 2 s. EPIs were acquired from 14 noncontiguous near axial planes (thickness=5 mm; inter-slice gap=1 mm; matrix size 64×64), parallel to the AC–PC line. For each paradigm blocks were presented in a pseudo-randomized order.

For the Emotional-Decision paradigm 188 images (376 s) were acquired for the entire session, the first 11 of which were discarded as "dummy scans" to allow for T1 equilibration effects, leaving a total of 176 images per session. Each activation (Unpleasant or Neutral) block consisted of 15 contiguous images and was repeated 4 times in each session(60 total images for Neutral or Unpleasant stimuli); resting periods comprised 8 images, and were repeated for a total of 7 times (56 total images).

For the Memory-Decision paradigm 241 images (482 s) were acquired for the entire session, the first 11 of which were discarded as "dummy scans" to allow for T1 equilibration effects, leaving a total of 230 images per session. Each activation (Unpleasant or Neutral) block consisted of 10 contiguous images and was repeated 6 times in each session (60 total images for Neutral or Unpleasant stimuli); resting periods comprised 10 images, and were repeated for a total of 11 times (77 total images).

3.4.5 Imaging acquisition and post processing of fMRI data

Data processing and analysis were accomplished using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Pre-processing steps comprised slice acquisition time correction, within-subject image realignment, spatial normalization to the MNI template (voxel size: 4×4×4 mm) and spatial smoothing using a Gaussian kernel (12-mm full-width at half-maximum). Data sets were rejected if head displacement was greater than 5 mm in any direction. The time series was high-pass filtered to remove low frequency noise, and the default SPM2 temporal frequency cutoff was used. The average hemodynamic response to each block was modelled using a canonical, synthetic hemodynamic response function.

Changes in blood oxygenation level-dependent (BOLD) contrast associated with the performance of the cognitive tasks were assessed on a pixel-by-pixel basis using the general linear model and the theory of Gaussian fields. Significant hemodynamic changes for each contrast were assessed using *t* statistical parametric maps (SPMt). For the analysis, we obtained a mean contrast for each task at each session. The intragroup activations and comparisons between groups were investigated using a random-effect analysis, with a one-sample or two-sample *t*-test performed as appropriate.

p-value threshold was ≤ 0.05 corrected for False Discovery Ratio at single-subject level and ≤ 0.001 uncorrected at the intragroup level; extent threshold ≥ 5 contiguous voxels.

Data will be shown according to MNI coordinates.

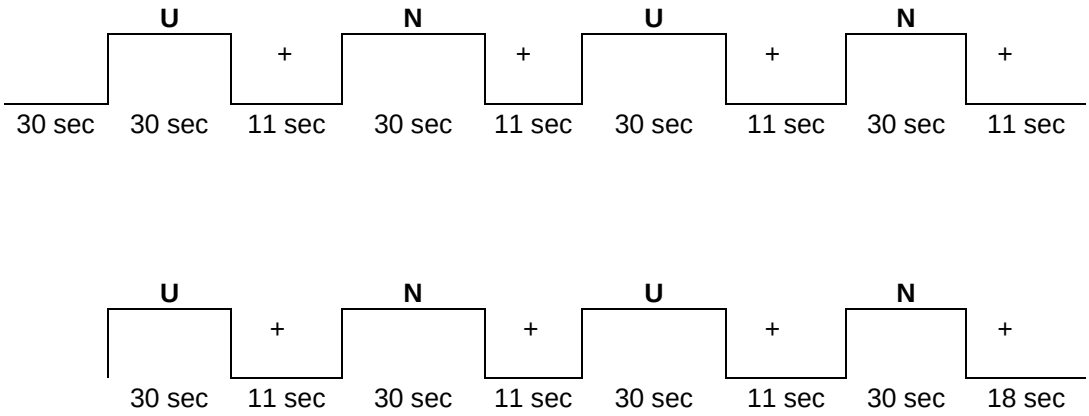
3.4.6 Statistical analyses of cognitive measures

Simple comparison between patients and control groups were conducted using parametric *t* test. Significance was determined for $p<0.05$

Figure 1

Emotional Decision Scan

(a)



(b)

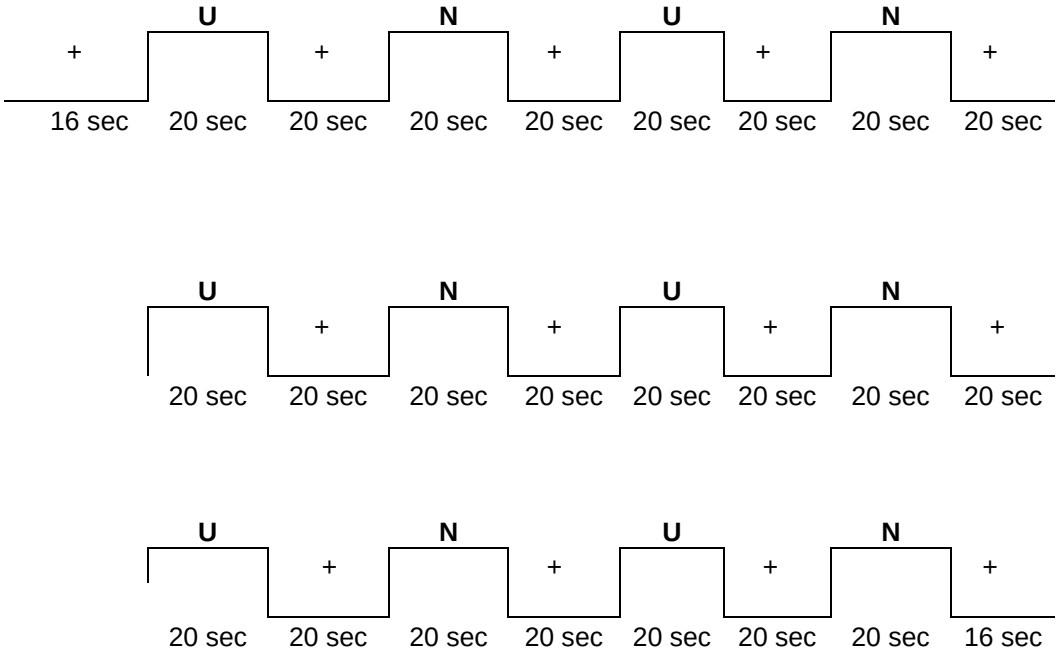
+	MALATTIA	+	TUMORE	+	MASSACRO	+	STUPRO	+	UCCISO
ISI	DROGA	ISI	PECCATO	ISI	RUBARE	ISI	MORTE	ISI	MISERIA
	POVERO		SOFFRIRE		SPORCO		VITTIMA		SCHIFO
2 sec	**4 sec**	**2 sec**	**4 sec**	**2 sec**	**4 sec**	**2 sec**	**4 sec**	**2 sec**	**4 sec**

Fig 1 (a): Overview of blocked stimulus presentation paradigm for the Emotional Decision Scan. Eight alternating blocks of neutral (N) and unpleasant (U) trials were separated by Rest Periods (+). Total scan time was 376 sec. (6min, 26 sec). (b) An example of the stimulus presentation parameters within a block of unpleasant trial for the Emotional Decision task.
ISI = second inter-stimulus interval.

Figure 2

Recognition Memory Scan

(a)



(b)

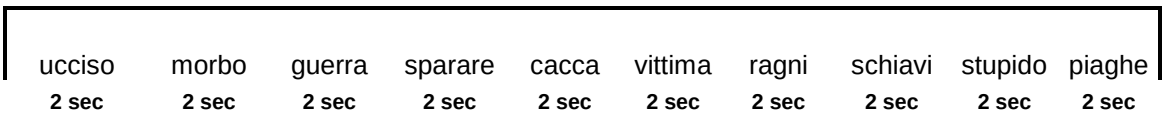


Fig 2 (a): Overview of blocked stimulus presentation paradigm for Recognition memory Scan. Twelve alternating blocks of Neutral (N) and Unpleasant (U) trials were separated by Rest Periods (+). Total scan was 492 sec (8 min 12 sec). (8) An example of a block of unpleasant trial and preceding baseline. The 30 unpleasant and 30 neutral words presented during scan 1 (targets) were randomly mixed with 30 foils of each word type (0.5 probability of target appearing). Subjects selected a word judged the most unpleasant or neutral for each word set in the previous emotional decision task.

3.5 RESULTS

3.5.1 Beahavioural data

During the emotional decision task scan, all subjects made an appropriate response (chose one word from each word set) on 100% of the trials. This demonstrates that subjects attended to the stimuli and responded as instructed for the entire duration of the scan. Given that the task instructions for the emotional decision task required subjects to make a subjective choice that was based on their own personal experiences and knowledge of the words involved in each word set, we did not include the behavioral data for the first scan here. As a manipulation check, we questioned subjects immediately following the experiment about their experience in tbc scanner. Debriefing revealed that ali subjects found the unpleasant word sets to be highly unpleasant, particularly when compared it the neutral word sets. During the recall task scan, subjects recognized more emotionally negative words as compared to neutral words. Overall, 88% of the unpleasant and 72% of the neutral targets were correctly identified demonstrating a significant memory enhancement for the unpleasant words.

3.5.2 Neuropsychological and Psychopathological results

Raw scores for state anxiety (33) were determined. State anxiety ratings went from a mean score of 35.1 ± 7.3 before scanning to 47.2 ± 6.8 after scanning (paired t = 2.13, P=0.033), demonstrating an overall significant increase in anxiety presumably due to the scanning procedure. State anxiety differente scores (scan report - prescan report), reflecting the change in anxiety from the pre-scan period to the report about the attual scanning period. Together, these findings suggest that state anxiety levels do increase as a result of the scanning procedure.

Average scores BDI scales were below the range of scores indicative of cut-off of depression, indicating that no group of patients or controls were clinically depressed. However, there was significant statistical difference in raw scores

between patients (mean=12.8, sd=3.5) and controls (mean= 5.6, sd=5.2) (t=2.23, p=0.03).

Comparison of mean test performance of patients with ALS and controls revealed similar performance in all neuropsychological domains. In particular, on measures of intellectual function there were no differences between the groups in premorbid scale of QI, as estimated by the TIB, and the Raven's SPM scores, or in the estimated premorbid Raven's SPM score. In addition the discrepancy between the actual and predicted Raven's score was not significant for any individual, and there was no significant difference between the means of the two groups. In MMSE, as well executive functioning, logical memory, short-term memory both verbal than visuo-spatial, visuo-constructional abilities and language, in terms of syntactic comprehension and naming, patients displayed significant differences in raw performance score in comparison with contro group.

3.5.3 fMRI Emotional Decision Scan

Within subjects analyses:

The *control* subjects group displayed during emotional recognition task significant higher activation for *unpleasant* word stimuli vs the rest in left cerebellum, right anterior cingolate, right angular gyrus, left postcentral gyrus, right inferior parietal lobule, left middle frontal gyrus (Table I, Fig c).

The *patients* group showed in the same task, for *unpleasant* stimuli vs rest, statistical greater activation in left cuneus and precuneus, left middle frontal gyrus, right anterior cingulate, left inferior occipital gyrus, right inferior frontal gyrus and left superior temporal gyrus (Table II, Fig d).

The *control* group exhibited greater statistically significant activation for *neutral* word stimuli vs rest in right posterior cingulate gyrus, right and left cerebellum,

right inferior frontal gyrus, left precentral gyrus, left middle frontal gyrus and right cuneus (Table V, Fig e).

The *ALS* group revealed greater activation in left inferior occipital gyrus and left middle frontal gyrus in *neutral* word in comparison with rest (Table VI, Fig f) .

Between subjects analyses:

As regard with between subjects analyses on emotional decision task, *controls* revealed significant greater activation of right middle frontal gyrus for *unpleasant* words in comparison with *patients.* (Table III).

Moreover, even if there is no significant difference between groups in this cognitive task lowering the statistical probability, threshold at $p<0.05$ a difference can be found, suggesting there is a trend for a grater involvement of anterior cingulate in controls vs patients.

In addition, *ALS* group displayed a greater significant activation in Left Middle Frontal gyrus (BA10, BA11) for *unpleasant* stimuli, in comparison with *control* subjects (Table IV).

Controls dslpayed greater activation as compared with *patients* in left precentral gyrus (BA6), right cerebellum and right inferior parietal lobule during exposition to *neutral* stimuli (Table VII)

Patients showed a significant, greater activation on left middle frontal gyrus during *neutral* stimuli decision in comparison with controls (Table VIII).

3.5.4 Memory Recognition Scan

Within subjects analyses:

The *control* subjects group displayed during memory recognition task significant higher activation in right inferior occipital gyrus, left inferior occipital gyrus, right inferior parietal lobule and left superior temporal gyrus for *unpleasant* word stimuli vs the rest (Table IX, Fig g).

The *patients* group showed in the same task, for *unpleasant* stimuli vs rest, statistical greater activation in left inferior occipital gyrus, right inferior occipital gyrus and right middle frontal gyrus (Table X, Fig h).

The *control* group exhibited greater statistically significant activation for *neutral* word stimuli vs rest right inferior parietal lobule, left precentral gyrus (BA6), right inferior occipital gyrus, left insula and left inferior occipital gyrus (Table XII, Fig i).

The *ALS* group revealed greater activation in left cerebellum, left inferior frontal gyrus, right cerebellum, right middle occipital gyrus, and left inferior occipital gyrus on *neutral* word stimuli in comparison with rest. (Table XII, Fig i).

Between subjects analyses:

As regard with between subjects comparison on recognition memory task, *controls* revealed significant greater activation of right posterior cingulate gyrus for *unpleasant* words in comparison with *patients* (Table XI).

In addition, *ALS* group displayed a greater significant activation in right posterior cingulate gyrus (BA10, BA11) for *unpleasant* stimuli in comparison with *control* subjects (Table XIV).

3.5.5 EMOTIONAL DECISION TASK: FIGURES AND TABLES

Tables of comparison *within* groups are in white, comparisons *between* groups are coloured in light blue

'vs' as indicating grater than (>)

*****MNI space, based on the reference template of the Montreal Neurological Institute in the Talairach & Tournoux atlas

Table I: Emotional decision task *control subjects – Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.42	4	-60	-12	Left cerebellum
4.31	-28	-64	-28	Left cerebellum
4.27	12	32	-4	Right Anterior Cingolate
4.23	48	-80	24	Right Angular gyrus
4.09	-44	-36	52	Left postcentral gyrus
4.06	36	-52	60	Right Inferior Parietal Lobule
3.88	-40	4	36	Left Middle Frontal Gyrus

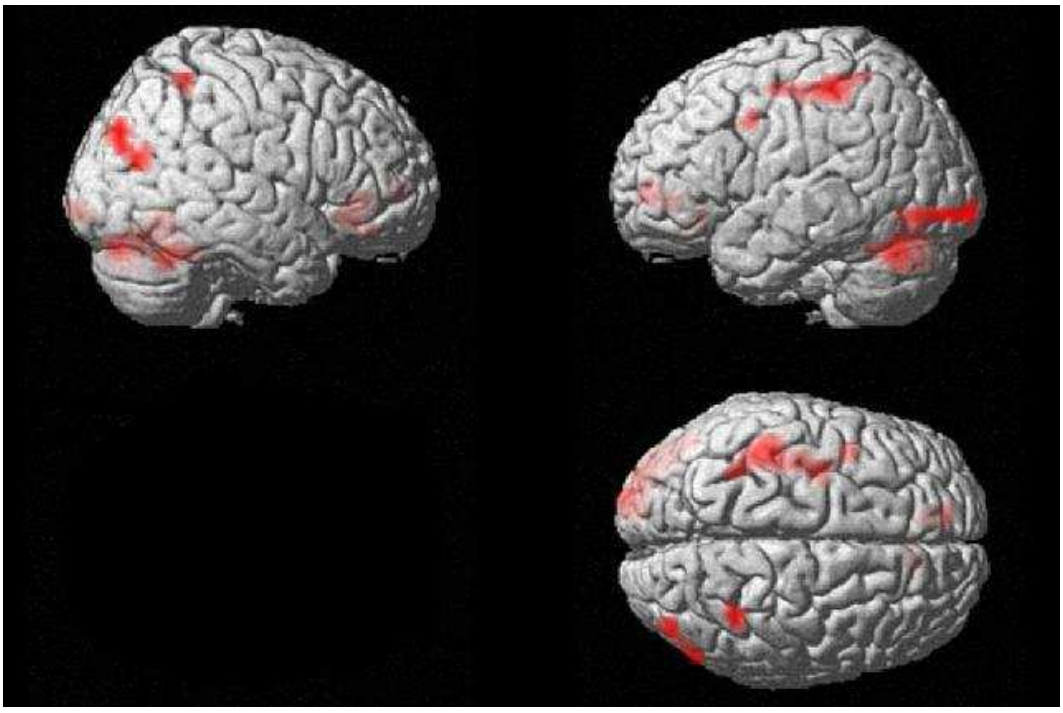


Fig c: Emotional decision task *control subjects – Unpleasant* stimuli vs rest

Table II: Emotional decision task *Patients – Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.67	-4	-80	12	Left Cuneus
4.43	-8	-48	44	Left Precuneus
4.07	-40	8	32	Left Middle Frontal Gyrus
3.97	4	24	12	Right Anterior Cingulate
3.95	-28	-100	-12	Left Inferior Occipital Gyrus
3.75	52	24	-12	Right Inferior Frontal Gyrus
3.65	-44	-36	12	Left Superior Temporal Gyrus

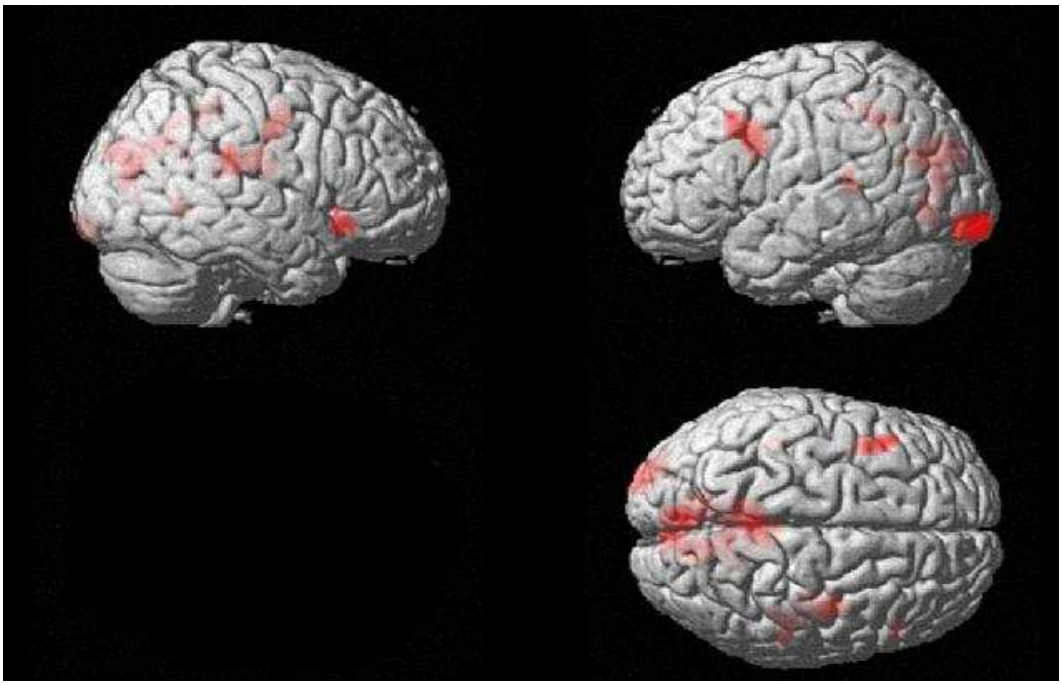


Fig d: Emotional decision task *patients – Unpleasant* stimuli vs rest

Table III: Emotional decision task *Control* subjects vs *Patients* – *Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.39	40	-4	44	Right Middle Frontal Gyrus

Table IV: Emotional decision task *Patients* vs *Control* subjects– *Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
3.93	-32	60	4	Left Middle Frontal G (BA10)
3.87	-24	36	-20	Left Middle Frontal G (BA11)

Table V: Emotional decision task *Control* subjects – *Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.40	4	-56	24	Right Posterior Cingulate G.
4.37	-12	100	-8	Left cerebellum
4.24	44	16	-8	Right inferior frontal Gyrus
4.13	20	-52	-24	Right cerebellum
3.95	-36	-56	-32	Left cerebellum
3.90	-32	-28	52	Left Precentral Gyrus
3.56	-52	8	32	Left Middle Frontal Gyrus
3.53	16	-104	-4	Right Cuneus

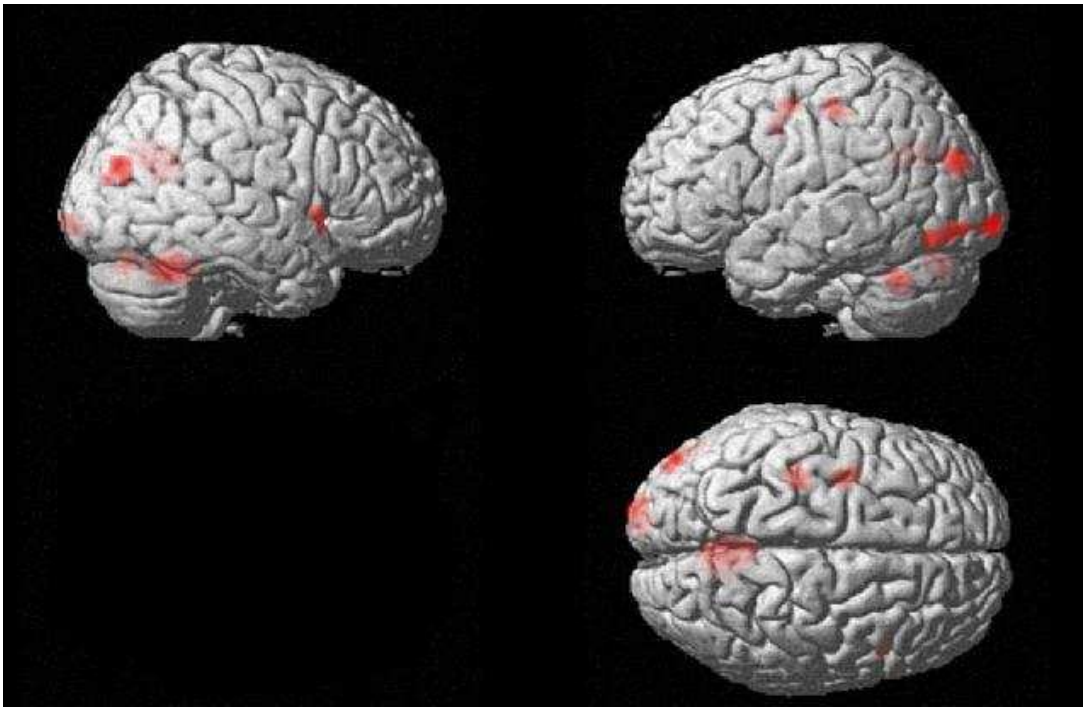


Fig e: Emotional decision task *control subjects – Neutral* stimuli vs rest

Table VI: Emotional decision task *Patients – Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.61	-40	-88	-4	Left Inferior Occipital Gyrus
3.77	-44	16	44	Left Middle Frontal Gyrus

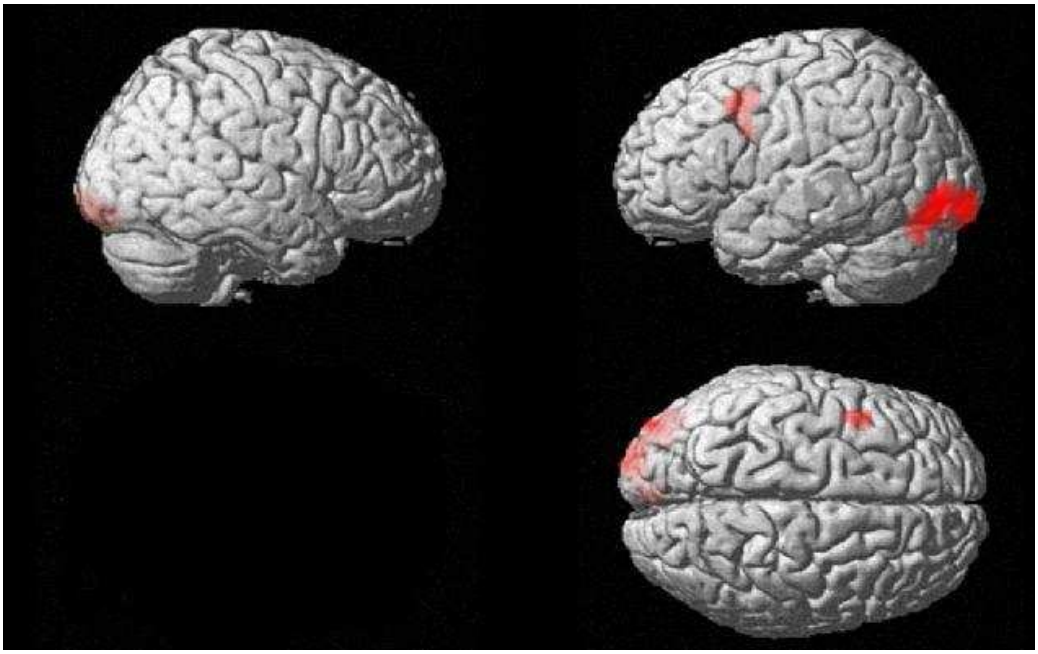


Fig f: Emotional decision task *Patients – Neutral* stimuli vs rest

Table VII: Emotional decision task *Control* subjects vs *Patients* – *Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.20	-36	-4	48	Left Precentral Gyrus (BA6)
3.68	20	-52	-16	Right cerebellum
3.59	56	-32	28	Right Inferior Parietal Lobule

Table VIII: Emotional decision task *Patients* vs *Control* subjects – *Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
3.66	-36	40	-16	Left Middle Frontal Gyrus

MEMORY RECOGNITION TASK: FIGURES AND TABLES

Tables of comparison *within* groups are in white, comparisons *between* groups are coloured in light blue

'*vs*' as indicating grater than (>)

*****MNI space, based on the reference template of the Montreal Neurological Institute in the Talairach & Tournoux atlas

Table IX: Memory recognition task *Control* subjects – *Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
5.05	32	-56	-28	Right Inferior Occipital Gyrus
4.98	-36	-76	-8	Left Inferior Occipital Gyrus
3.95	32	-60	48	Right Inferior Parietal Lobule
3.67	-64	-36	16	Left Superior Temporal Gyrus

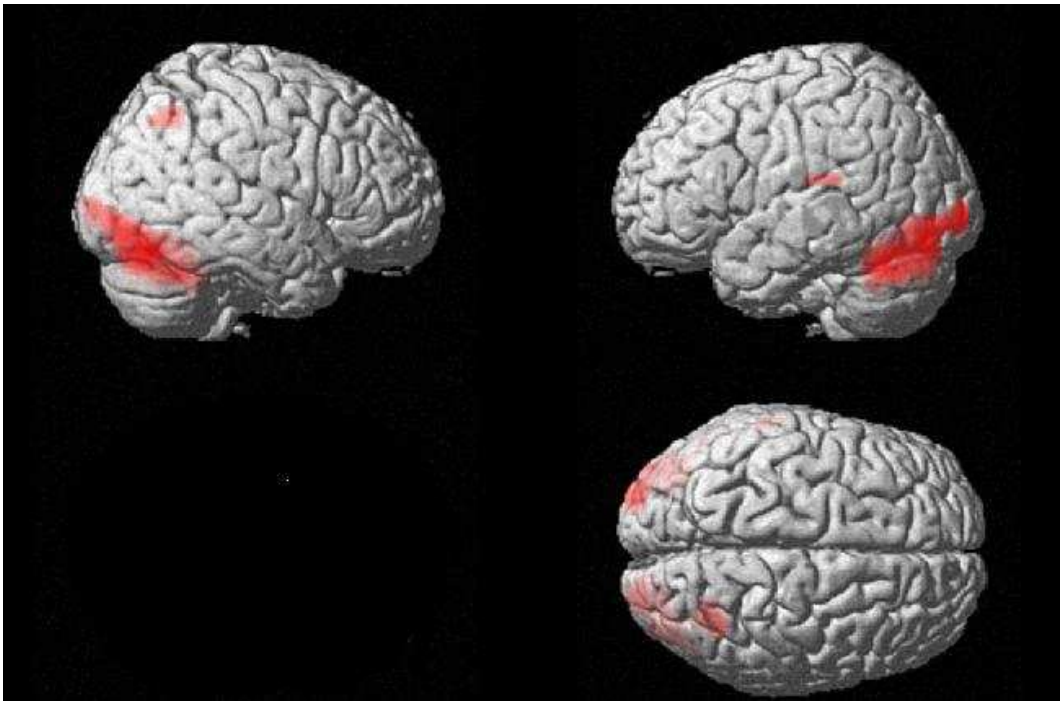


Fig g: Memory recognition task control subjects – Unpleasant stimuli vs rest

Table X: Memory recognition task *Patients – Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.50	-44	-84	-8	Left Inferior Occipital Gyrus
4.21	40	-84	-12	Right Inferior Occipital Gyrus
3.94	44	12	36	Right Middle Frontal Gyrus

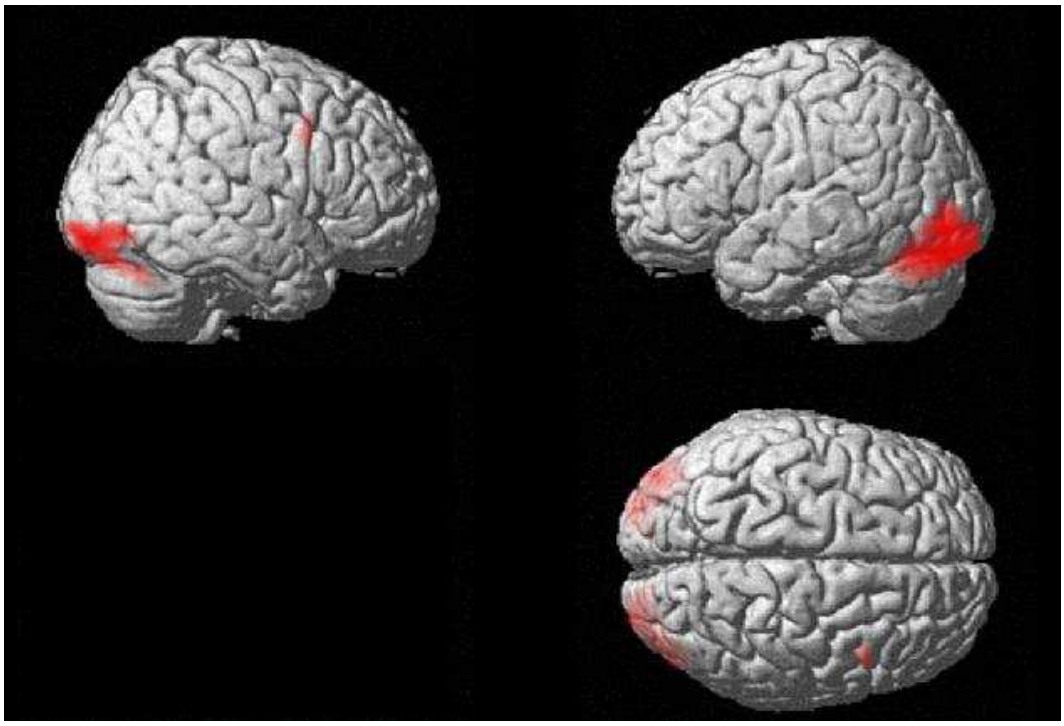


Fig h: Memory recognition task *Patients – Unpleasant* stimuli vs rest

Table XI :Memory recognition task *Control* subjects vs *Patients – Unpleasant* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.24	20	-68	8	Right Posterior Cingulate G.

Table XII :Memory recognition task *Control* subjects – *Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
4.37	32	-56	48	Right Inferior Parietal Lobule
4.04	-48	0	36	Left Precentral Gyrus (BA6)
3.92	32	-76	-16	Right Inferior Occipital Gyrus
3.74	-36	16	-4	Left Insula
3.48	-36	-88	-4	Left Inferior Occipital Gyrus

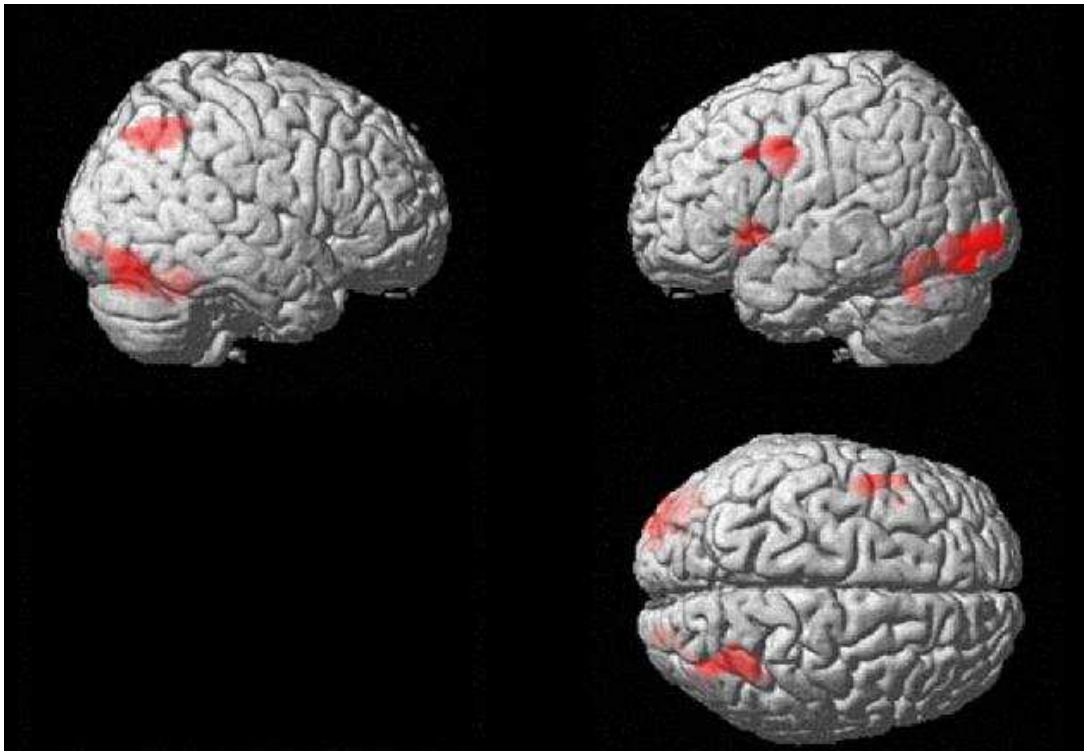


Fig i: Memory recognition task control subjects – Neutral stimuli vs rest

Table XIII: Memory recognition task *Patients – Neutral* stimuli vs rest

Z score	MNI* coordinates			Area
	x	y	z	
5.10	-36	-84	-20	Left cerebellum
4.78	-56	20	0	Left Inferior Frontal Gyrus
4.73	40	-60	-36	Right cerebellum
4.49	4	-68	-20	Right Middle Occipital Gyrus
4.38	-40	-88	-4	Left Inferior Occipital Gyrus

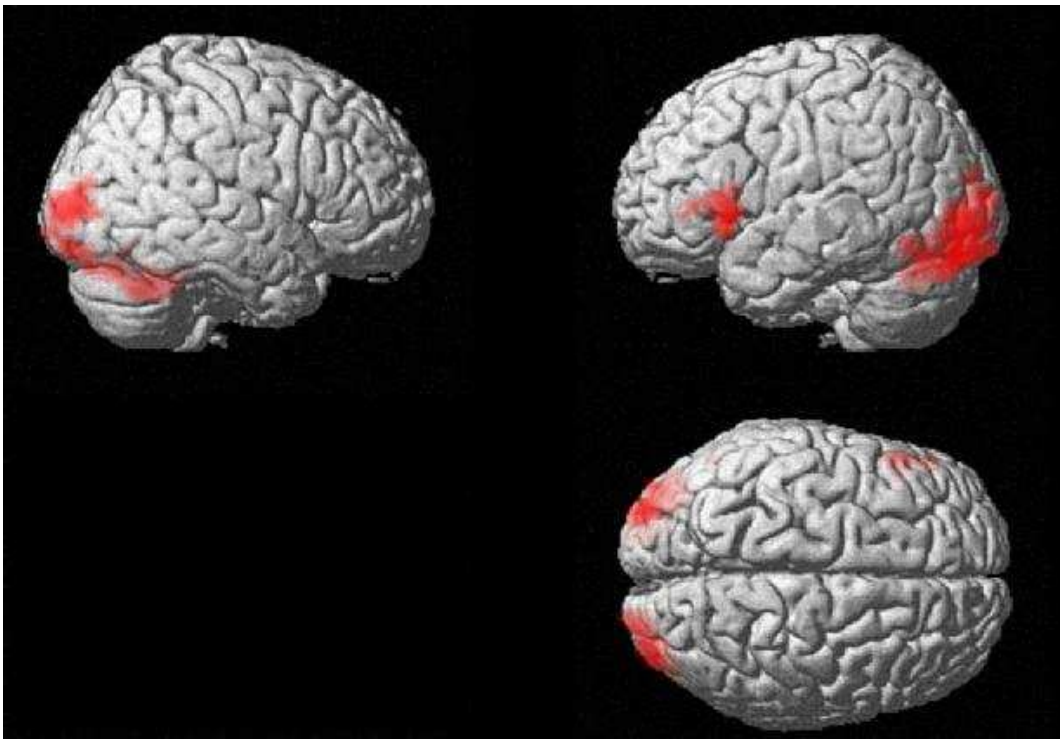


Fig L: Memory recognition task patients – Neutral stimuli vs rest

Table XIV: Memory decision task *Control* subjects vs *Patients* – *Neutral* stimuli vs rest

Z score	MNI coordinates			Area
	x	y	z	
4.22	20	-68	16	Right Posterior Cingulate G.

3.6 DISCUSSION

In addition to the extra-motor cortical involvement, some studies have also demonstrated evidence of changes in the limbic system in ALS. Moreover, frontotemporal dementia has been linked more generally with difficulty interpreting emotional facial expression, that is mediated by amygdala functioning, finding confirmed by Zimmerman et al. in ALS individuals. So, this study was designed to examine whether a pilot group of patients with ALS demonstrate emotional perceptual processing impairment, focusing particularly on amygdala activation. In order to reach this aim, we selected an emotional paradigm (30) to establish specifity of amygdale responses, and, more generally, pattern of activation during emotional stimulation. Alternating blocks of unpleasant and neutral trials were presented. During the emotional decision task, subjects viewed sets of three unpleasant or three neutral words while selecting the most unpleasant or neutral word, respectively. During the memory task, subjects identified words that have presented during the emotional decision task (0.5 probability).

Our study did not confirm amygdala activation using Tabert's paradigm. That can be due to a number of reasons. For example, we adapted the English paradigm in Italian language, following Tabert's guidelines: each word was comparable for frequency, length, imagery, concreteness and valance with each others. Nevertheless, something might have be changed after translation, and the effect on amygdala may result altered.

However, a numbers of relevant findings were detected. Most interesting results came from statistical analyses between subjects. During emotional decision task, was observed a significantly different activation in middle frontal gyrus in patients in comparison than controls, respectively in the right hemisphere and in the left hemisphere. The prefrontal cortex has been implicated in a variety of attentional, executive, and mnemonic mental operations, yet its functional organization is still highly debated. Anyhow, middle frontal gyrus appear unequivocally as involved in sustained attention and working memory and plays a

specific role in the cognitive processing of emotional stimuli (26,46). The reason of this different lateralisation in patients and controls in detection of unpleasant stimuli is not so clear. It was found that the mnemonic component of the working memory tasks affected the hemispheric pattern of pre-frontal cortical activation: in particular, the spatial (searching for localization) working memory task seem to preferentially activate the middle frontal gyrus in the right hemisphere, while the nonspatial (searching for shape) working memory task activate the middle frontal gyrus in both hemispheres (47). However, this dissociation can be hardly implicated with our emotional task. Anterior cingulate showed a trend towards impairment in patient versus control, but did not reach statistical significance; it was demonstate(48) the anterior cingulate gyrus was the only brain region with equivalent responses to attentional and emotional stimuli. This finding also explain that attentional and emotional functions are segregated into parallel dorsal and ventral streams that extend into prefrontal cortex and are integrated in the anterior cingulate. Moreover, anterior cingulate is the site of the origin for the final behaviour circuits, and the most obvious frontal type of apathy results from damege of this structure. Impaired activation in anterior cingulate in ALS patients who were specifically impaired on written verbal fluency test was yet found by Abrahams (49) in a PET study. So, a trend toward impairment in ALS patients of this structure during an emotional task can assume great importance in interpreting social cognition.

Similarly, statistical analyses between subjects in emotional task for neutral stimuli, revealed a significant more complex pattern of activation in controls than patients (left precentral gyrus, right cerebellum, right inferior parietal lobule). All these areas can be ascribed as well as to attentional processing (50,51,52). On the other hand, ALS patients group presented a significant grater activation in left middle frontal gyrus during neautrali stimuli presentation. Greater activation in left middle frontal gyrus in emotional task, persistent for unpleasant and for neutral stimuli, both implicated in a choice based on semantic valaence of presented words, may be interpreted also as compensotary cortical activation, or neuroplastic changes.

Different lateralization in patients than controls may appear as confirmed in memory recognition task. Patients showed statistical lower activation in right posterior cingulate in comparison with control subjects, both for unpleasant than for neutral stimuli. Functional imaging studies consistently find that emotional stimuli activate the posterior cingulate cortex, a region that appears to have memory-related functions. A recent study (53) showed that activation of the posterior cingulate cortex by emotional stimuli cannot be attributed to the memory-enhancing effects of non-emotional stimulus features sensuc strictu. The findings are consistent with the suggestion that this region may mediate interactions of emotional and memory-related processes (54).

All these findings can be interpreted with the Right-Hemisphere Hypothesis that posits that emotional stimuli are perceived more efficiently by the right hemisphere than by the left hemisphere, in particular unpleasant ones. This eventual dimish activation of right emisphere in ALS can also explain what is reported by Papps and colleagues (21), that ALS individuals are specifically impaired in attending to and recalling emotional words.

The potential clinical implications on cognitive-affective impairment in patients with ALS have major importance, as well as the hypothesis of a different activation of hemispheres during emotional task, a valance choice or emotional stimuli recall. Problems with judgment, alteration toward positive valence and decreased excitability for extreme emotional stimuli should be taken into account when patient care is planned. For example, changes on emotional processing can altered the ability to engage competently end-of-life decision, both for patients themselves than as regard with caregivers.

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4. QUALITY OF LIFE IN ALS: ALSAQ ITALIAN VALIDATION AND CORRELATION WITH MOTOR IMPAIRMENT

4.1 QUALITY OF LIFE IN ALS: AN OVERVIEW

As no effective treatment is so far available for ALS, most medical interventions aim to improve the quality of life (QoL) of patients (4,5). The QoL in ALS is related to patient psychological profile (6,7), environmental and social condition (8), spiritual aspiration (9) and coping style (10). The understanding of factors related to quality of life in chronic neurological disorder is becoming increasingly important, with the recent emphasis on the comprehensive management of patients' condition.

Great majority of authors (1) found the severity of depressive symptoms and quality of life showed a moderate positive relation to physical impairment and a weak negative relation to time since diagnosis. These findings are in contrast with results of a study by Norquist et al.(2), that found no major decrease in mental health score over time when compared with physical functioning scores. Similarly, Kiebert et al.(31) reported that appeared to be no direct association between the increase in physical impairment and subsequent development of major depressive disorder in patients with ALS. In the past, QoL assessment in ALS had typically involved very general or disease-specif questionnaires. More recently, researchers have attempted to develop QoL assessment that examine whether other factors may have an impact in the ALS population. Clarke et al (34) found that a patient-centred approach measuring psychological distress and illness severity showed greater internal validity and consistency than did standard disease-based QoL assessment. Bromberg and Forshew (4) further examined the patient-centred approach and found that patients and caregivers shared many similar concerns that revolved around marriage, family, friends, religion, recreational activities, disease progression and financial issues. These data are supported by Chiò (8), that found an appreciation of QoL relies mainly on psychological, supportive, and spirituals factors, and that physical status was not

relevant in determining QoL. Although physical status overall has not been though to affect QoL, it has been postulated that isolated aspects of decreased physical status such as fatigue may play a role in decreasing the patient's perception in his or her QoL.

4.2 INTRODUCTION TO ITALIAN VALIDATION OF ALSAQ

The evaluation of QoL has acquired increasing importance in degenerative diseases with poor prognosis such as ALS. The lack of treatments and the disease progression imply the need for palliative therapies to ameliorate both general health status and ultimately life quality of ALS patients. Further, protocols of ALS clinical trials usually include QoL assessment as a follow-up parameter. Most existing generic QoL instruments, as the 36-item Short Form Health Survey (SF-36) (11, 28), the Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) (14), the McGill Quality of Life Questionnaire (MQOL) (15) are not suitable for ALS because they do not assess features unique to this disease. Few questionnaires have been specifically designed to evaluate QoL in ALS, namely SIP/ALS-19 (13), ALSSQOL (29) and ALSAQ (24). SIP/ALS-19 is based on a subset of items selected by a panel of ALS specialists from the Sickness Impact Profile (SIP) whereas ALSSQOL (Amyotrophic Lateral Sclerosis Specific QoL instrument) is derived from the McGill Quality of Life questionnaire (MQOL) (15) modified by changes in format and by adding questions on religiousness and spirituality. To date only limited data are available on these two measures (30). ALSAQ-40 is otherwise a widely used ALS patient-focused disease questionnaire (31,32) and has been already validated in Japanese (20) and Dutch language (21). Unlike the other scales, ALSAQ-40 has been specifically designed for the use in ALS and other motor neuron diseases. It was developed on the basis of in-depth interviews with patients rather than relying on the literature of clinical scales in this field. The ALSAQ-40 reliability of the measures in terms of internal reliability, construct and content validity is high (18,19) and appears sensitive to changes that have an impact on the overall health status of patients. It therefore provides a meaningful and interpretable picture of disease impact on the subjective functioning and well being of patients on areas that are of concern to them (18). This scale has been already validated in Japanese (20) and Dutch language (21).

Our purpose is to validate an Italian version of ALSAQ-40 and ALSAQ-5 in a large cohort of Italian ALS patients and to further characterize ALSAQ-40 relation with muscle strength, motor disability and respiratory function.

4.3 METHODS

4.3.1 Patients

We considered patients affected with clinically definite or clinically probable ALS according to El Escorial criteria (22) and regularly followed at the Neuromuscular Clinic of the University of Padova. Exclusion criteria were closeness to death and a level of cognitive impairment not allowing patients to understand the questions. An informed consent was obtained from each patient.

4.3.2 Italian ALSAQ-40 and ALSAQ-5

Original Amyotrophic Lateral Sclerosis Questionnaire contains 40 questions that measure 5 areas of health: Physical Mobility (10 items), Activities of Daily Living and Independence (10 items), Eating and Drinking (3 items), Communication (7 items), and Emotional Functioning (10 items). The questions refer to the patient's condition during the past two weeks and the answers are given on a five-point Likert scale. The ALSAQ-40 indicates the amount of ill health in each domain assessed using a summary score from 0 (best health status) to 100 (worse health status). The ALSAQ-5 contains 5 questions, one from each of the five dimensions of the ALSAQ 40. The score of the 5 questions of ALSAQ-5 is recoded and ranges from 0 to 100, with 0 representing the best possible health status (16,18,23). Original questionnaires were translated to Italian by two native Italian speakers fluent in English who have not seen the scales before. The Italian version was back-translated to English by two native English speakers fluent in Italian, who also have not seen the scales before. Since there was no significant difference between the original and back-translated version of the scales, Italian version of scales was accepted. Questionnaire data were collected in a face-to-face setting at the end of the medical assessment. If the patient could write, (s)he filled out the questions of the measure. In case of writing impairment, the interviewer (psychologist) noted patient's answer to questionnaires. The interviewer noted also any further clarification about questionnaires items requested by the patient. Thirty patients underwent ALSAQ-

40 re-test by three months to analyse the validity and reliability of the Italian version of the scales.

4.3.3 Comparative Instruments

To test Italian ALSAQ-40 validity we used the following measures:

1. *The Amyotrophic lateral Sclerosis Functional Rating Scale Revised* (ALSFRS-R)(24). This is a 12-item scale, in which the patient's functioning for each item is rated on a scale from 0 (unable to attempt the task) to 4 (normal function). This scale includes evaluation of swallowing, speech, and respiratory function, and both strength and function of the upper and lower extremities musculature. A score of 48 points is normal whereas 0 points indicates maximal dysfunction.

2. *The 36 item Short form Health Survey questionnaire* (SF-36) (25). At present, this is the most widely used measure of general health status. It contains 36 items across eight multi-item scales: Physical Functioning (PF), Role limitations due Physical health problems (RP), Role limitations due to Emotional problems (RE) Social Functioning (SF), Bodily Pain (BP), Vitality (VT), Mental Health (MH) and General Health perceptions (GH). All raw scales are linearly converted to a 0 to 100 scale, with higher values indicating favourable health status.

3. *Medical Research Council MRC scale and forced vital capacity (FVC).* To evaluate patients motor disability we used the measure of muscle strength by the limb muscles (score from 0, absence of movement to 5, full strength). Muscles evaluated were: deltoids, triceps and biceps brachii, finger extensor, thumb adductor, thigh flexor, knee extensor, ankle extensor and flexor. All muscles were tested bilaterally. We considered the total MRC score (megascore) of both upper and lower limbs which respectively ranged from 0 to 60 and from 0 to 40. FVC was assessed by a standard manual spirometer (CYTEC 60) and expressed as a percentage of the expected value.

4.4 STATISTICAL ANALYSIS

All data were analyzed using the psychometric package as provided in the R language and environment for statistical computing (R Development Core Team, 2005) (26). Usual baseline data and ALS characteristics (including age, gender, type, marital status, time since onset, onset of disease) were evaluated.

The internal reliability of the translated ALSAQ-40 scales and the test-retest reliability were assessed by Cronbach ‘s alpha, as shown in Table III. Non-parametric Spearman correlation coefficients was used to analyze shortened version, ALSAQ-5, and it was hypothesized that scales with similar content would correlate strongly (0.73 or higher). For the item to scale correlation, corrected for overlap, a correlation of 0.40 was considered the required minimum. Construct validity is demonstrated by comparison of the novel rating instruments to other established ones (MOS SF-36, ALSFRS-R) and to functional or strumental measures (MS upper and lower, FVC) (Table IV).

Separate analysis was conducted for the ALSAQ-40 and for the reduced version of the questionnaire (ALSAQ-5).

Moreover, we assessed face validity on the percentage of motor and cognitive help asked.

Table I. Clinical features of 76 ALS patients

Age (Years)	**Type**		**Gender**		**Marital Status**		**Diagnosis**		**Onset**	
	S	F[a]	M	F[b]	married	single widow divorced	<2 years	>2 yeras	B	L
76 (mean: 61,39 ± 11,6)	73	16	39	37	66	10	45	31	15	61

S= Sporadic Type F[a]=Familiar Type; M =male F[b]= Female; B= Bulbar onset L= Limb onset

Table II. Baseline Measures and comparative data

Measurement	Number of Patients(%)	Mean	SD
ALSFRS-R	74 (97,4)	33,9	12,1
FVC%	50 (65,8)	79,2	21,8
MRC upper	74 (97,4)	47,1	15
MRC lower	74 (97,4)	28,5	11,8
SF-36	21 (27,6)		
ALSAQ-40 re-test	30 (39,5)		
Questionnaire completed with motor help from someone else	25 (32,9)		
Questionnaire completed with cognitive help from someone else	43 (56,6)		
Questionnaire completed without any kind of aid	13 (17,1)		

SD =Standard Deviation.
FVC: Forced Vital Capacity.
ALSFRS-R: Amyotrophic Lateral Sclerosis functional Rating Scale Revised
MRC upper and lower= Medical Research Council scale applied to upper districts (maximum score=60) and applied to lower districts(maximum score=40)

Table III. Internal reliability (Cronbach's alpha) of scales of the Italian version of ALSAQ-40 in the baseline (Time 1) survey and in the re-test (Time 2).

ALSAQ 40 I Scales	Time 1	Time 2
Physical Mobility	0.938	0.960
ADL/Independence	0.962	0.966
Eating and Drinking	0.962	0.965
Communication	0.971	0.965
Emotional Functioning	0.886	0.867

Table IV. Construct validity: subscales of Italian version of the ALSAQ-40, ALS-FRS and SF-36 [(a)]

ALSAQ 40	Physical Mobility	ADL/ Independence	Eating and Drinking	Communication	Emotional Functioning
ALSFRS subscales					
Speech	0.042	-0.155	**-0.718****	**-0.795****	**-0.234***
Salivation	0.079	-0.115	**-0.653****	**-0.636****	-0.087
Swallowing	0.033	-0.184	**-0.814****	**-0.761****	-0.212
Writing	**-0.441****	**-0.710****	-0.174	-0.151	0.014
Feeding	**-0.428****	**-0.808****	**-0.278***	-0.204	-0.143
Dressing	**-0.704****	**-0.736****	-0.014	-0.035	-0.118
Turning	**-0.739****	**-0.707****	-0.085	-0.041	-0.213
Walking	**-0.817****	**-0.399****	0.041	0.060	-0.223
Climbing	**-0.817****	**-0.343****	0,077	-0.051	**-0.279***
Dyspnea	-0.085	0.007	**-0.234***	**-0.305****	-0.129
Orthopnea	**-0.231***	-0.169	**-0.331****	**-0.403****	**-0.248***
Respiratory Insufficiency	**-0.261***	-0.142	**-0.308****	**-0.379****	-0.158
SF-36 Subscales					
PF	**-0.745****	**-0.497****	0,118	0,18	-0.173
RP	-0.160	0.066	-0.156	-0.260	**-0.478****
BD	**-0.531****	-0.190	**0.436****	0.097	0.067
GH	-0.351	-0.196	-0.231	-0.036	-0.345
VT	**-0.592****	**-0.681****	-0.285	-0.147	**-0.582****
SF	**-0.518****	**-0.483****	-0.004	-0.092	-0.295
RE	-0.046	0,14	0,107	-0.182	**-0.507****
MH	-0.008	-0.004	0.062	-0.188	**-0.561****
Functional measurement					
FVC	**-0.399****	**-0.337***	**-0.327***	**-0.393****	-0.125
MS-sup	**-0.397****	**-0.709****	-0.139	-0.167	-0.143
MS-inf	**-0.651****	**-0.332****	0.098	0.110	-0.071

*** p value* < 0.01, ** p* < 0.05 *Spearman correlation coefficients* **:** *all correlations are negative as high ALSAQ 40 scores correspond with low ALSFRS and SF 36 scores.*

[a] *PF= physical functioning; RP = Role limitations due to a physical health problems; RE = Role limitations due to an emotional problems; SF= Social Functioning; BP= Bodly Pain; VT = Vitality; MH = Mental Health*

Table V. Internal Reliability (Spearman's correlation) of the Italian version of the ALSAQ-5: Correlation of the ALSAQ-5 in the baseline (Time 1) and re-test (Time 2).

ALSAQ-5 I Items	**Time 1 vs Time 2**
Physical Mobility	0.777
ADL/Independence	0.924
Eating and Drinking	0.858
Communication	0.868
Emotional Functioning	0.737

4.5 RESULTS

Seventy-six patients completed ALSAQ-40 over a period of 20 months. There were no missing data. All patients were interviewed and assessed in hospital; the characteristics of total cohort of patients and their baseline measure are shown in Table I and Table II. They were similar to expectation and previous report in gender ratio, disease onset and disease type (27).

4.5.1 Internal reliability

The internal reliability involves examining the extent to which a number of items addressing the same concept actually are doing so. Cronbach's alpha values were greater than 0.88 for all dimensions of the Italian ALSAQ 40. Corrected item to subscale correlations were all above 0.60 and significant (ps< 0.001).

4.5.2 Test-retest reliability

Test-retest reliability represents the most popular indicator of survey reliability: it involves the administration of the measure on two separate occasion to the same population.. In our patients we separate administrations of questionnaires by three months follow-up. Internal reliability of scales of the Italian ALSAQ-40 in the baseline (Time 1) survey and in re-test (Time 2) are showed in Table III, and displayed an excellent internal consistency (Cronbach's alpha values greater than 0.886 for each scale). Likewise, also the test-retest reliability of ALSAQ-5 I items in the test-retest analysis (Table V), was very good (correlation greater than 0.73 for each item).

4.5.3 Construct validity

Construct validity describes the extent to which the scores on a scale reflect what current theory predicts the test will show: it is important to understand how our theories in QoL can provide evidence that they behave in practice the way we

think they should. It was examined by means of Spearman's correlations of scales for ALSAQ-40, with scales for ALS-FRS, SF-36and FVC and Muscular Strength Mega score (superior MS and inferior MS) (Table IV).

Excellent correlations in the ALSFRS-R were found between Eating and Drinking scale and Swallowing (*rho* = - 0,84), between Activity of Daily Living/Independence and Feeding (*rho* = - 0,80) and Physical Mobility and Walking (*rho*= - 0,82). The 5 items selected (ALSAQ-5) correlated as well with SF-36 in the same magnitudes as the ALSAQ-40. In particular, strong correlations were found with SF-36 subscales Mobilty and Physical functioning, and between ADL Independence and Vitality. All correlations are negative as high ALSAQ-40 scores correspond with low ALSFRS and SF 36 scores.

Construct Validity examined by means of Spearman's correlation of Italian ALSAQ-40 and Mega Score Upper and Lower revealed a significant correlation between Physical Mobility and ADL Independence and Mega Score Superior and Inferior. Forced Vital Capacity has a significant correlation with all of ALSAQ-40 scale exclusive of Emotional Functioning, as shown in Table IV.

4.5.4 Relationship of ALSAQ-40 subscales to patients' variables

To determine whether there were significant correlations between the scales of Italian ALSAQ-40 and patients demographic features, such as the gender, or patients behavioural data, in terms of requested cognitive or motor help. Speraman's correlation were performed. No significant correlation was observed between age gender or marital status (*p*s > 0,15) of the subject and any of the subscale of ALSAQ, nor with cognitive or motor help required (*p*s > 0,15) (data not shown).

4.5.5 Face validity

Face validity is the need for a questionnaire to apparently tap, unambiguous and easily understood, simple by item content, an underling dimension.

Most of respondents pointed out the scale as including statements relevant to how they were feel their condition. Even though the large patients' agreement for the questionnaire, 56.58% asked cognitive help to better understand ambiguous questions (for example, at the questions "I have found picking things up difficult" patients asked: "with which hand?").

4.6 DISCUSSION

QoL in ALS has been evaluated with different instruments, because there is no consensus on which scale are mot suitable for measuring QoL in these patients. The following scales are the mostly used in recent studies: the SF-36 (11,12), the SIP/ALS (13), the SEIQoL-DW (14), the McGill Quality of Life Questionnaire MQOL (15), the Amyotrophic Lateral Sclerosis Assessment Questionnaire-40-item scale and its shortened 5-item version (ALSAQ-40 and ALSAQ-5 respectively) (16,17). The aim of our study was to validate an Italian version of this latter measure, and its shortened form. Italian ALSAQ-40 showed high test-retest reliability and a good construct validity, as supported by comparison with the subscales of the SF-36 and ALSFR-S. Indeed, we found a strong correlation between Italian ALSAQ-40 and ALSFRS-R as shown by comparing the score of the Eating and Drinking subscale with the Swallowing item, and the Activity of Daily Living/Independence and Feeding subscale with the Physical Mobility and Walking item. Measures of muscle strength by MRC score and Forced Vitality Capacity by Spirometry (FVC) also correlated with the score of Physical Mobility and ADL/Independence ALSAQ-40 scales.

Our correlations outline a good construct validity and a relation between ALSAQ-40 subscales exploring both physical functioning and motor impairment. We found no relation between the ALSAQ-40 Emotional Functioning subscale and either muscle strength or functional ability. These outcomes support the theory that emotional distress and functional decline are partially independent: the relatively limited influence of health-related functional status on QoL in ALS patients has also been shown in recent studies comparing global QoL and the ALSFRS-R (10, 36-38).

Hence, ALSAQ-40 I suggests that the emotive connotations patients assign to their life can remain relatively positive even when their health status is severely impaired.

McDonald (1994) (35) showed that, when he compares the covariates of length of illness, severity of ALS disease and age, the relative risk of death per unit time for patients with psychological distress is 2.24 times higher than in patients with

psychological well-being. The risk of dying associated with psychological distress is higher than the risk associated with increased age and is similar to that of disease severity. So, psychological status and quality of life are important prognostic factors in ALS, irrespective of length of time since diagnosis, disease severity, age and marital status as observed in our study.

The distributions of sex and disease onset in our Italian sample were similar to those of previous reports (27). During the questionnaires the psychologist noted if patients asked for any further help (motor help or cognitive help, to better understand the questions). An high request rate for cognitive (56,6%) and motor (32,9%) help was observed, thus suggesting that a face to face interview is a good approach for ALSAQ-40 assessment.

In conclusion, we found the Italian ALSAQ-40 and ALSAQ-5 are valid, reliable disease-specific QoL instruments for Italian MND patients, as shown also in other language versions. The results of this study show that the Italian ALSAQ-40 and ALSAQ-5 are useful measures of health status in ALS and that their psychometric indexes are comparable to those of the original UK version.

A copy the instrument translated and validated in Italian is reproduced in Appendix III.

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5. EMOTIONAL LABILITY IN MND: STUDY ON NEUROPSYCHOLOGICAL AND PSYCHOPATHOLOGICAL CORREALTES, IMPACT ON CAREGIVERS AND ELQ ITALIAN VALIDATION

5.1 EMOTIONAL LABILITY IN MND: AN OVERVIEW OF LITERATURE DATA AND OUR PURPOSES

Emotional Lability (EL), is the involuntary occurrence of laughter and crying in the absence of a corresponding change in affect. It was first reported in Motor Neuron Disease (MND) in the last century and was found to occur in 19%-49% of Amyotrophic lateral Sclerosis (ALS) patients (1,2), the most common form of MND. EL is most often present in patients who have pseudo-bulbar symptomatology (1,3). Nevertheless, few studies have undertaken a systematic investigation of this phenomenon and hence it remains poorly understood.

In 1997 Moore and colleagues validated the CNS-LS (Centre of Neurological Study-Lability Scale) in ALS patients; a seven-item, self report measure of affective lability composed of two subscales measuring labile laughter and labile tearfulness (4). The CNS-LS represents a good clinical instrument, but lacks the details necessary to permit a thorough exam of the nature and the pervasiveness of emotional lability in the MND population. More recently, Newsom-Davies and colleagues (3) developed the Emotional Lability Questionnaire (ELQ), a measurement scale specifically designed to assess MND patients which includes a self-rated version for patients and independent-rated version for caregivers. The ELQ was modified from the Pathological Laughter and Crying scale (5) which was first developed for stroke patients. The ELQ presents good psychometric properties and in depth exploration of emotion and expression, such as the introduction of the ‘abnormal smiling’ subscale. We set out to validate an Italian version of the ELQ, to produce a measure able to detect lability in an Italian population of MND patients, and to distinguish between pathological laughing, crying and smiling.

A second aim of this study was also to investigate the relationship between EL and cognitive deficits, which are found in some patients with MND. Although EL can be found in patients with frontal and temporal lobe involvement, the traditional view is that EL is due to damage to pathways that arise in the motor areas of the cerebral cortex and descend to the brainstem and inhibit putative centres for laughter and crying. Recent neuroanatomical findings suggest that the critical areas are in the cerebro-ponto-cerebellar pathways (6,7). The abnormal cognitive profile found in MND/ALS is well-known, and consists of predominant executive dysfunction and in some cases language and memory dysfunction (8,-11, 46-50). Visuospatial functions appear well preserved. This profile of impairment is consistent with frontotemporal involvement as found in neuroimaging studies of MND patients (12,13,14). In one of the largest studies of cognition in ALS to date (15), 47% of patients showed executive dysfunction, and 15% of them had severe cognitive impairment with features that were consistent with fronto-temporal dementia. The presence of cognitive impairment in MND appears more prominent in patients with pseudo-bulbar palsy (10,16). In previous studies emotional lability was also found to significantly correlate with bulbar scores (3). However, the relationship between EL and cognitive dysfunction in MND has received little attention other than a small study reported by McCullagh and colleagues (17) in which a difference was found between 8 ALS patients with EL and 10 patients without, in errors on Wisconsin Card Sorting Test.

Moreover, the relationship between EL and psychopathology has not previously been investigated in MND. Estimated prevalence rates for depression or mild depressive-symptomatology has appeared low, between 0-44% in MND populations (18,19,20,21). In recent studies depression has appeared to be relatively more common (prevalence rates up to 50%), as were other forms of psychological distress, and was not associated with illness severity and functional status (22). Estimated prevalence rates for anxiety have ranged 11-30% (23,24,25). A number of studies have shown the importance of including patients' families in psychological research on MND. Social factors have been reported to

be the best predictor of ALS patients' self-esteem during the disease (26). In addition Gauthier et al.(27) found that patients' level of disability and caregivers' depression were related with caregivers' perception of burden. While Goldstein (23) showed that carers also demonstrated signs of anxiety and depression, with the latter correlating with aspects of the patients' functional impairment. Carers depression and strain appeared to be related to their attributional style and perceived strain was greater in carers who viewed their partners' illness as having a more global impact on their lives (28). Hence, our third aim was to investigate the relationship between EL and psychological status in patients and their caregivers.

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5.2 METHODS AND MATERIALS

5.2.1 Participants

We recruited 41 patients with Motor Neuron Disease in the Neurosciences Department of Padua, in the period from March 2007 and November 2007. The sample consisted of 16 females and 25 males; 32 of 41 had ALS, 6 had Primary Lateral Sclerosis, 1 was affected by Progressive Bulbar Palsy , 1 was affected by Progressive Muscular Atrophy and 1 had Flail Arm Syndrome. Mean age of the sample was 58.19 (11.59sd, range 23-77). Mean educational level was 9.39 years. All of the ALS patients fulfilled the criteria of "probable" or "definite" ALS (29). We excluded patients with a clinical diagnosis of dementia according to Neary's criteria (30), those in receipt of 24-hour care and those with cerebral injury or cerebrovascular accident. We assessed their respective caregivers in 39 cases of 41; two patients reported not to have a single referential caregiver. The carers sample consisted of 11 males and 18 females (mean age was 52.56 , 15.42sd); 74% of them were the patient's spouse. More detailed data of patients and caregivers are showed in Table I.

We also tested as controls 39 healthy subjects. The control group did not significantly differ from the patient group in gender, age and educational level. Thirty-nine pseudo-caregivers (i.e. who spent the day with the 39 healthy subjects) were also tested. The pseudo-caregivers did not significantly differ from the carers in gender, age and educational level. Similar exclusion criteria were applied.

5.2.2 ELQ translation and back-translation

The original Emotional Lability Questionnaire, (3) consisted of two components: the self-rated version, given to MND patients, and the independent rated version given to carers. Each questionnaire contains 33 items, including three subscales measuring: Laughing (11 items), Crying (11 items), and Smiling (11 items). The

questions refer to the patients' condition during the past four weeks and the answers are given on a four-point Likert scale. The higher the score, the higher the level of perceived emotional lability.

The translation and back-translation process included three phases: the first, in which two native Italian speakers fluent in English, translated the original version of the ELQ; then, using the back-translation approach, two native English speakers fluent in Italian, translated the English version to Italian. In the third phase, four raters compared the two versions. No relevant differences between the original and back-translated versions of the questionnaires were found.

5.2.3 Procedure

MND patients and caregivers were interviewed separately by a psychologist, following neurological examination. The interview took an average of 1.5 hours to complete. The same method was employed to assess controls and pseudocaregivers. The ELQ, both self-rated and independent rated versions, and other psychodiagnostic instruments, were administered as a structured interview to each participant. MND patents were asked to return to our Neurological department no longer than two months after first assessment, for a more comprehensive neuropsychological test battery. The great majority of patients (93%) accepted. The complete neuropsychological evaluation took an average of 1 hour, however not every patient was able to complete all of the tasks due to severity of motor impairment or bulbar involvement.

5.2.4 Neuropsychological Measures

Thirty-eight of 41 MND patients undertook the neuropsychological battery, which was designed to assess intelligence, executive functions, memory and language. An initial general screening was undertaken using the *Mini Mental State Examination* (32). Intelligence was assessed with the *Raven's Coloured Matrices* (33) and with the *Brief Intelligence Test* (T.I.B.), designed to estimate pre-morbid intellectual ability (34). Executive functions were explored using the *Modified*

Wisconsin Card Sorting Test (35), *Phonemic Verbal Fluency* (F,A,S) (36), *Digit Span Backward* (37), *Trail Making Test A and B.* The latter was performed according to Reitan's protocol (38). Long and short-tem Memory were respectively investigated with *Babcock's Prose* (36), *Verbal Digit Span Forward* (37) and *Corsi Blocks tapping test* (36). Language was investigated with *Semantic verbal fluency* (modified version from Spinnler) (37). To exclude the effect of dysarthria on verbal fluency, both phonemic and semantic, a motor control condition was performed in which patients were asked to read aloud all the words generated previously during the task as quickly as possible and the examiner recorded the time taken to perform this phase. The difference between the specified time for the generation condition and the time taken for the control condition, the fluency index (*fi*) was calculated according to guidelines of Abrahams et al.(*Neuropsychologia,* 38:734-747, 2000) (11).

5.2.5 Psychodiagnostic Mesaures

Depression was assessed using the *Beck Depression Inventory* (BDI) (39). State and trait anxiety were respectively evaluated with Spielberger's *State and Trait Anxiety Inventory* (STAI Y-1 and STAI Y-2) (40). Emotional fragility and sense of inadequacy were investigated with *Emotional Fragility questionnaire* (FE) (41), a questionnaire focusing on sense of frailty and inadequacy.

5.2.6 Functional Mesaures

The Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) is a 12-item scale, in which the patient's functioning for each item is rated on a scale from 0 (unable to attempt the task) to 4 (normal function). This scale includes evaluation of swallowing, speech, and respiratory function, and both strength and function of the upper and lower extremities musculature. *Medical Research Council* (MRC) scale was used to obtain a more specific strength measure for upper and lower extremity muscles groups.

5.3 STATISTICS

5.3.1 Validation of the Italian version of the ELQ

Spearman's correlations were applied to establish the internal validity of the ELQ, both self-rated and independent rated versions, between Laughing, Crying, Smiling subscales and global scores. Spearman's correlation was also undertaken to explore construct validity, separately for patients and controls group, and for caregivers and pseudo-caregivers. MND characteristics (including age, educational level, time since onset, onset of disease in terms of bulbar or limb, functional scores such as ALFRS-R and MRC for upper and lower extremities) were compared with ELQ scores with Spearman's correlation.

5.3.2 Neuropsychological and Psychopathological battery and ELQ scores

The cognitive and psychopathological data were analyzed with Mann Whitney U non-parametric tests (as the data were not normally distributed), comparing patients' performance with controls. Spearman's correlations between ELQ data and the neuropsychological and psychopathological variables were applied to those variables on which the ALS group were impaired. Due to the number of correlations significance was set at $p=0.01$ to reduce the incidence of Type 1 errors.

5.4 RESULTS

5.4.1 Validation of the Italian version of the ELQ

Seventy-one per cent of patients indicated that they suffered from at least of one of the three emotional lability domains (Laughter, Crying, Smiling), as opposed to 5% of healthy controls. Significant results relating to validity are displayed in Tables III and IV. In addition, correlational analyses were used to explore the relationship of EL to demographic variables and clinical data. MND patients displayed a positive correlation between time since onset of disease (in months) and Laughing ($r=0.48$; $p<0.00$). Global Lability revealed a significant correlation with ALFRS-R total scores ($r=0.36$; $p<0.01$); in particular, significant correlations were found between Global Lability and ALSFRS-R 1-language ($r=0.50$; $p < 0.000$) and ALSFRS-R 3 -swallowing ($r=0.47$; $p < 0.001$). The MRC did not exhibit any significant correlations.

5.4.2 Neuropsychological tests and ELQ

Neuropsychological results are reported in Table II.. In the comparison of the patient and control groups, MND patients showed a trend towards impaired performance on digit span backwards and Corsi block tapping test and were significantly impaired relative to controls on the Raven's Coloured Progressive Matrices. (you don't need to put in the U and p values here as they are in the table) No significant correlations were found between neuropsychological performance and emotional lability. Semantic Verbal Fluency Index was found to correlate with level of swallowing (ALSFRS-R 3) ($r=0.49$; $p<0.00$). MRC did not exhibited any significant correlation with these cognitive tasks.

Psychodiagnostic questionnaires and ELQ

Thirty-nine per cent of MND patients revealed BDI scores from 16 to 33; 34% showed the presence of state anxiety (STAY-Y1) and trait anxiety (STAI Y-2)

with greater than one standard deviation above the cut off; 51% of patients' scores were greater than the 75th percentile in Emotional Fragility questionnaire. While, 18% of caregivers had depression scores from moderate to severe on the BDI; 79% showed STAI-Y1 scores over the clinical cut off, and 44% were over the clinical cut off on the STAI-Y2; 46% went greater than the 75 percentile of emotional fragility scores. –Scores for the BDI, STAI Y1 and STAI Y2 revealed significant differences between patients and healthy controls. Caregivers had significantly greater scores on the BDI and STAI Y2 than pseudocaregivers. The results are presented in Table V.

Finally, psychological results obtained from questionnaires administered to the four groups were compared with Spearman correlations with ELQ scores. In the ALS/MND patients ELQ Global Lability correlated with state anxiety (STAI Y1) scores, ($r=0.36$. $p<0.01$) and with Emotional Fragility questionnaire scores ($r=0.4$; $p<0.00$). The Crying subscale showed a significant correlation with Emotional Fragility ($r=0.44$; $p<0.00$), BDI scores ($r=0.41$; $p<0.00$), STAI Y1($r=0.38$; $p<0.01$), STAI Y 2 ($r=0.37$; $p<0.01$). In caregivers, Smiling subscale of independent rated version showed a strong trend towards a significant correlation with Emotional Fragility questionnaire at our raised significance threshold ($r=0.33$; $p<0.05$). No significant correlation were found in healthy controls and pseudo-caregivers with respect to emotional lability and psychopathological features.

Both validated questionnaires, for patients and caregivers, are presented respectively in appendix IV and V

Table I: Features of MND patients and caregivers

Patients (n=41)	Values
Men, n (%)	25 (60.9)
Mean Age(SD)	58.19(11.6)
Mean Educational level (years)(SD)	9.4 (4.5)
Mean length from diagnosis (months) (SD)	40.58(33.8)
Spinal onset (%)	30(73.2)
Married, n (%)	33 (80.4)
Mean MRC upper limbs (SD)	38.6(10.9)
Mean MRC lower limbs(SD)	29.2(11.5)
Mean ALSFRS-R(SD)	32.7 (7)
Caregivers (n=39)	
Men, n (%)	11(28.2)
Mean Age(SD)	52.5(15.4)
Mean Educational level (years)(SD)	9.4(4.8)
Spouses	29 (74.4)
Sons or daughters	7(17.9)
Parent	1(2.6)
Brothers or sisters	2(5.2)

ALSFRS-R= Amyotrophic Lateral Sclerosis Functional Rating Scale Revised;
MRC upper and lower= Medical Research Council scale applied to upper extremities (maximum score=50) and applied to lower extremities(maximum score=40)

Table II: Neuropsychological assessment of patients and controls

	Patients n Mean (SD) *n=38*	Controls Mean (SD) *n=39*	Mann Whitney U Coefficient	P Value
General Screening				
MMSE	28.26 (1.77) *n=28*	28.51(1.79)	326	0.375
Intelligence				
Rs CPM	28.76 (5.61) *n=38*	31.86 (3.98)	**332.5**	**0.002**
TIB	108,78 (6,54) *n=30*	104,41 (9)	470	0.594
Memory				
Digit Span Forward	5.51 (0.94) *n=30*	5.94 (1.59)	468	0.233
Digit Span Backward	**3.3 (0,81) *n=24***	**3.72 (1.38)**	**411**	**0.052**
Babcock Prose	12.36 (2,56) *n=30*	12.97 (2.40)	450.5	0.309
Corsi Blocks Tapping	5 (1.02) *n=30*	5.5 (1.24)	**490**	**0.037**
Language				
Semantic Fluency	35.19 (12.46)	37.02 (10.95)	381	0.714
Semantic Index (*Sfi*)	*n=30* 2,44 (0,95) *n=30*	2,51 (1,21)	429	0.838
Phonemic Fluency	30.55 (11.15)	32.47 (13.36)	374	0.381
Phonemic Index(*Pfi*)	*n=30* 5.1 (2.32) *n=30*	5.1 (1.96)	466.5	0.714
Attention/Planning				
TMT A	44.6 (7.43) *n=24*	51.37 (30.50)	349	0.411
TMT B	126.88 (110.73) *n=24*	120.09 (33.62)	442.5	0.494
TMT A-B	82.28 (106.37) *n=24*	68.71 (60.23)	467	0.381
WCST (categories)	3.90 (1.89) *n=24*	4.41 (1.56)	324	0.309
WCST (errors)	17.35 (13.38) *n=24*	13.37 (8.31)	447.5	0.199
WCST (perseverations)	8.74 (9.61) *n=24*	5.7 (4.58)	439	0.254

$p<0.01$ and $p<0.05$ are highlighted in bold

MMSE=Mini Mental State Examination; RsCPM=Raven's Coloured Matrices; TIB=Brief Intelligence Test; TMT=Trail Making Test; WCST=Wisconsin Cards Sorting Test Modified Version (Nelson)

Table III: Statistically significant correlations between ELQ items for the patients and caregivers groups

ELQ scores correlating	Spearman's coefficient	P Value
Within self-rated version (n patients=41):		
Smiling-Total	0.52	0.000
Within independent-rated version (n caregivers=39):		
Crying-Total	0.69	0.000
Between self-rated and independent-rated version		
Self/Laughter-Independent/Laughter	0.57	0.000
Self/Total- Independent/Total	0.51	0.000
Self/Laughter- Independent/Total	0.46	0.000
Self/Total- Independent/Laughter	0.57	0.000

Table IV: Statistically significant correlations between ELQ items for the controls and pseudo-caregivers groups

ELQ scores correlating	Spearman's coefficient	P Value
Within self-rated version (n controls=39):		
Laughter-Total	0.91	0.000
Crying-Total	0.69	0.000
Smiling-Total	0.50	0.001
Within independent-rated version(n pseudo-caregivers=39):		
Laughter-Total	0.94	0.000
Crying-Total	0.43	0.000
Smiling-Total	0.76	0.000
Smiling- Laughter	0.72	0.000
Between self-rated and independent-rated version		
Self/Laughter- Independent/Smiling	0.82	0.000
Self/Laughter- Independent/Total	0.57	0.000

Table V: Participants psychopathological features and significant results[a]

	MND (SD) N=41	CONTROLS (SD) n=39	Mann Whitney U Coefficient	CAREGIVERS (SD) n=39	CAREGIVER'S CONTROLS(SD) n=39	Mann Whitney U Coefficient
BDI	15.92 (11.55)	7.38 (6.03)	**U=1203 (p<0.000)**	10.71 (6.48)	5.94 (6.30)	**U=1137 (p<0.000)**
STAI Y1	43.48 (13.45)	35.20 (9.66)	**U =1085 (p<0.005)**	47.76 (10.05)	35.64 (9.19)	**U=1247 (p<0.000)**
STAI Y2	44.39 (12.43)	32.56 (15.84)	**U =1155.5 (p<0.000)**	41.97 (8.61)	37.76 (9.45)	U=966.5 (p<0.05)
FE	74.2 (29.53)	58.27 (24.49)	U=1011 (p<0.05)	65.68 (24.21)	59 (27.04)	U=86.5 (p=0.312)

[a]Significant results are highlighted in bold

BDI=Back Depression Inventory; STAI = State-Trait anxiety Inventory; Y1= State Form; Y2= Trait Form; FE= EmotionalFragility

5.5 DISCUSSION

The Italian version of the ELQ showed good internal validity as determined by the relationship between the subscales (Laughing, Crying, Smiling) and global scores. Construct validity was corroborated by significant correlations between self rated version subscales and independent rated version subscales. Seventy-one per cent of MND patients reported that they suffered from at least one of the three aspects of emotional lability. This percentage appears greater than reported in previous studies (1,2,44). MND patients displayed a positive correlation between time since onset of disease (in months), Laughing and Smiling. Global Lability (total score derived from sum of the three subscales) was significantly related to ALFRS-R total scores and in particular with Language and Swallowing items. Our findings are therefore consistent with the view that the Emotional Lability correlates with disease progression and bulbar symptomatology (3).

The neuropsychological battery revealed significantly impaired performance in the MND group in the Raven's Coloured Progressive Matrices only as compared with controls. Two tests of working memory, Digit Span Backward and Corsi Block Tapping test, showed trends towards an impairment. Although the Raven's matrices is considered to be a test of fluid intelligence it can also be viewed as reliant on other more specific cognitive processes such as working memory, attention and problem solving and hence is dependent on intact executive functions. However, our group, unlike many previous studies, did not display a deficit on other tests of executive processes such as Verbal Fluency, Trail Making Test and the Wisconsin Card Sorting Test. Moreover, the neuropsychological scores did not correlate significantly with any aspect of emotional lability. This data are in contrast with McCullogh's and colleagues study (17), who implicated an association between prefrontal cortex dysfunction, as represented by deficits on the Wisconsin Card Sorting Test and emotional lability. The current findings suggest that different underlying neuronal pathways are involved with cognitive dysfunction in MND and emotional lability and provide further support for the concept of MND as a multisystem disorder. Cognitive change in MND has been

previously associated with extra-motor frontotemporal dysfunction (12, 13, 14) while it is possible that dysfunction of cerebro-cerebellar pathways are involved in the regulation of emotional expression (7).

With regard to the presence of psychopathology in MND, the scientific literature varies: the two most common features investigated, depression and anxiety have been reported in 0-44% and 10-36% of cases respectively. In our sample, 36% of patients showed a level of depression from moderate to severe, while very high levels of anxiety were reported with 70% exhibiting a high level of state anxiety and 60% and high level of trait anxiety. Furthermore high levels of emotional fragility were reported in 48% of cases. Wicks demonstrated that the estimated prevalence of mood disorder amongst patients with ALS may vary significantly depending on the measure used (21). Regardless of the lack of unanimous consensus of standard utilization of psychopathological measures, it was clear that our sample of MND patients revealed predominant anxiety, but with also depression and emotional fragility in many cases.

Moreover, the current study revealed a relationship between total scores on the ELQ and both state anxiety and Emotional Fragility indicating an association between lability and psychopathology in MND patients. The Crying subscale showed a significant relationship with all psychopathological measures. These findings suggest that the presence of psychopathological symptoms in MND patients may be a predisposing factor for emotional lability or in contrast that such psychopathology may be a reaction to emotional lability. Interviews with carers also demonstrated clear evidence of psychopathology with 20% reporting depression from moderate to severe levels on the BDI, while 85% and 72% showed state and trait anxiety scores over the clinical cut off, respectively. As for the relationship between patients and carers mood, some data in the literature have reported an association (23-28) but despite high levels of affective conditions in our patients and carers we did not find an association.

In conclusion, emotional lability appears to be more prevalent in the MND population than previously thought. However cognitive change was not associated with the presence of lability suggesting differential neurological pathways involved and indicating that extramotor involvement in MND is widespread. Moreover, the lack of ability to control one's own emotions and the expression of inconsistent emotions, seems to relate to high levels of anxiety and emotional frailty in people with MND. Hence, the relatively low number of patients' asking for a drug treatment for emotional lability (44) may not be representative of real discomfort caused by such emotion dyscontrol. Clinicians should be more aware of the effects of emotional lablity and provide appropriate support to the both the patients and caregivers during the course of the illness.

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6 . PSYCHOPATHOLOGICAL FEATURES AND SUICIDAL IDEATION IN ALS

6.1 PSYCHOLOGICAL CHARACTERISTICS IN ALS: A LITERATURE BRIEF REVIEW

Over the last four decades, few studies have been typically devoted to the psychological aspects of the Amyotrophic Lateral Sclerosis (ALS) -even if increasing attention has been focused on it- because of the comparisons between results are difficult mainly for evolution of disease stages and different assessment methodologies (1).

Most of these studies (2,3,4) evidenced poorly adjusted patients suggested somatic preoccupation plus a distress syndrome as anxiety, depression, impaired concentration, fatigue, loss of emotional control, alienation. Ratings scales such as the Neuropsychiatric Inventory, shown that up to 63% of patients are apathetic, irritable, inflexible, restless and disinhibited (4,5). Moreover, there remains an impression that patients with ALS are also cheerful, stoical, and positive (6, 7, 8, 9). Estimated prevalence rates for depression or mild depressive-symptomatology appeared in fact quite low and have varied between 0-44% (10, 11, 12), whilst prevalence rates for anxiety have ranged 0-30% (13). The estimated prevalence of mood disorder amongst ALS patients depends on the measure used, which causes results to vary significantly between different studies (14). Evidences enhances that depressive mood and psychological state may influence the survival span in ALS, and psychological well-being can prolong survival in patients with ALS and predict it after diagnosis. (15; 16). For these reasons cognitive insights in ALS patients appear as important prognostic features for the length of the disease and must be investigated, as yet observed by Kim (17).

Role of physical impairment in psychological status of ALS patients appear controversial: some authors found that the severity of patients' depression or low quality of life directly correlated with the level of physical disability (18; 19, 20);

otherwise, different studies displayed that positive mood and satisfying quality of life could be maintained as physical functions declines (21,22;7, 23, 24).

The presence of suicidal ideation represents another psychological aspect which has been scarcely investigated so far: it has been suggested that most ALS patients in end-stage of life had a living will, and only little percentage express the desire to hasten dying (25,26). Anyway, suicidal ideation in ALS has been deepen just in months before death and not in months after diagnosis.

6.2 STUDY PORPUSES

In order to gain a better understanding in ALS psychological profile, we set out to: 1) determine psychological features in our sample of people with ALS respect to strength (assessed with MRC), functionality (evaluated with ALSFRS-R) (27), and forced vital capacity (FVC);

2) correlate psychopathological features with quality of life domains (performed with ALSAQ-40); 3) investigate whether there is a cognitive-affective typical pattern in our ALS patients, divided in recent diagnosis versus longer than two years, and compared to Mystenia Gravis (MG) patients. MG is an autoimmune disorder resulting from the production of antibodies against acetylcholine receptors leading to the destruction of the postsynaptic membrane at the neuromuscular junction, and was chose as representative sample of neuromuscular pathology not leading to death, as in ALS. This last comparison was mainly addressed to investigate differences in suicidal ideation.

Exner's Rorschach Inkblot test (28), firstly used for ALS patients in our study, was chosen as elective instrument in order to obtain a detailed insight in ALS cognitive and affective profile: this measure represents a very different approach to the understanding of personality than self-reports test: on the one hand cognitive complexities inherent this test response elaboration includes conscious processes, like semantic processing and short-term visual storage, and unconscious affective process (29); on the other hand, Rorschach method can yield information about underling personality dimensions that individuals may not be aware of or his unwilling to expose (30, 31, 32).

6.3 METHODS AND MATERIALS

6.3.1 Participants

We recruited 42 ALS patients via the Neurosciences Department of Padova University, in the period between March 2005 to March 2007. All patients were evaluated in Outpatients Clinic by two neurologist, a psychologist and a speech therapist and fulfilled the criteria for “probable” or “definite” ALS according to El Escorial Criteria (33). Each patient was underwent to a neuropsychological evaluation, different according to everyone physical impairment, to exclude patients with clinical dementia or severe cognitive impairment. Three patients (two males, one female) were excluded for this reason. The bulbar severe impairment have reduced opportunities to investigate all patients completely enable to speech.

In the second part of analysis our ALS patients were dived into two target sample groups: the first, called ALS1, composed by people who have received the diagnosis less than two years before the evaluation, and the second, called ALS2, composed by patients who have received the diagnosis more than two years before the evaluation. Twenty-one Myastenia Gravis (MG) patients, matched for age, sex and educational level were compared to ALS subgroups.

Participation to psychological testing was voluntary and the patients gave their informed written consent. All of the ALS patients fulfilled the criteria of “probable” or “definite” ALS (27). We excluded patients with a clinical diagnosis of dementia according to Neary’s criteria (34), and those in receipt of 24-hour care. Demographic and clinical data on two ALS study group and comparative myastenic group are presented in Table I.

6.3.2 Measures

To evaluate patients motor disability we used the measure of muscle strength by the limb muscles (score from 0, absence of movement to 5, full strength). Muscles evaluated were: deltoids, triceps and biceps brachii, finger extensor, thumb adductor, thigh flexor, knee extensor, ankle extensor and flexor. All muscles were tested bilaterally. We considered the total *MRC score* (megascore) of both upper and lower limbs which respectively ranged from 0 to 60 and from 0 to 40.

Forced Vital Capacity (FVC) was assessed by a standard manual spirometer (CYTEC 60) and expressed as a percentage of the expected value.

To assess functional abilities we used the *Amyotrophic lateral Sclerosis Functional Rating Scale Revised* (ALSFRS-R), a 12-item scale, in which the patient's functioning for each item is rated on a scale from 0 (unable to attempt the task) to 4 (normal function). This scale includes evaluation of swallowing, speech, and respiratory function, and both strength and function of the upper and lower extremities musculature, as reported in chapter 4. A score of 48 points is normal whereas 0 points indicates maximal dysfunction.

Quality of life and subjective health were measured with the *ALSAQ-40* (35, 36), a 40-items questionnaire specifically dedicated to ALS, measuring five dimensions of health: 'Physical Mobility', 'Activities of Daily Living', 'Eating and Drinking', 'Communication' and 'Emotional Functioning'. The instrument has a 0-4 Likert type scaling and we considered for this study only the five global dimensions (for more information see chapter 4).

To evaluate psychological profile was employed *Rorschach Inkblot test*; this famous projective-cognitive test is notoriously composed by ten official inkblots. Five inkblots are black ink on white, two are black and red ink on white, three are multicolored. Using the scores for these categories, the examiner then performs a series of mathematical calculations producing a structural summary of the test

data. The results of the structural summary are interpreted using existing empirical research data on personality characteristics that have been demonstrated to be associated with different kinds of responses. Rorschach protocols followed Exner's Comprehensive System (CS) guidelines. This system of scoring represents the standard method in psychology for interpreting the Rorschach: it has demonstrated significant refinements in reliability, validity, statistical power and interrater-reliability as a result of the procedural standardization and scoring innovations introduced (37,38). Thanks to this method we can investigated suicidal ideation and more than 300 other psychological indices for every protocol. The test was administered and scored by a psychologist trained in Rorschach Exner's CS We performed both the calculations of scores and then the first steps of interpretation through the ROR-SCAN software (*2006 by Philip F. Caracena).*

6.4 STATISTICS

Data analysis were performed using the Statistical Package for the Social Sciences (SPSS) (39). Rorschach indices correlation, in the entire ALS sample, was calculated for clinical measures (ALSFRS, MRC FVC) and all five dimension of ALSAQ-40 with Pearson parametric test.

Three group differences (recent ALS diagnosis, longer ALS diagnosis, Myastenia Gravis) in psychological variables were determined using T-test. Bonferroni's correction was applied to significant overall group effects, accounting for the multiple comparison.

The significant level was set up at $p<0.05$, and all tests were two-tailed.

6.5 RESULTS

Forty-two patients affected by ALS (mean age 60,5 s.d. 13.8; 18 females and 24 males, 5 with bulbar onset and 37 with limb onset), and 21 myastenic controls (mean age 58.3 ; standard deviation 16.7; 8 females and 13 males) were assessed. Demographic and pathological characteristics for ALS group and MG group are shown in Table I.

In the first part of our study, each patients received neurological assessment respect of strength, (MRC), ALSFRS-R, FVC and quality of life (ALSAQ-40).

In the second part, ALS group was divided in two subgroups: ALS1 (21 patients, 13 males and 8 females mean age 58.5 sd 8.9, mean length of disease since diagnosis 11.5 months), who have received the diagnosis less than two years before the evaluation, and ALS2 (21 patients, 11 males, 10 females, mean age 60.33, sd 14, mean length of disease since diagnosis 32.5 months) who have received the diagnosis more than two years before the evaluation.

The three groups (ALS recent diagnosis-ALS longer diagnosis-MG patients), did not show significant differences for age, gender, or years of education, and were compared for psychological features evaluated by Rorschach test.

6.5.1 Clinical Measures (MRC, FVC, ALSFRS-R)

In ALS patients sample was shown a significant negative correlation ($p<0.01$) between loss of strength in upper limbs (MRC upper) and Rorschach variables indicating affective resources (W Sum C)($r=-0.712$), all available resources both affect than ideation (EA)($r=-0.688$), pure H<2($r=-0.626$). Positive correlation emerged between strength in upper limbs and abilities in management of actual stress perceived (D) ($r=0.477$; $p<0.05$), chronic stress perceived (ADj D)($r=0.716$; $p<0.00$), interpersonal behaviour ineffective or maladaptive (PHR) ($r=0.476$; $p<0.05$), uncontrolled, unmodulated expression of feelings CF+C<F ($r=0.459$; $p<0.05$).

Impairment in lower limb strength negatively correlated with distortion of reality (FX-%) ($r=-0.454$; $p<0.05$), whereas positive correlations were found lack of interest in people (Pure H<2) ($r=0.562$; $p<0.01$). Forced Vital Capacity negatively correlated with chronic stress perceived (D) ($r=-0.363$; $p<0.05$), overburden of stress (D>AdjD) ($r=-0.447$; $p<0.01$), overburden of actual stress (es>EA) ($r=-0.483$; $p<0.05$), anxiety (XuY) ($r=-0.710$; $p<0.01$), rigid use of escapist fantasy (M passive) ($r=-0.358$; $p<0.05$), and anger (S<3)($r=-0.353$; $p<0.01$). Higher ratings of introspection ability (FD) was associated with higher FVC)($r=0.430$; $p<0.05$).

Correlation between these clinical measures and Rorschach variables are showed in Table II.

Regarding ALSFRS-R, item concerning 'Feeding' (item 5) was the one that showed more significant correlation: greater impairment was associated with lack of feelings and ideation (EA)($r=-0.422$; $p<0.05$), with distortion of reality and cognitive defects (X-)($r=-0.390$; $p<0.05$), and with anger (S<3) ($r=-0.316$; $p<0.05$). Lower speech abilities (item 1) were correlated with uncontrolled, unmodulated expression of feelings (CF+C>F) ($r=0.321$; $p<0.05$). Greater impairment in writing (ALSFRS-R item 4) was associated with correlated with lack of feelings and ideation (EA)($r=-0.313$; $p<0.05$), as in the case of Feeding.

Impairment in Dispnea (item 10) correlated with isolation ((H+Hd+(H)+(Hd)) ($r=0.342$; $p<0.05$) and severe interpersonal problems and coping defect (CDI)) ($r=0.318$; $p<0.01$).

Correlation between ALSFRS-R functional measures and Rorschach variables are displayed in Table III.

6.5.2 Quality of life

For ALSAQ-40 domains, 'Physical Mobility' correlated with avoidant style and lost of interest n reality (R<17) (r=0.339; p<0.05).

Loss of 'Activities in daily Living and Independence' correlated with overburden of stress (D>AdjD) (r=0.492; p<0.05), self introspective tendencies in pessimistic view of themselves, sense of guilt (SumV+FD>2) (r=0.450; p<0.01), = presence of uncertainty, confusion, or ambivalence about feelings*;* (C-S Bl>0) (r=0.339; p<0.05), uncontrollated, unmodulated expression of feelings (CF+C>FC) (r=0.304; p<0.05).

Impairment in 'Eating and Drinking' correlated with Depressive way of thinking and morbid ideation (MOR>3) (r=0.339; p<0.05).

Lower score in 'Communication' domain was associated with rigidity of thinking (a>p+1) (r=0.467; p<0.01), and avoidant style, lost of interest in reality (R<17) (r=0.357; p<0.05).

Disturbed, suffering Emotional Functioning correlated with positive Depressive Constellation (DEPI<5) and positive coping defect Index (CDI=3) (r=0.390; p<0.05).

Correlation between ALSAQ-40 measures and Rorschach variables are displayed in Table IV.

6.5.3 Psychopathological features

ALS 1 group responded differently in a number of indices from ALS group 2. In particular, significant differences were found for anxiety (FY) (p<0.05), distrust (Hd+(Hd)+Ad+(Ad)) (p<0.01) and interpersonal relations deficit (CDI) (p<0.05) were grater in patients with recent diagnosis than in patients with longer one. Accurate detection of reality appeared, on the other hand, significant poorer in ALS1 respect of ALS 2 (p<0.05). Suicidal Ideation index showed significant higher scores (p<0.000) for ALS1 respect to ALS2.

Compared to MG patients, ALS 1 group showed greater anger (S, S-), ($p<0.05$), elevate situational stress perceived (es), ($p<0.05$), overburden of stress (D) ($p<0.01$), morbid ideation (MOR) ($p<0.05$), uncertainty, emotional confusion (C-Sh Bl) ($p<0.05$), positive coping defect Index (CDI) ($p<0.05$), depressive thoughts (DEPI) ($p<0.01$) and suicide ideation (S-CON) ($p<0.01$).

ALS 2 group, compared to MG patients, displayed : less intellective abilities (M) ($p<0.05$), greater overburden of stress, (D) ($p<0.05$), severe cognitive defect (INC2) ($p<0.05$), cooperative tendency (COP) ($p<0.05$), Depressive thoughts (DEPI) ($p<0.05$), and suicidal ideation (S-CON) ($p<0.01$).

Tab I.: Demographic and clinical characteristics of ALS and MG patients

	ALS 1 (n=21)	**ALS 2 (n=21)**	**MG (n=21)**
Age (SD)	58,47 (8,87)	60,33 (14,01)	58,33 (16,69)
Years of education (SD)	9,47 (3,05)	9,8 (5,08)	9,24 (4,7)
Males (n)	11	12	13
Married (n)	17	15	18
Time since Diagnosis (SD)	11,5 (4,94)	32,47 (6,72)	
Bulbar onset (n)	5	2	
ALSFRS-R	38,57(5,67)	29,5 (6,41)	
FVC (SD)	81,01 (20,24)	65,93 (6,41)	
MRC upper (SD)	45,28 (8,11)	35,8 (12,9)	
MRC lower (SD)	31,28(10,52)	19,8 (12,14)	

ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
FVC=Forced Vital Capacity
MRC upper and lower= Medical Research Council scale applied to upper districts (maximum score=50) and applied to lower districts(maximum score=40)

Table II: Correlation between clinical measures and Rorschach variables

	Rorschach Variables	Pearson Coefficient (P value)
MRC upper (n=41)	W Sum C	-0.712**(0.000)
	EA	-0.688**(0.003)
	Pure H<2	-0.626**(0.002)
	D	0.477*(0.029)
	Adj D	0.716**(0.000)
	PHR	0.476*(0.029)
	CF+C>F	0.459*(0.036)
MRC lower (n=41)	FX-%	-0.454*(0.039)
	Pure H<2	0.562**(0.008)
FVC (n=33)	D	-0.363*(0.038)
	D>AdjD	-0.447**(0.009)
	es>EA	-0.483*(0.04)
	XuY	-0.710**(0.000)
	M passive	-0.358*(0.041)
	S>3	-0.353**(0.004)
	FD	0.430*(0.013)

** *p value* < 0.01, * *p* < 0.05 *Pearson correlation coefficients*
FVC=Forced Vital Capacity
WSumC *=affective resources; EA=all available resources, both affect than ideation; Pure H<2 =lack of interest in people, incapacity to identify themselves with entire, complete human being; D=presence of distress; AdjD =chronic stress perceived; PHR=interpersonal behaviour ineffective or maladaptive ; CF+C>F= uncontrolled, unmodulated expression of feelings ; FX-%=distortion of reality; D>AdjD =overburden of stress;* es>EA *= experienced stimulation greater than experience actual, available individual resources are not sufficient to substain actual situation XuY=anxiety; M passive=use of escapist fantasy; S>3=anger; FD=introspection*

Table III: Correlation between ALSFRS-R [c] and Rorschach variables

ALSFRS items/Rorschach variables	Pearson Coefficient (P value)
Speech /CF+C>F	-0.321*(0.047)
Writing /EA	0.313*(0.044)
Feeding /EA	0.422*(0.05)
Feeding /X-%	-0.390*(0.047)
Feeding /S>3	-0.316*(0.041)
Dyspnea/ H+Hd+(H)+(Hd)	0.342*(0.02)
Dyspnea /CDI	-0.318**(0.004)

** *p value* < 0.01, * *p* < 0.05 *Pearson correlation coefficients*
[c] *Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised*

CF+C>F= uncontrollated, unmodulated expression of feelings; EA=all available resources, both affect than ideation; X%=distortion of reality; H=interest in people; H+Hd+(H)+(Hd)=interest in people/isolation; CDI=severe interpersonal problem

Table IV: Correlation between Quality of life subscales (ALSAQ-40) [b] and Rorschach variables

ALSQA-40 subscales / Rorschach variables	Pearson coefficient value (P value)
Physical Mobility /R<17	0.339 * (0.039)
Activities of daily Living and Independence/D>AdjD	0.492* (0.04)
Activities of daily Living and Independence/Sumv+FD>2	0.450** (0.008)
Activities of daily Living and Independence/C-S Bl>0	0.338* (0.039)
Activities of daily Living and Independence/CF+C>FC	0.340* (0.039)
Eating and Drinking/MOR>3	0.338* (0.039)
Communication/a>p+1	0.467** (0.006)
Communication/R<17	0.357* (0.031)
Emotional Functioning/DEPI<5;CDI=3	0.390* (0.02)

** *p value* < 0.01, * *p* < 0.05 *Pearson correlation coefficients*

[b]*Amyotrophic Lateral sclerosis Questionnaire-40 Items*

R<17=avoidant style, lost of interest n reality; D>AdjD = overburden of stress; *SumV+SumFD>2=self introspective tendencies, pessimistic view of themselves, sense of guilt; C-S Bl>0 = presence of uncertainty, confusion, or ambivalence about feelings; CF+C>F = uncontrolled, unmodulated expression of feelings ;* MOR>3 = *Depressive way of thinking, morbid ideation; a>p+1 =rigidity of thinking;* DEPI<5;CDI-3= *Major Depression* es>EA = *experienced stimulation greater than experience actual, available individual resources are not sufficient to substain actual situation ;*

Table V: Mean ratings and p values for between group ALS 1 and ALS 2 analyses

Rorschach Variables	Mean (SD) ALS 1	Mean (SD) ALS 2	T test (p<0,05)
Anxiety (FY)	0.78(0.7)	0.61(0.83)	0.047
Distrust (Hd+(Hd)+Ad+(Ad))	5.10(2.5)	2.95(1.88)	0.000
Interpersonal problems (CDI)	3,62(1.3)	3.33(1.1)	0.015
Accurate detection of reality (X+%)	51.67(8.5)	58.95(017)	0.015
Suicidal Ideation (S-CON)	8(1.7)	6(1.3)	0.000

Table VI: Mean ratings and p values for between group ALS 1 and MG analyses

Rorschach Variables	Mean (SD) ALS 1	Mean (SD) MG	T test (p<0,05)
Anger (S)	3.48(1.9)	1.76(1.6)	0.012
Destruptive Anger (S-)	1.10(0.8)	07(1.2)	0.012
Situational stress perceived (es)	11.8 (4.3)	8.9(4.6)	0.012
Overbuden of stress (D)	- 1.62 (0.9)	- 0.43(1.39)	0.000
Morbid Ideation (MOR)	2.67(1.8)	1.5(1.2)	0.048
Uncertainty, emotional confusion(C-Sh Bl)	1(1)	0.33(0.5)	0.048
Depressive thoughts (DEPI)	5(1.2)	3.33(1.5)	0.006
Interpersonal Defect Index (CDI)	3,62(1.3)	2.67(1.3)	0.006
Suicide Constellation (S-CON)	8 (1.7)	4(1.4)	0.000

Table VII: Mean ratings and p values for between group ALS 2 and MG analyses

Rorschach Variables	Mean (SD) ALS 2	Mean (SD) MG	T test (p<0,05)
Intellective abilities, thoughts (M)	2.9 (1.8)	4.1(2.9)	0.042
Overbuden of stress (D)	- 1.56 (0.9)	- 0.43(1.39)	0.027
Severe Cognitive defect (INC2)	0.5(0.2)	0.33(0.6)	0,047
Cooperative tendency (COP)	0.76(1.22)	1.86(1.2)	0.021
Depressive thoughts (DEPI)	4.38(1.3)	3.33(1.5)	0.027
Suicide Constellation (S-CON)	6(1.3)	4(1.4)	0.000

6.5 DISCUSSION

A common misconception of the Rorschach test is that its interpretation is based primarily on the content of the response. In fact, it is only a comparatively small portion of a broader cluster of variables that are used to interpret the Rorschach data, that, according to Exner's comprehensive system guidelines (37, 38), are elaborated according to a very restrictive scoring. The great vantage of this method is that it can reflects unconscious thoughts and wishes, or ideas that patients do not want to expose, such as death desire. Our initial purposes were to examine the correlates between physical impairment and quality of life with psychopathological features, assessed by Rorschach, in ALS patients. Secondly, we investigated how length of time since diagnosis can be associated with psychological features, in particular with suicidal ideation. Regarding the first point, correlations between Rorschach psychological indices and functional, clinical aspects were performed to all 42 ALS patients data. In the second part of the study our ALS sample was divided into two groups, according to length of the diagnosis (recent versus longer than two years), and were compared with a group of patients affected by Myasthenia Gravis, representing a good comparison as a neuromuscular disorder not leading to death. Patients' physical strength was assessed according to Muscular Research Council scale and scores were grouped in upper and lower muscular districts. Upper districts strength loss revealed correlation with greater emotional impulsiveness, action involving less cognitive adaptation, presence of emotion such as irritation, suggestiveness, sensitivity (40). Moreover, this loss appear to correlate with interpersonal behaviour as unaffective or maladaptive, with decline of interest in people or incapacity to identify themselves with entire, global human being and with diminish of available resources. The concept of resources refers to affective and cognitive capabilities that are been developed, including the manner by which feelings are identified and utilized. The more resources available, the more likely the person is able to form and direct behaviours: stress tolerance relates directly with lack of available resources. In fact, upper limb loss of functionality appear also linked to increase

of stress intolerance: in particular, whilst 5% of the adult non-patient show negative values in stress tolerance index, 60% of ALS patients of our sample present negative values (37). Functional loss in lower muscular districts seems to concern lesser psychopathological involvement than upper muscular impairment. In decreasing of functionality of lower districts we observed diminished interest in other people, as in upper areas, and cognitive distortion of, or disregard for, reality; this latter aspect could be caused by a host of reasons. Some can be caused by faulty cognitive processing, however, in most instances, the processing is adequate but emotional elements and/or preoccupations prompt a misidentification of the stimulus set. The decrease of pulmonary capacity shows the rising of anger, anxiety, chronic and actual difficulty in stress management, overburden of stress, self-introspective tendencies and excessive, rigid use of escapist fantasy; this latter aspect can suggest the tendency toward interpersonal passivity. So, in our data, loss of strength in upper muscular districts appear more psychologically traumatic respect to the loss of lower districts strength. In both cases, physical impairment confirmed the relation with psychological distress rising. Our findings permitted moreover to define a different pattern of psychological reaction to upper and lower muscular strength loss. As with ALSFRS-R, correlation with psychological features showed great number of correlation in the item concerning autonomous feeding. The more the independence in this ability declines, the more appear to emerge feelings of anger, anxiety, distortion of reality and to diminish cognitive and affective resources. Similarly, also impairment in writing ability seems to be linked to decreasing in personal resources, language loss appear associated with emotional discontrol and level of dyspnea presents correlation with lack of interest in other people and coping defect in interpersonal relations. In particular, the link between loss of language (indicating bulbar involvement) and emotional discontrol may be consistent with emotional lability. This is a typical phenomena found to occur in 19%-49% of ALS patients (41, 42), and it is most often present in patients who have pseudo-bulbar symptomatology (41, 43). ALSAQ-40, a disease-specific measure recently validated in Italian language (see chapter 4) (36), was employed to assess quality of life and well-being perceived in patients: we considered

correlations with measure's global domains and Rorschach variables. 'Emotional Functioning', domain confirmed the construct validity of both measures, thanks to correlation with coping defect constellation and depressive constellation. The depressive constellation, called DEPI, includes 14 variables, each of which is tested against a criterion, and ultimately yield this DEPI scores from zero to seven. This includes dystimics (neurotic depression), unipolar depressives, bipolar disorders. The coping defect constellation, called CDI, consist of 11 variables that are used in criterion tests yielding a CDI scores of zero to five. Although CDI is not a depression index, the presence of positive CDI among individuals diagnosed as depressed reflects social deficits that worsen depressive symptomatology (44). In our ALS sample, 60% of patients showed the positivity in DEPI constellation, 75% displayed positivity in CDI constellation and 43% of them showed the co presence of both constellation as positive. Difficulty in 'Activities of Daily Living and Independence' appeared involved with high stress perceived, shame and embarrassment, presence of uncertainty, confusion in feelings, and lack of control in emotional expression. Loss of 'Physical Mobility' correlated with low number of responses production, that can indicate low interest in task or an effort to simplify the reality. The reason of this correlation may be accounted in a number of ways, such as an expression of opposition and anger. 'Eating and Drinking' domain difficulties appear involved in morbid ideation: this index underlines the presence of pessimistic view of the feature, and self-image marked by negative characteristics. (37). Impairment in 'Communication' domain correlated with the inflexibility of thoughts, yet detected in literature as typical feature of the disease, (8) and with efforts to simplify reality. After correlating demographic data with Rorschach variables we divided ALS sample into two groups respect of time of length of diagnosis, as mentioned earlier, and the two ALS groups were compared to each other and respectively with myastenic patients. Most striking differences between two groups of ALS patients was suicidal ideation, greater in patients with recent diagnosis respect of patients with length of diagnosis longer than two years. Suicide ideation was assessed with Rorschach Suicide Constellation (S-CON) and consists of 12 seemingly heterogeneous psychological variables, each of which is reviewed against a

criterion to determine if finding is positive or negative; it is reported as ecologically valid, real-world behaviours of serious suicide attempts, rather than assessing general impulsivity or self-destructive trends (45). Sixty-eight per cent of our patients with recent diagnosis versus 30% of longer one were assessed as potential suicide, using a cut-off of eight or more variables in S-CON. Few studies have investigated wish of hasten death in ALS patients so far. Albert and colleagues (25) found a prevalence as 18.9% for the wish to die in ALS patients in the end-sage patient sample: this percentage is consistent with our findings in our cohort of patients with time since first diagnosis longer than two years. Similar findings have been reported in other studies for ALS (46 ,26) and for other kind of patients near death, including people with cancer, AIDS, and those receiving hospice and in-home palliative care (47, 48, 49). According to a recent ALS cross-cultural study wish to die (50), great variations in this percentage were respect to the living country and to the cultural factors. However, all researches were nowadays focused on the last period of life of ALS patients.

Other interesting different indices between these two groups were anxiety, distrust in other people and less accurate detection of reality: these features appeared significantly higher in patients with recent diagnosis. In a longitudinal study on quality of life and depression (51), Gauthier and colleagues found a substantial steadiness of depression in ALS patients in different stages of disease. Rabkin et al (12) found that multiple measures of depression and distress converged to indicate that major depression in people with late-stage ALS is rare, although transient depressive symptoms may occur, and depression does not generally increase as death approaches. According to the same author (7), depressive symptoms and psychological distress were not related to the amount of time since diagnosis, to the degree of disability, or to the progression of the illness. On the contrary, in our research emerges a worsening psychological condition in the first phase of illness. This inconsistent finding can be due to the fact that previous studies have employed self-report measure, focusing on what patients decide to voice.

Comparison between ALS patients with recent diagnosis and myastenic patients was the one that revealed greater differences. Also in this case, suicidal ideation

appear significantly higher in ALS patients. In particular, among Rorschach variables that constitutes suicide constellation, the most important aspects leading to statistic significance were morbid ideation, confusive emotions, anger and overburden of stress. Other dramatic aspect greater in ALS patients with recent diagnosis respect of myastenic controls appear as coping defect in social relations and depressive symptoms.

Last comparison was performed between ALS patients with longer diagnosis and myastenic controls. Similarly to previous analyses, statistics showed significant presence of suicidal ideation greater in ALS patients than in myastenic sample: psychological index more present in this constellation is the overburden of stress. Another important difference higher in ALS patients is the severe incongruous combination, such as the presence in the responses of the highly implausible, or impossible, features or activities attributed to a single object. It can be the result of ideational negligence, or of strained, disrupted, inappropriate thinking that departs noticeably from reality and can reflects neuropsychological impairment or psychotic aspects. This datum is supported by the low frequency of Human Movement index, that reflects intellective abilities and represents a significant correlation with Intellective Quotient (52). This finding could be representative of cognitive decline in ALS patients: early in the disease course, over one third of the ALS subjects appear to develop cognitive deficits in longitudinal studies, supporting the hypothesis that cognitive deficits in ALS become more prominent over time (53, 54).

Moreover, ALS patients appeared less cooperative respect to myastenic sample and displayed higher coping defect in social relation.

In conclusion, we investigated cognitive and affective patterns linked to physical impairment in a sample of 42 ALS patients: as described elsewhere, people with ALS exhibited psychological distress. From our data emerged a more dramatic psychopathological profile associated with lost of upper limb districts respect of lower districts, mainly in terms of affective impulsiveness, lack of interest and environment with others and incapacity to tolerate the quote of stress perceived. Greater anxiety and various psychological features appear correlate to loss of forced vital capacity, such as the presence of anger.

Quality of life domain more involved with psychopathological reaction appeared the loss of independence in daily living and autonomous feeding.

Patients belonging to the group of diagnosis more recent than two years present higher suicidal ideation respect if compared to patients belonging to longer diagnosis group. In both group suicidal ideation is higher than controls. This constellation, if found as positive, identifies 75% of the effected suicides (55). Patients probably do not act the suicidal purpose because they are conscious of their fatal disease: it remains that the first phase appeared the most critical and thy need specific psychological support. Wish to hasten death appeared as more common than previously thought in MND, and the stereotype of "cheerful, stoical, and positive" individuals must be revised.

All of these observations raise many questions, and suggest the necessity to undertake longitudinal studies. Patients should be evaluated in the months following the disclosure of the diagnosis, and then every six months during the evaluation of the disease. These evaluations should include neurological, psychological, psychopathological and cognitive assessment. The psychological evaluation should focus on suicidal ideation and coping strategies, but also on the evaluation of depression, anxiety and anger. Particular attention must be paid to suicidal ideation in the first, critical period after diagnosis, and must be considered that the more painful areas seem to be loss of strength in upper muscular districts, loss of breath and diminished abilities in autonomous feeding and independence. Mc Donald et al. observed that the psychological status at the beginning of their study was related to the mortality rate (15). So, a more accurate knowledge of the psychological and emotional aspects, as well the adaptive patterns observed, would allows us to provide better clinical treatments and to tailor psychological interventions for these patients and their families.

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7. ABSTRACT / RIASSUNTO

UN APPROFONDIMENTIMENTO NEUROPSICOLOGICO E COGNITIVO NELLA MALTTIA DEL MOTENURONE / SCLEREOSI LATERALE AMIOTROFICA
(MND/ALS)

1) Si sono valutate le funzioni cognitive di 128 pazienti MND (vs 113 controlli sani), con una esaustiva batteria di test neuropsicologici: disfunzioni significativamente presenti appaiono nel 40% dei casi (soprattutto a carico delle funzioni esecutive e della memoria a breve termine, confermando le disfunzioni esecutive come il più frequente deficit in questa patologia); il 7% presenta una franca demenza frontale o fronto-temporale (capitolo 2).

2) Nove pazienti ALS (vs 10 controlli sani) sono stati sottoposti ad indagine con fMRI: si sono evinte differenze significative soprattutto nella lateralizzazione nell'attivazione tra pazienti e controlli durante il compito di attenzione, sia per parole-stimolo neutre che nagative (attivazione statisticamente maggiore nel giro frontale sinistro nei pazienti, e di aree frontali, parietali e cerebellari sinistre nei controlli) e di una minore attivazione da parte dei pz del cingolo posteriore destro nel recupero mnesico di parole sia neutre che negative (capitolo 3).

3) Si è validato in italiano un questionario specifico di qualità di vita per la MND/ALS, l'ALSAQ-40, verificandone la validità psicometria su 76 pazienti: correlazioni funzionali sono discusse nel testo (capitolo 4).

4) Si è validato in italiano l'ELQ, un questionario per la valutazione della labilità emotiva su 41 pazienti MND e 39 rispettivi caregiver (vs 39 controlli e 39 pseudo-caregivers): la mancanza di correlazione con il profilo neuropsicologico e la correlazione con aspetti psicopatologici, sia nei pazienti che nei caregivers, sono descritte nel testo (capitolo 5).

5) Il test di Rorschach (metodo Exner) è stato somministrato a 21 pazienti ALS con esordio recente, 21 con esordio superiore ai due anni e 21 controlli miastenici: tra i numerosi risultati, di rilievo segnalare come l'ideazione suicidaria appaia statisticamente maggiore nel sottogruppo ALS con diagnosi più recente rispetto a quello con diagnosi più remota (capitolo 6).

A NEUROPSYCHOLOGICAL AND COGNITIVE INSIGHT INTO MOTOR NEURON DISEASE/ AMYOTROPHIC LATERAL SCLEROSIS
(MND/ALS)

1) We evaluated cognitive functioning in 128 MND patients (vs 113 healthy controls), with a comprehensive neuropsychological battery. Dysfunctions were significantly present in 40% of cases (mainly for executive functioning and short-term memory); 7% of them showed clear frontal or fronto-temporal dementia (chapter 2).

2) Nine ALS patients (vs 10 healthy controls) underwent the fMRI study: significant differences were displayed in lateralized activation between patients and controls during the attentional task, both for unpleasant and for neutral word stimuli (statistically greater activation in right middle frontal gyrus for patients, greater activation for frontal, parietal and cerebellar areas in controls) and lower activation was shown in patients in the posterior cingulate during mnesic recall, for both unpleasant and neutral stimuli (chapter 3).

3) We validated an Italian version of a specific quality of life questionnaire for MND/ALS: the ALSAQ-40, psychometric reliability in terms of internal reliability, construct validity, test-retest reliability and face validity were evaluated on the basis of 76 patients' responses. Correlation with functional and clinical measures are discussed in the text (chapter 4).

4) Similarly, we validated an Italian version of the ELQ, (a questionnaire for detecting emotional lability) on 41 MND patients and 39 respective caregivers (vs 39 healthy controls and 39 pseudo-caregivers). The lack of correlation with neuropsychological profile and correlations with psychopathological indices, both in patients and in caregivers, are described in the text (chapter 5).

5) The Rorschach test (according to Exner's guidelines) was administred to 21 ALS patients with early onset, 21 with onset longer than two years and 21 myasthenic controls. Among the numerous findings obtained, suicidal ideation was significantly more present in the ALS group with a recent diagnosis compared to those with a more remote one (chapter 6).

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APPENDICES

APPENDIX I: UNPLEASANT WORD STIMULI USED IN THE FMRI PARADIGMA (chapter 3)

	Words selected for the emotional task	Words added for the memory task
1	BOMBA	TRISTE
2	CATTIVA	STANCO
3	CIMITERI	PRIGIONE
4	COLPA	CANCRO
5	DIAVOLO	CADUTA
6	DOLORE	LADRO
7	DROGA	OFFESA
8	GUERRA	CIMITERI
9	MALATTIE	PIANGERE
10	MASSACRO	PESTE
11	MISERIA	PERDITA
12	MORIRE	ATTACCO
13	MORTO	REATO
14	ODIARE	PASSIVO
15	PECCATO	DELUSO
16	PERDITA	ANSIOSO
17	PERICOLO	DEBOLE
18	POVERO	DELUSO
19	RUBARE	INUTILE
20	SCHIAVO	ISOLATA
21	SCHIFO	NOIOSO
22	SOFFRIRE	ORRENDO
23	SPORCO	PESSIMO
24	STUPIDO	TRISTE
25	TRADIRE	UMILIATA
26	TRAGEDIA	PASSIVA
27	TUMORE	FALLITA
28	UCCISO	SCIEMA
29	VIOLENZA	SANGUE
30	VITTIMA	FERITA

APPENDIX II: NEUTRAL WORD STIMULI USED IN THE FMRI PARADIGMA (chapter 3)

	Words selected for the emotional task	Words added for the memory task
1	ADESIONE	ABITUATO
2	AFFATTO	ADEGUATA
3	ALBERO	AFFINCHè
4	ANGOLO	APERTO
5	ANIMALE	INIZIALE
6	BINARIO	OVVERO
7	CAMBIANO	PIOGGIA
8	CARTE	SCHIENA
9	CICLO	STANZA
10	CONTINUA	TETTO
11	COPRIRE	TRACCIA
12	FRUTTA	VANNO
13	IMPERO	PENNELLO
14	MONETA	PIANTA
15	ORIGINE	STAMPATO
16	PIATTO	PRESENTE
17	PIEDE	MENTALE
18	PORTE	REGOLARE
19	PRESENTE	CONFORME
20	RADICE	LISCIO
21	SCARPE	AZZURRA
22	SEGUENDO	ALCUNO
23	SPENDERE	FINCHè
24	STRADE	ORARIO
25	USANDO	SIMILE
26	VELOCE	PIOGGIA
27	VENTO	SIMBOLO
28	VESTITO	SERALE
29	VETRO	SUOLO
30	VOLUME	COTTO

APPENDIX III: ITALIAN VERSION OF AMYOTROPHIC LATERAL SCLEROSIS ASSESSMENT-40 ITEMS (ALSAQ-40)

ALSAQ-40

Le seguenti affermazioni si riferiscono ad alcune difficoltà che lei potrebbe aver riscontrato durante le ultime due settimane. Indichi per favore, ponendo una crocetta sulla casella appropriata, come si è sentito riguardo le seguenti affermazioni.

Se lei non può compiere affatto l'azione indicata dall'affermazione, la preghiamo di segnare la casella corrispondente a: ***Sempre / Non posso farlo affatto***

Quanto spesso durante le ultime due settimane ha pensato che le seguenti affermazioni fossero vere?

Ponga per favore una crocetta nella casella corrispondente ad ogni affermazione

	Mai	Raramente	Qualche Volta	Spesso	Sempre / non posso camminare affatto
1) Ho trovato difficile camminare anche per brevi distanze, per esempio in casa					
2) Sono caduto/a e mentre camminavo					
3) Sono inciampato/a mentre camminavo					
4) Ho perso l'equilibrio mentre camminavo					

5) Ho dovuto concentrarmi
nel camminare

---

6) Camminare mi ha
stancato moltissimo

---

7) Ho sentito male alle gambe
mentre camminavo

---

8) Ho trovato difficile
salire e scendere le scale

---

9) Ho trovato difficile
stare in piedi

---

10) Ho trovato difficile
alzarmi dalle sedie

---

11) Ho trovato difficile
usare le braccia e le mani

---

12) Ho trovato difficile
girarmi e muovermi nel letto

---

13) Ho avuto difficoltà
nell'afferrare gli oggetti

---

14) Ho trovato difficile
tenere in mano libri o giornali,
o girarne le pagine

---

15) Ho trovato difficile

scrivere con chiarezza

---

16) Ho trovato difficile
fare i lavori in casa

---

17) Ho avuto difficoltà
nel mangiare con le posate

---

18) Ho avuto difficoltà
nel pettinarmi o nel
lavarmi i denti

---

19) Ho trovato difficile
vestirmi

---

20) Ho trovato difficoltà
nel lavarmi sul lavabo del bagno

---

21) Ho trovato difficoltà
nel deglutire

---

22) Ho trovato difficoltà
nel mangiare cibi solidi

---

23) Ho trovato difficoltà
nel bere bevande liquide

---

24) Ho trovato difficoltà
nel partecipare alle conversazioni

---

25) Credo che non sia stato
facile capirmi quando parlavo

---

26) Ho balbettato o
farfugliato mentre parlavo

---

27) Ho dovuto parlare
molto lentamente

---

28) Ho parlato meno
di quanto fossi solito/a fare

---

29) Mi sono sentito/a frustrato/a
a causa del mio modo di parlare

---

30) Mi sono sentito/a a disagio
a causa del mio modo di parlare

---

31) Mi sono sentito/a solo/a

---

32) Mi sono annoiato/a

---

33) Mi sono sentito imbarazzato/a
nelle situazioni sociali

---

34) Mi sono sentito/a
senza speranza per il futuro

---

35) Ho temuto di essere
un peso per gli altri

---

36) Mi sono chiesto/a
perché andare avanti

---

37) Ho provato rabbia
a causa della mia malattia

---

38) Mi sono sentito depresso/a

---

39) Mi sono preoccupato/a
di come la malattia
potrà colpirmi nel futuro

---

40) Mi sono sentito/a privato/a
della mia libertà

Per favore si assicuri di aver segnato una casella per ciascuna domanda.

Grazie di aver compilato questo questionario.

APPENDIX IV: ITALIAN VERSION OF EMOTIONAL LABILITY QUESTIONNAIRE (ELQ) FOR MND PATIENTS

QUESTIONARIO SULLA LABILITA' EMOTIVA PAZIENTI CON MALATTIA DEL MOTONEURONE

Questo questionario riguarda l'espressione emotiva, in particolare il riso e il pianto. Leggi per favore attentamente ogni domanda e cerchia il numero accanto alla risposta che descrive meglio le tue reazioni emotive nelle ultime quattro settimane.

1. Ti sono capitati episodi improvvisi di **riso** nelle ultime quattro settimane? Quanto spesso?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 1, passa direttamente alla domanda 12. Se hai segnato 1), 2) o 3) alla domanda 1, prosegui alla domanda 2.

2. Quanti di questi episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

3. Quanti di questi episodi si sono verificati in un momento o in un luogo inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

4. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente (più di 30 sec.)

5. Quanti di questi episodi ti sembra di essere riuscito a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

6. Quanti di questi episodi sono avvenuti a causa di divertimento o felicità?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

7. In quanti di questi casi la risata è stata maggiore di quanto ti saresti aspettato/a in base al divertimento o felicità che provavi?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

8. In quanti episodi la risata è avvenuta in un momento in cui provavi tristezza (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

9. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

Specifica……
……

10. Quanti di questi episodi ti hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

11. Questa modalità di ridere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si

Se hai saltato dalla domanda 1, inizia qui.

12. Ti sono capitati episodi improvvisi di **pianto** nelle ultime quattro settimane?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 12, salta alla domanda 23. Se hai segnato 1), 2) o 3) alla domanda 12, continua dalla domanda 13.

13. Quanti episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

14. Quanti di questi episodi si sono verificati in un momento o in un luogo Inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

15. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente (più di 30 sec.)

16. Quanti di questi episodi ti sembra di essere riuscito a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

17. Quanti di questi episodi sono avvenuti a causa della tristezza?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

18. In quanti di questi casi il pianto è stato maggiore di quanto ti saresti aspettato/a in base al tuo dispiacere del momento?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

19. In quanti episodi il pianto è avvenuto in un momento in cui provavi felicità o divertimento (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

20. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

21. Quanti di questi episodi ti hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

22. Questa modalità di piangere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si

Se hai saltato dalla domanda 12,
comincia qui:

23. Ti sono capitati episodi inusuali di **sorriso** nelle ultime quattro settimane? Quanto spesso?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 23, ometti pure il resto del questionario. Se hai segnato 1), 2) o 3) alla domanda 23, prosegui alla domanda 24.

24. Quanti di questi episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

25. Quanti di questi episodi si sono verificati in un momento o in un luogo inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

26. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente (più di 30 sec.)

27. Quanti di questi episodi ti sembra di essere riuscito/a a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

28. Quanti di questi episodi sono avvenuti a causa di divertimento o felicità?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

29. In quanti di questi casi il sorriso è stato maggiore di quanto ti saresti aspettato/a in base al divertimento o felicità che provavi?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

30. In quanti episodi il sorriso è avvenuto in un momento in cui provavi tristezza (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

31. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

Specifica……
……

32. Quanti di questi episodi ti hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

33. Questa modalità di sorridere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si

APPENDIX V: ITALIAN VERSION OF EMOTIONAL LABILITY QUESTIONNAIRE (ELQ) FOR MND CAREGIVERS

QUESTIONARIO SULLA LABILITA'
EMOTIVA PER PARENTI E
ACCOMPAGNATORI

Questo questionario riguarda l'espressione emotiva, in particolare il riso e il pianto. Leggi per favore attentamente ogni domanda e cerchia il numero accanto alla risposta che descrive meglio le reazioni emotive di……nelle ultime quattro settimane.

1. Sono capitati al/alla paziente episodi improvvisi di **riso** nelle ultime quattro settimane? Quanto spesso?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 1, passa pure alla domanda 12. Se hai segnato 1), 2) o 3) alla domanda 1, prosegui alla domanda 2.

2. Quanti di questi episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

3. Quanti di questi episodi si sono verificati in un momento o in un luogo inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

4. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente (più di 30 sec.)

5. Quanti di questi episodi ti sembra che lui/lei sia riuscito a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

6. Quanti di questi episodi sono avvenuti a causa di divertimento
o felicità?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

7. In quanti di questi casi la risata è stata maggiore di quanto ti saresti aspettato/a in base al divertimento o felicità che lui/lei provava?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

8. In quanti episodi la risata è avvenuta in un momento in cui lui/lei provava tristezza (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

9. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

Specifica……
……

10. Quanti di questi episodi gli/le hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

11. Questa modalità di ridere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si

Se hai saltato dalla domanda 1, inizia qui.

12. Sono capitati al/alla paziente episodi improvvisi di **pianto** nelle ultime quattro settimane? Quanto spesso?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 12, salta alla domanda 23. Se hai segnato 1), 2) o 3) alla domanda 12, continua dalla domanda 13.

13. Quanti di questi episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

14. Quanti di questi episodi si sono verificati in un momento o in un luogo inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

15. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente (più di 30 sec.)

16. Quanti di questi episodi ti sembra che lui/lei sia riuscito a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

17. Quanti di questi episodi sono avvenuti a causa della tristezza?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

18. In quanti di questi casi il pianto è stato maggiore di quanto ti saresti aspettato/a in base al dispiacere momentaneo di lui/lei?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

19. In quanti episodi il pianto è avvenuto in un momento in cui lui/lei provava felicità o divertimento (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

20. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

Specifica……
……

21. Quanti di questi episodi gli/le hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

22. Questa modalità di piangere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si

Se hai saltato dalla domanda 12,
comincia qui:

23. Sono capitati a lui/lei episodi inusuali di **sorriso** nelle ultime quattro settimane?Quanto spesso?

0) Mai
1) A volte
2) Abbastanza spesso
3) Frequentemente

Se hai segnato 0) alla domanda 23, ometti pure il resto del questionario. Se hai segnato 1), 2) o 3) alla domanda 23, prosegui alla domanda 24.

24. Quanti di questi episodi si sono verificati indipendentemente dall'ambiente esterno?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

25. Quanti di questi episodi si sono verificati in un momento o in un luogo inadeguato, o quando tu non te lo saresti aspettato?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

26. In media, quanto sono durati questi episodi?

0) Molto poco
1) Poco (alcuni secondi)
2) Moderatamente (meno di 30 sec.)
3) Prolungatamente(più di 30 sec.)

27. Quanti di questi episodi ti sembra che lui/lei sia riuscito/a a controllare?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

28. Quanti di questi episodi sono avvenuti a causa di divertimento o felicità?

0) Tutti o quasi
1) La maggior parte
2) La minor parte
3) Nessuno

29. In quanti di questi casi il sorriso è stato maggiore di quanto ti saresti aspettato/a in base al divertimento o felicità che lui/lei provava?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

30. In quanti episodi il sorriso è avvenuto in un momento in cui provavi tristezza (sia subito prima che contemporaneamente) ?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

31. Quanti di questi episodi sono avvenuti insieme ad altre emozioni, come nervosismo, rabbia o paura (sia subito prima della risata che contemporaneamente)?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

Specifica……
……

32. Quanti di questi episodi gli/le hanno creato disagio sociale o imbarazzo?

0) Nessuno
1) La minor parte
2) La maggior parte
3) Quasi tutti

33. Questa modalità di sorridere rappresenta un cambiamento rispetto a prima dell'esordio della malattia del motoneurone?

0) No
1) Si